WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

VOLUME 98

Painting, Firefighting, and Shiftwork

LYON, FRANCE
2010

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This publication represents the views and expert opinions
of an IARC Monographs Working Group on the
Evaluation of Carcinogenic Risks to Humans,
which met in Lyon,

2–9 October 2007

2010

IARC MONOGRAPHS

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans involving the production of critically evaluated monographs on individual chemicals. The programme was subsequently expanded to include evaluations of carcinogenic risks associated with exposures to complex mixtures, lifestyle factors and biological and physical agents, as well as those in specific occupations. The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for agents to which humans are known to be exposed and on specific exposure situations; to evaluate these data in terms of human risk with the help of international working groups of experts in chemical carcinogenesis and related fields; and to indicate where additional research efforts are needed. The lists of IARC evaluations are regularly updated and are available on the Internet at http://monographs.iarc.fr/.

This programme has been supported since 1982 by Cooperative Agreement U01 CA33193 with the United States National Cancer Institute, Department of Health and Human Services. Additional support has been provided since 1986 by the Health, Safety and Hygiene at Work Unit of the European Commission Directorate-General for Employment, Social Affairs and Equal Opportunities, and since 1992 by the United States National Institute of Environmental Health Sciences, Department of Health and Human Services. The contents of this volume are solely the responsibility of the Working Group and do not necessarily represent the official views of the U.S. National Cancer Institute, the U.S. National Institute of Environmental Health Sciences, the U.S. Department of Health and Human Services, or the European Commission Directorate-General for Employment, Social Affairs and Equal Opportunities.

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NOTE TO THE READER

The term ‘carcinogenic risk’ in the *IARC Monographs* series is taken to mean that an agent is capable of causing cancer under some circumstances. The *Monographs* evaluate cancer hazards, despite the historical presence of the word ‘risks’ in the title.

Inclusion of an agent in the *Monographs* does not imply that it is a carcinogen, only that the published data have been examined. Equally, the fact that an agent has not yet been evaluated in a *Monograph* does not mean that it is not carcinogenic.

The evaluations of carcinogenic risk are made by international working groups of independent scientists and are qualitative in nature. No recommendation is given for regulation or legislation.

Anyone who is aware of published data that may alter the evaluation of the carcinogenic risk of an agent to humans is encouraged to make this information available to the Section of IARC Monographs, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France, in order that the agent may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the monographs as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the Section of IARC Monographs, so that corrections can be reported in future volumes.

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

VOLUME 98
PAINTING, SHIFTWORK, AND FIREFIGHTING

Lyon, 2–9 October 2007

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[1] Working Group Members and Invited Specialists serve in their individual capacities as scientists and not as representatives of their government or any organization with which they are affiliated. Affiliations are provided for identification purposes only.

[2] Each participant was asked to disclose pertinent research, employment, and financial interests. Current financial interests and research and employment interests during the past 3 years or anticipated in the future are identified here. Minor pertinent interests are not listed and include stock valued at no more than US$10 000 overall, grants that provide no more than 5% of the research budget of the expert's organization and that do not support the expert's research or position, and consulting or speaking on matters not before a court or government agency that does not exceed 2% of total professional time or compensation. All grants that support the expert's research or position and all consulting or speaking on behalf of an interested party on matters before a court or government agency are listed as significant pertinent interests.

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[3] Dr Landrigan is an inactive member of the Medical Advisory Committee of the John P. Redmond Foundation, which is affiliated with the International Association of Fire Fighters. He has not received any compensation or research support from these organizations.

[4] Dr LeMasters served as a factual witness for the Claimant in a 2006 court case in Vermont to decide whether the Claimant's non-Hodgkin lymphoma was causally related to his work as a firefighter. For this she received compensation of less than 5% of her total annual professional compensation. Dr LeMasters has no other recent or anticipated activities in this area.

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[5] Dr Arendt is a director and major shareholder of Stockgrand Ltd (UK), which sells melatonin measurement methodology. She also holds royalty rights on blue-light lamps manufactured by Philips Lighting (Netherlands), which also funds some of her research. In addition, she serves as a consultant to Alliance Pharmaceuticals (UK), which is developing melatonin products.

[6] Dr Austin worked as a consultant for McCarter & English LLP (formerly Cummings & Lockwood LLP), representing General Electrical Company in litigation involving a GE transformer fire, from January 2002 to July 2004.

[7] Dr Cherrie's employer, the Institute of Occupational Medicine, has done exposure assessment, litigation support, or other consulting work for several solvent manufacturers and related trade associations, including Euro Chlor, the European Chemical Industry Council (CEFIC), Akzo Nobel, and Ciba Specialty Chemicals.

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Jane Mitchell's colleagues gratefully acknowledge her many years of service in the *IARC Monographs* programme, beginning with Volume 29 (October 1981).

[8] Dr Sim has submitted a proposal as a co-principal investigator for a firefighter cohort study to the Melbourne, Australia, Metropolitan Fire Brigade.

PREAMBLE

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

PREAMBLE

The Preamble to the *IARC Monographs* describes the objective and scope of the programme, the scientific principles and procedures used in developing a *Monograph*, the types of evidence considered and the scientific criteria that guide the evaluations. The Preamble should be consulted when reading a *Monograph* or list of evaluations.

A. GENERAL PRINCIPLES AND PROCEDURES

1. Background

Soon after IARC was established in 1965, it received frequent requests for advice on the carcinogenic risk of chemicals, including requests for lists of known and suspected human carcinogens. It was clear that it would not be a simple task to summarize adequately the complexity of the information that was available, and IARC began to consider means of obtaining international expert opinion on this topic. In 1970, the IARC Advisory Committee on Environmental Carcinogenesis recommended '...that a compendium on carcinogenic chemicals be prepared by experts. The biological activity and evaluation of practical importance to public health should be referenced and documented.' The IARC Governing Council adopted a resolution concerning the role of IARC in providing government authorities with expert, independent, scientific opinion on environmental carcinogenesis. As one means to that end, the Governing Council recommended that IARC should prepare monographs on the evaluation of carcinogenic risk of chemicals to man, which became the initial title of the series.

In the succeeding years, the scope of the programme broadened as *Monographs* were developed for groups of related chemicals, complex mixtures, occupational exposures, physical and biological agents and lifestyle factors. In 1988, the phrase 'of chemicals' was dropped from the title, which assumed its present form, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*.

Through the *Monographs* programme, IARC seeks to identify the causes of human cancer. This is the first step in cancer prevention, which is needed as much today as when

IARC was established. The global burden of cancer is high and continues to increase: the annual number of new cases was estimated at 10.1 million in 2000 and is expected to reach 15 million by 2020 (Stewart & Kleihues, 2003). With current trends in demographics and exposure, the cancer burden has been shifting from high-resource countries to low- and medium-resource countries. As a result of *Monographs* evaluations, national health agencies have been able, on scientific grounds, to take measures to reduce human exposure to carcinogens in the workplace and in the environment.

The criteria established in 1971 to evaluate carcinogenic risks to humans were adopted by the Working Groups whose deliberations resulted in the first 16 volumes of the *Monographs* series. Those criteria were subsequently updated by further ad-hoc Advisory Groups (IARC, 1977, 1978, 1979, 1982, 1983, 1987, 1988, 1991; Vainio *et al.*, 1992; IARC, 2005, 2006).

The Preamble is primarily a statement of scientific principles, rather than a specification of working procedures. The procedures through which a Working Group implements these principles are not specified in detail. They usually involve operations that have been established as being effective during previous *Monograph* meetings but remain, predominantly, the prerogative of each individual Working Group.

2. Objective and scope

The objective of the programme is to prepare, with the help of international Working Groups of experts, and to publish in the form of *Monographs*, critical reviews and evaluations of evidence on the carcinogenicity of a wide range of human exposures. The *Monographs* represent the first step in carcinogen risk assessment, which involves examination of all relevant information in order to assess the strength of the available evidence that an agent could alter the age-specific incidence of cancer in humans. The *Monographs* may also indicate where additional research efforts are needed, specifically when data immediately relevant to an evaluation are not available.

In this Preamble, the term ‘agent’ refers to any entity or circumstance that is subject to evaluation in a *Monograph*. As the scope of the programme has broadened, categories of agents now include specific chemicals, groups of related chemicals, complex mixtures, occupational or environmental exposures, cultural or behavioural practices, biological organisms and physical agents. This list of categories may expand as causation of, and susceptibility to, malignant disease become more fully understood.

A cancer ‘hazard’ is an agent that is capable of causing cancer under some circumstances, while a cancer ‘risk’ is an estimate of the carcinogenic effects expected from exposure to a cancer hazard. The *Monographs* are an exercise in evaluating cancer hazards, despite the historical presence of the word ‘risks’ in the title. The distinction between hazard and risk is important, and the *Monographs* identify cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher.

In the *Monographs*, an agent is termed 'carcinogenic' if it is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity. The induction of benign neoplasms may in some circumstances (see Part B, Section 3a) contribute to the judgement that the agent is carcinogenic. The terms 'neoplasm' and 'tumour' are used interchangeably.

The Preamble continues the previous usage of the phrase 'strength of evidence' as a matter of historical continuity, although it should be understood that *Monographs* evaluations consider studies that support a finding of a cancer hazard as well as studies that do not.

Some epidemiological and experimental studies indicate that different agents may act at different stages in the carcinogenic process, and several different mechanisms may be involved. The aim of the *Monographs* has been, from their inception, to evaluate evidence of carcinogenicity at any stage in the carcinogenesis process, independently of the underlying mechanisms. Information on mechanisms may, however, be used in making the overall evaluation (IARC, 1991; Vainio *et al.*, 1992; IARC, 2005, 2006; see also Part B, Sections 4 and 6). As mechanisms of carcinogenesis are elucidated, IARC convenes international scientific conferences to determine whether a broad-based consensus has emerged on how specific mechanistic data can be used in an evaluation of human carcinogenicity. The results of such conferences are reported in IARC Scientific Publications, which, as long as they still reflect the current state of scientific knowledge, may guide subsequent Working Groups.

Although the *Monographs* have emphasized hazard identification, important issues may also involve dose–response assessment. In many cases, the same epidemiological and experimental studies used to evaluate a cancer hazard can also be used to estimate a dose–response relationship. A *Monograph* may undertake to estimate dose–response relationships within the range of the available epidemiological data, or it may compare the dose–response information from experimental and epidemiological studies. In some cases, a subsequent publication may be prepared by a separate Working Group with expertise in quantitative dose–response assessment.

The *Monographs* are used by national and international authorities to make risk assessments, formulate decisions concerning preventive measures, provide effective cancer control programmes and decide among alternative options for public health decisions. The evaluations of IARC Working Groups are scientific, qualitative judgements on the evidence for or against carcinogenicity provided by the available data. These evaluations represent only one part of the body of information on which public health decisions may be based. Public health options vary from one situation to another and from country to country and relate to many factors, including different socioeconomic and national priorities. Therefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of individual governments or other international organizations.

3. Selection of agents for review

Agents are selected for review on the basis of two main criteria: (a) there is evidence of human exposure and (b) there is some evidence or suspicion of carcinogenicity. Mixed exposures may occur in occupational and environmental settings and as a result of individual and cultural habits (such as tobacco smoking and dietary practices). Chemical analogues and compounds with biological or physical characteristics similar to those of suspected carcinogens may also be considered, even in the absence of data on a possible carcinogenic effect in humans or experimental animals.

The scientific literature is surveyed for published data relevant to an assessment of carcinogenicity. Ad-hoc Advisory Groups convened by IARC in 1984, 1989, 1991, 1993, 1998 and 2003 made recommendations as to which agents should be evaluated in the *Monographs* series. Recent recommendations are available on the *Monographs* programme website (http://monographs.iarc.fr). IARC may schedule other agents for review as it becomes aware of new scientific information or as national health agencies identify an urgent public health need related to cancer.

As significant new data become available on an agent for which a *Monograph* exists, a re-evaluation may be made at a subsequent meeting, and a new *Monograph* published. In some cases it may be appropriate to review only the data published since a prior evaluation. This can be useful for updating a database, reviewing new data to resolve a previously open question or identifying new tumour sites associated with a carcinogenic agent. Major changes in an evaluation (e.g. a new classification in Group 1 or a determination that a mechanism does not operate in humans, see Part B, Section 6) are more appropriately addressed by a full review.

4. Data for the *Monographs*

Each *Monograph* reviews all pertinent epidemiological studies and cancer bioassays in experimental animals. Those judged inadequate or irrelevant to the evaluation may be cited but not summarized. If a group of similar studies is not reviewed, the reasons are indicated.

Mechanistic and other relevant data are also reviewed. A *Monograph* does not necessarily cite all the mechanistic literature concerning the agent being evaluated (see Part B, Section 4). Only those data considered by the Working Group to be relevant to making the evaluation are included.

With regard to epidemiological studies, cancer bioassays, and mechanistic and other relevant data, only reports that have been published or accepted for publication in the openly available scientific literature are reviewed. The same publication requirement applies to studies originating from IARC, including meta-analyses or pooled analyses commissioned by IARC in advance of a meeting (see Part B, Section 2c). Data from government agency reports that are publicly available are also considered. Exceptionally,

doctoral theses and other material that are in their final form and publicly available may be reviewed.

Exposure data and other information on an agent under consideration are also reviewed. In the sections on chemical and physical properties, on analysis, on production and use and on occurrence, published and unpublished sources of information may be considered.

Inclusion of a study does not imply acceptance of the adequacy of the study design or of the analysis and interpretation of the results, and limitations are clearly outlined in square brackets at the end of each study description (see Part B). The reasons for not giving further consideration to an individual study also are indicated in the square brackets.

5. Meeting participants

Five categories of participant can be present at *Monograph* meetings.

(a) The Working Group is responsible for the critical reviews and evaluations that are developed during the meeting. The tasks of Working Group Members are: (i) to ascertain that all appropriate data have been collected; (ii) to select the data relevant for the evaluation on the basis of scientific merit; (iii) to prepare accurate summaries of the data to enable the reader to follow the reasoning of the Working Group; (iv) to evaluate the results of epidemiological and experimental studies on cancer; (v) to evaluate data relevant to the understanding of mechanisms of carcinogenesis; and (vi) to make an overall evaluation of the carcinogenicity of the exposure to humans. Working Group Members generally have published significant research related to the carcinogenicity of the agents being reviewed, and IARC uses literature searches to identify most experts. Working Group Members are selected on the basis of (a) knowledge and experience and (b) absence of real or apparent conflicts of interests. Consideration is also given to demographic diversity and balance of scientific findings and views.

(b) Invited Specialists are experts who also have critical knowledge and experience but have a real or apparent conflict of interests. These experts are invited when necessary to assist in the Working Group by contributing their unique knowledge and experience during subgroup and plenary discussions. They may also contribute text on non-influential issues in the section on exposure, such as a general description of data on production and use (see Part B, Section 1). Invited Specialists do not serve as meeting chair or subgroup chair, draft text that pertains to the description or interpretation of cancer data, or participate in the evaluations.

(c) Representatives of national and international health agencies often attend meetings because their agencies sponsor the programme or are interested in the subject of a meeting. Representatives do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations.

(d) Observers with relevant scientific credentials may be admitted to a meeting by IARC in limited numbers. Attention will be given to achieving a balance of Observers

from constituencies with differing perspectives. They are invited to observe the meeting and should not attempt to influence it. Observers do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations. At the meeting, the meeting chair and subgroup chairs may grant Observers an opportunity to speak, generally after they have observed a discussion. Observers agree to respect the Guidelines for Observers at *IARC Monographs* meetings (available at http://monographs.iarc.fr).

(e) The IARC Secretariat consists of scientists who are designated by IARC and who have relevant expertise. They serve as rapporteurs and participate in all discussions. When requested by the meeting chair or subgroup chair, they may also draft text or prepare tables and analyses.

Before an invitation is extended, each potential participant, including the IARC Secretariat, completes the WHO Declaration of Interests to report financial interests, employment and consulting, and individual and institutional research support related to the subject of the meeting. IARC assesses these interests to determine whether there is a conflict that warrants some limitation on participation. The declarations are updated and reviewed again at the opening of the meeting. Interests related to the subject of the meeting are disclosed to the meeting participants and in the published volume (Cogliano *et al.*, 2004).

The names and principal affiliations of participants are available on the *Monographs* programme website (http://monographs.iarc.fr) approximately two months before each meeting. It is not acceptable for Observers or third parties to contact other participants before a meeting or to lobby them at any time. Meeting participants are asked to report all such contacts to IARC (Cogliano *et al.*, 2005).

All participants are listed, with their principal affiliations, at the beginning of each volume. Each participant who is a Member of a Working Group serves as an individual scientist and not as a representative of any organization, government or industry.

6. Working procedures

A separate Working Group is responsible for developing each volume of *Monographs*. A volume contains one or more *Monographs*, which can cover either a single agent or several related agents. Approximately one year in advance of the meeting of a Working Group, the agents to be reviewed are announced on the *Monographs* programme website (http://monographs.iarc.fr) and participants are selected by IARC staff in consultation with other experts. Subsequently, relevant biological and epidemiological data are collected by IARC from recognized sources of information on carcinogenesis, including data storage and retrieval systems such as PubMed. Meeting participants who are asked to prepare preliminary working papers for specific sections are expected to supplement the IARC literature searches with their own searches.

For most chemicals and some complex mixtures, the major collection of data and the preparation of working papers for the sections on chemical and physical properties, on

analysis, on production and use, and on occurrence are carried out under a separate contract funded by the US National Cancer Institute. Industrial associations, labour unions and other knowledgeable organizations may be asked to provide input to the sections on production and use, although this involvement is not required as a general rule. Information on production and trade is obtained from governmental, trade and market research publications and, in some cases, by direct contact with industries. Separate production data on some agents may not be available for a variety of reasons (e.g. not collected or made public in all producing countries, production is small). Information on uses may be obtained from published sources but is often complemented by direct contact with manufacturers. Efforts are made to supplement this information with data from other national and international sources.

Six months before the meeting, the material obtained is sent to meeting participants to prepare preliminary working papers. The working papers are compiled by IARC staff and sent, prior to the meeting, to Working Group Members and Invited Specialists for review.

The Working Group meets at IARC for seven to eight days to discuss and finalize the texts and to formulate the evaluations. The objectives of the meeting are peer review and consensus. During the first few days, four subgroups (covering exposure data, cancer in humans, cancer in experimental animals, and mechanistic and other relevant data) review the working papers, develop a joint subgroup draft and write summaries. Care is taken to ensure that each study summary is written or reviewed by someone not associated with the study being considered. During the last few days, the Working Group meets in plenary session to review the subgroup drafts and develop the evaluations. As a result, the entire volume is the joint product of the Working Group, and there are no individually authored sections.

IARC Working Groups strive to achieve a consensus evaluation. Consensus reflects broad agreement among Working Group Members, but not necessarily unanimity. The chair may elect to poll Working Group Members to determine the diversity of scientific opinion on issues where consensus is not readily apparent.

After the meeting, the master copy is verified by consulting the original literature, edited and prepared for publication. The aim is to publish the volume within six months of the Working Group meeting. A summary of the outcome is available on the *Monographs* programme website soon after the meeting.

B. SCIENTIFIC REVIEW AND EVALUATION

The available studies are summarized by the Working Group, with particular regard to the qualitative aspects discussed below. In general, numerical findings are indicated as they appear in the original report; units are converted when necessary for easier comparison. The Working Group may conduct additional analyses of the published data and use them in their assessment of the evidence; the results of such supplementary

analyses are given in square brackets. When an important aspect of a study that directly impinges on its interpretation should be brought to the attention of the reader, a Working Group comment is given in square brackets.

The scope of the *IARC Monographs* programme has expanded beyond chemicals to include complex mixtures, occupational exposures, physical and biological agents, lifestyle factors and other potentially carcinogenic exposures. Over time, the structure of a *Monograph* has evolved to include the following sections:

1. Exposure data
2. Studies of cancer in humans
3. Studies of cancer in experimental animals
4. Mechanistic and other relevant data
5. Summary
6. Evaluation and rationale

In addition, a section of General Remarks at the front of the volume discusses the reasons the agents were scheduled for evaluation and some key issues the Working Group encountered during the meeting.

This part of the Preamble discusses the types of evidence considered and summarized in each section of a *Monograph*, followed by the scientific criteria that guide the evaluations.

1. Exposure data

Each *Monograph* includes general information on the agent: this information may vary substantially between agents and must be adapted accordingly. Also included is information on production and use (when appropriate), methods of analysis and detection, occurrence, and sources and routes of human occupational and environmental exposures. Depending on the agent, regulations and guidelines for use may be presented.

(*a*) *General information on the agent*

For chemical agents, sections on chemical and physical data are included: the Chemical Abstracts Service Registry Number, the latest primary name and the IUPAC systematic name are recorded; other synonyms are given, but the list is not necessarily comprehensive. Information on chemical and physical properties that are relevant to identification, occurrence and biological activity is included. A description of technical products of chemicals includes trade names, relevant specifications and available information on composition and impurities. Some of the trade names given may be those of mixtures in which the agent being evaluated is only one of the ingredients.

For biological agents, taxonomy, structure and biology are described, and the degree of variability is indicated. Mode of replication, life cycle, target cells, persistence, latency, host response and clinical disease other than cancer are also presented.

For physical agents that are forms of radiation, energy and range of the radiation are included. For foreign bodies, fibres and respirable particles, size range and relative dimensions are indicated.

For agents such as mixtures, drugs or lifestyle factors, a description of the agent, including its composition, is given.

Whenever appropriate, other information, such as historical perspectives or the description of an industry or habit, may be included.

(*b*) *Analysis and detection*

An overview of methods of analysis and detection of the agent is presented, including their sensitivity, specificity and reproducibility. Methods widely used for regulatory purposes are emphasized. Methods for monitoring human exposure are also given. No critical evaluation or recommendation of any method is meant or implied.

(*c*) *Production and use*

The dates of first synthesis and of first commercial production of a chemical, mixture or other agent are provided when available; for agents that do not occur naturally, this information may allow a reasonable estimate to be made of the date before which no human exposure to the agent could have occurred. The dates of first reported occurrence of an exposure are also provided when available. In addition, methods of synthesis used in past and present commercial production and different methods of production, which may give rise to different impurities, are described.

The countries where companies report production of the agent, and the number of companies in each country, are identified. Available data on production, international trade and uses are obtained for representative regions. It should not, however, be inferred that those areas or nations are necessarily the sole or major sources or users of the agent. Some identified uses may not be current or major applications, and the coverage is not necessarily comprehensive. In the case of drugs, mention of their therapeutic uses does not necessarily represent current practice nor does it imply judgement as to their therapeutic efficacy.

(*d*) *Occurrence and exposure*

Information on the occurrence of an agent in the environment is obtained from data derived from the monitoring and surveillance of levels in occupational environments, air, water, soil, plants, foods and animal and human tissues. When available, data on the generation, persistence and bioaccumulation of the agent are also included. Such data may be available from national databases.

Data that indicate the extent of past and present human exposure, the sources of exposure, the people most likely to be exposed and the factors that contribute to the exposure are reported. Information is presented on the range of human exposure, including occupational and environmental exposures. This includes relevant findings

from both developed and developing countries. Some of these data are not distributed widely and may be available from government reports and other sources. In the case of mixtures, industries, occupations or processes, information is given about all agents known to be present. For processes, industries and occupations, a historical description is also given, noting variations in chemical composition, physical properties and levels of occupational exposure with date and place. For biological agents, the epidemiology of infection is described.

(*e*) *Regulations and guidelines*

Statements concerning regulations and guidelines (e.g. occupational exposure limits, maximal levels permitted in foods and water, pesticide registrations) are included, but they may not reflect the most recent situation, since such limits are continuously reviewed and modified. The absence of information on regulatory status for a country should not be taken to imply that that country does not have regulations with regard to the exposure. For biological agents, legislation and control, including vaccination and therapy, are described.

2. Studies of cancer in humans

This section includes all pertinent epidemiological studies (see Part A, Section 4). Studies of biomarkers are included when they are relevant to an evaluation of carcinogenicity to humans.

(*a*) *Types of study considered*

Several types of epidemiological study contribute to the assessment of carcinogenicity in humans — cohort studies, case–control studies, correlation (or ecological) studies and intervention studies. Rarely, results from randomized trials may be available. Case reports and case series of cancer in humans may also be reviewed.

Cohort and case–control studies relate individual exposures under study to the occurrence of cancer in individuals and provide an estimate of effect (such as relative risk) as the main measure of association. Intervention studies may provide strong evidence for making causal inferences, as exemplified by cessation of smoking and the subsequent decrease in risk for lung cancer.

In correlation studies, the units of investigation are usually whole populations (e.g. in particular geographical areas or at particular times), and cancer frequency is related to a summary measure of the exposure of the population to the agent under study. In correlation studies, individual exposure is not documented, which renders this kind of study more prone to confounding. In some circumstances, however, correlation studies may be more informative than analytical study designs (see, for example, the *Monograph* on arsenic in drinking-water; IARC, 2004).

In some instances, case reports and case series have provided important information about the carcinogenicity of an agent. These types of study generally arise from a suspicion, based on clinical experience, that the concurrence of two events — that is, a particular exposure and occurrence of a cancer — has happened rather more frequently than would be expected by chance. Case reports and case series usually lack complete ascertainment of cases in any population, definition or enumeration of the population at risk and estimation of the expected number of cases in the absence of exposure.

The uncertainties that surround the interpretation of case reports, case series and correlation studies make them inadequate, except in rare instances, to form the sole basis for inferring a causal relationship. When taken together with case–control and cohort studies, however, these types of study may add materially to the judgement that a causal relationship exists.

Epidemiological studies of benign neoplasms, presumed preneoplastic lesions and other end-points thought to be relevant to cancer are also reviewed. They may, in some instances, strengthen inferences drawn from studies of cancer itself.

(*b*) *Quality of studies considered*

It is necessary to take into account the possible roles of bias, confounding and chance in the interpretation of epidemiological studies. Bias is the effect of factors in study design or execution that lead erroneously to a stronger or weaker association than in fact exists between an agent and disease. Confounding is a form of bias that occurs when the relationship with disease is made to appear stronger or weaker than it truly is as a result of an association between the apparent causal factor and another factor that is associated with either an increase or decrease in the incidence of the disease. The role of chance is related to biological variability and the influence of sample size on the precision of estimates of effect.

In evaluating the extent to which these factors have been minimized in an individual study, consideration is given to a number of aspects of design and analysis as described in the report of the study. For example, when suspicion of carcinogenicity arises largely from a single small study, careful consideration is given when interpreting subsequent studies that included these data in an enlarged population. Most of these considerations apply equally to case–control, cohort and correlation studies. Lack of clarity of any of these aspects in the reporting of a study can decrease its credibility and the weight given to it in the final evaluation of the exposure.

Firstly, the study population, disease (or diseases) and exposure should have been well defined by the authors. Cases of disease in the study population should have been identified in a way that was independent of the exposure of interest, and exposure should have been assessed in a way that was not related to disease status.

Secondly, the authors should have taken into account — in the study design and analysis — other variables that can influence the risk of disease and may have been related to the exposure of interest. Potential confounding by such variables should have been dealt with either in the design of the study, such as by matching, or in the analysis,

by statistical adjustment. In cohort studies, comparisons with local rates of disease may or may not be more appropriate than those with national rates. Internal comparisons of frequency of disease among individuals at different levels of exposure are also desirable in cohort studies, since they minimize the potential for confounding related to the difference in risk factors between an external reference group and the study population.

Thirdly, the authors should have reported the basic data on which the conclusions are founded, even if sophisticated statistical analyses were employed. At the very least, they should have given the numbers of exposed and unexposed cases and controls in a case–control study and the numbers of cases observed and expected in a cohort study. Further tabulations by time since exposure began and other temporal factors are also important. In a cohort study, data on all cancer sites and all causes of death should have been given, to reveal the possibility of reporting bias. In a case–control study, the effects of investigated factors other than the exposure of interest should have been reported.

Finally, the statistical methods used to obtain estimates of relative risk, absolute rates of cancer, confidence intervals and significance tests, and to adjust for confounding should have been clearly stated by the authors. These methods have been reviewed for case–control studies (Breslow & Day, 1980) and for cohort studies (Breslow & Day, 1987).

(*c*) *Meta-analyses and pooled analyses*

Independent epidemiological studies of the same agent may lead to results that are difficult to interpret. Combined analyses of data from multiple studies are a means of resolving this ambiguity, and well-conducted analyses can be considered. There are two types of combined analysis. The first involves combining summary statistics such as relative risks from individual studies (meta-analysis) and the second involves a pooled analysis of the raw data from the individual studies (pooled analysis) (Greenland, 1998).

The advantages of combined analyses are increased precision due to increased sample size and the opportunity to explore potential confounders, interactions and modifying effects that may explain heterogeneity among studies in more detail. A disadvantage of combined analyses is the possible lack of compatibility of data from various studies due to differences in subject recruitment, procedures of data collection, methods of measurement and effects of unmeasured co-variates that may differ among studies. Despite these limitations, well-conducted combined analyses may provide a firmer basis than individual studies for drawing conclusions about the potential carcinogenicity of agents.

IARC may commission a meta-analysis or pooled analysis that is pertinent to a particular *Monograph* (see Part A, Section 4). Additionally, as a means of gaining insight from the results of multiple individual studies, ad-hoc calculations that combine data from different studies may be conducted by the Working Group during the course of a *Monograph* meeting. The results of such original calculations, which would be specified in the text by presentation in square brackets, might involve updates of previously conducted analyses that incorporate the results of more recent studies or de-novo

analyses. Irrespective of the source of data for the meta-analyses and pooled analyses, it is important that the same criteria for data quality be applied as those that would be applied to individual studies and to ensure also that sources of heterogeneity between studies be taken into account.

(*d*) *Temporal effects*

Detailed analyses of both relative and absolute risks in relation to temporal variables, such as age at first exposure, time since first exposure, duration of exposure, cumulative exposure, peak exposure (when appropriate) and time since cessation of exposure, are reviewed and summarized when available. Analyses of temporal relationships may be useful in making causal inferences. In addition, such analyses may suggest whether a carcinogen acts early or late in the process of carcinogenesis, although, at best, they allow only indirect inferences about mechanisms of carcinogenesis.

(*e*) *Use of biomarkers in epidemiological studies*

Biomarkers indicate molecular, cellular or other biological changes and are increasingly used in epidemiological studies for various purposes (IARC, 1991; Vainio *et al.*, 1992; Toniolo *et al.*, 1997; Vineis *et al.*, 1999; Buffler *et al.*, 2004). These may include evidence of exposure, of early effects, of cellular, tissue or organism responses, of individual susceptibility or host responses, and inference of a mechanism (see Part B, Section 4b). This is a rapidly evolving field that encompasses developments in genomics, epigenomics and other emerging technologies.

Molecular epidemiological data that identify associations between genetic polymorphisms and interindividual differences in susceptibility to the agent(s) being evaluated may contribute to the identification of carcinogenic hazards to humans. If the polymorphism has been demonstrated experimentally to modify the functional activity of the gene product in a manner that is consistent with increased susceptibility, these data may be useful in making causal inferences. Similarly, molecular epidemiological studies that measure cell functions, enzymes or metabolites that are thought to be the basis of susceptibility may provide evidence that reinforces biological plausibility. It should be noted, however, that when data on genetic susceptibility originate from multiple comparisons that arise from subgroup analyses, this can generate false-positive results and inconsistencies across studies, and such data therefore require careful evaluation. If the known phenotype of a genetic polymorphism can explain the carcinogenic mechanism of the agent being evaluated, data on this phenotype may be useful in making causal inferences.

(*f*) *Criteria for causality*

After the quality of individual epidemiological studies of cancer has been summarized and assessed, a judgement is made concerning the strength of evidence that the agent in question is carcinogenic to humans. In making its judgement, the Working Group

considers several criteria for causality (Hill, 1965). A strong association (e.g. a large relative risk) is more likely to indicate causality than a weak association, although it is recognized that estimates of effect of small magnitude do not imply lack of causality and may be important if the disease or exposure is common. Associations that are replicated in several studies of the same design or that use different epidemiological approaches or under different circumstances of exposure are more likely to represent a causal relationship than isolated observations from single studies. If there are inconsistent results among investigations, possible reasons are sought (such as differences in exposure), and results of studies that are judged to be of high quality are given more weight than those of studies that are judged to be methodologically less sound.

If the risk increases with the exposure, this is considered to be a strong indication of causality, although the absence of a graded response is not necessarily evidence against a causal relationship. The demonstration of a decline in risk after cessation of or reduction in exposure in individuals or in whole populations also supports a causal interpretation of the findings.

A number of scenarios may increase confidence in a causal relationship. On the one hand, an agent may be specific in causing tumours at one site or of one morphological type. On the other, carcinogenicity may be evident through the causation of multiple tumour types. Temporality, precision of estimates of effect, biological plausibility and coherence of the overall database are considered. Data on biomarkers may be employed in an assessment of the biological plausibility of epidemiological observations.

Although rarely available, results from randomized trials that show different rates of cancer among exposed and unexposed individuals provide particularly strong evidence for causality.

When several epidemiological studies show little or no indication of an association between an exposure and cancer, a judgement may be made that, in the aggregate, they show evidence of lack of carcinogenicity. Such a judgement requires firstly that the studies meet, to a sufficient degree, the standards of design and analysis described above. Specifically, the possibility that bias, confounding or misclassification of exposure or outcome could explain the observed results should be considered and excluded with reasonable certainty. In addition, all studies that are judged to be methodologically sound should (a) be consistent with an estimate of effect of unity for any observed level of exposure, (b) when considered together, provide a pooled estimate of relative risk that is at or near to unity, and (c) have a narrow confidence interval, due to sufficient population size. Moreover, no individual study nor the pooled results of all the studies should show any consistent tendency that the relative risk of cancer increases with increasing level of exposure. It is important to note that evidence of lack of carcinogenicity obtained from several epidemiological studies can apply only to the type(s) of cancer studied, to the dose levels reported, and to the intervals between first exposure and disease onset observed in these studies. Experience with human cancer indicates that the period from first exposure to the development of clinical cancer is sometimes longer than 20 years; latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity.

3. Studies of cancer in experimental animals

All known human carcinogens that have been studied adequately for carcinogenicity in experimental animals have produced positive results in one or more animal species (Wilbourn *et al.*, 1986; Tomatis *et al.*, 1989). For several agents (e.g. aflatoxins, diethylstilbestrol, solar radiation, vinyl chloride), carcinogenicity in experimental animals was established or highly suspected before epidemiological studies confirmed their carcinogenicity in humans (Vainio *et al.*, 1995). Although this association cannot establish that all agents that cause cancer in experimental animals also cause cancer in humans, it is biologically plausible that agents for which there is *sufficient evidence of carcinogenicity* in experimental animals (see Part B, Section 6b) also present a carcinogenic hazard to humans. Accordingly, in the absence of additional scientific information, these agents are considered to pose a carcinogenic hazard to humans. Examples of additional scientific information are data that demonstrate that a given agent causes cancer in animals through a species-specific mechanism that does not operate in humans or data that demonstrate that the mechanism in experimental animals also operates in humans (see Part B, Section 6).

Consideration is given to all available long-term studies of cancer in experimental animals with the agent under review (see Part A, Section 4). In all experimental settings, the nature and extent of impurities or contaminants present in the agent being evaluated are given when available. Animal species, strain (including genetic background where applicable), sex, numbers per group, age at start of treatment, route of exposure, dose levels, duration of exposure, survival and information on tumours (incidence, latency, severity or multiplicity of neoplasms or preneoplastic lesions) are reported. Those studies in experimental animals that are judged to be irrelevant to the evaluation or judged to be inadequate (e.g. too short a duration, too few animals, poor survival; see below) may be omitted. Guidelines for conducting long-term carcinogenicity experiments have been published (e.g. OECD, 2002).

Other studies considered may include: experiments in which the agent was administered in the presence of factors that modify carcinogenic effects (e.g. initiation–promotion studies, co-carcinogenicity studies and studies in genetically modified animals); studies in which the end-point was not cancer but a defined precancerous lesion; experiments on the carcinogenicity of known metabolites and derivatives; and studies of cancer in non-laboratory animals (e.g. livestock and companion animals) exposed to the agent.

For studies of mixtures, consideration is given to the possibility that changes in the physicochemical properties of the individual substances may occur during collection, storage, extraction, concentration and delivery. Another consideration is that chemical and toxicological interactions of components in a mixture may alter dose–response relationships. The relevance to human exposure of the test mixture administered in the animal experiment is also assessed. This may involve consideration of the following aspects of the mixture tested: (i) physical and chemical characteristics, (ii) identified

constituents that may indicate the presence of a class of substances and (iii) the results of genetic toxicity and related tests.

The relevance of results obtained with an agent that is analogous (e.g. similar in structure or of a similar virus genus) to that being evaluated is also considered. Such results may provide biological and mechanistic information that is relevant to the understanding of the process of carcinogenesis in humans and may strengthen the biological plausibility that the agent being evaluated is carcinogenic to humans (see Part B, Section 2f).

(*a*) *Qualitative aspects*

An assessment of carcinogenicity involves several considerations of qualitative importance, including (i) the experimental conditions under which the test was performed, including route, schedule and duration of exposure, species, strain (including genetic background where applicable), sex, age and duration of follow-up; (ii) the consistency of the results, for example, across species and target organ(s); (iii) the spectrum of neoplastic response, from preneoplastic lesions and benign tumours to malignant neoplasms; and (iv) the possible role of modifying factors.

Considerations of importance in the interpretation and evaluation of a particular study include: (i) how clearly the agent was defined and, in the case of mixtures, how adequately the sample characterization was reported; (ii) whether the dose was monitored adequately, particularly in inhalation experiments; (iii) whether the doses, duration of treatment and route of exposure were appropriate; (iv) whether the survival of treated animals was similar to that of controls; (v) whether there were adequate numbers of animals per group; (vi) whether both male and female animals were used; (vii) whether animals were allocated randomly to groups; (viii) whether the duration of observation was adequate; and (ix) whether the data were reported and analysed adequately.

When benign tumours (a) occur together with and originate from the same cell type as malignant tumours in an organ or tissue in a particular study and (b) appear to represent a stage in the progression to malignancy, they are usually combined in the assessment of tumour incidence (Huff *et al.*, 1989). The occurrence of lesions presumed to be preneoplastic may in certain instances aid in assessing the biological plausibility of any neoplastic response observed. If an agent induces only benign neoplasms that appear to be end-points that do not readily undergo transition to malignancy, the agent should nevertheless be suspected of being carcinogenic and requires further investigation.

(*b*) *Quantitative aspects*

The probability that tumours will occur may depend on the species, sex, strain, genetic background and age of the animal, and on the dose, route, timing and duration of the exposure. Evidence of an increased incidence of neoplasms with increasing levels of exposure strengthens the inference of a causal association between the exposure and the development of neoplasms.

The form of the dose–response relationship can vary widely, depending on the particular agent under study and the target organ. Mechanisms such as induction of DNA damage or inhibition of repair, altered cell division and cell death rates and changes in intercellular communication are important determinants of dose–response relationships for some carcinogens. Since many chemicals require metabolic activation before being converted to their reactive intermediates, both metabolic and toxicokinetic aspects are important in determining the dose–response pattern. Saturation of steps such as absorption, activation, inactivation and elimination may produce non-linearity in the dose–response relationship (Hoel *et al.*, 1983; Gart *et al.*, 1986), as could saturation of processes such as DNA repair. The dose–response relationship can also be affected by differences in survival among the treatment groups.

(*c*) *Statistical analyses*

Factors considered include the adequacy of the information given for each treatment group: (i) number of animals studied and number examined histologically, (ii) number of animals with a given tumour type and (iii) length of survival. The statistical methods used should be clearly stated and should be the generally accepted techniques refined for this purpose (Peto *et al.*, 1980; Gart *et al.*, 1986; Portier & Bailer, 1989; Bieler & Williams, 1993). The choice of the most appropriate statistical method requires consideration of whether or not there are differences in survival among the treatment groups; for example, reduced survival because of non-tumour-related mortality can preclude the occurrence of tumours later in life. When detailed information on survival is not available, comparisons of the proportions of tumour-bearing animals among the effective number of animals (alive at the time the first tumour was discovered) can be useful when significant differences in survival occur before tumours appear. The lethality of the tumour also requires consideration: for rapidly fatal tumours, the time of death provides an indication of the time of tumour onset and can be assessed using life-table methods; non-fatal or incidental tumours that do not affect survival can be assessed using methods such as the Mantel-Haenzel test for changes in tumour prevalence. Because tumour lethality is often difficult to determine, methods such as the Poly-K test that do not require such information can also be used. When results are available on the number and size of tumours seen in experimental animals (e.g. papillomas on mouse skin, liver tumours observed through nuclear magnetic resonance tomography), other more complicated statistical procedures may be needed (Sherman *et al.*, 1994; Dunson *et al.*, 2003).

Formal statistical methods have been developed to incorporate historical control data into the analysis of data from a given experiment. These methods assign an appropriate weight to historical and concurrent controls on the basis of the extent of between-study and within-study variability: less weight is given to historical controls when they show a high degree of variability, and greater weight when they show little variability. It is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls, particularly when historical controls show high between-study variability and

are, thus, of little relevance to the current experiment. In analysing results for uncommon tumours, however, the analysis may be improved by considering historical control data, particularly when between-study variability is low. Historical controls should be selected to resemble the concurrent controls as closely as possible with respect to species, gender and strain, as well as other factors such as basal diet and general laboratory environment, which may affect tumour-response rates in control animals (Haseman *et al.*, 1984; Fung *et al.*, 1996; Greim *et al.*, 2003).

Although meta-analyses and combined analyses are conducted less frequently for animal experiments than for epidemiological studies due to differences in animal strains, they can be useful aids in interpreting animal data when the experimental protocols are sufficiently similar.

4. Mechanistic and other relevant data

Mechanistic and other relevant data may provide evidence of carcinogenicity and also help in assessing the relevance and importance of findings of cancer in animals and in humans. The nature of the mechanistic and other relevant data depends on the biological activity of the agent being considered. The Working Group considers representative studies to give a concise description of the relevant data and issues that they consider to be important; thus, not every available study is cited. Relevant topics may include toxicokinetics, mechanisms of carcinogenesis, susceptible individuals, populations and life-stages, other relevant data and other adverse effects. When data on biomarkers are informative about the mechanisms of carcinogenesis, they are included in this section.

These topics are not mutually exclusive; thus, the same studies may be discussed in more than one subsection. For example, a mutation in a gene that codes for an enzyme that metabolizes the agent under study could be discussed in the subsections on toxicokinetics, mechanisms and individual susceptibility if it also exists as an inherited polymorphism.

(*a*) *Toxicokinetic data*

Toxicokinetics refers to the absorption, distribution, metabolism and elimination of agents in humans, experimental animals and, where relevant, cellular systems. Examples of kinetic factors that may affect dose–response relationships include uptake, deposition, biopersistence and half-life in tissues, protein binding, metabolic activation and detoxification. Studies that indicate the metabolic fate of the agent in humans and in experimental animals are summarized briefly, and comparisons of data from humans and animals are made when possible. Comparative information on the relationship between exposure and the dose that reaches the target site may be important for the extrapolation of hazards between species and in clarifying the role of in-vitro findings.

(*b*) *Data on mechanisms of carcinogenesis*

To provide focus, the Working Group attempts to identify the possible mechanisms by which the agent may increase the risk of cancer. For each possible mechanism, a representative selection of key data from humans and experimental systems is summarized. Attention is given to gaps in the data and to data that suggests that more than one mechanism may be operating. The relevance of the mechanism to humans is discussed, in particular, when mechanistic data are derived from experimental model systems. Changes in the affected organs, tissues or cells can be divided into three non-exclusive levels as described below.

(i) *Changes in physiology*

Physiological changes refer to exposure-related modifications to the physiology and/or response of cells, tissues and organs. Examples of potentially adverse physiological changes include mitogenesis, compensatory cell division, escape from apoptosis and/or senescence, presence of inflammation, hyperplasia, metaplasia and/or preneoplasia, angiogenesis, alterations in cellular adhesion, changes in steroidal hormones and changes in immune surveillance.

(ii) *Functional changes at the cellular level*

Functional changes refer to exposure-related alterations in the signalling pathways used by cells to manage critical processes that are related to increased risk for cancer. Examples of functional changes include modified activities of enzymes involved in the metabolism of xenobiotics, alterations in the expression of key genes that regulate DNA repair, alterations in cyclin-dependent kinases that govern cell cycle progression, changes in the patterns of post-translational modifications of proteins, changes in regulatory factors that alter apoptotic rates, changes in the secretion of factors related to the stimulation of DNA replication and transcription and changes in gap–junction-mediated intercellular communication.

(iii) *Changes at the molecular level*

Molecular changes refer to exposure-related changes in key cellular structures at the molecular level, including, in particular, genotoxicity. Examples of molecular changes include formation of DNA adducts and DNA strand breaks, mutations in genes, chromosomal aberrations, aneuploidy and changes in DNA methylation patterns. Greater emphasis is given to irreversible effects.

The use of mechanistic data in the identification of a carcinogenic hazard is specific to the mechanism being addressed and is not readily described for every possible level and mechanism discussed above.

Genotoxicity data are discussed here to illustrate the key issues involved in the evaluation of mechanistic data.

Tests for genetic and related effects are described in view of the relevance of gene mutation and chromosomal aberration/aneuploidy to carcinogenesis (Vainio

et al., 1992; McGregor *et al*., 1999). The adequacy of the reporting of sample characterization is considered and, when necessary, commented upon; with regard to complex mixtures, such comments are similar to those described for animal carcinogenicity tests. The available data are interpreted critically according to the end-points detected, which may include DNA damage, gene mutation, sister chromatid exchange, micronucleus formation, chromosomal aberrations and aneuploidy. The concentrations employed are given, and mention is made of whether the use of an exogenous metabolic system *in vitro* affected the test result. These data are listed in tabular form by phylogenetic classification.

Positive results in tests using prokaryotes, lower eukaryotes, insects, plants and cultured mammalian cells suggest that genetic and related effects could occur in mammals. Results from such tests may also give information on the types of genetic effect produced and on the involvement of metabolic activation. Some end-points described are clearly genetic in nature (e.g. gene mutations), while others are associated with genetic effects (e.g. unscheduled DNA synthesis). In-vitro tests for tumour promotion, cell transformation and gap–junction intercellular communication may be sensitive to changes that are not necessarily the result of genetic alterations but that may have specific relevance to the process of carcinogenesis. Critical appraisals of these tests have been published (Montesano *et al*., 1986; McGregor *et al*., 1999).

Genetic or other activity manifest in humans and experimental mammals is regarded to be of greater relevance than that in other organisms. The demonstration that an agent can induce gene and chromosomal mutations in mammals *in vivo* indicates that it may have carcinogenic activity. Negative results in tests for mutagenicity in selected tissues from animals treated *in vivo* provide less weight, partly because they do not exclude the possibility of an effect in tissues other than those examined. Moreover, negative results in short-term tests with genetic end-points cannot be considered to provide evidence that rules out the carcinogenicity of agents that act through other mechanisms (e.g. receptor-mediated effects, cellular toxicity with regenerative cell division, peroxisome proliferation) (Vainio *et al*., 1992). Factors that may give misleading results in short-term tests have been discussed in detail elsewhere (Montesano *et al*., 1986; McGregor *et al*., 1999).

When there is evidence that an agent acts by a specific mechanism that does not involve genotoxicity (e.g. hormonal dysregulation, immune suppression, and formation of calculi and other deposits that cause chronic irritation), that evidence is presented and reviewed critically in the context of rigorous criteria for the operation of that mechanism in carcinogenesis (e.g. Capen *et al.*, 1999).

For biological agents such as viruses, bacteria and parasites, other data relevant to carcinogenicity may include descriptions of the pathology of infection, integration and expression of viruses, and genetic alterations seen in human tumours. Other observations

that might comprise cellular and tissue responses to infection, immune response and the presence of tumour markers are also considered.

For physical agents that are forms of radiation, other data relevant to carcinogenicity may include descriptions of damaging effects at the physiological, cellular and molecular level, as for chemical agents, and descriptions of how these effects occur. 'Physical agents' may also be considered to comprise foreign bodies, such as surgical implants of various kinds, and poorly soluble fibres, dusts and particles of various sizes, the pathogenic effects of which are a result of their physical presence in tissues or body cavities. Other relevant data for such materials may include characterization of cellular, tissue and physiological reactions to these materials and descriptions of pathological conditions other than neoplasia with which they may be associated.

(*c*) *Other data relevant to mechanisms*

A description is provided of any structure–activity relationships that may be relevant to an evaluation of the carcinogenicity of an agent, the toxicological implications of the physical and chemical properties, and any other data relevant to the evaluation that are not included elsewhere.

High-output data, such as those derived from gene expression microarrays, and high-throughput data, such as those that result from testing hundreds of agents for a single end-point, pose a unique problem for the use of mechanistic data in the evaluation of a carcinogenic hazard. In the case of high-output data, there is the possibility to overinterpret changes in individual end-points (e.g. changes in expression in one gene) without considering the consistency of that finding in the broader context of the other end-points (e.g. other genes with linked transcriptional control). High-output data can be used in assessing mechanisms, but all end-points measured in a single experiment need to be considered in the proper context. For high-throughput data, where the number of observations far exceeds the number of end-points measured, their utility for identifying common mechanisms across multiple agents is enhanced. These data can be used to identify mechanisms that not only seem plausible, but also have a consistent pattern of carcinogenic response across entire classes of related compounds.

(*d*) *Susceptibility data*

Individuals, populations and life-stages may have greater or lesser susceptibility to an agent, based on toxicokinetics, mechanisms of carcinogenesis and other factors. Examples of host and genetic factors that affect individual susceptibility include sex, genetic polymorphisms of genes involved in the metabolism of the agent under evaluation, differences in metabolic capacity due to life-stage or the presence of disease, differences in DNA repair capacity, competition for or alteration of metabolic capacity by medications or other chemical exposures, pre-existing hormonal imbalance that is exacerbated by a chemical exposure, a suppressed immune system, periods of higher-than-usual tissue growth or regeneration and genetic polymorphisms that lead to

differences in behaviour (e.g. addiction). Such data can substantially increase the strength of the evidence from epidemiological data and enhance the linkage of in-vivo and in-vitro laboratory studies to humans.

(*e*) *Data on other adverse effects*

Data on acute, subchronic and chronic adverse effects relevant to the cancer evaluation are summarized. Adverse effects that confirm distribution and biological effects at the sites of tumour development, or alterations in physiology that could lead to tumour development, are emphasized. Effects on reproduction, embryonic and fetal survival and development are summarized briefly. The adequacy of epidemiological studies of reproductive outcome and genetic and related effects in humans is judged by the same criteria as those applied to epidemiological studies of cancer, but fewer details are given.

5. Summary

This section is a summary of data presented in the preceding sections. Summaries can be found on the *Monographs* programme website (http://monographs.iarc.fr).

(*a*) *Exposure data*

Data are summarized, as appropriate, on the basis of elements such as production, use, occurrence and exposure levels in the workplace and environment and measurements in human tissues and body fluids. Quantitative data and time trends are given to compare exposures in different occupations and environmental settings. Exposure to biological agents is described in terms of transmission, prevalence and persistence of infection.

(*b*) *Cancer in humans*

Results of epidemiological studies pertinent to an assessment of human carcinogenicity are summarized. When relevant, case reports and correlation studies are also summarized. The target organ(s) or tissue(s) in which an increase in cancer was observed is identified. Dose–response and other quantitative data may be summarized when available.

(*c*) *Cancer in experimental animals*

Data relevant to an evaluation of carcinogenicity in animals are summarized. For each animal species, study design and route of administration, it is stated whether an increased incidence, reduced latency, or increased severity or multiplicity of neoplasms or preneoplastic lesions were observed, and the tumour sites are indicated. If the agent produced tumours after prenatal exposure or in single-dose experiments, this is also mentioned. Negative findings, inverse relationships, dose–response and other quantitative data are also summarized.

(*d*) *Mechanistic and other relevant data*

Data relevant to the toxicokinetics (absorption, distribution, metabolism, elimination) and the possible mechanism(s) of carcinogenesis (e.g. genetic toxicity, epigenetic effects) are summarized. In addition, information on susceptible individuals, populations and life-stages is summarized. This section also reports on other toxic effects, including reproductive and developmental effects, as well as additional relevant data that are considered to be important.

6. Evaluation and rationale

Evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data are made, using standard terms. The strength of the mechanistic evidence is also characterized.

It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity. In considering all of the relevant scientific data, the Working Group may assign the agent to a higher or lower category than a strict interpretation of these criteria would indicate.

These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency). A classification may change as new information becomes available.

An evaluation of the degree of evidence is limited to the materials tested, as defined physically, chemically or biologically. When the agents evaluated are considered by the Working Group to be sufficiently closely related, they may be grouped together for the purpose of a single evaluation of the degree of evidence.

(*a*) *Carcinogenicity in humans*

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

***Sufficient evidence of carcinogenicity*:** The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. A statement that there is *sufficient evidence* is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.

***Limited evidence of carcinogenicity*:** A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

***Inadequate evidence of carcinogenicity*:** The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

***Evidence suggesting lack of carcinogenicity*:** There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

When the available epidemiological studies pertain to a mixture, process, occupation or industry, the Working Group seeks to identify the specific agent considered most likely to be responsible for any excess risk. The evaluation is focused as narrowly as the available data on exposure and other aspects permit.

(*b*) *Carcinogenicity in experimental animals*

Carcinogenicity in experimental animals can be evaluated using conventional bioassays, bioassays that employ genetically modified animals, and other in-vivo bioassays that focus on one or more of the critical stages of carcinogenesis. In the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models that address several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals.

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

***Sufficient evidence of carcinogenicity*:** The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single

species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide *sufficient evidence*.

A single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites.

***Limited evidence of carcinogenicity*:** The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

***Inadequate evidence of carcinogenicity*:** The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available.

***Evidence suggesting lack of carcinogenicity*:** Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent is not carcinogenic. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the species, tumour sites, age at exposure, and conditions and levels of exposure studied.

(*c*) *Mechanistic and other relevant data*

Mechanistic and other evidence judged to be relevant to an evaluation of carcinogenicity and of sufficient importance to affect the overall evaluation is highlighted. This may include data on preneoplastic lesions, tumour pathology, genetic and related effects, structure–activity relationships, metabolism and toxicokinetics, physicochemical parameters and analogous biological agents.

The strength of the evidence that any carcinogenic effect observed is due to a particular mechanism is evaluated, using terms such as ‘weak’, ‘moderate’ or ‘strong’. The Working Group then assesses whether that particular mechanism is likely to be operative in humans. The strongest indications that a particular mechanism operates in humans derive from data on humans or biological specimens obtained from exposed humans. The data may be considered to be especially relevant if they show that the agent in question has caused changes in exposed humans that are on the causal pathway to carcinogenesis. Such data may, however, never become available, because it is at least conceivable that certain compounds may be kept from human use solely on the basis of evidence of their toxicity and/or carcinogenicity in experimental systems.

The conclusion that a mechanism operates in experimental animals is strengthened by findings of consistent results in different experimental systems, by the demonstration of

biological plausibility and by coherence of the overall database. Strong support can be obtained from studies that challenge the hypothesized mechanism experimentally, by demonstrating that the suppression of key mechanistic processes leads to the suppression of tumour development. The Working Group considers whether multiple mechanisms might contribute to tumour development, whether different mechanisms might operate in different dose ranges, whether separate mechanisms might operate in humans and experimental animals and whether a unique mechanism might operate in a susceptible group. The possible contribution of alternative mechanisms must be considered before concluding that tumours observed in experimental animals are not relevant to humans. An uneven level of experimental support for different mechanisms may reflect that disproportionate resources have been focused on investigating a favoured mechanism.

For complex exposures, including occupational and industrial exposures, the chemical composition and the potential contribution of carcinogens known to be present are considered by the Working Group in its overall evaluation of human carcinogenicity. The Working Group also determines the extent to which the materials tested in experimental systems are related to those to which humans are exposed.

(*d*) *Overall evaluation*

Finally, the body of evidence is considered as a whole, in order to reach an overall evaluation of the carcinogenicity of the agent to humans.

An evaluation may be made for a group of agents that have been evaluated by the Working Group. In addition, when supporting data indicate that other related agents, for which there is no direct evidence of their capacity to induce cancer in humans or in animals, may also be carcinogenic, a statement describing the rationale for this conclusion is added to the evaluation narrative; an additional evaluation may be made for this broader group of agents if the strength of the evidence warrants it.

The agent is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent is a matter of scientific judgement that reflects the strength of the evidence derived from studies in humans and in experimental animals and from mechanistic and other relevant data.

Group 1: The agent is *carcinogenic to humans*.

This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Group 2.

This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of

carcinogenicity in experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*.

Group 2A: The agent is *probably carcinogenic to humans*.

This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

Group 2B: The agent is *possibly carcinogenic to humans*.

This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Group 3: The agent is *not classifiable as to its carcinogenicity to humans*.

This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals.

Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents that do not fall into any other group are also placed in this category.

An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed, especially when exposures are widespread or the cancer data are consistent with differing interpretations.

Group 4: The agent is *probably not carcinogenic to humans*.

This category is used for agents for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group.

(*e*) *Rationale*

The reasoning that the Working Group used to reach its evaluation is presented and discussed. This section integrates the major findings from studies of cancer in humans, studies of cancer in experimental animals, and mechanistic and other relevant data. It includes concise statements of the principal line(s) of argument that emerged, the conclusions of the Working Group on the strength of the evidence for each group of studies, citations to indicate which studies were pivotal to these conclusions, and an explanation of the reasoning of the Working Group in weighing data and making evaluations. When there are significant differences of scientific interpretation among Working Group Members, a brief summary of the alternative interpretations is provided, together with their scientific rationale and an indication of the relative degree of support for each alternative.

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GENERAL REMARKS

This ninety-eighth volume of *IARC Monographs* contains evaluations of the carcinogenic hazard to humans of shiftwork, painting, and firefighting. This is the first evaluation of shiftwork and firefighting by IARC. Painting had been evaluated previously in Volume 47, and newer epidemiological and experimental studies are reviewed in this volume. A common feature that led to the assessment of these human activities in one volume is that each is associated with diverse and complex exposures.

Firefighters can work in the profession full time or on a volunteer basis, holding other jobs at the same time. They can battle household fires, chemical fires, oil fires, forest fires, and fires of many other types, resulting in exposures to a vast variety of smoke, dusts, and chemical agents. Exposures are generally intermittent but intense. Many occupational records apply the term "firefighter" rather broadly, including logistics and support personnel as well as the people who enter a fire. The average time spent actually in fires is rather short overall, raising some concern that results for subgroups of highly exposed individuals might be difficult to observe in cohorts that are more broadly defined.

Painters, too, can work in the profession full time, but the term also includes artists and day workers who take different odd jobs on other days. Several studies include job categories such as decorators and wallpaper hangers along with painters, and there are also studies involving residential exposure to freshly painted rooms. Painters can work indoors or outdoors, with varying degrees of ventilation and protective equipment, and some work in construction zones with exposure to various dusts and chemical substances. The paints and coatings themselves have changed in composition over time and can be based on natural oils, synthetic oils, or latex. They include pigments derived from metals and chemical additives for many purposes, including those with pesticidal properties. In addition, painters are exposed to dusts and chlorinated solvents during preparation and cleanup operations.

Shiftwork is perhaps the most wide-ranging classification of all, with various definitions of shiftwork used in the epidemiological studies. As a causal factor, shiftwork is difficult to disentangle from related measures such as circadian disruption, sleep deprivation, and exposure to light at night. Analysis of epidemiological studies is further complicated by the fact that reference populations, too, are invariably exposed to these factors to some degree. The social and physical

environment associated with working at night provides additional factors that complicate the analysis of these studies. The strongest evidence so far is for breast cancer, which is associated with childbearing history, which in turn might affect willingness to take on shiftwork. There are surprisingly few studies of the effects of shiftwork for men working in industrial settings, however.

It is hoped that the critical reviews that appear in this volume will stimulate further research that addresses these aspects and leads to a resolution of the cancer hazards associated with firefighting and shiftwork.

A summary of the findings of this volume appears in *The Lancet Oncology* (Straif et al., 2007).

Reference

Straif K, Baan R, Grosse Y et al. (2007). Carcinogenicity of shift-work, painting, and fire-fighting. *Lancet Oncol*, 8:1065–1066 doi:10.1016/S1470-2045(07)70373-X. PMID:19271347 http://www.thelancet.com/journals/lanonc/article/PIIS147020450770373X/fulltext

THE MONOGRAPHS

PAINTING AND PAINT MANUFACTURE

OCCUPATIONAL EXPOSURES IN PAINT MANUFACTURE AND PAINTING

1. Exposure Data

1.1 Description of paint products

1.1.1 *Introduction*

The term *organic coating* encompasses conventional paints, varnishes, enamels, lacquers, water-emulsion and solution finishes, nonaqueous dispersions (organosols), plastisols, and powder coatings. The following definitions have been used commonly, although not always in a consistant manner (IARC, 1989a; Stoye & Freitag, 1998; Brock *et al.*, 2000; Goldschmidt & Streitberger, 2002). Glossaries for short explanations of paint and painting terms are available on the internet (e.g. www.occa.org.za/paintopedia/glossary.htm # Sect. S).

Paint is a suspension of finely divided pigment particles in a liquid composed of a binder (resin) and a volatile solvent or water, normally with additives to impart special characteristics. The volatile components evaporate from the drying film after application, while the binder holds the pigment in the dry film, causing it to adhere to the substrate. Some high quality, hard gloss paints are referred to as enamels.

Lacquer is defined as a coating that dries primarily by evaporation rather than by oxidation or polymerization. Because the solvents or water used in lacquers are relatively volatile and no chemical change is required for formation of the film, lacquers dry very rapidly.

Varnish is defined as a homogeneous, transparent or translucent liquid that is converted to a solid transparent film after being applied as a thin layer.

The basic components of paints vary widely in terms of chemical composition, depending on the colour, durability, and other properties required from the paint. Table 1.1

lists the main substances and classes of substances present in paints and to which workers may be exposed in the painting trades.

At the time of writing, solvent-borne paints contain much less solvent (high-solids paints) and less hazardous solvents than a decade ago. Sometimes, the solvent content is reduced to such an extent that volatile organic compounds (VOCs) emission levels are similar to those of waterborne paints.

Waterborne paints are used for private end consumers, as well as in several industries, including:

- the construction industry, for interior and exterior decoration
- the metal industry,
- the wood industry, including the furniture-making industry,
- the car industry, and
- the plastics industry.

Research and development for higher performance focuses on faster drying, and decrease of the residual solvents used in formulation. In countries where the ambiant air temperature is high together with elevated air humidity, waterborne paints are less convenient because of their very slow drying time. In these environments, high-solids paints or powder coatings are preferred.

The quality of powder coatings has much improved since their introduction, and now often reaches that of conventional paints. Future developments will allow their application onto heat-sensitive substrates such as wood-fibre plates or plastics.

1.1.2 *Pigments and extenders (fillers)*

Pigments can be classified as (i) inorganic, and (ii) organic pigments (Bentley & Turner, 1998; Stoye & Freitag, 1998; Brock *et al.*, 2000; Smith, 2002). They can also be classified into whites, colours, and effect pigments. Pigments are generally added in considerable proportion (3–60% by weight) to paint formulations and are used to provide colour, opacity, and sheen. They also affect the viscosity, flow, toughness, durability, and other physical or chemical properties of the coating, such as corrosion protection. The physical properties of pigments (particle shape and size) vary; the diameter of pigment particles is mostly <3 µm, and for special performance up to 15 or 20 µm. The particles in dry pigment powders are 0.5–10 µm in diameter (Oyarzún, 2000).

Dyes (soluble in paint medium, unlike pigments) are used only in very few instances or products because they provide much less long-term stability against light and other influences. Examples of use are the extremely transparent wood stains (see 1.3.2) (Zollinger & Iqbal, 2003), and the limited use of transparent colorants in automotive clear coats for special effects in Japan (Streitberger & Dössel, 2008).

Hazardous pigments and fillers, especially chromate- or lead-based products, are being increasingly replaced even though many of the new products possess lower performance in coloristics, corrosion protection or mechanical properties of paint layers. The speed and type of changes depends mainly on local legislation, costs, suitability and simplicity of

substituting for the newer products. Many paint systems for industrial or individual use are free of lead and chromate, especially in western Europe, but the situation is extremely heterogeneous across countries worldwide.

Besides nanoparticle-based pigments (see below), new colour-effect pigments are being developed, such as interfering mica pigments, liquid-crystal pigments, inorganic or organic pigments with better performance in colour or stability, and corrosion-protection pigments with better corrosion effects for chromate substitution. New fillers with better mechanical properties are also being formulated and produced.

(a) Inorganic pigments and fillers

Inorganic pigments are an integral part of numerous decorative, protective and functional coating systems, as found in automobile finishes, marine paints, industrial coatings, traffic paints, maintenance paints, and exterior and interior oil, alkyd and latex house paints. Inorganic pigments belong to several different chemical classes, i.e. primary elements, oxides, carbonates, chromates, phosphates, sulfides and silicates (Brock *et al.*, 2000; Smith, 2002; Buxbaum & Pfaff, 2005).

Many forms of lead have been used for over 200 years in pigments including: carbonate (white lead), oxides (litharge, red lead), sulfate, oxychloride (Turner's yellow), acetate, borate, and chromates (IARC, 2006a). During the last few decades, they have been substituted to a large extent by organic pigments or lead-free inorganic pigments. Alternatives to lead are the very resistant and insoluble mixed-phase oxide pigments such as nickel (or chromium) titanium yellow ($NiO.Sb_2O_5.20TiO_2$), and bismuth vanadate (BiO_4V^{-5}). New oxide pigments include the spinel-structured cobalt blue $Co(Al,Cr)_2O_4$ and cobalt green $(Co,Ni,Zn)_2(Ti,Al)O_4$ (Winkler, 2003; Buxbaum & Pfaff, 2005).

Zinc chromate was widely employed to protect against rust formation on all sorts of equipment until recently (Buxbaum & Pfaff, 2005). Currently, its use is restricted to a few applications such as in primer formulations for airplanes. Other chromium pigments that had been used in paint for many years included lead chromates, barium chromate and chromium oxide (see IARC, 1990). Cadmium sulfide, cadmium sulfoselenide and antimony trioxide are now substituted with various grades of naturally occurring, or synthetic, ferric oxide which provide yellow, red and brown pigments (Buxbaum & Pfaff, 2005).

Today, the most common pigment employed in paint is the white pigment titanium dioxide, TiO_2 (IARC, 2010a), produced in two different crystal forms – rutile and anatase – with distinct colour properties. The rutile crystal structure has an almost 25% greater opacity than the anatase form. Because of its chemical inertness, extreme whiteness, excellent covering power and lack of toxicity compared to white lead, titanium dioxide is the dominant component in the manufacture of white paint, and represents 90% of all pigments on the market worldwide. Lithopone, a coprecipitate of 28–30% zinc sulfide and 70–72% barium sulfate (Buxbaum & Pfaff, 2005) introduced before the First World War, is hardly ever used any more.

Table 1.1 Main substances (and classes of substances) which workers may be exposed to in the painting trades[a]

Material	Principal uses or sources of emissions	Agent evaluated	*IARC Monographs*	Evaluation
Acrylates (e.g., ethyl acrylate, methyl methacrylate)	Acrylic resins, ultraviolet curing paints	Ethyl acrylate Acrylic acid Methyl acrylate Methyl methacrylate	IARC (1999a) IARC (1999a) IARC (1999a) IARC (1999a)	2B 3 3 3
Acrylic resins	Binders	As above		
Alcohols, aliphatic (e.g., methanol, isopropanol, *n*-butanol)	Solvents (lacquers), paint removers	Methanol Ethanol Isopropanol *n*-Butanol	– – IARC (1999a) –	– – 3 –
Alkalis (e.g., sodium hydroxide, potassium hydroxide)	Paint removers	–	–	–
Alkyd resins	Binders	–	–	–
Aluminium, powder	Pigment	–	–	–
Amides, aliphatic (e.g., dimethylformamide)	Solvents	Dimethylformamide	IARC (1999a)	2A
Amines (mono), aliphatic (e.g., diethylamine) and alkanolamines (e.g., 2-amino-2-methyl-1-propanol)	Water-based paints	Triethanolamine	IARC (2000)	3
Amines (poly), aliphatic (e.g., diethylenetriamine)	Curing agents (epoxy resins)	–	–	–
Amines, aromatic (e.g., *meta*-phenylenediamine, 4,4-methylenedianiline)	Curing agents (epoxy resins)	*meta*-Phenylenediamine 4,4-Methylenedianiline	IARC (1987) IARC (1987)	3 2B
Amino resins (e.g., urea-formaldehyde resins, melamine-formaldehyde resins)	Binders	See Formaldehyde		

Table 1.1 (Contd)

Material	Principal uses or sources of emissions	Agent evaluated	*IARC Monographs*	Evaluation
Ammonia	Water-based paints	–	–	–
Anhydrides, organic (e.g., maleic anhydride, phthalic anhydride, trimellitic anhydride)	Alkyd resin synthesis, curing agents (epoxy resins)	Succinic anhydride	IARC (1987)	3
Antimony compounds (e.g., antimony trioxide)	Pigments, fire retardant pigments	Antimony trioxide Antimony trisulfide	IARC (1989a) IARC (1989a)	2B 3
Arsenic compounds (e.g., copper aceto-arsenate)	Antifouling agents	–	IARC (1987)	1
Asbestos	Filler, spackling and taping compounds, talc	Asbestos	IARC (1987)	1
Barium compounds (e.g., barium sulfate, barium carbonate)	Pigments	–	–	–
Benzoyl peroxide	Catalyst	Benzoyl peroxide	IARC (1999a)	3
Bisphenol A	Epoxy resins		IARC (1999a)	3
Cadmium compounds (e.g., cadmium sulfide, cadmium sulfoselenide)	Pigments	Cadmium and Cadmium compounds	IARC (1993)	1
Calcium compounds (e.g., calcium sulfate, calcium carbonate)	Fillers	–	–	–
Camphor	Plasticizer	–	–	–
Carbon black	Pigment	Carbon black	IARC (2010a)	2B
Cellulose ester resins (e.g., cellulose nitrate, cellulose acetate)	Binders	–	–	–
Chloracetamide	Fungicide (water-based paints)	–	–	–

Table 1.1 (Contd)

Material	Principal uses or sources of emissions	Agent evaluated	*IARC Monographs*	Evaluation
Chlorofluorocarbons	Spray-can paint propellants	Chlorofluoromethane	IARC (1999a)	3
Chromium and chromium compounds (e.g., chromic oxide, chromates)	Pigments	Chromium (III) compounds	IARC (1990)	3
		Chromium (VI) compounds	IARC (1990)	1
		Chromium, metallic	IARC (1990)	3
Clays (e.g., bentonite)	Fillers	–	–	–
Coal-tar and asphalt	Special waterproof coatings (ships, tanks, pipes)	Coal tar	IARC (1987)	1
		Coal-tar pitches	IARC (1987)	1
		Bitumen extracts	IARC (1987)	2B
		Bitumen refined	IARC (1987)	3
Cobalt compounds	Pigments, driers	Cobalt and cobalt compounds	IARC (1991a)	2B
		Cobalt, metallic	IARC (2006a)	2B
Copper and copper compounds (e.g., bronze powder, cuprous oxide)	Pigments, antifouling agents	–	–	–
Dyes and pigments, organic (e.g., aromatic azo dyes, phthalocyanines, rhodamine)	Pigments	CI Basic Red 9 }		2B
		Magenta production }		1
		2-naphthylamine }	IARC (1982)	1
		4-aminobiphenyl }	IARC (2010b)	1
		Auramine production }		1
		Benzidine }		1
		Benzidine-based dyes }		1
Epichlorohydrin	Epoxy resins	Epichlorohydrin	IARC (1999a)	2A
Epoxy resin	Binders	–	IARC (1976)	–
Esters, aliphatic (e.g., ethyl acetate, isopropyl acetate)	Solvents	–	–	–

Table 1.1 (Contd)

Material	Principal uses or sources of emissions	Agent evaluated	*IARC Monographs*	Evaluation
Ethers, aliphatic (e.g., isopropyl ether, tetrahydro-furan) and glycol ethers (e.g., methyl cellosolve)	Solvents	2-Butoxyethanol 1-*tert*-Butoxypropan-2-ol	IARC (2006b) IARC (2006b)	3 3
Formaldehyde	Amino resin varnishes, biocide (water-based paints)	Formaldehyde	IARC (2006b)	1
Gasoline	Solvent	Gasoline	IARC (1989b)	2B
Glycidyl ethers (e.g., *n*-butyl glycidyl ether and bisphenol A diglycidyl ether)	Epoxy resin diluents and constituents	Phenylglycidyl ether Triethylene glycol diglycidyl ether Bisphenol A diglycidyl ether	IARC (1999a) IARC (1999a) IARC (1999a)	2B 3 3
Glycols (e.g., ethylene glycol)	Polyester resins, water-based paints	–	–	–
Hydrocarbons, aliphatic (e.g., hexanes, heptanes)	Solvents (naphthas, white spirits)	–	–	–
Hydrocarbons, aromatic (e.g., benzene, toluene, xylenes, trimethylbenzene)	Solvents (naphthas, white spirits), paint removers	Benzene Toluene Xylene Ethylbenzene	IARC (1987) IARC (1999a) IARC (1999a) IARC (2000)	1 3 3 2B
Hydrocarbons, chlorinated (e.g., dichloromethane, 1,1,1-trichloroethane, carbon tetrachloride, trichloroethylene)	Solvents, paint removers, metal degreasers	Dichloromethane 1,1,1-Trichloroethane Carbon tetrachloride Trichloroethylene	IARC (1999a) IARC (1999a) IARC (1999a) IARC (1995)	2B 3 2B 2A
Hydrochloric acid (hydrogen chloride)	Catalyst (amino resins)	–	IARC (1992)	3
Iron compounds (e.g., iron oxides, ferric ferrocyanide)	Pigments	Ferric oxide	IARC (1987)	3

Table 1.1 (Contd)

Material	Principal uses or sources of emissions	Agent evaluated	*IARC Monographs*	Evaluation
Isocyanates (e.g., 1,6-hexamethylene diisocyanate, toluene diisocyanate)	Two-component polyurethane resins	Toluene diisocyanate	IARC (1999a)	2B
Isothiazolones (e.g., 1,2-benzisothiazolin-3-one)	Biocides in tinned foods	–	–	–
Kerosene	Solvent	Jet fuel	IARC (1989c)	3
Ketones, aliphatic (e.g., acetone, methyl ethyl ketone, cyclohexanone, isophorone, diacetone alcohol)	Solvents, lacquers, paint removers	Cyclohexanone	IARC (1999a)	3
Lead compounds (e.g., lead chromate, lead oxides, basic lead carbonate, lead naphthenate)	Primers, pigments, driers	Lead Lead compounds, inorganic	IARC (1987) IARC (2006c)	2B 2A
Magnesium compounds (e.g., magnesium carbonate)	Fillers	–	–	–
Manganese naphthenate	Drier	–	–	–
Mercury compounds (e.g., mercuric oxide, phenyl mercuric acetate)	Fungicides (water-based paints)	Mercury and inorganic mercury compounds	IARC (1993)	3
Methyl cellulose	Thickener (water-based paints)	–	–	–
Mica	Filler	–	–	–
Molybdenum compounds (e.g., lead molybdate)	Pigments	–	–	–
Nickel, metal powder	Pigment	Nickel compounds Nickel, metallic and alloys	IARC (1990) IARC (1990)	1 2B 2B
Nitroparaffins (e.g., nitroethane, 2-nitropropane)	Solvents	2-Nitropropane	IARC (1999a)	2B
Oils, vegetable (e.g., linseed oil, tung oil)	Binders	–	–	–

Table 1.1 (Contd)

Material	Principal uses or sources of emissions	Agent evaluated	*IARC Monographs*	Evaluation
Oximes (e.g., methyl ethyl ketoxime)	Anti-oxidants, anti-skinning agents	–	–	–
Petroleum solvents (e.g., Stoddard solvent, VM & P naphtha)	Solvents, paint removers	Petroleum solvents	IARC (1989a)	3
Phenol	Phenol-formaldehyde resins, paint remover (formerly)	Phenol	IARC (1999a)	3
Phenol-formaldehyde resins	Binders	See Phenol, and Formaldehyde		
Phenols, chlorinated (e.g., pentachlorophenol)	Fungicides (water-based paints)	Polychlorophenols and their sodium salts	IARC (1999a)	2B
		Pentachlorophenol	IARC (1991b)	2B
Phosphates, organic (e.g., tricresyl-*ortho*-phosphate, tributyl phosphate)	Plasticizers	–	–	–
Phthalate esters (e.g., dibutyl phthalate, dioctyl phthalate	Plasticizers	Di(2-ethylhexyl)phthalate	IARC (2000)	3
		Butyl benzyl phthalate	IARC (1999b)	3
Polychlorinated biphenyls	Plasticizers	Polychlorinated biphenyls	IARC (1987)	2A
Polycyclic aromatic hydrocarbons	Special waterproof coatings (ships, tanks, pipes)	Selected polycyclic aromatic hydrocarbons	IARC (2010c)	
Polyester resins	Binders	–	–	–
Polyurethane resins	Binders	Polyurethane foams	IARC (1987)	3
Polyvinylacetate resins	Binders	Polyvinyl acetate	IARC (1987)	3

Table 1.1 (Contd)

Material	Principal uses or sources of emissions	Agent evaluated	*IARC Monographs*	Evaluation
Pyrolysis fumes	Removal of paint by burning; heat-curing operations	–	–	–
Rosin	Binder	–	–	–
Rubber, synthetic (e.g., butyl rubber, styrene-butadiene rubber)	Binders (special paints, water-based paints)	Rubber industry	IARC (1987)	1
Shellac resin	Binder	–	–	–
Silica, amorphous (e.g., diatomaceous earth)	Filler	Silica, amorphous	IARC (1997)	3
Silica, crystalline (e.g., quartz)	Filler, sand-blasting operation	Silica, crystalline	IARC (1997)	1
Silicates (e.g., sodium silicate, aluminium silicate)	Fillers	–	–	–
Stearates (e.g., aluminium stearates, zinc stearates)	Soaps, flattening agents	–	–	–
Strontium compounds (e.g., strontium chromate, strontium sulfide)	Pigments	Strontium chromate see Chromium and chromium compounds		
Styrene	Polyester resins	Styrene	IARC (2002)	2B
Styrene oxide	Diluent (epoxy resins)	Styrene-7,8-oxide	IARC (1994)	2A
Sulfuric acid	Metal cleaner	–	–	–

Table 1.1 (Contd)

Material	Principal uses or sources of emissions	Agent evaluated	*IARC Monographs*	Evaluation
Talc	Filler	Talc containing asbestiform fibres	IARC (1987)	1
		Talc, not containing asbestiform fibres	IARC (2010a)	3
Tin, metal powder	Lacquers (tinplate containers)	–	–	–
Tin, organic compounds (e.g., tri-*n*-butyltin oxide, dibutyltin laurate)	Antifouling agents, catalysts	–	–	–
Titanium dioxide	Pigment	Titanium dioxide	IARC (2010a)	2B
para-Toluenesulfonic acid	Catalyst (amino resins)	–	–	–
Turpentine	Solvent	–	–	–
Vinyl acetate	Polyvinylacetate resins	Vinyl acetate	IARC (1995)	2B
		Vinyl chloride – vinyl acetate copolymers	IARC (1987)	3
Zinc and compounds (e.g., zinc metal powder, zinc oxide, zinc chromate)	Pigments, catalysts, bodying agents	Zinc chromate see Chromium and chromium compounds		

[a] Updated from IARC (1989); –, not evaluated by IARC

The use of iron-blue pigments $M^{I}[Fe^{II}Fe^{III}(CN)_6]$ (Milori blue, Vossen blue, Berlin blue, Prussian or Turnbull´s blue) is in decline as they are too sensitive to chemicals and alkaline water.

The term *earth pigments* is obsolete, as these iron or chromium(III) oxide pigments (Fe_2O_3, Fe(O)OH, Cr_2O_3) are now produced synthetically from ores in a similar manner to titanium dioxide, the most widely used of the coloured pigments derived from natural sources (Buxbaum & Pfaff, 2005). Natural iron oxides are processed from several different ores, including haematite (see IARC, 1987), limonite, siderite and magnetite, and provide a range of reds, yellows, purples, browns and blacks. Iron oxide particles of around 10 nm are highly transparent and additionally, offer good ultraviolet (UV) protection of wood.

Bismuth vanadate pigments are a relatively new class of pigments that have steadily gained importance over the last three decades. Formulations range from BiO_4V^{-5} to the mixed pigment $4BiVO_4x3Bi_2MoO_6$. The pigments are lead- and chromate-free inorganic yellow pigments used to manufacture high-peformance brillant yellow, orange, red, and green shades. Bismuth vanadate has become an increasingly important substitute for lead chromate in the last 10–20 years. Nevertheless, lead chromate and lead wolframate are still used in some countries (Smith, 2002).

Traditionally, the most important black pigment, carbon black (microcrystalline carbon, graphite-similar), belongs to inorganic pigments (Buxbaum & Pfaff, 2005). The small particles (10–40 nm) can have surface areas as large as 1000 m^2/g.

Nanoparticles, mostly inorganic, are chemically similar to pigments and fillers, but they are discussed together with additives because of their special additive-like functions, and the low contents at which they are used in formulations.

(i) *Lustre pigments (effect pigments)*

This group includes metallic, pearlescent and iridescent pigments. The most common metallic dusts and powders used in paint are aluminium powder or fine flakes and bronze powders, which consist of metals in a finely divided state; e.g. gold bronzes are alloys of copper with varying proportions of zinc or aluminium (Glausch *et al.*, 1998; Wissling, 2006).

Additional effect pigments developed for new optical effects include mica plates, which have been increasingly used over the last 20 years (often inorganically coated with silicium dioxide, iron(III)oxide, chromium(III)oxide or aluminium oxide). The thickness and the kind of metal oxide used has an impact on the optical effect, especially the colour and the interference effect [where the angle of watching determines the colour]. Other plate-like effect pigments are based on silicium dioxide, thin polymer flakes or haematite (Wissling, 2006).

(ii) *Fillers*

Materials used as fillers (extenders) are not pigments as they do not contribute to the coloristic or functional properties of the coating (Stoye & Freitag, 1998; Brock *et al.*, 2000;

Nanetti, 2000). Typical fillers are barium sulfate (barytes), calcium carbonate (ground limestone and chalk), silica (diatomaceous or amorphous, pyrogenic or precipitated; see IARC, 1997), clays (hydrated aluminium silicate), talcum (hydrated magnesium silicate; see IARC, 1987) and mica (hydrated potassium aluminium silicate). Fillers are often added to paint to reduce cost, improve physical characteristics, and increase resistance to wear; their effects are largely governed by their average particle size. This size is normally about 1–10 µm, and under 0.1 µm for special performances.

(b) Organic pigments

Hundreds of organic pigments, comprising a broad spectrum of structural classes, are used in the paint industry (Brock *et al.*, 2000; Smith, 2002; Zollinger & Iqbal, 2003). The most important and established uses for organic pigments include the coloration of coating compositions for interior, exterior, trade and automotive applications, including oil and water emulsion paints and lacquers. Azo pigments are formed by successive diazotization of a primary amine and coupling.

After the discovery of Perkins' mauve in 1856, the development of synthetic colouring materials continued with the discovery of fuchsin in 1858 and of other triphenylmethane dyes, such as alkali blue, methyl violet, and malachite green. Large amounts of these dyes were used as the first synthetic organic pigments. The largest single advance in pigment technology after the First World War was the discovery in the 1930s of phthalocyanine blue and, later, its halogenated green derivatives, which are still widely used in automotive finishes. Other main categories of organic pigments used in paints and related products include quinacridones, thioindigos, perinones, perylenes, diketo-pyrrolopyrroles and anthraquinone.

Organic effect pigments have reached some commercial significance. In particular, liquid crystals (spiro compounds), fixed in the binder matrix by polymerization, permit extreme colour changes depending on the viewing angle.

In the 1960s, there were probably more than 200 different organic pigments used in paints. At the time, azo pigments such as Benzidine Yellow were considered to have relatively low toxicity, and were widely used. These pigments are of relatively low solubility, and although they are based on the aromatic amine 3,3′-dichlorobenzidine, the free amine is not bioavailable. IARC (1982) identified eight pigments based on 3,3′-dichlorobenzidine. Three 3,3′-dichlorobenzidine-based paint pigments were commonly used in architectural finishes in the mid-to-late 1960s. Benzidine was used as the basis for the paint pigment pyrazolone maroon (see IARC, 2010b).

Free aromatic amines used in the synthesis of azo pigments can be found in trace amounts as impurities. The aromatic amines 4-aminobiphenyl, benzidine, 2-naphthylamine and 2-methyl-4-chloroaniline [4-chloro-*ortho*-toluidine] have been found in azo pigments (see IARC, 2010b).

1.1.3 *Binders (resins)*

The 'vehicle' part of paints contains components collectively termed 'binders' or film formers. Binders protect the substrate and hold the pigment in the dry film when required, and cause it to adhere to the surface to be painted. Almost all binders in modern paint films are composed of polymer materials such as resins and drying oils, whose main functions are to provide film hardness, gloss, surface adhesion, and resistance of the film to the weather, atmospherilics, acids, alkalis, and other agents (Stoye & Freitag, 1998; Brock *et al.*, 2000; Müller & Poth, 2006). A large variety of both natural and mainly synthetic resins has been used in paints.

The chemical composition and variety of binders have not changed fundamentally with new paint systems or better awareness of health hazards. Binders (in principle oligomers and polymers) of waterborne and UV-curing paints or powder coatings are similar to those of conventional paints, with slight modifications. Water-thinnable resins contain more carboxyl (acid) groups and can be used as stable emulsions when they are neutralized with amines or caustic soda (pH 7–9). Thus, waterborne paints nearly always contain tertiary amines, ammonia or alkali. During drying, the amines evaporate and the hydrophilic binder becomes hydrophobic and resistant. These paints contain only little solvent (up to 10%), often even none. UV-curing paints contain fixed unsaturated groups for polymerization by UV-radiation, as well as monomers and oligomers as thinners (which then polymerize), mostly acrylates, therefore generally not requiring any solvent. The ozone that forms during UV irradiation is removed automatically by the radiation machinery, and bled with the air waste. New developments include less harmful monomers and further technical improvements (Müller & Poth, 2006).

(a) Natural resins and oils

From early times, various natural resins have been used to reinforce linseed oil and other drying oils, since paints based on pigment and oil only yield very soft films. Shellac and insect exudations are natural oleoresins that have been used in paints for centuries (Brock et *al.*, 2000).

Another useful natural resin is rosin (colophony), which is obtained as a residue after distilling pine oleoresin for the production of turpentine. Rosin consists of about 85% rosin acids (abietic acid) and 15% neutral substances, and can be classified into two main types – gum rosin and wood rosin. Rosin has been used in paints (principally alkyd resins) for many years, and is nowadays still used in printing inks. Rosin is often upgraded to yield higher quality resins by chemical reactions, including liming (calcium rosinate), salification, esterification with glycerol, and reactions with trimethylolpropane, phthalic anhydride, maleic anhydride, adipic acid and sebacic acid (Brock *et al.*, 2000).

Vegetable and fish oils have long been used as binders in traditional paints and varnishes. White linseed oil has been the most important oil in standard exterior paints, despite its moderately slow drying rate. It is infrequently used in interior paints because of

yellowing. Other important oils include castor oil, tall oil, soya bean oil, coconut oil, cottonseed oil, tung oil and various fish oils (Brock *et al.*, 2000).

Although raw oils have been useful as paint binders, it is advantageous to use them in conjunction with refined oils and oils treated with heat (heat-bodied oils), which isomerize the raw oil and improve the drying rate of the films. Oleoresinous varnishes are made by cooking oils with natural or synthetic resin, which results in more rapid drying and a harder film (Brock *et al.*, 2000). Today, natural resins are used mainly as raw material to modify synthetic resins, and used in 'bio paints'.

(b) Synthetic resins

A wide variety of synthetic resins has been commercially available since the early 1900s. Those that have been most frequently employed in paints, varnishes and lacquers include cellulosic, phenolic, alkyd, vinyl, acrylic and methacrylic, polyesters and polyurethane resins, chlorinated rubber derivatives, styrene-butadiene, and silicone oils. Mixtures of different synthetic resins provide characteristic properties that cannot be obtained from a single resin. While the amount of resin in paint varies, concentrations of 20–60% are common. The choice of a resin(s) for a particular application depends on factors such as appearance, ease of application, cost, and resistance to mechanical forces, chemicals, heat and wear. Some resins (polyurethanes, epoxys; see IARC, 1999a) are blended with crosslinking agents immediately before use, which results in a hard, serviceable film. Alkyd, acrylic, polyurethane and polyester resins have a broad spectrum of use in paints, including paints for houses, automobiles, furniture and appliances, as well as in the protection of metal surfaces, e.g. in chemical plants and oil refineries (Brock *et al.*, 2000).

(i) *Phenolic resins*

Depending on the type and proportion of components and on the reaction conditions, phenolic resins may be heat-reactive or not. The first product of the reaction is methylol phenol. With an excess of formaldehyde under alkaline conditions, methylol groups react slowly with phenol, are retained in the reaction product (resoles) and can act as reactive sites in varnish preparations or for crosslinking in finished products (Brock *et al.*, 2000).

Heat-sensitive phenolic resins that are insoluble in oil may be dissolved in solvents and used as the sole vehicle for metal coatings, e.g. for wires. Specially formulated water-soluble resoles with free neutralisable carboxyl groups are used in waterborne coatings.

(ii) *Alkyd resins*

The advent of alkyd resins was a major breakthrough in modern paint technology. Alkyds are oil-modified polyester resins produced by the condensation reaction of polyhydric alcohols, polybasic acids and monobasic fatty acids, e.g. linseed or soja fatty acids. The terms 'non-oil' and 'oil-free' alkyd describe polyesters formed by the reaction of polybasic acids with polyhydric alcohols in excess of stoichiometric amounts. These

products are best described as saturated polyesters containing unreacted hydroxyl or carboxyl groups (Bentley & Turner, 1998; Brock *et al.*, 2000).

For example, nitrocellulose lacquers are formulated with alkyd resins, and can have a nitrocellulose content of up to 55%. These lacquers are produced in large quantities. Alkyds modified with short-chain acids, such as those from coconut oil and castor oil, are widely used in high-grade furniture lacquers.

Some water-thinnable alkyd resins that contain sufficient carboxyl (hydrosols) groups or an emulgator (added or incorporated, self-emulsifying) are used for wood protection or to inhibit corrosion (Brock *et al.*, 2000).

Alkyd resins have been used in protective coatings for over 40 years, constituting about 45% of all resins used in organic coatings. Their use in product finishes (machines, equipment, wood and metal) is decreasing because of their slow hardening and low performance compared with modern two-component systems (Stoye & Freitag, 1998).

(iii) *Vinyl resins*

Vinyl polymers and copolymers were among the first synthetic polymers on the market and are widely used in trade paints. Vinyl monomers can polymerize readily by the addition of initiators, such as peroxides and azo compounds, which decompose at reactor temperature to generate free radicals. Polymerization processes involve radical formation, initiation, propagation including chain transfer, and termination (Bentley & Turner, 1998; Brock *et al.*, 2000). The principal vinyl resins of importance in the paint industry are polyvinyl chloride, polyvinyl acetate and polyvinyl butyrate. These are available in a range of different compositions for specific uses, and in grades that can be handled as true solutions in organic solvents, as high-solid dispersions (‘organosols’ or ‘plastisols’), as dry powders or as waterborne latices. Polyvinyl acetate is extensively used in emulsion paints, providing exceptional flexibility, toughness, and water and chemical resistance. Vinyl chloride copolymer coatings are still used in coil coatings, and in industrial and marine coatings (Stoye & Freitag, 1998).

Water emulsions of high molecular-weight polyvinyl acetate are widely used in interior house paints. Copolymers of vinyl acetate with acrylic monomers are also used in exterior emulsion house paints. Latexes of vinyl chloride polymers and copolymers have been commercially important for several years, e.g. as copolymers in exterior house paints, which often include a vinyl chloride–acrylic ester copolymer modified with a specially designed alkyd resin. Polyvinyl acetate and vinyl acetate copolymers are used in latex-based interior and exterior paints. The principal modifying monomers for vinyl acetate include dibutyl maleate and fumarate, butyl-, 2-ethylhexyl- and isodecyl acrylates, and higher vinyl esters. Copolymers of the acrylates and vinyl acetate are commonly called vinyl acrylics and generally contain l5% acrylic monomer by weight.

Polyvinylidene fluoride is a base for organosols for extremely weather-resistant metal coatings, used mainly in coil-coating applications for façades.

(iv) *Acrylic and methacrylic ester resins*

Acrylic resins are divided into four specific types: water-based, solvent-based thermoplastic (lacquer types), solvent-based thermosetting or room temperature-drying, and powder coating resins (Brock *et al.*, 2000).

Acrylic and methacrylic polymers are made from a variety of acrylic and methacrylic monomers (see IARC, 1999a). The major monomers used are the methyl, ethyl, butyl and 2-ethylhexyl esters of acrylic and methacrylic acids, which readily undergo polymerization in the presence of free-radical initiators, such as peroxides, to yield high molecular-weight polymers (Schwartz & Baumstark, 2001). The acetone–cyanohydrin process is the major method for the production of monomeric methacrylate esters.

Several functional groups can be incorporated into acrylic and methacrylic monomers. These are principally amides, carboxyls, hydroxyls and epoxys and are used to confer crosslinking capabilities and thermosetting properties to the resulting polymers. Other monomers, including vinyl acetate (see IARC, 1995), styrene (see IARC, 2002), vinyl toluene (see IARC, 1994), acrylonitrile (see IARC, 1999a) and methylacrylamide are used in conjunction with the acrylic monomers to achieve different properties.

Acrylic and methacrylic polymers are used in the formulation of clear and pigmented lacquers. Dispersions in water and in organic solvents yield latex and organosol coatings, respectively (Schwartz & Baumstark, 2001). In the late 1950s, lacquers of greatly improved durability, based on polymethylmethacrylate or thermosetting acrylic enamels, were adopted by the automobile industry (Fettis, 1995; Goldschmidt & Streitberger, 2002). By the 1960s, the acrylic emulsion polymers had been firmly established in exterior coatings for wood surfaces, a field long dominated by oil paints (Schwartz & Baumstark, 2001). Currently, acrylic resins – solvent-borne or waterborne – are state-of-the-art in the field of top coats for car paints, lacquers and many others high-performance coatings. For best performance, they are used in one-component or two-component products, and cured to improve their functionality. Those containing hydroxyl groups are cured with isocyanates or melamines, those containing carboxyl groups are cured with epoxy-groups, those containing epoxy-groups are cured with (poly)acids or amines, while those containing isocyanate groups are crosslinked with air humidity.

(v) *Epoxy resins*

Epoxy resins were first derived from bisphenol A and epichlorohydrin (see IARC, 1999a), and introduced into the paint industry in the late 1940s. Two major types of epoxy resin exist – glycidyl ether epoxy resins (see IARC, 1989a) and epoxidized olefins, the former being the most common. Epoxy resins based on bisphenol A and epichlorohydrin are the most prominent of the glycidyl ether category. They are produced by a condensation reaction in which bisphenol A and epichlorohydrin are reacted in the presence of alkali. The resultant diglycidyl ether resin has a functionality of two reactive epoxy groups per molecule. Epoxy resins can be polymerized through their reactive epoxy group using acids, amines or polyamides (Brock *et al.*, 2000).

Epoxy resins of a second major type, epoxidized olefins, are based on epoxidation of the carbon-carbon double bond.

To proceed from the relatively low molecular weight of the coating composition, as applied, to the high molecular-weight polymer necessary for optimal film properties, a 'curing' or polymerization must take place. Some of the principal reactions that have been used include chemical crosslinking via the amine–epoxide reaction [anhydride–epoxide reaction], reaction with methylol groups (e.g. between the secondary hydroxyl groups of the higher molecular-weight resins and the methylol groups of phenol–formaldehyde and urea–formaldehyde resins), crosslinking via the isocyanate–hydroxyl reaction and esterification reactions between solid-grade epoxy resins and carboxyl-containing compounds, particularly drying-oil fatty acids (Brock *et al.*, 2000).

Glycidyl ether resins of high molecular weight (number average,[1] about 7000; weight average,[2] about 200 000) are unique among epoxy coatings in that they form coatings by solvent evaporation alone. Because of their toughness, adhesion and corrosion resistance, epoxy resins are used in many applications, including industrial maintenance, automobile primers and coatings for appliances and steel pipes. Epoxys combined with phenolic resins and thermosetting acrylic resins yield high-bake finishes with hardness, flexibility, and resistance to chemicals and solvents (Brock *et al.*, 2000).

(vi) *Polyurethane resins*

Although polyurethanes were synthesized in 1937, the utility of weather-resistant polyurethane coatings became apparent only in the 1960s. Polyurethanes are obtained from the reaction of polyhydric alcohols and (poly- or oligo-)isocyanates. Nonreactive polymers can be prepared by terminating the polymer chains with monofunctional isocyanates or alcohols. Crosslinked polymers are formed from polyfunctional isocyanates or alcohols (Bentley & Turner, 1998; Brock *et al.*, 2000). Isocyanates that have been used include toluene diisocyanate (see IARC, 1999a), isophoronediisocyanate and 1,6-hexamethylene diisocyanate (HDI).

As a result of the wide range of physical properties obtained by varying the formulations of polyurethane coatings, they can be used in industrial and maintenance coatings as well as in coatings for wood, concrete, and flexible structures (Goldschmidt & Streitberger, 2002; Stoye & Freitag, 1998). Polyurethane coatings are being used increasingly for automobiles and aircraft, for wood and plastics, and in architectural coatings. The nomenclature of polyurethanes is sometimes difficult: the term is used for polyurethanes ready to be applied on a substrate as well as for two-pack mixtures of an acrylic resin to be crosslinked with an (oligo)isocyanate. The two-component systems are used as high-performance coatings for maintenance and product finishes.

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[1] Molecular weight value from number of molecules each multiplied by molecular weight and total divided by number of molecules

[2] Molecular weight value from sum of number of grams of materials with a particular molecular weight each multiplied by its molecular weight and total divided by total number of grams

Blocked (capped) isocyanates are used for one-component stoving coatings or coating powders. They are polyisocyanates in which acidic compounds such as phenols, ε-caprolactams, alcohols, malonic esters or secondary amines have been added to the isocyanate group. The blocking agents are separated at a characteristic temperature between 100 and 180°C followed by the rapid start of the curing reaction with a hydroxyl partner.

(vii) *Silicone resins*

Silicones are characterized by a siloxane backbone [-Si-O-Si-O-] with organic groups that determine the properties of the final polymer. The monomeric precursors of silicone polymers are mono-, di- and trisubstituted halosilanes (usually chlorosilanes). Monosubstituted silanols can undergo a condensation reaction to form highly crosslinked polymers, which are mainly used in coatings. The degree of crosslinking and consequent physical properties are controlled by adjusting the ratio between mono- and disubstituted chlorosilanes. Alkyd resins with terminal hydroxyl groups can be reacted with silicones in a condensation reaction to produce hybrid polymers (Heilen, 2005).

Silicone resins are used to waterproof masonry, and are blended with alkyds to formulate industrial maintenance coatings for storage tanks and other metal structure (Heilen, 2005).

Silicone chemistry is an important part of a new class of nano-coatings: the sol-gel chemistry for producing nano-thin layers is mainly based on hydrolysis of alkoxy-substituted silanes, followed by a condensation step at a surface. The result is a very thin layer with good protection properties (Sepeur, 2008).

(viii) *Cellulose derivatives*

Cellulose nitrate, commonly misnamed nitrocellulose, was the first cellulose derivative produced. The development of stable cellulose nitrate with low viscosity resulted in fast-drying lacquer coatings, which were used extensively in automobile and furniture production. In the USA, three types of commercially available cellulose nitrates are distinguished by their nitrogen content and solubility. Each of these types is available in a variety of viscosity grades, which are a measure of the polymer chain length (Stoye & Freitag, 1998).

Cellulose nitrate lacquers have also been formulated to contain resins, plasticizers, solvents and thinners. Plasticizers are usually added at about 10% of the weight of cellulose nitrate. Plasticizers such as triphenyl phosphate, tricresyl phosphate, dibutyl phthalate and butyl tartrate are being used in increasing amounts. The principal solvents used initially with cellulose nitrate include ethyl, butyl and amyl acetates, acetone, ‘diacetone alcohol’, ethanol and mixtures of alcohol with toluene, and of alcohol with esters (Stoye & Freitag, 1998). The main disadvantage of nitro lacquers is their high solvent content.

Another cellulose derivative, ethyl cellulose, is made by treating cellulose from wood pulp or cotton with a solution of sodium hydroxide to obtain primarily what is commonly referred to as ‘alkali’ or ‘soda’ cellulose. Further treatment with ethyl chloride under heat

and pressure yields ethyl cellulose, which can be produced in different viscosities. It is widely used in clear, dyed or pigmented lacquers for flexible substrates.

Cellulose acetate is a linear high-molecular weight polymer obtained by first treating cellulose with a reduced amount of acetic acid to cause a certain amount of swelling, and then reacting it with acetic anhydride in the presence of sulfuric acid. Cellulose acetate lacquers are stable to light and heat and have good resistance to oils, greases and weak acids (Brock *et al.*, 2000).

Methylcellulose, carboxymethyl cellulose and hydroxyethyl cellulose are water-soluble polymers that are used as thickeners in latex-based coatings. Cellulose acetate butyrate is used as a resin modifier in solvent-borne automobile base coats, deposited (underneath a clear coat) based on polymethylmethacrylate or other resins.

1.1.4 *Solvents*

A solvent is a liquid consisting of one or more component(s) that is able to dissolve binder, and is volatile under aplication (Stoye & Freitag, 1998). Solvents are widely used to keep paints in liquid form for easy application. The typical solvent content of paints and coating materials in western Europe is listed in Table 1.2.

Table 1.2. Typical solvent content of paints and coating materials in western Europe, 2006

Coating material		Solvent content in %
Coating powders, silicate paints		0
Emulsion paints for interior use		0–2
Emulsion paints for exterior use, plasters		3–5
Electrodeposition coatings		1–5
Latex coatings (environment-friendly)		5–9
Waterborne coatings (industrial)		3–18
High-solids coatings		20–35
General medium-solids and low-solids paints/coatings		40–50
Dilutions, thinners, cleaning agents	for solvent-borne coatings	100
	for waterborne coatings	0–50

Compiled by the Working Group

Until the late nineteenth century, the solvents used were almost exclusively turpentine and alcohol. Since the early 1900s, the number of solvents has increased considerably to encompass a broad range of petroleum and coal-tar distillates, alcohols, esters, ketones, glycols, synthesized glycol ethers and esters (mainly ethylene), and propylene glycol derivates. A large variety of mixtures of these classes of chemicals is also used. The choice

of solvent depends on properties such as adequate polarity, possibility of hydrogen-bridge linkages, volatility and evaporation, cooling effects while atomization, surface tension, viscosity, flash point and flammability and – more and more importantly – physiological harmlessness. Derivatives of ethyleneglycol monoethylether (ethyl glycol) have been removed from many formulations since the 1980s in western Europe. Since 1990, the use of styrene, the main reactive solvent in putties and paints based on unsaturated polyesters, has been reduced by legislation of the European Community.

Waterborne coatings generally require water-soluble solvents such as glycol ethers (butylglycol), *n*-butanol or sometimes *N*-methyl-pyrrolidone.

1.1.5 *Additives*

Additives are defined as those chemicals that perform a special function or impart a special property to paints or coatings. They are present at low concentrations, generally 0.1–5% wt. Additives include surfactants and dispersing agents, driers, rheological agents, plasticizers, biocides, anti-skinning agents, antifoam agents (defoamers), corrosion inhibitors, light (UV) stabilizers and catalysts (Brock *et al.*, 2000; Stoye & Freitag, 1998).

In the last 5 years, nanoparticle-based additives have appeared on the market (see below under ix). Many additives are adapted to the new paint systems, by modifications of the existing products rather than by the development of new ones.

(a) Surfactants and dispersing additives

Surfactants, which are classified into anionic, cationic, amphoteric or nonionic are used as pigment dispersants in both nonaqueous and aqueous systems. Dispersants employed in nonaqueous systems include lecithin, zinc or calcium naphthenate or octoate, oleates, and oleic acid. Polymeric organic surfactants (polyurethanes, polyamides and others) are also used increasingly because of their better colloidal stabilizing properties. Ionizable dispersants usually used in aqueous systems include polyphosphates, pyrophosphates, salts of arylalkyl-sulfonic acids and salts of polycarboxylic acids, e.g. polyacrylic acid (Oyarzún, 2000; Müller & Poth, 2006).

In addition to pigment dispersion, surfactants are used in paints as emulsifying agents, protective colloids, wetting agents and antifoaming agents.

Surfactants used in waterborne paints include aluminium stearate, cellulose ethers, polydimethyl siloxanes, polyethylene, alkali metal phosphates and sodium dioctyl sulfosuccinate.

A variety of other surface-active agents are added to paints to control flow, levelling, sagging, settling and viscosity, including hydrogenated castor oils, lecithin, metallic soaps (e.g. linoleates, palmitates and stearates), treated montmorillonite clays, peptized oil gels, polyol esters, siloxan-polyester resins, silicas, and soap solutions (Brock *et al.*, 2000; Müller & Poth, 2006).

Defoaming agents must be able to enter the foam lamellae. There, they destabilize the lamella, whereupon the foam collapses. The two main groups of defoaming agents are mineral oils and specially modified siloxanes.

(b) Driers

The driers (siccatives) used in solvent-borne and waterborne paints containing unsaturated polymers are principally metal salts (lead, calcium, cobalt, manganese, zirconium, vanadium, barium, zinc, cerium and lanthanum) of naphthenic acid, tall oil acid, 2-ethylhexanolic acid and neodecanoic acid, generally at concentrations ranging from 0.3 to 0.8% (Brock *et al.*, 2000). Cobalt-based driers are the most commonly used commercially and are active catalysts in both air-drying and heat-cure systems. Other metal driers serve as auxiliary driers and are usually used in combination with cobalt and manganese. Lead (IARC, 2006a) driers were at one time the major auxiliary driers, but legislation limiting the amount of lead that can be used in coatings has practically elimininated its use since 1990–2000. The most suitable replacements for lead are reported to be zirconium, calcium and cobalt-zirconium compounds (Müller & Poth, 2006).

(c) Rheological additives

The rheological properties of a coating material are of prime importance for optimum performance during application (‘good flow without dripping’). They also influence its storage life.

Water-soluble hydrophilic colloids include agents such as gum arabic, gum tragacanth, starch, sodium alginate, methyl cellulose, hydroxyethyl cellulose, polyvinyl alcohol, ammonium caseinate, polyurethane derivates, and polyacrylates. Acrylate salts, casein and cellulosics are widely used in acrylic paints, while the major thickeners for styrene–butadiene paints are alkali-soluble proteins (soya bean proteins). Methyl cellulose and hydroxyethyl cellulose are common thickeners for polyvinyl acetate paints (Brock *et al.*, 2000).

Non-cellulosic agents used in waterborne and solvent-borne paints include maleic anhydride copolymers, mineral fillers, such as colloidal attapulgite (see IARC, 1997), and treated magnesium montmorillonite clays, pyrogenic silicic acid (SiO_2), natural products (e.g. alginic acid, casein and soya bean protein), polyacrylamides, polyacrylic acid salts and acid-containing crosslinked acrylic emulsion copolymers. Associative thickeners consist of molecules with hydrophilic and hydrophobic moieties (Brock *et al.*, 2000).

(d) Plasticizers

Following the use of castor oil and glycerine in the late nineteenth century and of triphenyl phosphate after 1912, the use of plasticizers expanded by the mid-1920s with the introduction of di(2-ethylhexyl)phthalate (see IARC, 2000), and dibutylphthalate in the mid-1930s.

Plasticizers are generally added in quantities of up to about 2% wt and include dibutyl-, diethyl-, diethylhexyl- and dioctylphthalates and, to a lesser extent, the low molecular-weight esters of adipic and sebacic acid, tributyl phosphate, and castor oil. Polyester resins, including maleic residues, sulfonamides, triorthocresyl phosphate and chlorinated diphenyls, are used occasionally (Stoye & Freitag, 1998).

(e) Biocides (fungicides, preservatives and 'mildewcides')

Waterborne paints contain organic substances and represent an ideal growth medium for fungi, algae and bacteria. With the reduced content of residual monomers and organic solvents, which often have anti-microbial action, the risk for microbial contamination is increased in new formulations. This is followed by discoloration of the paint, changes in rheological behaviour and pH, coagulation, odour, and gas evolution. The growth of microorganisms in the coating or later in the film can be reduced or even prevented by adding chemical biocides to paint at concentrations below 1% wt (Brock *et al.*, 2000; Schwartz & Baumstark, 2001).

In-can preservatives protect against attack during production, transportation and storage. Commonly used substances are formaldehyde (decreasingly so) and its reaction products with alcohols, amines and amides, as well as *N*,*S*-heterocyclic compounds such as isothiazolinones and chloroacetamide (Brock *et al.*, 2000).

In-film preservation is the protection of the applied film against attack by bacteria, moulds, algae or mosses. Their need depends on the exposition of the applied film to humidity, shadow, heat, etc. Substances that are used currently include several *S*- and *N*-containing compounds, often cyclical compounds such as dithiocarbamates, thiophthalimide derivates, benzimidazole derivates and trialkyl compounds, as well as some ecologically unsafe substances such as organic mercury compounds. This category also compasses *antifouling additives* in marine paints, which are designed to prevent marine growth on ships´ hulls and port installations (Brock *et al.*, 2000).

(f) Antiskinning agents

Antiskinning agents are added to paints to retard the formation of skin on the surface of the liquid coating, in either closed or open tins, without delaying the drying of the product. The principal antiskinning agents are oximes or phenol derivatives. The oxime used most commonly is methyl ethyl ketoxime; smaller quantities of butyraldoxime and cyclohexanone oxime are used. The phenol derivatives used are mainly methoxyphenol, *ortho*-aminophenol, and polyhydroxyphenol. Minor quantities of cresols, guaiacol, hydroquinone (see IARC, 1999a), isobutoxysafrol and lignocol have also been used as antiskinning agents.

(g) Corrosion inhibitors

Corrosion inhibitors can be divided into inorganic pigments and organic inhibitors (Brock *et al.*, 2000).

Red lead and chromate-containing pigments have both a chemical and an electrochemical action. Pigments containing red lead are still used in heavy-duty anti-corrosion systems because they possess excellent protection properties. Some zinc chromates are still essential for the protection of aluminium on aircraft.

Lead and chromate-containing pigments are increasingly being substituted by phosphates (zinc, chromium(III), aluminium, calcium and magnesium phosphates). Zinc dust primers are widely used in the protection of steel structures. The synthetic micaceous iron oxide pigment (haematite, Fe_2O_3) acts through a physical mechanism, mainly by the barrier effect of its crystal lattice structure (platelets).

The most important member of the group of organic inhibitors is the zinc salt of 5-nitrophthalic acid.

(h) Asbestos

In the early twentieth century, asbestos was used as a filler to improve the technical properties of paints, particularly those used in shipyards and those applied to bridges. The paints may have contained up to about 20% asbestos. Usage decreased after about 1950, although specialist textured paints or coatings continued to be widely used in home decoration until the early 1990s. These paints contained approximately 5% chrysotile asbestos (Williams *et al.*, 2007).

(i) Nanoparticles

Nanoparticles [substances of < 100 nm in more than one dimension] are mostly metal oxides such as special transparent titanium dioxide, silver or silver compounds, aluminium oxide, fullerenes, and other organic compounds. The use of particles in the range of 10–100 nm – contained in amounts of 0.5-5% wt – remarkably improves the properties of paint layers in terms of scratch resistance, hardness, gloss, wheather stability and crosslinking/hardening. Interestingly, nanoparticles have been used for a long time: carbon black, silicas and ferrous oxides, which have been used for hundreds of years, can have particle sizes down to about 20–100 nm.

Nanoparticles are present as single particles only at the time of manufacturing. Single particles increase in size by agglomeration and by absorption of polymers and tensides onto their surface (which is important for better stabilization, preservation of the required properties and better flow behaviour of the paint). During drying of the paint, the particles continue to agglomerate and are incorporated irreversibly into the polymer matrix. As a result, painters are not exposed to single nanoparticles as such. In addition, since nanoparticles are made by special manufacturers and sold as slurry (aqueous or solvent-

based), because of the strong potential for agglomeration, workers in the paint manufacture do not come into contact with individual nanoparticles either (Aitken *et al.*, 2006).

(j) Light stabilizers

Platelet-shaped aluminium pigments (with their "mirror effect") have been used for many years in high-weather resistant masonry coatings. Modern light stabilizers for coatings are multifunctional. They can be divided according to their mode of action into UV absorbers and radical captors (Brock *et al.*, 2000).

UV absorbers convert UV radiation into heat. Four classes of substances possess the appropriate absorption coefficient: 2-hydroxybenzophenones, 2-hydroxyphenylbenzitriazoles, oxalanilides, and 2-hydroxyphenyltriazines.

Radical interceptors quench the reactive radicals being formed in upper layers and convert them into stable compounds. This interrupts the radical reaction chain of photochemical degradation of the binder. The most commonly used types are the HALS type products (hindered amine light stabilizer), which are all derived from 2,2,6,6-tetramethyl piperidine.

1.2 Production and use of paint products

1.2.1 *Production*

(a) Production processes

The modern manufacture of paints, which are produced mostly in batches, sometimes also continuously, involves three major steps: (i) mixing and grinding of raw materials; (ii) tinting (shading) and thinning; and (iii) filling operations.

Manufacturers first load an appropriate amount of pigment, resin and various liquid chemicals for homogenizing into a stirrer. The homogenized mixture is then transferred to a roller mill, which is a large rotor-stator steel cylinder. Mills for grinding primers or dark pigments are partly filled with steel balls or ceramic pearls of about 0.1–3 mm in diameter. Mills for grinding light colours usually contain flattened ceramic or zirconium dioxide spheres (pebbles) of about 0.1–2 mm in diameter. Depending on the type of mill used, the grinding process lasts for about 0.5–2 hours or until the pigment has been ground to a sufficiently fine paste. After that stage, the grinding pearls are removed and more resin and solvent are added to the paste, and the process repeated. The paste is then pumped out of the mill through a strainer to a holding tank (Brock *et al.*. 2000; Goldschmidt & Streitberger, 2002).

The 'tinting' step involves comparing samples in the holding tank with colour standards. Small amounts of shading pastes, which are highly concentrated blends of ground pigments, and a vehicle are added as required to match the standard. After the batch has been shaded to specifications, it is thinned to the desired viscosity by the addition of solvent, filtered and poured into containers for shipment (Brock *et al.*, 2000; Goldschmidt & Streitberger, 2002).

The complexity of paint technology is indicated by the numerous types of raw material required. A plant that produces a broad line of trade, maintenance, and industrial paints requires over 1000 different raw materials as well as intermediates including oils, pigments, extenders, resins, solvents, plasticizers, surfactants, metallic driers, and other materials.

The modern manufacture of unpigmented lacquers is generally a cold-cutting or simple mixing operation. For example, cellulose nitrate solutions are made by adding the nitrated cellulose from alcohol-wet cotton to the solvent mixture and agitating for 1–2 hours in a paddle or turbine blade mixer. Alkyd resins, which are supplied in solution, can be added directly to the cotton-based solution. Hard resins may be dissolved separately and added as solutions, or the lumps may be dissolved directly in the cotton-based solution by stirring.

The new paint systems are usually produced in the same sequence and with similar equipment as solvent-borne paints. Coating powders, by contrast, need other machineries, such as the extruders used in the plastics industry.

A general trend in the production is the reduction of exposure of workers to the material. Pigment, fillers and solvents (and solvent-based binder solutions) are increasingly removed by ventilation exhausts or by totally-closed automatized production lines. However, many small manufacturers, especially in low-resource countries, still produce paints with a technology without exhausts.

(b) Production volume

Traditionally, two types of coatings are produced: trade sale paints and industrial product finishes.

Trade sale paints are primarily for exterior and interior coatings for houses and buildings, although sizeable amounts of automobile and machinery refinishes, traffic paints and marine shelf-goods are also dispensed through trade sales outlets.

Industrial product finishes or chemical coatings are produced to user specification and sold to manufacturers for factory applications on such items as automobiles, aircraft, appliances, furniture, plastic parts, and metal containers. They also include the category of industrial maintenance coatings, which are specially formulated and are used to maintain industrial plants and equipment (e.g. as resistance to corrosion).

World production of surface coatings in 2005 by selected countries or regions is given in Table 1.3. In 2005, North America produced 6.3 million tonnes (23.1%), western Europe 6.6 million tonnes (24.1%), and eastern Europe 2.5 million tonnes (9.1%). China produced 3 million tonnes (10.9%), with a strong trend in increasing production.

Table 1.3. World production of surface coatings by selected country or regions in 2005

Region	Production (in thousands of tonnes)	%
USA	5373	19.6
NAFTA	6330	23.1
Western Europe	6600	24.1
Germany	1810	6.6
Eastern Europe	2500	9.1
Russia	750	2.7
Asia	8700	31.7
Japan	1512	5.5
China	3000	10.9
Latin America	1540	5.6
Brasil	674	2.5
Rest	1750	6.4
Total	27430	100.0

NAFTA, North American Free Trade Agreement
From CHEM Research GmbH (2006)

The worldwide production of industrially applied paints grew from 6.3 million tonnes in 1980 to 10.5 million tonnes in 2006. In contrast, for the same period, solvent consumption barely increased from 4.1 to 4.2 million tonnes – a consequence of the increasing use of solvent-reduced paints (Streitberger, 2007). Table 1.4 gives details of the production of paints and coatings in Germany by type of resin.

Table 1.4. Production of paints and coatings

Type of resin	Production (in thousands of tonnes) by type of resin
Solvent-borne	
Alkyd	110.4
Acryl	50.9
Natural oils	6.1
Vinyl, styrene	26.2
Epoxy	68.4
Urethane	68.2
Cellulosic	26.7
Polyester	55.7
Phenolic, melamine, urea	4.2
Bitumen, tar	28.5

Table 1.4 (contd)

Type of resin	Production (in thousands of tonnes) by type of resin
Shellac etc.	5.7
High Solids	32.9
Other resins	42.9
Total	526.9
Powder coatings	73.5
Waterborne	
Dispersions (interior)	639.5
Dispersions (exterior)	174.7
Primers	80.3
Synthetic resin plasters	199.2
Glue paints etc.	22.7
Silicate wall paints	30.4
Silicate plasters	27.1
Dispersion laquers	91.7
Electrodip coatings	36.7
Phenolic, melamine, urea	1.0
Putties	189.4
Silicon resin paints	10.6
Silicon resin plasters	19.3
Other resins, synthetic	121.3
Other resins, natural	2.2
Total	1646.1
Thinners (organic solvents)	231.3

From Verband Der Deutschen Lackindustrie (2007)

1.2.2 *Application methods*

The uses and properties of polymer systems in industrial coatings are described in Table 1.5 and 1.6. The various methods of paint application are presented in Table 1.7.

Most paints are applied by simple methods such as brushing or rolling, yielding high transfer efficiency, and with no spray dust formation. Electrodeposition of paint, introduced during the 1960s, was an important milestone in industrial painting and has proven especially advantageous for painting automobile bodywork and other parts thanks to its superior corrosion resistance. In this technique, the coating is an aqueous dispersion of low solid content. The binder particles carry ionized functional groups which may be positive or negative, thus having either anodic or cathodic deposition.

Table 1.5. Uses of polymer systems in industrial coatings

Polymer systems	Coil	Metal	Appli-ance	Furni-ture	Hard-board	Lumber and plywood	Marine	Main-tenance	Auto-mobile OEM	Auto-mobile refinish	Tins
Natural and modified polymers											
Drying oils				**(+)**	**(+)**	+	+	+			**(+)**
Cellulose esters		+		+		+			+	+	
Cellulose ethers				+						+	
Condensation systems											
Alkyd resins	+	+	+	+	+	+	+	+	**(+)**	**(+)**	**(+)**
Polyesters, high molecular weight	+	+	+		+	+					
Amino resins	+	+	+	+	+	+			+	+	
Phenolic resins	+	+	+				+	+	+		+
Polyamides		+					+	+			+
Polyurethanes		+	+	+	+	+	+	+	+	+	+
Epoxy resins	+	+	+	+	+		+	+	+	+	+
Silicones	+	+	+				+	+		+	+
Vinyl polymers and copolymers based on:											
Butadiene								+			+
Acrylic or methacrylic ester	+	+	+	+	+		+	+	+	+	+
Vinyl acetate				+	+	+	+	+			

Table 1.5 (contd)

Polymer systems	Coil	Metal	Appli-ance	Furni-ture	Hard-board	Lumber and plywood	Marine	Main-tenance	Auto-mobile OEM	Auto-mobile refinish	Tins
Vinyl chloride	+	+	+	+	+	+	+	+	+		+
Vinylidene chloride							+	+			
Styrene		+	+		+			+	+	+	+
Vinyl acetal or butyral	+	+		+				+		+	+
Fluorocarbons	+							+			
Resin combinations											
Acrylic and amino	+	+	+	+	+				+		+
Acrylic and epoxy		+	+						+		+
Acrylic and silicone	+	+						+			
Alkyd and amino	+	+	+	+	+				+	+	+
Alkyd and acrylic		+	+	+				+	+	+	+
Alkyd and epoxy		+	+					+	+		
Alkyd and silicone	+	+	+								
Polyester and epoxy		+	+					+	+		+
Polyester and silicone	+	+			+						

Table 1.5 (contd)

Polymer systems	Coil	Metal	Appli-ance	Furni-ture	Hard-board	Lumber and plywood	Marine	Main-tenance	Auto-mobile OEM	Auto-mobile refinish	Tins
Cellulose ester and urethane				+							
Alkyd, acrylic and amino					+						
Polyester and amino											+
Phenolic and epoxy							+	+			+
Epoxy and amino											+
Phenolic and amino											+
Alkyd and vinyl chloride polymers							+	+			

Updated from IARC (1989a) by Working Group
OEM, original equipment manufacturer

Table 1.6. Properties of paint systems for different uses

System	Use for	Advantages	Limitations	Use trends
(Nitro)cellulosics physical drying	Furniture, small mass articles	Fast drying, scratch resistant, alcohol resistant, thin layers possible	Poor light and solvent stability, poor solids content, high solvent content	Declining
2K-PUR (‘DD-paints’) and 1K-PUR-heat curing paints	Furniture (kitchen), high performance exterior, e.g. vehicles, ships, metal, aircraft	Mechanically and chemically very stable, elastic	Expensive, time in which the material must be used before hardening in the can	Increasing
Acid-curing enamels, urea–formaldehyde resin +Alkyd resin	Similar to 2K-PUR	Similar to 2K-PUR	Formaldehyde emission	Declining
Oil-based resins (alkyd resins)	Exteriors, wall paints, DIY	Good gloss and surface, resistant against weather and chemicals	Slow hardening, often brittling, sensitive against alkali	Declining
Unsaturated Polyesters (UP-paints)	High performance, glossy surfaces e.g. pianos. Putties	Scratch resistant high gloss, low solvent content, high thickness possible	Not light stable, short processing time (2K), poor storage stability and adhesion	Constant for special uses
Waterborne: Acrylate- and PUR-dispersions	Interior furniture, DIY	Low VOC content, light stable	Slow drying, expensive, strong roughening at wood surfaces	Increasing
UV-curing paints, also: electron beam coating	Furniture, specially in schools, parquet	Extremely fast and resilient curing, very low VOC	UV: limited pigmentability	Increasing
Powder coatings (esp. acryl-, polyester-based)	Metal, appliance, machineries, automotive parts	Solvent-free, fast hardening	Heatability of object (plastics and wood very difficult)	Increasing

Table 1.6 (contd)

System	Use for	Advantages	Limitations	Use trends
Polyester (1K, 2K)	Primers, various interior uses	Cheap, mechanically resistant	Poor weather and chemical stability	Declining
Thermoplastic acrylates	Industrial metal coating, low performance appliances	Weather stability, flexible, chemically stable	Poor hardness, heat-softening, expensive	Declining
Melamin resins (oven-curing with OH-polyester, -acrylate,- alkyd)	Weather-stable top coats: vehicles, machinery, appliances, coil coating	Hardness, resistance, adhesion to substrate	Properties not really at level of 2K-PUR	Declining
Epoxy resins (esp. 2K)	Vehicle primers, corrosion and construction protection, Tank interior	Excellent adhesion (especially on zinc, a difficult substrate), resistance, flexibility	Poor weather stability: yellowing, chalking	Constantly high level
Phenolic resins and similars, different hardeners	Primers, electro insulation, tin interiors	Temperature- and chemical-resistant	Yellowing	Special uses
Polyvinylbutyral	Metal primer, e.g. washprimer, shop primer	Excellent adhesion, corrosion protection, also on aluminium	Not for top coats	Constant
Silicon resins	Construction protection	Temperature and weather resistance	Expensive	Increasing
Chlorine-, fluorine-containing polymers	Corrosion protection, coil coating, dirt repellent top coats	Good adhesion on plastics, temperature- and weather-stable	Halogen content (environment, waste disposal), expensive	Special uses, declining

1K, 1-component material; 2K, 2-components material (also two-pack material); 1K-PUR, 1-component polyurethane; 2K-PUR 2-components polyurethane; DIY, Do-It-Yourself
Compiled by the Working Group

Table 1.7. Application methods

Application	Surface quality	Limitations			Throughput	Solvent emissions	Transfer efficiency
		Dimensions	Geometry	Others			
Brushing	Medium to good	Small areas	-	-	Very low	Low	Very good
Rolling	Good		Accessibility	-	Medium	Low	Very good
Drawing (putty)	-	Small areas	-	-	Low	Low	Very good
Wiping	Poor	Large parts	-		Low	Low	Very good
Conventional dipping	Medium	Limit in object volume	No scooping parts	Edge covering	High	Low	Very good
Coating in barrel	Poor	Small parts	Pourable	-	High	Low	Very good
Centrifuging	Poor	Small parts	Pourable	-	High	Low	Very good
Flooding	Medium	Limit in object volume	No scooping parts	Edge covering	High	Low	Very good
Flow Coating	Medium	Working width	No scooping parts	Edge covering	High	Low	Very good
Curtain coating	Very good	Working width	Nearly flat objects	-	High	Low	Very good
Roller coating/Coil coating	Medium	Working width	Flat surfaces	-	Very high	Low	Very good
Electrodipping	Low	Limit in object volume	No scooping parts	-	High	Low	Very good

Table 1.7 (contd)

Application	Surface quality	Limitations			Throughput	Solvent emissions	Transfer efficiency
		Dimensions	Geometry	Others			
Air – low-pressure atomization	Good	-	-	-	Low	High	Poor
Air – high-pressure atomization	Excellent	-	-	-	Low-to-medium	Very high	Very poor
Air – high-pressure HVLP	Very good	-	-	-	Low	High	Poor
Airless atomization	Medium	-	-	-	High	Medium	Medium
Airmix atomization	Good	-	-	-	Medium	High	Medium
Electrostatically aided air atomization	Very good	-	No Faraday cages	Electricity-conducting substrate	Medium	High	Good
High speed rotation atomization	Very good	-	No Faraday cages	Electricity-conducting substrate	Medium	High	Good
Electric powder coating	Good	-	-	Electricity-conducting substrate	Medium	No	Good
Fluidized bed coating	Poor	-	-	Thick layers	Medium	Low	Very good

HVLP, high-volume low-pressure
Compiled by the Working Group

The anodic type typically uses amino- or alkali-solubilized polycarboxylic resins and the cathodic type, salts of amine-treated resins, such as epoxy resins (Stoye & Freitag, 1998).

For high quality surface requirements ("appearance," gloss, smoothness), paints are often applied by direct contact or by deposition by atomization processes.

Deposition by atomization processes includes conventional spray, hot spray, electrostatic spray, and powder coating (Brock *et al.*, 2000).

Probably the greatest advance during the early 1900s in the field of paint technology was the introduction of the spray gun. Its advent helped the introduction of cellulose nitrate lacquers and their application to automobile assembly line production. Electrostatic spraying was first introduced in the USA in the 1940s, and then later in the United Kingdom.

The solvent-free electrospray powder spray application was introduced in 1965 in the coating industry. In this process, the powder is first fluidized in a closed container by compressed air. The so-formed aerosol is transported by an injector to the spray gun. There, the powder particles are charged electrostatically and sprayed onto the object, which is earthed. The electrostatic charge allows the transport of the particles to the object and their adhesion to it.

Since the early-to-mid 1990s, – initiated mainly by Rule 1151 in southern California – the high-volume low-pressure technique has allowed savings on paint material by reducing spray dust. The modified spray technique, which requires new nozzles and a new spray gun interior, allows a 10–20% reduction in paint consumption. This technique is applied worldwide.

1.3 Formulation and application methods by trade

1.3.1 *Construction painting*

Paints that are used on architectural structures (indoor and outdoor surfaces) are comprised of primers or undercoats and matt, semigloss or gloss-finishing coats. The primers and finishing coats differ primarily in the pigment/vehicle balance and in additive and vehicle types. Primers (usually called 'primers/sealers') are used to seal the variable porosity of the substrate (e.g. wood) and to adhere to the substrate and to subsequent coats of paints.

(a) Exterior house paints

Traditionally, linseed oil and oleoresinous vehicles have accounted for the bulk of architectural (house) paints. Several other oils have been used, but to a much lesser degree and often in conjunction with linseed oil. The most important have been tung oil, perilla oil, soybean oil, fish oils, safflower oil, and dehydrated castor oil. More modern oil-based house paints generally contain a combination of untreated drying oil (unbodied oil) and drying oil treated (polymerized) so that its viscosity is increased (bodied oil). A wide variety of

thinners and solvents were employed in the formulation – white spirits, benzene and solvent naphtha.

Between 1950 and 1960, the first exterior water-based house paints were introduced. Most of these were based on acrylic-type latexes, and the paint had excellent colour retention on exterior exposure. Since that time, water-soluble and emulsified linseed oil house paints have been marketed, which combine the advantage of an oil paint and a water-based paint in one product. Because of the ease of application, cleaning ability with soap and water and good service, latex paints constitute most of the exterior paint market. Among the more common latexes are the acrylics, polyvinylacetate–dibutylmaleate copolymers, ethylene copolymers and acrylate copolymers (Schwartz & Baumstark, 2001).

The pigments used in interior and exterior construction or architectural paints include primarily inorganic and organic pigments that are stable against UV light, water and acid rain.

(b) Interior paints

The principal pigments used for interior white paints are titanium dioxide, zinc oxide and iron oxides as well as various carbonates and siliceous extenders, which are used to control pigment volume and gloss. Since 1927, with the development of alkyd resins, a variety of architectural enamels for interior and exterior use have been based on these resins. The bulk of enamels produced for interior use contains oil treated to increase viscosity (bodied oil), and/or varnish.

Water-based interior paints contain three types of latex polymers: styrene–butadiene types, polyvinyl acetate types, and acrylics. Copolymer blends of styrene and acrylate have also been used, combining the most durable features of each monomer into a single polymer (Schwartz & Baumstark, 2001).

Extender pigments used in latex paints include clays, calcium carbonates, silicates, diatomaceous earths, silicas, barytes, and talcs (IARC, 1997, 1987, 2010a), as well as white and coloured pigments. Surfactants, pigments and other additives are usually incorporated into the formulation along with latex to obtain a stable and satisfactory product. These other additives include thickeners, defoaming agents, freeze–thaw stabilizers, coalescents, and pH adjusters (ammonia amines or potassium hydroxide). The thickeners used most commonly are cellulosics – principally hydroxyethyl cellulose and methyl cellulose – polyacrylates, polyacrylamide, polyvinyl alcohols, and many others. Propylene glycol and monoethers of this glycol and other glycols serve as freeze–thaw stabilizers. Coalescents are additives designed to optimize the coalescence of latex particles and include hexylene glycol, butyl cellosolve, and butyl carbitol. In the last 20 years, the solvent content has decreased from about 3–5% to nearly 0%. As a result, interior paints must be protected against microbial attack (fungi, bacteria) by in-can preservatives such as imidazoline derivatives (Schwartz & Baumstark, 2001).

(c) Masonry paints

Latex-based primers/sealers are state-of-the-art for masonry surfaces. The latex vehicle is generally more resistant to alkali than earlier casein-based paints and permits evaporation of water from masonry surfaces without disruption of the film. Both alkyd and latex vehicles adequately seal porous surfaces (Schwartz & Baumstark, 2001). Oil paints and styrene–butadiene copolymer, polyvinyl acetate emulsion, resin emulsion and chlorinated rubber paints are also used on masonry surfaces.

Concrete floor coatings – and coatings for other cementitious substrates – must possess good water and alkali (saponification) resistance and adhesion over damp surfaces. Concrete is first covered with a solvent primer. A satisfactory floor paint can be formulated using a styrene–butadiene latex fortified with an epoxy ester. An example of a concrete floor enamel formulation is presented in Table 1.8. Acrylic emulsion paints are widely used outdoors on concrete, stucco and cinder block because of their durability, adhesion, and flexibility (Stoye & Freitag, 1998).

Table 1.8. Example of formulation of vinyl acetate-based masonry paint for interior use

Component	Percentage
Water	26.9
Dispersant (polycarbonate, polyacrylate)	0.7
Thickener (polyurethane, cellulose derivates)	0.5
Defoamer (mineral oil)	0.1
Sodium hydroxide (25 %)	0.1
Dipropylene glycol-*n*-butyl ether	0.5
In-can preservative (isothiazolinone)	0.2
Titanium dioxide (rutile)	5.7
Calcite	29.7
Chalk	12.5
Calcium carbonate (precipitated)	8.0
Talc	9.1
Vinyl acetate-ethylene copolymer dispersion, 53 %	6.0
Total	100.0

From Müller & Poth (2006)

(d) Waterproof paints

Waterproof paints are applied on the outside of unpainted concrete, brick, stucco, and so forth and are formulated in a variety of ways to include components such as wax, aluminium stearate, and silicone resins. A significant advance in the manufacture of waterproofing paints in the mid-1950s involved the use of silicone resins. Typically, silicone waterproof paints contain silicone resin and solvent or water, or special silicones, such as sodium methyl siliconate, in aqueous solution (Heilen, 2005).

1.3.2 *Surface coating in the wood industry*

Five properties are considered to be essential in furniture varnish: quick, hard, tough drying (3–4 hour); good sanding and polishing properties; good resistance to water, heat and chemicals; good processing properties; and environment friendliness (e.g. free of formaldehyde, low VOC emissions). Table 1.9 gives an example of a formulation for a parquet lacquer of matt clear varnish.

The types of organic dyes found in wood stains (IARC, 1981) include anthraquinones, acid azo metal complexes, phthalocyanines, triphenylmethane salts, coumarins, perinones, methines, pyrazolones, quinophthalones, various other metal complexes, and several food dyes (Prieto & Kiene, 2007).

Finishing operations for wood include staining, 'wash coating' [the application of a clear thin coat of lacquer before use of a filler], filling (if necessary), sealing, sanding, application of one or two lustre coats, and polishing. Two types of oil or water stains – soluble and suspended pigment type – impart the desired colour to wood. Wood stains are dissolved in a vehicle that enables them to seep into the wood rather than simply stick to its surface as a film. After the staining operation, 'wash coating' stiffens the protruding fine wood fibres, and can be removed by light sanding. In some procedures, a filler is used to fill the depressions before the sealer and finish coats are applied. These finishes are dried by evaporation of solvent or water; finish coats usually contain physically drying dispersions, UV-curing lacquers or two-component polyurethane systems. Formulations of paint used for furniture depend on the end-use. Nursery furniture, for example, requires extremely hard, tough coatings containing non-toxic pigments. A wide variety of coatings has been used on furniture, based on the chemical systems mentioned above.

Current trends are towards solventless UV-curing paints, often as replacement for existing waterborne systems. The main advantages are a higher performance and longer lifetime of the coated parts. The first attempts with powder coatings on fibre plates are under way.

1.3.3 *Painting in the metal industry*

(a) Metal primers, finish coats and corrosion inhibition paints

As iron and steel rust in contact with moisture and oxygen, many products made with these metals are coated with rustproof primers and finishing coats.

Primers are vehicle-rich coatings intended for application as foundation and adhesion-promoting coats. Metal primers are used to form a firm adhesive bond with the surface and also serve as an impermeable barrier between the environment and the metal surface.

Table 1.9. Example of formulation of a parquet lacquer of matt clear varnish in western Europe, 2000

Type of product and ingredients	Parts per weight
Mixture 1	
Solvents	
Propylene glycol-*n*-butyl-ether	40
Propylene glycol	10
Dipropylene glycol monomethyl ether	20
Additives – total	25
Water	30
Butyl glycol	20
Mixture 2	
Acrylic dispersion, 45% wt	400
Polyurethane dispersion, 40% wt	400
Wax dispersion	45
Defoamer, levelling agent	10
Procedure	
Introduce mixture 2 and add mixture 1 while stirring	

From Schwartz & Baumstark (2001)

When active rust prevention is essential, rust-inhibitive pigments that retard oxidation chemically are used.

Zinc chromate (zinc yellow; [a double salt of zinc and potassium and chromic acid]) was introduced in the early 1940s and is still used in some areas, especially for aircraft. Because of restrictions on the use of lead and chromates in the early 1960s, the pigments favoured in the past 20 years in industrial maintenance coatings have been mainly zinc metal, zinc oxide, zinc molybdates and zinc phosphates (Brock *et al.*, 2000; Buxbaum & Pfaff, 2005).

Finishing coats cover the metal primer and seal it. Some metal products are covered by enamels that contain alkyd resins, and dry by oxidation. The most durable coatings available are generally used on machinery and other industrial equipment, and are based on epoxy or polyurethane resins that are cured by chemical reaction. Typical formulations are shown in Table 1.10.

Since the 1980-1990s, an increasing percentage of metal parts used in the industry, household and machinery are coated with coating powders. The use of powders however is limited by the following factors inherent to the system: geometry (not too complex), resistance against oven temperature of 160–220°C, and electrical conductivity. Until the mid-1990s, the technologically very good hardener triglycidyl isocyanurate was used. Because of its teratogenicity, this hardener is no longer used in western and northern Europe, although it is still used in southern Europe, and in many other countries outside Europe. Other aromatic glycidylesters and β-hydroxyalkylamide may be used as substitute (Gillis de Lange, 2004).

Table 1.10. Examples of formulations of metal paints

Type of paint and ingredients	Weight (%)
Iron oxide primer (from 2000)	
Water soluble alkyd resin (75% in butyl glycol)	16.7
Styrene–butadiene copolymer dispersion	25.4
Ammonia (25%)	1.0
n-Butoxypropanol	1.2
Butyl glycol	1.7
Fillers (talc, calcite)	11.5
Zinc phosphate	7.4
Metal complex dryer (catalyst) 10%	0.4
Iron oxide pigment	6.7
Wetting and dispersing agent	3.6
Defoamer	0.3
Water	26.2
White epoxy powder indoor paint (from 2002)	
Epoxy resin (Bisphenol A-based)	55.7
Dicyanamide curing agent	2.8
Calcium carbonate (extender)	1.5
Titanium dioxide (pigment)	24.4
Barium sulfate (filler)	12.7
Acrylic polymer flow additive	2.9
Water-based red epoxy enamel for can coating (from 2000)	
Phenol epoxy resin emulsion (55% solids)	68.2
Butyl glycol	10.0
Hexamethoxy melamine curing agent	2.0
Iron oxide red pigment	9.8
Water	10.0
Polyurethane clear coat, solvent-borne, 2-pack, for metal (from 2000) (similar for wood or plastics)	
Hydroxyl-functional acrylic resin (60% in solvents)	81.0
Cellulose acetobutyrate (20% in butyl acetate)	2.0
Dibutyl tin dilaurate (catalyst) (1% in butyl acetate)	1.0
Hydroxyphenyl benzotriazol (UV absorber)	0.8
N-Alkyl piperidine derivative (radical catcher)	0.6
Silicone oil (1% in xylene)	1.0
Glycol monobutyl ether acetate	4.0
Polyisocyanate (90% in solvents)	32.2
Butyl acetate	18.5
Xylene	8.9
Total (100 of component 1 + 50 of component 2)	150.0

From Müller & Poth (2006)

(b) Marine paints

Paints for surfaces that are continuously immersed in seawater must be formulated with antifouling properties to resist the growth of marine flora and fauna. The accumulation of vegetable and animal vegetation at the hull produces a "biological roughness", which leads to weight gain of the ship and the loss of its hydrodynamic form (Grüner, 2007).

Antifouling coatings based on derivatives of triphenyl or tributyl tin have been introduced since the 1990s. In some coatings, an organotin compound, such as the acetate, chloride, fluoride or oxide, is simply mixed into the formulation. These coatings are known as 'free-association' coatings and are characterized by a high leach rate of organotin when the coating is new which rapidly diminishes, until the concentration of the coating becomes insufficient to prevent fouling. A more useful formulation is obtained when the organotin in 'copolymer' coatings is covalently bound to the resin of the coating and is released when the bond hydrolyses in sea water. Due to the high toxicity of these combinations, the use of organotin compounds is forbidden since 2003. According to the Navy Environmental Protection Committee of the International Maritime Organization (IMO), their presence on ships is illegal since 2008 (IMO, 2008).

More recent strategies have focused on nontoxic alternatives. These include the use of fluoropolyurethane foulant-release coatings. Paints based on "Controlled Depletion Polymer" have a high rosin content (> 50%) and few film formers, so that water-soluble films are formed in which the biocides are soluted. The "Self-Polishing Copolymer" is based on an acrylate resin, which is largely hydrophobic, water swellable. The biocides are bound to the polymer chemically and their activity occurs through hydrolysis (Grüner, 2007).

(c) Automobile coatings

Cellulose nitrate lacquers, introduced in the early 1920s, were followed by the introduction of alkyd enamels to the automobile industry in the early 1930s. These compositions were usually modified with small amounts of amino resins to provide harder, more thoroughly crosslinked films. These were followed by the adoption of thermosetting acrylic enamels in which alkyds were replaced by acrylic copolymers containing hydroxyl groups which could still react with melamine modifiers (Fettis, 1995).

In the late 1950s, lacquers of greatly improved durability and gloss, based on polymethylmethylacrylate or thermosetting acrylic enamels, were adopted by the automobile industry (Fettis, 1995).

Nowadays, many polymers (including maleic resins, amino resins (urea–formaldehyde and melamine–formaldehyde polymers), silicones, epoxides, polyesters and polyurethanes) form the basis of highly diverse coating systems. In addition, nonaqueous dispersion lacquers and acrylic enamels have been developed. Steel used in automobiles is pretreated with a conversion coating (phosphating or bonderizing) to improve corrosion resistance and

adhesion. Today, most cars are galvanized and phosphated (Goldschmidt & Streitberger, 2002).

The earlier solvent-borne primers have been almost completely replaced since 1960 by waterborne electrodeposited primers. The original anodic type has been largely replaced since 1980 by the cathodic type, which is superior in corrosion protection. The binders for cathodic deposition are typically acid salts of amino-treated epoxy. The formulations contain polyepoxides or mostly blocked polyisocyanates which crosslink the coating when it is baked. Prior to application of the top coat, a coat of solvent or waterborne epoxyester primer–surfacer is applied (Fettis, 1995; Goldschmidt & Streitberger, 2002).

Waterborne base coats have been used in Europe since 1980–1990 and are still state-of-the-art today. In other regions, their use is increasing. Very high solid content top coats are being used increasingly; conventional thermosetting acrylic enamels that can be applied in about 60–65% volume solids are now available (Fettis, 1995; Goldschmidt & Streitberger, 2002). Top coats (especially clear coats) have been used in only a few plants since the mid-1990s. Some manufacturers already apply powder clear coats. The trends are towards more waterborne products, more powder and less paint consumption by application of thinner layers as well as by elimination of whole layers (surfacer).

A broad range of inorganic and organic pigments is used in automotive finishes (top coats). These include inorganic types such as titanium, nickel titanium and iron oxides, carbon black, aluminium and other effect pigments (Fettis, 1995). Organic pigments include diarylide yellow, anthrapyrimidine, isoindolinones, quinacridones, thioindigos, perinones (diimides of naphthalene-1,4,5,8-tetracarboxylic acid), perylenes (diimides of perylene-3,4,9,10-tetracarboxylic acid), copper phthalocyanines and anthraquinones, naphthol reds and maroons (monoazo pigments such as the copper precipitation product from the coupling of diazotized 4-nitroanthranilic acid with Naphthanil RC).

Table 1.11 gives a typical formulation of a lacquer for an automobile top coat.

Table 1.11. Formulation of a metallic base coat for automobile paint in western Europe, 2004

Type of paint and ingredients	Weight (%)
Blue metallic lacquer	
Polyacrylate dispersion (24% in water)	48.0
Melamin resin (80% in water)	4.7
Butyl glycol	7.4
Dimethylethanolamine (10% in water)	1.1
Aluminium flakes pigment (65% in aliphatic hydrocarbon)	3.8
Saturated polyester (60% in butyl glycol)	5.0
Water	30.0

From Müller & Poth (2006)

(d) Car repair finishes

Automotive repair finishing coatings, unlike assembly line coatings, are not stoved but instead dried or cured at temperatures below 80°C. They are usually force-dried at 50–60°C. Increasingly, they are coated by portable infrared radiators. Nevertheless, the coating is both visually and technologically comparable with the stoved primary coat, even though the coating systems are completely different, particularly in terms of binders and solvents (Brock *et al.*, 2000; Goldschmidt & Streitberger, 2002).

To meet these requirements, mainly products of the rapid and high peformance two-component polyurethane and two-component epoxy coating chemistry have been used since the 1970s. Alkyd resins, cellulose nitrate combination products and other older systems are also widely used, being tailored to local equipment and to requirements (Brock *et al.*, 2000).

The preparation zone is used for cleaning, degreasing, dust removal, levelling, priming, filling and sanding. The coating/drying station may be combined as one station or separated into two booths (Brock *et al.*, 2000).

Primer, surfacer and clearcoat are usually solvent-based. The base coat is also solvent-based in most countries. Since 2007, only waterborne basecoats are allowed in the European Community (EC).

(e) Coil coatings

One of the growing areas of industrial coating is coil coating. The coil stock consists of enormous rolls of thin-gauge (galvanized) steel or aluminium, which are coated at steel mills, aluminium mills or by specially equipped contractors. The coils are unwound, coated on high-speed roller coaters, heat-cured, sometimes then laminated and rewound. Binder compositions include alkydamino–formaldehyde combinations, vinyl chloride–vinyl acetate copolymers (see IARC, 1987, 1995, 2008) and thermosetting acrylics, often modified with small amounts of epoxy, which produces coatings that are flexible, durable and adhesive. In the coil-coating industry, which still uses solvent-borne materials only, solvent vapours are collected and disposed of by incineration (thermal recycling) (Goldschmidt & Streitberger, 2002).

Powder coating and UV-curing systems are used increasingly. Where this is not possible for technical reasons, waterborne paints are introduced.

1.3.4 *Other painting trades and paint products*

(a) Traffic paints

The major requirements for traffic (road) paints are fast and hard drying, and environmental compatibility. Since the 1990s, many public authorities in Europe demand the use of waterborne materials as much as possible for coating bus fleets, trains, and trams.

The paints generally contain a high pigment volume, fast-drying vehicles, such as resin combinations with low oil content or oil-free synthetic resins, and low-boiling solvents (e.g. petroleum fractions with distillation ranges of 100–150°C) or water.

Conventional alkyd formulations account for many traffic paints still used in numerous countries. However, there has been a significant increase in the use of more durable pavement-marking materials, such as two-component polyester, polyurethane and epoxy systems and one-component hot extruded thermoplastic types.

(b) Fire-retardant paints

Fire-retardant or intumescent paints, when applied to wood or other combustable, as well as to steel and aluminium surfaces, retard the spread of fire by foaming at elevated (but less than charring) temperatures. Several intumescent formulae contain a chemical combination of polyol (e.g. pentaerythritol), a mono- or diammonium phosphate or polyphosphate, aluminium hydroxide (as water degasser), and an amide. Certain pigments such as red phoshorous (glassy polyphosphoric acid protects against oxygen) and borates are also added to enhance the fire-resistant properties of such paints. Other intumescent paint formulae contain polyvinyl acetate and acrylic latexes.

(c) Aerosol colours

A large variety of paints have been packaged in aerosol tins for touching up and painting small areas, graffitis, hobby aircrafts and other such objects. The principal types of paint used are of alkyd composition, are thinned out to a low viscosity (generally with ketones and aromatic hydrocarbons) to allow atomization, and contain a gaseous propellant which is liquid under pressure (propane, butane, isobutane or sometimes dichloromethane, which has replaced dichlorofluoromethane in many countries). Other aerosol paint compositions include acrylic and cellulosic lacquers and epoxyester systems. In early 2000, the first two-component aerosol tins appeared. The two components are brought into contact by crashing a hardener cartridge inside, followed by intensive shaking.

(d) Paint and varnish strippers

Dichloromethane (see IARC, 1999a) was for a long time a widely used and effective paint stripper base. Other chlorinated hydrocarbons that were used with dichloromethane were, in order of decreasing effectiveness, perchloroethylene 1,2-dichloroethane (see IARC, 1999a), propylene dichloride, dichloroethyl ether and *ortho*-dichlorobenzene (see IARC, 1999b). Today, halogenated solvents are avoided in many countries. Other solvents that can soften paint films are, in approximate decreasing order of effectiveness, ketones (e.g. methyl ethyl ketone), dibasic and other esters, aromatic hydrocarbons, alcohols and aliphatic hydrocarbons, often combined with the use of ultrasonic impulses (Brock *et al.*, 2000; Goldschmidt & Streitberger, 2002).

The main inorganic paint strippers are alkalis, principally in the form of a hot solution of sodium hydroxide and, to a lesser degree, potassium hydroxide and lime or soda ash (anhydrous sodium carbonate). Additives such as sequestering agents (e.g. gluconic acid and alkali metal gluconates), surfactants (e.g. sodium resinate, fatty acid soaps, sodium lignin sulfonate, alkylarenesulfonates and petroleum sulfonates), water-soluble activators (e.g. phenolic compounds and their sodium salts – cresol, chlorocresol, sodium pentachlorophenate) and solvents (e.g. monoethers of ethylene glycol and diethylene glycol) are often used to increase the stripping rates of inorganic paint removers. Plants today use hot alkaline tenside solutions when possible. Paint removers that are used on steel, aluminium and other nonferrous alloys often contain corrosion inhibitors such as phosphates (Goldschmidt & Streitberger, 2002).

Molten and fused alkali baths are also employed sometimes to salvage ferrous metal parts with defective finishes. At temperatures of up to 500°C, even heavy films of epoxy and silicone coatings can be removed rapidly.

(e) Substrate preparation by sanding and air blasting

Substrates contaminated with corrosion products, dirt, dust, oil, grease and other contaminants must be sanded or – if possible or necessary – cleaned by air blasting (Goldschmidt & Streitberger, 2002).

Sanding is performed wet or dry, by hand or machines. The resulting dust may contain old paint, rust, zinc salts, and metal dust from the underlayer.

(f) Paints for artists

Art painters use pigments in oil paints, acrylics, watercolour paints, gouache, encaustic, poster paints, casein paints, and tempera. The range of pigments used in art paints is greater than that used in commercial paints. McCann (2008) highlights the following toxic metals in pigments used in art paints: arsenic in emerald green and cobalt violet (cobalt arsenate); antimony in true Naples yellow (lead antimonate); cadmium in various cadmium pigments; chromium in chromium oxide green, zinc yellow, strontium yellow, viridian; lead in flake white, mixed white, true Naples yellow; manganese in manganese blue, manganese violet, burnt umber, raw umber, Mars brown; and mercury in vermillion.

1.4 Exposures in the workplace

1.4.1 *Inhalation exposures*

(a) Introduction

Occupational exposure results predominantly from the inhalation of gases and vapours from solvents and additives, of pigment dust, and of complex inorganic and organic mixtures such as dusts from binders, dried coatings, and mists generated during the spraying of paint. The other major route of occupational exposure is through cutaneous contact with the various paint compounds, many of which can be absorbed through the skin. Ingestion related to personal work habits constitutes another potential route of entry.

Workers in the painting trades may also be exposed to several chemical agents originating from other operations that they or fellow workers are involved in, such as cleaning and preparing – by chemical or mechanical means – the object to be painted. Workers may be exposed to crystalline silica dust produced by other construction trades on a building site.

The main substances to which workers may be exposed are listed in Table 1.1. The main agents for which quantitative occupational inhalation exposure data are available are presented in Tables 1.2–1.6, which cover the major painting trades.

Exposure to solvent mixtures is often described using a summary measure, the cumulative exposure index (CEI), i.e. the sum of ratios of various measured levels to the respective occupational exposure limits. If this index exceeds unity, the combined exposure to different components of a solvent mixture is considered to exceed the recommended exposure limit. The values of the CEI are not always comparable because the exposure limits may vary by country and over time.

In some painting operations, personal protective equipment is worn. However, it is common industrial hygiene practice to determine potential exposure by monitoring the breathing zone outside such protective gear.

(b) Manufacture of paints and related products

The potential for occupational exposure depends largely on the types of products being manufactured, the degree of automation of the manufacturing process, the availability of exposure control measures, and the nature of the specific job held. Various job classification systems have been developed for the paint manufacturing industry. Workers have thus been regrouped according to the basic product manufactured – water-based paints, solvent-based paints, lacquer and vehicle – and their function: pre-batch assembler, mixer, tinter, filler, tank and tub cleaner, reactor operator, varnish cooker, filter press operator (Morgan *et al.*, 1981). Additional functions are raw materials handler, laboratory personnel, and others such

as packagers, maintenance personnel, shippers, and warehouse workers (National Institute for Occupational Safety and Health, 1984).

Exposures, both by inhalation and skin contact, occur specifically in operations that can involve manual handling procedures such as weighing ingredients (pigments, extenders, resins, additives), loading them into mixing equipment, adding solvents to mills, and cleaning equipment (mixers, mills, reactors, kettles, tanks, filters). Additional exposure to solvents occurs in thinning, tinting and shading procedures, filling operations, and filtering of varnishes. The cooking of varnishes may produce emissions of various aldehydes such as acrolein, of phenol, ketones, glycerine and fatty acids as well as dusts or vapours of maleic, phthalic and fumaric anhydrides during the loading of kettles. The production of powder coatings can be associated with significant exposure to dust from resin powders, pigments, curing agents and other additives. In the manufacture of radiation-curable coatings, exposures may occur to monomers such as ethyl acrylate, other acrylates, and photoinitiators. Caustic solutions may be used in the cleaning of dispersion equipment (National Institute for Occupational Safety and Health, 1984). In general, the greatest potential for exposure results from spills and the continuous spattering from machines (Adams, 1983).

(i) *Exposure to solvents* (Table 1.12)

Heavy naphthas, toluene and benzene are reported to have been the most commonly used solvents during the 1930s, presumably with high exposure levels. Substitutes for aromatic hydrocarbons, including turpentine, decaline and tetraline, were used in the following decades. Among the solvents most commonly reported from exposure measurements in the paint industry since the 1980s are toluene, xylene, ethyl acetate, *n*-butylacetate, *n*-butanol and ethylbenzene (Table 1.12).

In the paint-manufacturing industry in Sweden, manual cleaning of equipment was associated with outstandingly high exposures to solvents, including dichloromethane/methylene chloride (Ulfvarson, 1977; Lundberg & Håkansson, 1985). Exposure estimates for solvents (CEI) in the Swedish paint-manufacturing industry showed a decreasing trend from 2 in 1950–69, 1.5 in 1970–74, 0.7 in 1975–79 to 0.3 since 1980 (Lundberg, 1986), due in large part to better control measures and to the increasing production of water-based paints.

In two paint-producing factories in the People's Republic of China, the mean benzene concentrations determined by grab samples were 21.4 and 159.5 mg/m^3 (Yin *et al.*, 1987).

More recent studies from Taiwan (China), China, Poland, Germany, Korea, and France reported mean or median exposures to the most frequently reported solvents toluene and xylene to be less than 30 ppm and CEI to be less than 0.7 ppm (Table 1.12). However, the wide ranges of exposure levels indicate that workers, at times, are exposed to high a concentration of solvents.

In two German studies of varnish production, the mean concentrations of various glycol ethers reported were in the range of <0.1–7.0 ppm (Angerer *et al.*, 1990; Söhnlein *et al.*, 1993).

Table 1.12. Paint manufacture - concentration of solvents in air

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm [a]		Comments
					Mean [a]	Range	
Ulfvarson (1977) Sweden	Personal sampling, 3–66 min	9 paint factories	Organic solvents		CEI		Most common solvents were xylene, toluene, butanol and esters; local exhaust common, respirators not often used. CEI based on Swedish OEL or ACGIH
		Charging solvents		33	2.0	0.2–16	
		Pigment dispersion		18	1.5	0.2–4.4	
		Tinting, thinning		14	0.9	0.1–2.0	
		Can filling, paints		39	1.3	0.02–6.6	
		Can filling, thinners		14	1.8	0.1–7.4	
		Manual cleaning of equipment		51	5.7	0.5–30	
Haglund *et al*. (1980) Sweden	Breathing zone, 30 min; 17 workers	7 paint factories			8h-TWA median (mg/m^3)		Workers presumed to have the highest exposure were measured (17 out of 47)
			Xylene	16	111	14–6074	
			Toluene	16	11	1–1257	
			Isobutanol	15	5	1–354	
			Ethylacetate	14	20	1–129	
			n-Butylacetate	13	14	7–1676	CEI based on Swedish OEL from 1978
			Ethanol	13	13	5–971	
			n-Butanol	13	7	1–1541	
			Methylacetate	8	12	3–169	
			Dichloromethane	3	719	635–2421	
			White spirits	3	45	5–52	
			Isopropanol	1	129		
			CEI	17	0.5	0.1–40	

Table 1.12 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm [a]		Comments
					Mean [a]	Range	
Lundberg & Håkansson (1985) Sweden	Breathing zone, 30 min; 47 workers	7 paint manufacturing industries			8h-TWA median (mg/m^3)		Outstandingly high exposures occurred during manual cleaning of paint mixing equipment (9 workers included)
			Xylene	44	82	1–6070	
			Toluene	43	10	1–1260	
			Isobutanol	36	4	1–1040	
			n-Butanol	35	6	1–1540	
			Ethanol	33	12	1–1090	
			Ethylacetate	32	26	1–767	
			n-Butylacetate	31	9	1–1680	
			White spirits	18	44	5–74	
			Methylacetate	11	13	3–169	
			Dichloromethane	5	719	10–2420	
			Methyl ethyl ketone	5	39	8–124	
			Isopropanol	3	129	6–258	
Angerer *et al*. (1990), Germany	Personal full shift diffusive sampling; 12 workers	Production of varnishes containing glycolethers	2-Butoxyethanol	12	1.1	<0.1–8.1	
			2-Ethoxyethanol	12	2.8	<0.1–7.8	
			2-Ethoxyethyl acetate	12	2.7	<0.1–11.1	
			1-methoxypropanol-2-ol	12	7.0	<0.1–24.1	
			2-methoxypropyl-1-acetate	12	2.8	<0.1–13.8	
			Xylene	12	1.7	0.4–6.7	

Table 1.12 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm [a]		Comments
					Mean [a]	Range	
Söhnlein *et al*. (1993) Germany	Personal full shift sampling; 12 workers	Varnish production Day 1	2-Butoxyethanol	12	0.5	<0.1–1.4	
			2-Ethoxyethanol	12	2.9	<0.6–15.2	
			2-Ethoxyethyl acetate	12	0.5	<0.1–3.7	
		Day 2	2-Butoxyethanol	12	0.6	<0.1–1.0	
			2-Ethoxyethanol	12	2.1	<0.1–6.2	
			2-Ethoxyethyl acetate	12	0.1	<0.1–0.4	
Wesołowski & Gromiec (1997) Poland	Personal full shift sampling	5 paint and lacquer production plants, including two modern plants – workers in production, laboratory and transport plants		179 total			40 organic solvents measured; only those with a mean concentration >3 mg/m^3 included here; The two modern plants had lower CEI
			Ethylacetate		7.4 mg/m^3	0–182	
			Toluene		4.7	0–88.2	
			n-Butyl acetate		3.1	0–127	
			2-Methoxypropyl acetate		3.8	0–25.7	
			Ethylbenzene		7.0	0.1–95.1	
			Xylene		21.6	0.4–314.1	
			Trimethylbenzene (all isomers)		5.6	0–88.4	
			C-9 Aromatic HC		11.9	0.2–174	
			White spirit		16.9	0.15–274	
			CEI		0.65	0.1–4.94	

Table 1.12 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm [a]		Comments
					Mean [a]	Range	
Tsai *et al.* (1997) Taiwan, China	Passive personal sampling	6 paint factories		245 total	Median		CEI based on ACGIH, 1990. Lower exposure in other departments-not included . Benzene found in 4 samples at <2 ppm
		Mixing	Toluene	29	3.1	0–15.1	
			Xylene		4.3	0–18.6	
			n-Hexane		0	0–6.0	
			Methyl isobutyl ketone		0	0–5.3	
			n-Butyl acetone		1.9	0–15.9	
			CEI		0.11	0–0.45	
		Grinding/thinning	Toluene	18	13.7	0–106.5	
			Xylene		15.9	1.2–108.1	
			n-Hexane		0	0–18.8	
			Methyl isobutyl ketone		0	0–36.6	
			n-Butyl acetone		5.0	0–39.5	
			CEI		0.31	0.02–1.51	
		Tinting	Toluene	25	2.3	0–232.4	
			Xylene		4.6	0–391.6	
			n-Hexane		0	0–62.4	
			Methyl isobutyl ketone		0	0–11.6	
			n-Butyl acetone		1.9	0–18.6	
			CEI		0.11	0.01–7.61	

Table 1.12 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm [a]		Comments
					Mean [a]	Range	
Tsai *et al.* (1997) Taiwan, China	Passive personal sampling	Packaging	Toluene	39	11.9	0–57.3	
			Xylene		13.7	1.3–89.4	
			n-Hexane		0	0–19.9	
			Methyl isobutyl ketone		0	0–6	
			n-Butyl acetone		4.4	0–14.6	
			CEI		0.3	0.01–1.21	
Krämer *et al.* (1999) Germany	Ambient air, 8 h	Paint production (13 men)	Xylene	13	29	5–58	
			Ehylbenzene		9	2–17	
			Toluene			<1	
		Paint spraying (10 men)	Xylene	10	8	3–21	
			Ehylbenzene		2	1–6	
			Toluene			<1	
Nassiri & Golbabai (1999) Iran	Personal sampling, samples collected 5 days a week for 8 weeks; 54 workers	1 paint manufacturer		175	Range of means		
		Mixing, grinding, tinting, packaging	Toluene	NR	0.6-11.2		
			Xylenes		2.3-25.1		
					Mean		
		Tank cleaning	Toluene	NR	9.5		
			Xylenes		57.1		
		Control laboratory	Toluene	NR	7.6		
			Xylenes		40.0		

Table 1.12 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm [a]		Comments
					Mean [a]	Range	
Truchon *et al.* (1999) Canada	Personal full shift passive dosimeters	2 paint production plants		50	Range of 2 means (TWA)		
			Toluene		12–58	1–157	
			Methyl ethyl ketone		4–18	ND–95	
			Xylene		7–13	ND–45	
			Stoddard solvent		ND–13	ND–39	
			VM&P Naphta		12–39	ND–129	
			Methyl isobutyl ketone		1–2	ND–7	
			n-Butyl acetate		2–7	ND–24	
			Ethyl acetate		ND–2	ND–10	
			Methyl isoamyl ketone		ND–1	ND–3	
			Isopropyl alcohol		ND–3	ND–17	

Table 1.12 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm [a]		Comments
					Mean [a]	Range	
Yang *et al.* (2000) Korea	Personal full shift low flow sampling	1 paint manufacturer			GM		
		Paint mixing, synthesis	*N,N*-dimethylformamide	13	1.2	0.1–7.4	
			Toluene		1.2	0.2–15.9	
			Methyl ethyl ketone		0.6	0.1–17.8	
			CEI		0.11	0.01–1.0	
		Packing	*N,N*-dimethylformamide	5	0.4	0.1–2.7	
			Toluene		1.8	0.2–14.5	
			Methyl ethyl ketone		0.4	0.1–6.0	
			CEI		0.06	0.01–0.44	
Delcourt & Sandino (2001) France	Personal sampling, mean duration of 420 min	1 car paint manufacturer – Preparation drum cleaning, grinding and packaging	*n*-Butanol	58	6.1 mg/m^3	1.1–16.6	
			Isobutanol	59	2.3	0.5–9.3	
			Methyl ethyl ketone	59	7.5	1.2–27.9	
			Methyl isobutyl ketone	56	28.1	3.3–115.6	
			Ethyl acetate	59	8.1	0.6–29.1	
			n-Butyl acetate	56	38.3	7.2–160.7	
			Toluene	58	12.3	2.5–33.6	
			Ethylbenzene	57	8.1	0.7–19.9	
			m-Xylene	56	21.3	2.1–54.6	

Table 1.12 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm [a]		Comments
					Mean [a]	Range	
Purvis *et al.* (2001) Kenya	Full shift (8–10 h) over 3 days	3 paint manufacturers		96	Ranges of 3 means		Number of samples from the respective section not reported
		Laboratory	Ethylbenzene		1.5–12.1		
			Styrene		ND–0.04		
			Toluene		1.2–39.3		Workers expected to have the highest exposure cross-section in each section were selected.
			Xylenes		5.9–40.9		
			CEI		0.09–0.57		
		Mixing, tinting, filling, transport of raw materials and resins	Benzene		ND–0.13		
			Ethylbenzene		0.4–31.3		
			Styrene		ND–0.35		
			Toluene		1.2–50.3		CEI based on ACGIH TLVs
			o-Xylene		1.4–107.5		
			CEI		0.06–1.7		

[a] Unless otherwise stated

ACGIH, American Conference of Governmental Industrial Hygienists; CEI, cumulative exposure index; ND, not detected; GM, geometric mean; TLV, threshold limit value; TWA, time-weighted average

In the United Kingdom, a total of 341 toluene measurements in paint manufacturing were available in the National Exposure DataBase, covering the period between 1985 and 2002 (Creely *et al.*, 2006a). The mean airborne concentration of toluene was 77.6 ppm (range <0.01–8698 ppm), and a decline in concentration of 11% per year was observed. Based on industry data ($n = 253$), the decrease in the airborne concentration of toluene in paint manufacturing was –44% per year. [The decline is likely due to increased production of paints with low-solvent contents.] While operations were largely manual before the late 1960s, improvements such as local exhaust ventilation were gradually introduced into factory environments in the mid-1960s.

(ii) *Exposure to dusts* (Table 1.13)

In a Swedish investigation covering ten factories manufacturing paint and industrial coatings, exposure to quartz, asbestos, chromium including Cr(VI), and lead was documented in some air samples during the charging operation in some of the companies (Table 1.13).

(iii) *Other exposures*

Exposure to ammonia was reported while charging it during manufacture of water-based paints in a paint industry in Sweden, at average airborne concentrations of 50–80 ppm (35–56 mg/m^3). The levels of pentachlorophenol and phthalic anhydride were below the national occupational health standards of 0.5 mg/m^3 and 2 ppm (12 mg/m^3), respectively (Ulfvarson, 1977). The concentration of diethylene triamine was below the detection limit (0.01 mg/m^3) in the breathing zone of two workers canning epoxy paint-curing agents in a paint factory in Finland (Bäck & Saarinen, 1986).

In a paint-manufacturing company in the USA, the 8-hour time-weighted average (TWA) airborne concentration of vinyl acetate were in the range of 1.0–8.4 ppm (3.6–30.6 mg/m^3; four samples). Personal and area air samples indicated concentrations of ethyl acrylate ranging from below the limit of detection to 5.8 ppm (23.8 mg/m^3); concentrations of butyl acetate were all below the limit of detection (16 samples), except one sample at 0.9 ppm (4.7 mg/m^3; Belanger & Coye, 1980).

(c) Construction painting and lacquering

Usually in the construction industry, the work of painters involves the use of a limited number of types of coatings – mainly decorative water- or solvent-based paints, and wood lacquers and varnishes. The potential for exposure to a variety of substances (mainly solvents and pigments) is high: painting performed inside buildings, where there is poor ventilation, especially in confined spaces such as small rooms, cupboards or bathrooms, can lead to very high levels of air contaminants; whereas when painting the outside of buildings (façades, windows, roofs), natural ventilation is usually effective at reducing exposures. The painting of new buildings usually involves water-based paints and spraying equipment; however, during renovation or maintenance, solvent-based paints are still widely used, and work is usually performed by hand with a brush or roller.

Table 1.13. Exposure to paint mist, dust, silica and metals in air

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm		Comments
					Mean	Range	
PRODUCTION							
Ulfvarson (1977) Sweden	Personal sampling during charging operations, 5 min–8h	10 paint factories – Charging operations, tinting, handling of bags, compressing empty bags, floor cleaning and emptying air-cleaner filters	Total dust Quartz (5*) Asbestos (4*) CrO_3 (7*) Pb (7*)	61 5 6 14 7		1.7–70 mg/m^3 0.01–0.9 mg/m^3 0.31–5 fibres/m^3 0.003–1.6 mg/m^3 0.006–4 mg/m^3	* Number of factories
CONSTRUCTION INDUSTRY							
Rosensteel (1974) USA	Breathing zone samples; 5 workers	Bridge girders plant – Spraying lead silico-chromate paint			**mg/m^3**		NIOSH report
			Chromium Lead	5 5	0.08 0.02	0.01–0.25 0.01–0.04	
Landrigan *et al.* (1982) USA	NR	Bridge Scraping lead-based paint and priming it Recoating with lead-based paint	Lead			24–1017 µg/m^3 6–30 µg/m^3	
Spee & Zwennis (1987) Netherlands	Personal, 90–135 min; 5 workers	Steel bridge coated with lead-based paint – Flame torch cutting	Lead	13	12.2 mg/m^3	2.3–38.1	

Table 1.13 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm		Comments
					Mean	Range	
Norbäck *et al.* (1995) Sweden	Personal full-shift sampling for 6 days, 3–5 h painting per day; 12 painters	House painters		12	8h-TWA		
		Roller painting water-based paint inside old and new buildings, removing old wall paper, manual sanding, filling walls and sizing wall paper	Total dust		4.1 mg/m^3	0.04–14.3 mg/m^3	
			Organic dust		1.4	0.1–3.7	
			Calcium		0.3	0.07–0.90	
			Iron		0.02	0.004–0.05	
			Titanium		0.01	<0.001–0.05	
			Zinc		0.02	<0.001–0.08	
			Lead		0.001	<0.001–0.003	
			Cobalt		0.001	<0.001–0.003	
Conroy *et al.* (1996) USA	Personal samples, 8–10hrs	**Steel bridge – Abrasive blasting**			Median		
		During blasting:	Lead				
		Blasters and sweepers		64	366 µg/m^3	12–4401	
		Equipment operators		12	219	14–1400	
		Foremen		17	160	26–3423	
		Moving containment, painting, cleaning, maintenance	Lead				
		Blasters and sweepers		11	130	42–2500	
		Equipment operators		15	440	13–1900	
		Foremen		6	46	12–180	
	Area samples, 8–10 hrs	*Bridge*	Lead	9	10970 µg/m^3	196–29950	
			Chromium	4	23.5	1.26–43.7	
			Cadmium	4	15.7	13.5–18.3	
		Viaduct	Lead	10	3277	533–18200	
			Chromium	5	369	9.41–657	
			Cadmium	3	1.31	1.06–1.60	

Table 1.13 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm		Comments
					Mean	Range	
Lipton et *al.* (1996) USA	Personal sampling, 62–327 min; inside respirator-helmet for abrasive blasters	Steel bridge	Crystalline silica		Median TWA		Silica content in respirable dust: 7.1–37.5%
		Abrasive blasting with silica sand		7	0.02 mg/m^3	ND–0.2	
		Traffic control within area		6	0.08	0.04–0.53	
		Flaggers		3	0.02	ND–0.02	
		Hopper loader		9	0.08	0.04–0.35	
Lange & Thomulka (2000) USA	Personal breathing zone	Steel construction lead-paint removal with needle gun	Lead	13	TWA 7.5 µg/m^3	1.7–20.9	
Daniels *et al.* (2001) USA	Personal	Wet abrasive blasting of lead-based paint from:	Lead		8h-TWA		
		Wood - method 1		3	70.9 µg/m^3		
		Wood - method 2		3	55.1		
		Bricks - method 1		6	68.4		
		Bricks - method 2		6	81.5		

Table 1.13 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm		Comments
					Mean	Range	
Reames *et al.* (2001) USA	Personal approx. 30 min	Dwellings – Lead-paint removal	Lead		GM		Data from 45 samples of multiple tasks not included
		All tasks		175	4.2 μg/m^3	<0.5–146.0	
		External scraping		64	5.1	0.3–123.0	
		Clean-up		25	2.3	0.3–17.1	
		Internal scraping		19	7.7	0.5–139.0	
		Demolition		15	10.3	2.5–80.2	
		Chemical stripping		14	10.2	3.3–20.9	
		Internal wet sanding		14	1.0	0.5–4.9	
		Component removal		8	2.4	0.5–8.0	
		Internal wet sanding and scraping		7	1.0	0.5–6.8	
		External wet sanding and scraping		5	1.0	0.4–3.6	
		Containment preparation		4	1.3	0.5–4.9	
		Water application		4	3.9	3.0–5.4	
Scholz *et al.* (2002) USA	Personal full-shift sampling	Surface preparation on building with lead paint	Lead	25	TWA 57 μg/m^3	0.8–550 μg/m^3	
	30 min task-specific sampling	Heat gun	Lead	6	2.3 μg/m^3	<1(ND)–5	
		Wet sanding		3	3.3	<1(ND)–7	
		Open flame burning		5	9.8	<1(ND)–20	
		Power sanding with exhaust		7	33	4–60	
		Dry scraping		18	71	≤4–230	
		Dry manual sanding		9	420	29–1200	
		Uncontrolled power sanding		10	580	65–3400	

Table 1.13 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm		Comments
					Mean	Range	
Rappaport *et al*. (2003) USA	Personal respirable air samples; 12 workers	7 construction sites – Abrasive blasting	Dust Crystalline silica	14 14	13.5 mg/m^3 1.28	1.2–833 0.26–26.2	
Golla & Heitbrink (2004) USA	Task-based respirable dust, breathing zone outside mask	*Concrete parking house – Wet abrasive blasting* at ground level on platform helper	Crystalline silica	 7 9 8	GM 0.22 mg/m^3 0.13 0.06	 0.12–0.43 0.04–0.41 <0.02–0.12	Silica content in respirable dust: 20%
METAL INDUSTRY							
Vandervort & Cromer (1975) USA	Breathing zone samples, 1–3h	Truck body and refuse handling equipment manufacturing – Spray painting operations	Paint mist Lead Chromium$_{tot}$	7 7 7	24.4 mg/m^3 1374 µg/m^3 194 µg/m^3	4.8–47 20–3000 10–400	NIOSH report
Kominsky *et al*. (1978) USA	Personal, 8–174 min	Manufacturing of aeromechanical systems – Spraying primer with zinc chromate	Chromium (VI)	12	606.7 µg/m^3	13.3–2900 µg/m^3	NIOSH report
Elofsson *et al.* (1980) Sweden		*Car refinishing workshops* Spraying activities Grinding activities	 Paint mist Lead Chromium$_{tot}$ Paint mist Lead Chromium$_{tot}$		 7 mg/m^3 100 µg/m^3 26 µg/m^3 3 mg/m^3 20 µg/m^3 6 µg/m^3		

Table 1.13 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm		Comments
					Mean	Range	
O'Brien & Hurley (1981) USA	Sampling time,				GM	GSD	NIOSH report
	25–41 min	Light aircraft finishing, primer	Paint mist	3	23.3 mg/m^3	1.6	
			Lead		ND		
			Chromium$_{tot}$		1600 µg/m^3		
	27–62 min	Light aircraft finishing, topcoat	Paint mist	6	23.3 mg/m^3	1.7	
			Lead		ND		
	19–35 min	Light aircraft finishing, stripping	Paint mist	6	14.1 mg/m^3	2.0	
			Lead			ND–5000	
	15–45 min	Car refinishing	Paint mist	7	8.7 mg/m^3	1.6	
			Lead		52 µg/m^3	1.5	
	8 h	Car refinishing	Paint mist	7	5.0 mg/m^3		
			Lead		30 µg/m^3		
	15–60 min	Railroad car	Paint mist	13	43.3 mg/m^3	1.4	
			Lead		211 µg/m^3	1.7	
			Chromium$_{tot}$		220 µg/m^3	2.2	
	60 min	Heavy equipment	Paint mist	3		2.0–36.5	
			Lead			230–1300	
			Chromium$_{tot}$			31–230	
	8 h	Metal furniture	Paint mist	6		3.7–27.6	
			Lead			ND–1050	
	8 h	Metal furniture, high solids paints	Paint mist	6		0.5–6.2	
			Lead			5–26	
			Chromium$_{tot}$			5–9	
	8 h	Small appliance parts, powder coating electrostatic spraying	Paint mist	3	1.3	1.1	
	8 h	Appliance finishing	Paint mist	4		21.7–54.5	
			Lead			<6–20	

Table 1.13 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm		Comments
					Mean	Range	
Hellquist *et al.* (1983) Sweden		Fireplace manufacturing plant – Spray painters	Total dust Chromium oxide Zinc oxide		1.7 mg/m^3 5–8 µg/m^3 20–30 µg/m^3		
Jayjock & Levin (1984) USA	Personal 55–197 min	Car body repair shop – Sanding and grinding of plastic filler	Total dust Respirable dust	2 2		5–40 mg/m^3 0.3–1.2 mg/m^3	
Zey & Aw (1984) USA	Personal	Bus manufacturing – Employees in and around paint booth	Chromium (VI) Lead	5 8	0.23 mg/m^3 0.78 mg/m^3	0.03–0.45 mg/m^3 ND–2.01 mg/m^3	NIOSH report
Booher (1988) USA	Personal full shift	Ship overhaul facility – Paint removal	Lead		GM		
		Chipping with needle gun		10	2.36 µg/m^3	1.0–4.9	
		Sanding		22	60.6	2.6–1570	
Zedd *et al.* (1993) USA	Personal full shift	Shipboard – Lead-paint removal	Lead		TWA		
		Chipping with needle gun		38	91.6 µg/m^3	<2–785	
		Grinding		37	400.5	<2–2500	
		Chipping/grinding		19	375.2	8.2–1610	
		Supervision		13	493.9	2.1–2300	

Table 1.13 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm		Comments
					Mean	Range	
Aizenberg *et al.* (2000) USA	Personal 4–6 h sampling (Button sampler)	4 U.S. Air Force facilities – paint and primer removal from aircraft parts or ground equipment by abrasive blasting			Range of 7 means (TWA)		Range of means for 7 surfaces or tasks. Data read from graph
			Lead	67	0.003–0.13 mg/m^3		
			Chromium (VI)	77	0.003–0.2 mg/m^3		
			Cadmium	67	0.001–0.5 mg/m^3		
Jarrett (2003) USA	Personal samples over 28 days	Shipyard – Paint removal	Lead		Range of means		Range of means per worker
		Abrasive blasting (10 workers)		104	824–3187 µg/m^3	308–6522 µg/m^3	
		Labourers within containment structure (6 workers)		11	1194–3852 µg/m^3	577–3852 µg/m^3	
Sabty-Daily *et al.* (2005) USA	Personal 8h breathing zone	Aerospace facility – Spray painting in booths			Range of means (8h-TWA)		
		Field study 1	Chromium$_{tot}$	18	5.3–256 µg/m^3	1.0–364 µg/m^3	6 means
		Field study 2	Chromium$_{tot}$	12	56–332	22–390	4 means
			Chromium (VI)	12	70–214	19–327	4 means

Table 1.13 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm		Comments
					Mean	Range	
Vitayavirasuk *et al*. (2005) Thailand	Personal sampling – full-shift 8 hrs respirable dust, 70 workers	Autobody repair workshop– spray painting not in booth					
		Painters wearing respirators	Lead	20	0.97 μg/m^3	0.08–5.75	
			Cadmium	20	0.01	ND–0.02	
			Chromium	20	0.73	0.31–3.07	
		Painters not wearing respirators	Lead	50	0.62	0.05–5.60	
			Cadmium	50	0.30	ND–5.74	
			Chromium	50	0.64	0.25–2.55	
Blade *et al*. (2007) USA	Personal full shift	Painting and coating facility using chromate-containing paint	Chromium (VI)		GM		
		Spraying, sanding and cleanup		5	16 μg/m^3	3.8–55 μg/m^3	
		Spraying and sanding		13	0.23	<0.02–4.3	
		Helper		4	7.9	2.4–22	
		Steel bridge – Abrasive blasting of chromate-containing paint	Chromium (VI)	8	0.43	0.10–1.3	

GM, geometric mean; GSD, geometric standard deviation; ND, not detected; NR, not reported; TWA, time-weighted average

Surfaces to be coated can be made from plaster- or gypsum-based wall-board composite materials, concrete, wood (for windows, doors and flooring), and more rarely, metal. Construction painters may spend a good proportion of their time in preparatory or accessory work. In a Finnish study of construction painters, 40% of the 231 painters estimated that they spent more time on such work than actual painting (Riala *et al.*, 1984). Removing old paint and preparing surfaces in general may involve the use of paint strippers containing solvents such as dichloromethane, of gas-operated blow torch units or hot air guns which may generate organic pyrolysis fumes, metallic fumes, and dusts from pigments. Other accessory tasks may be polishing, sanding or sandblasting operations, which may generate aerosols of old paint, quartz, concrete, plaster, wood, and metal dusts. Acid or alkali washing solutions may be used, as well as steam generators for removing wallpaper, which can release exhaust gases that contain carbon monoxide. Preparing surfaces also involves filling cracks and holes using plaster, cement, sealers, spackling, taping and dry wall materials, putties and wood fillers, which may result in possible additional exposure to inorganic dusts and fibres (including asbestos), and solvents. Further exposure arises from the use of solvents during the cleaning of equipment as well as from personal cleaning (Ringen, 1982; Huré, 1986; Swedish Work Environment Fund, 1987).

(i) *Exposure to solvents* (Table 1.14)

In a Danish investigation in 1974, exposure to benzene (55 ppm) and trichloroethylene (91 ppm) were particularly elevated. Benzene originated from turpentines used for thinning and for cleaning of painting equipment, and for hand washing (Mølhave & Lajer, 1976). Renovation spray painters in Sweden were exposed to very high concentrations of white spirits (1200–1500 ppm) (Bobjer & Knave, 1977). In a study in Finland involving mainly maintenance construction workers, the overall average airborne concentration of solvents expressed as solvent naphtha exposure, was 132 ppm (77 samples). The solvent naphta contained 17% aromatic hydrocarbons (Riala *et al.*, 1984).

A total of 45 maintenance painters in the Netherlands who worked on 12 different projects were exposed to an 8-hour TWA airborne concentration of combined solvents of 101 mg/m^3 (geometric mean). Benzene was detected at two of the sites at low concentrations (up to 0.2 mg/m^3). C_2- and C_3-substituted benzenes and C_8-C_{11} alkanes were found at most sites, originating mainly from the use of white spirits.

Workers using chlororubber paint in a pumping station were exposed to carbon tetrachloride at concentrations in the range of 10–17 mg/m^3 (Scheffers *et al.*, 1985).

During the application of water-based paints, ethylene glycol butyl ether (2–60 mg/m^3) was measured in concentrations of up to 40% of the Danish occupational exposure limit (Hansen *et al.*, 1987). Swedish housepainters renovating old buildings and painting new buildings by application of water-based paint were exposed to low concentrations of VOCs, formaldehyde and ammonia during indoor work (Norbäck *et al.*, 1995). In the Netherlands, outdoor house painting behind screening also resulted in low exposure to VOCs (Spee *et al.*, 2005).

Table 1.14. Construction industry - concentration of solvents, formaldehyde and ammonia in air

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm		Comments
					Mean	Range	
Mølhave & Lajer (1976) Denmark, 1974	Personal, 1 h	Indoor painting				Max. value	In total, 13 solvents investigated
			Benzene	41	55	289	
			Trichloroethylene	33	91	390	
			Toluene	43	23	91	
			Xylene	31	5	68	
			1,2,4-trimethylbenzene	32	15.8	177	
			CEI	44		<1 (7 samples)–34.6	
Riala *et al.* (1984) Finland	Personal, 15 min–3 h	Indoor painting in houses	Solvent naphtha	77	132		16 maintenance and 2 new sites. Alkyd and urethane painting, and varnishing
		Without ventilation:					
		- Roller and brush painting		43	194		
		- Spray painting		3	235		
		With ventilation:					
		- Roller and brush painting		26	38		
		- Spray painting		5	39		

Table 1.14 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm		Comments
					Mean	Range	
Hansen *et al.* (1987) Denmark	Personal, 20 min	15 workplaces – Application of water-based paint	Butyl acrylate			0–2 mg/m^3	
			Diethylene glycol butyl ether			4–5	
			Diethylene glycol methyl ether			8–32	
			Dipropylene glycol methyl ether			30–40	
			Ethylene glycol butyl ether			2–60	
			Ethylene glycol phenyl ether			0–0.7	
			Propylene glycol			2–70	
			2,2,4-Trimethylpentane-1,3-diol monoisobutyrate			0.5–12	
			Triethylamine			4–6	
			White spirits			40–75	
			Formaldehyde			0–0.4	

Table 1.14 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm		Comments
					Mean	Range	
Norbäck *et al.* (1995) Sweden	Personal full shift sampling, except for formaldehyde and ammonia. Measurements done in two time periods (phase I and II)	House painters – Roller painting with water-based paint, removing old wall paper, manual sanding, filling walls and sizing wall paper; 3–5 h painting per day			2 means	Max. value	Means of phase I and phase II are given
			Toluene	8; 20	109–216 µg/m^3	2120 (µg/m^3)	
			Xylene		107–132	620	
			Ethylbenzene		49–56	170	
			n-Nonane		74–200	2240	
			n-Decane		29–80	4670	
			n-Undecane		29–202	2030	
			Limonene		44–237	2770	
			n-Butanol		103–302	2500	
			Isobutanol		380–750	6570	
			Propylene glycol	20	2630	12700	
			Diethyleneglycol monoethyl ether		820	8060	
			Formaldehyde (8 h)	12	0.05	<0.03–0.10	
			Formaldehyde (peak)	5	0.08	<0.03–0.14	
			Ammonia (8 h)	12	0.9	<0.4–3.9	
			Ammonia (peak)	17	6.2	<1–25	

Table 1.14 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm		Comments
					Mean	Range	
Burstyn & Kromhout (2002) Netherlands	Personal, 176 min (full-shift)	House painting, mainly rolling and paintbrush					Data from 5 studies in 1980–1998, which include 105 workers. Solvent-based and water-based include 29 and 6 samples, respectively, from shipyards
		Water-based paint (acrylate)	Toluene	49	0.61 mg/m^3	0.004–9.4 mg/m^3	
			Xylenes	48	1.15	0.01–13.1	
			Ethylbenzene	48	0.23	0.002–1.7	
			n-Hexane	48	0.04	0.007–0.3	
			n-Decane	48	1.75	0.01–23.5	
		Solvent-based paint (alkyd, synthetic, turpentine, chloro-rubber)	Toluene	147	1.93	0.004–43.0	
			Xylenes	108	15.26	0.085–233.5	
			Ethylbenzene	108	4.95	0.023–86.0	
			n-Hexane	72	0.20	0.007–10.9	
			n-Decane	94	13.90	0.006–210.0	
Spee *et al.* (2005) Netherlands	Personal	Outdoor painting behind screen			GM		CEI based on MAC in The Netherlands
			VOCs	5	11.7 mg/m^3	3.4–22.9	
		6 painters from 3 sites (4–8 h)	CEI	5		0.01–0.05	
		33 painters from 10 sites (225–520 min)	VOCs	33		31 samples <1	
			CEI	33		<0.05–0.11	31 samples <0.05

CEI, cumulative exposure index; GM, geometric mean; VOC, volatile organic compound

Based on 304 measurements of solvent exposure from 137 house and shipyard painters in the Netherlands between 1980 and 1999, Burstyn & Kromhout (2002) reported a decreasing trend for solvent exposure. Toluene was selected as a marker for solvent exposure. A 12% annual decrease in toluene exposure concentration during application of solvent-based paint was observed. Use of solvent-based paint, painting in small rooms and spray-painting (versus manual painting) was associated with increased exposures. The reduction in exposure over time was comparable to that observed by others in a wide variety of industrial processes (Creely *et al.*, 2006a, 2007).

(ii) *Exposure to metals, dust and silica (*Table 1.13*)*

Substantial exposure to airborne lead was reported for workers in the USA involved in scraping old lead-based paint from the metallic structure of a bridge and priming it (24–1017 µg/m^3) (Landrigan *et al.*, 1982). In this situation, workers wore a respirator. In the Netherlands, workers involved in flame-torch cutting of a bridge steel structure coated with lead-based paints were shown to be exposed to very high concentrations of airborne lead (2.3–38.1 mg/m^3) (Spee & Zwennis, 1987).

During abrasive blasting of a steel bridge in the USA, lead concentrations of personal samples collected inside the air helmet (but outside the half-mask respirators) ranged from 12 to 4401 µg/m^3. A total of 85% of the 125 personal air samples exceeded the 50 µg/m^3 level allowed by OSHA. High lead exposure was also measured during painting, cleaning and setting up or moving the containment structure (range 12–2500 µg/m^3) (Conroy *et al.*, 1996).

When performing lead paint abatement on steel structure surfaces inside a building by needle gun methodology, personal full-shift airborne lead concentrations were in the range of 1.7–20.9 µg/m^3 (Lange & Thomulka, 2000). Personal exposure to lead during wet abrasive blasting of lead-based paint from wood and brick exterior house surfaces (range of mean exposure, 55.1–81.5 µg/m^3) exceeded the Permissible Exposure Limit (PEL) of OSHA (50 µg/m^3) (Daniels *et al.*, 2001). In a residential lead hazard reduction project in the USA, lead concentrations were in the range of <1.0–146.0 µg/m^3 (Reames *et al.*, 2001). The highest exposure occurred during external or internal paint scraping, demolition, and chemical stripping. In another study of surface preparation of buildings in the USA, the airborne lead concentrations measured from full-shift personal samples were in the range of 0.8–550 µg/m^3. Six of the samples were above the PEL of OSHA; all of these involved dry manual sanding and uncontrolled power sanding (Scholz *et al.*, 2002).

Swedish housepainters renovating old buildings and painting new buildings were exposed to relatively high dust levels, sometimes exceeding the Swedish PEL (10 mg/m^3). The highest exposure to dust was recorded during 2 days when manual sanding was taking place (Norbäck *et al.*, 1995).

Crystalline silica concentrations inside the respirator worn in the helmet were reported in the range from below the detection limit to 0.2 mg/m^3 (median, 0.02 mg/m^3) during abrasive blasting of a steel bridge in the USA (Lipton *et al.*, 1996). Painters had high exposure to respirable crystalline silica (n = 14, range 0.26–26.2 mg/m^3) during abrasive

blasting at seven construction sites in the USA from 1992 to 2000 (Rappaport *et al.*, 2003). Task-based exposure to crystalline silica was lower during wet abrasive blasting of the exterior walls of a parking garage (range <0.02–0.43 mg/m^3) (Golla & Heitbrink, 2004).

(d) Painting, varnishing and lacquering in the wood industry (Table 1.15)

Application of clear varnish or lacquer finishes on furniture represents the main use of coatings in the wood industry. Paints, varnishes and lacquers are also used in the production of various wooden raw materials (e.g. composite wood boards) and miscellaneous wooden articles (e.g. toys, tableware). Until the mid-1950s, cellulose ester-type lacquers were almost the only ones used in the furniture industry; however, amino-resin-based, polyurethane, and polyester coatings now constitute the main coatings in the industry (Swedish Work Environment Fund, 1987).

Workers are exposed mainly through the inhalation of solvents either from paint mist or from vapours generated by spraying operations, from vapours evolved from finished products or from auxiliary work such as mixing the coatings, cleaning the equipment or applying other products such as wood fillers and sealants. The exposure is influenced by the method of applying coatings; the most common are spraying, usually at low pressure, curtain and roller coating, and dipping. Low molecular-weight resin constituents such as formaldehyde and isocyanates may be released during the application or curing of coatings. Another possible exposure agent is wood dust from the general factory environment, and from preparatory work (sanding).

In an Italian art furniture factory, the average 4-hour airborne toluene concentration to which 20 workers employed in painting and hand-finishing were exposed was 27–182 mg/m^3(Apostoli *et al.*, 1982).

In a wood furniture company in the USA, overall, low air concentrations (0.05–0.24 mg/m^3) of paint mist and organic solvents were reported (O'Brien & Hurley, 1981). The mean short-term exposure to formaldehyde in furniture and plywood factories in Finland, Sweden and Denmark from the period 1975 to 1993 was in the range of 0.20–1.2 ppm (Table 1.15). Exposure to solvents in these studies was relatively low. Priha *et al.*, (1986) reported a decreasing time trend for exposure to formaldehyde between the years 1975 to 1984. A more recent Norwegian study covering 27 woodworking and furniture factories reported the geometric mean airborne formaldehyde concentration to be 0.15 ppm, with about 10% of the samples exceeding the Norwegian Occupational Exposure Limit (OEL) of 0.5 ppm (Thorud *et al.*, 2005). The CEI for solvents in this study was low.

In two studies of parquet lacquerers in Finland, the exposure to glycol ethers measured when primer and final lacquering were spread by steel comb and smooth comb was well below the OEL values (Laitinen & Pulkkinen, 2005; Laitinen *et al.*, 2006).

Table 1.15. Wood industry - concentration of solvents and formaldehyde in air

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm		Comments
					Mean	Range	
O'Brien & Hurley (1981) USA	27 workers	Furniture company – Spray painting and finish wiping		27			
		Acrylic base coat	CEI			0.05–0.11	
		Oil-based glaze	CEI			0.06–0.10	
		Cellulose nitrate lacquer	CEI			0.08–0.24	
		All tasks	Paint mist (8h-TWA)		0.1–2.5 mg/m^3		
Apostoli *et al.* (1982) Italy	20 workers Personal 4h sampling	Art furniture factory – Painting and hand-finishing	Toluene			27–182 mg/m^3	Acetone, isobutanol, ethanol, ethyl acetate were also found
Kauppinen (1986) Finland	Personal sampling for solvents; area sampling for formaldehyde	Plywood industry – Coating				ppm (mg/m^3)	
		Polyurethane paint 1975–1984	Methyl isobutyl ketone	12		2–28 (8.2–115)	
			Butylacetate	12		8–50 (38–238)	
			Xylene	12		10–25 (43–108)	
			Cyclohexane	12		1–28 (3.4–95)	
		Alkyd paint 1975–1984	Toluene	8		2–3 (7.5–11.3)	
			Xylene	8		7–12 (30.4–52)	
			Isobutanol	8		7–11 (21–33)	
			Trimethylbenzene	8		1–9 (5–44)	
		Coating	Formaldehyde				
		1965–74		7	1.0	0.5–1.8	
		1975–84		28	0.26	<0.01–0.6	

Table 1.15 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm		Comments
Priha *et al.* (1986) Finland 1975–84	Sampling during active painting. Personal for solvents (0.5–1.5 h); personal and area for formaldehyde (15–30min)	50 furniture factories					
		Spray painting	Formaldehyde	60	0.97	0.2–4.0	Decreasing time trend for formaldehyde, not for solvents
		Spray painting assistance		10	1.02	0.2–1.6	
		Operation of curtain painting		18	1.11	0.2–6.1	
		Feeding of painting machine		14	1.11	0.3–2.7	
		Receiving painted pieces		34	1.48	0.1–4.2	
		Receiving painted pieces after drying oven		14	0.94	0.2–5.4	
		Overall tasks	Xylene	394	19		Only those solvents present in >50% of samples given
			Butanol	394	17		
			Ethanol	394	32		
			Toluene	394	17		
			Butylacetate	394	11		

Table 1.15 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm		Comments
Alexandersson & Hedenstierna (1988) Sweden	Breathing zone, 15 min; 38 workers	Furniture factory – Acid-hardening varnishes and paint	Formaldehyde				Short-term samples basis for calculation of 8h-TWA
			(8h-TWA)	38	0.4 mg/m^3	0.12–1.3	
			(15 min)	38	0.7	0.14–2.6	
			Xylene		18		
			Ethanol		17		
			Toluene		15		
			Isobutanol		10		
			All solvents (8h-TWA)	38	0.15	0.02–0.52	
Vinzents & Laursen (1993) Denmark	Personal sampling; formaldehyde, 15 min; solvents, 2h	Furniture factories – Painting			GM	GSD	CEI based on Danish OEL
			Formaldehyde (28 factories)	43	0.20 mg/m^3	2.25	
			CEI for organic solvents	55	8h-TWA		
					0.21	2.57	
Laitinen & Pulkkinen (2005) Finland	22 workers	Parquet lacquer spread with steel comb and smooth comb			8h-TWA	SD	8h-TWA based on personal task samples
			DEGME	3	0.23	0.07	
			DEGEE	16	0.08	0.07	
			DEGBE	16	0.05	0.03	

Table 1.15 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm		Comments
Thorud *et al*. (2005) Norway	86 workers Personal parallel samples Sampling time, 141 min (range 21–291 min); 2–3 consecutive samples per worker per shift; sampling during 3 years	27 woodworking and furniture factories – Surface coating with acid-curing lacquers and paint: manual and automatic spray painting, curtain painting, dip painting, manual painting (roller, brush etc.), grinding, mounting			GM		
			Formaldehyde	557	0.15	0.01–1.48	
			n-Butyl acetate	550	2.09	0.02–155	
			Ethanol	521	6.73	0.06–397	
			Ethyl acetate	500	0.86	0.02–65.2	
			1-Butanol	496	0.81	0.02–32.6	
			2-Methyl-1-propanol	327	0.39	0.02–13.0	
			Aliphatics C4-C8	313	0.54	0.02–33.7	
			m & *p*-Xylene	288	0.19	<0.01–3.73	
			1-Methoxy-2-propylacetate	284	0.35	0.01–11.6	
			o-Xylene	269	0.06	<0.01–1.12	
			1-Methoxy-2-propanol	241	0.99	0.01–19.7	
			2-Propanol	228	1.45	0.03–37.7	
			Toluene	216	0.29	0.02–72.7	
			Ethylbenzene	185	0.06	<0.01–1.98	
			Aliphatics C9-C13	124	0.32	0.02–6.17	
			Ethyl 3-ethoxypropionate	45	0.55	0.09–2.52	
			1-Propanol	33	0.53	0.10–1.82	
			2-Butanone	22	0.48	0.12–2.83	
			4-Methyl-2-pentanone	20	0.44	0.07–8.40	
			Acetone	19	0.36	0.04–1.70	
			Styrene	9	0.10	0.01–1.47	
			CEI	557	0.13	<0.01–5.08	

Table 1.15 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm		Comments
Laitinen *et al.* (2006) Finland	22 workers, 30–242 min	Parquet lacquer spread with steel comb and smooth comb			8h-TWA	SD	8h-TWA based on personal task samples
			PGME	15	1.9	1.3	
			PGBE	11	1.0	1.4	
			DPGME	11	0.2	0.3	

DEGME: 2-(2-methoxyethoxy)ethanol
DEGEE: 2-(2-ethoxyethoxy)ethanol
DEGBE: 2-(2-butoxyethoxy)ethanol
PGME: 1-methoxy-2-propanol
PGBE: 1-butoxy-2-propanol
DPGME: 1-(2-methoxy-1-methylethoxy)-2-propanol
CEI, cumulative exposure index; SD, standard deviation; GM, geometric mean; GSD, geometric standard deviation

(e) Painting in the metal industry

Protection from corrosion is the primary purpose of painting metal. Mild steel is thus almost always subjected to the application of a primer coat containing corrosion inhibitors such as iron and lead oxides or of zinc powder, further covered with a decorative paint. Aluminium may be covered with a zinc chromate primer before a decorative coat is applied.

During the preparation of metal parts, painters may be exposed to cleaning and degreasing agents, such as solvents, alkalis and acids, and to abrasive dusts, such as crystalline silica generated during blast cleaning. Depending on the industry, metal painters may be exposed to a variety of dusts, solvents, fumes and gases resulting from operations such as mixing paints, maintaining equipment, applying fillers, sealers or putty, or background metal welding or assembling operations. Many coatings used in the metal industry are solvent-based, and spray painting is the main method of application, leading to potential exposures to paint mist and solvents. Two-component paints, such as those based on epoxy and polyurethane resins, play a major role, implying potential exposure to reactive substances such as isocyanates and epoxides. Air-drying or baking after application results in the release of solvents and, possibly, thermal degradation products of resins (Peterson, 1984).

(i) *Exposure to organic solvents* (Table 1.16)

Aircraft industry: Exposure of spray painters to solvents was measured in several industries in the USA, including aircraft finishing. Three studies on spray painting of aircraft up to 1977 reported exposure to relatively high concentrations of organic solvents such as toluene, methyl ethyl ketone and ethylacetate (Table 1.16). In another study, overall exposure levels were found to be low, except in railroad car painting. Analyses of bulk air samples indicated no detectable benzene (O'Brien & Hurley, 1981). Exposure concentrations to organic solvents were, however, still relatively high during spray painting of aircraft in France in 1994, with a mean CEI of 3.4–4.9 (Vincent *et al.*, 1994). The exposure concentration of ethylene glycol monoethyl ether acetate largely exceeded the French VME (permissible exposure level) of 5 ppm (27 mg/m^3). In a recent study from Taiwan, China, xylene and toluene concentrations and personal exposure to these during spray painting of primer and surface paint were low. Benzene was detected in all series of spraying samples (range of six means, 0.14–0.94 ppm) (Uang *et al.*, 2006).

Employees in the USA working in and around jet aircraft during the paint stripping process were exposed to dichloromethane ranging from 38 to 2820 mg/m^3 (Okawa & Keith, 1977). In a French study (Vincent *et al.*, 1994), very high levels of methylene chloride (mean 783.4 mg/m^3) was also measured during paint stripping of an aircraft. Personal respiratory protection was not used during the stripping process. During paint stripping of aircraft in Taiwan, China (Uang *et al.*, 2006), the range of mean airborne methylene chloride concentrations in different areas was 20.4–42.0 ppm. Exposure was highest during the first 4 hours of stripping.

Table 1.16. Metal industry - concentration of solvents, isocyanates and other agents in air

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm [a]		Comments
					Mean	Range	
SOLVENTS - Aircraft							
Greenburg *et al.* (1942) USA	106 painters	Large airplane factory	Toluene (8h-TWA)			ppm (mg/m^3) 100–1100 (377–4147)	
Hervin & Thoburn (1975) USA	Personal samples Short-term sampling (10–50 min)	Large aircrafts – Spray painting of intermediate and final coat	Toluene	12	583 mg/m^3	140–1230	NIOSH report
			Methyl ethyl ketone	12	1436	240–3250	
			Ethyl acetate	12	1231	160–3520	
			Naphtha	12	44	20–120	
			Butyl acetate	12	64	20–150	
			Xylene	12	318	60–1330	
			Cellosolve acetate	12	4843	670–25170	
			Dichloromethane	12	654	ND–2840	
	Long-term sampling (1–3h)	Spray painting of intermediate and final coat	Ethyl acetate	10	264	10–1100	
			Methyl ethyl ketone	10	197	20–440	
			Toluene	10	162	30–450	
			Butyl acetate	10	11	ND–50	
			Naphta	10	10	ND–160	
			Xylene	10	69	10–270	
			Cellosolve acetate	10	640	70–2490	
			Dichloromethane	10	100	ND–760	

Table 1.16 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm [a]		Comments
					Mean	Range	
Okawa & Keith (1977) USA	Breathing zone	Aircraft maintenance facility			mg/m^3		NIOSH report
		Paint stripping					CEI based on short time samples, not recalculated into TWA
		Wide body aircraft (56–126 min)	Dichloromethane	23	393	79–950	
		Narrow body aircraft (16–33min)	Dichloromethane	20	795	38–2820	
		Prime coat application (19–38 min sampling)	Toluene	13	112	51–179	
			Methyl ethyl ketone		39	8–77	
			Butylacetate		72	29–130	
			n-Butanol		25	9–47	
			Isopropanol		51	ND–132	
			Cyclohexanone		10	ND–23	
			CEI		0.74	0.28–1.35	
		Top coat application with white enamel (25–37 min sampling)	Ethyl acetate	11	333	ND–857	All the highest values were from the same sample
			Methyl ethyl ketone		69	ND–219	
			Methyl isobutyl ketone		44	ND–117	
			Butyl acetate		80	ND–210	
			Xylene		21	ND–49	
			Cellosolve acetate		18	ND–46	
			CEI		0.76	ND–1.76	

Table 1.16 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm [a]		Comments
					Mean	Range	
O'Brien & Hurley (1981) USA	Personal Sampling time, 25–41 min	Light aircraft finishing, primer			GM	GSD	CEI based on OSHA permissible exposure levels
			2-Butanone	3	42 mg/m^3	2.1	
			Toluene		60	1.2	
			Ethanol		26	1.6	
			Isopropanol		19	1.6	
			CEI		0.9	1.5	
	Sampling time, 27–62 min	Light aircraft finishing, topcoat	Ethylacetate	7	77	1.3	
			Ethoxyethylacetate		44	1.4	
			Aliphatic hydrocarbons		34	1.2	
			CEI		0.15	1.3	
	Sampling time, 19–35 min	Light aircraft finishing, stripping	Ethylacetate	6	52	2.5	
			Ethoxyethylacetate		30	2.7	
			Aliphatic hydrocarbons		73	1.5	
			CEI		0.13	2.5	
	Sampling time, 15–60 min	Railroad car	Toluene	14	188	1.5	
			Xylene		14	2.6	
			Other aromatic compounds		217	1.4	
			Aliphatic hydrocarbons		840	1.4	
			CEI		1.3	1.4	
	Sampling time, 60 min	Heavy equipment	Refined solvents	12		21–96 (range)	
			Other solvents		<5		
			CEI			0.01–0.05	

Table 1.16 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm [a]		Comments
					Mean	Range	
O'Brien & Hurley (1981) USA	Sampling time, 8h	Metal furniture, solvent and water-based paints	Toluene	5		12–61	
			Xylene			7–48	
			n-Butyl acetate			22–109	
			Diisobutyl ketone			<1–23	
			2-Ethoxyethyl acetate			1–14	
			Aliphatic hydrocarbons			33–180	
			CEI			0.10–0.46	
	Sampling time, 8h	Metal furniture, high-solids paints	Xylene	6		6–55	
			Aromatic distillates			5–60	
			Other solvents			<10	
			CEI			0.07–0.31	
	Sampling time, 8h	Appliance painting	Toluene	4		88–204	
			Xylene			112–225	
			CEI			0.38–0.79	

Table 1.16 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm [a]		Comments
					Mean	Range	
Vincent *et al.* (1994) France	13 painters Personal sampling, 120–330 min	Aeronautical industry Paint stripping (2 days): application, scraping and brushing, washing			mg/m^3		No personal respiratory protection during stripping
			Methylene chloride	38	783.4	299–1888	
			Phenol (area sampling)	9	5.7	3.4–9.5	
					Range of 3 means		
	Personal sampling, 95–250 min	Painting (3 days): Surface cleaning, mixing paint, spray painting, cleaning equipment	Methyl ethyl ketone	23	14.7–33.3	<0.3–79.5	
			Ethyl acetate		64.4–123.2	29.1–187.2	
			n-Butyl alcohol		<0.3–45.9	<0.3–68.7	
			Methyl isobutyl ketone		<0.4–37.7	<0.4–52.5	
			Toluene		94.5–199.8	57.0–259.1	
			n-Butyl acetate		16.1–122.5	11.8–162.7	
			Ethylbenzene		15.2–66.5	7.8–89.6	
			Xylenes		30.9–122.2	14.3–167.0	
			EGEEA		63.2–110.2	29.2–150.1	
			CEI		3.39–4.90	1.49–6.75	

Table 1.16 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm [a]		Comments
					Mean	Range	
Uang *et al.* (2006) Taiwan, China	Personal samples, 2h	Aircraft maintenance – Paint stripping	Methylene chloride			SD	
		Ground		11	42.0	31.9	
		Platform, right wing		9	23.4	12.8	
		Platform, left wing		13	20.4	11.4	
		Platform, nose		8	21.6	14.9	
					Range of 3 means	Range	
	Area sampling, 4h	Paint stripping	Phenol	17	0.83–1.21	0.23–3.81	
					Range of 6 means		
	Personal samples, 1–2h	Spray painting	Methyl isobutyl ketone	39	0.9–3.7		
			n-Butyl acetate	39	1.3–4.6		
			Butanone	39	ND–1.8		
			Xylene	39	0.5–7.3		
			Acetone	39	0.2–18.9		
			Isobutyl ketone	39	0.1–14.3		
			Toluene	39	3.1–10.7		
			Benzene	39	0.1–0.9		
			Cyclohexanone	39	0.1–3.3		
			Ethyl acetate	39	ND–2.5		
			Styrene	39	ND–2.0		

Table 1.16 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm [a]		Comments
					Mean	Range	
Shipyard							
Mikulski *et al*. (1972) Poland	Area samples; at least 6 samples at 1-h intervals during 1 shift	Shipyard – Painting in small spaces and in large holds with chlorinated rubber and epoxy			Range of 4 means	ppm	
			Benzene	6	ND–9	ND–11	
			Toluene	6	7–53	7–88	
			Xylene	6	59–398	23–538	
Cherry *et al*. (1985) UK 1980	8 painters studied over 2 days	Dockyard – Painting with:	Main solvent:		TWA		
		- White interior (4 painters)	White spirits	NR	577.4 mg/m^3		
		- Paint stripper (1 painter)	Dichloromethane	NR	214.7		
		- Chlorinated rubber (3 painters)	White spirits	NR	124.6		
Sparer *et al*. (1988) USA	Personal sampling over 3 days; 36 workers	Shipyard – Brush painting (n=76), spray painting (n=8) and not painting (n=6)			ppm (mg/m^3)	ppm (mg/m^3)	
			2-Ethoxyethanol	90	2.6 (9.9)	0–21.5 (0–80.5)	
			2-Methoxyethanol	81	0.8 (2.6)	0–5.6 (0–17.7)	

Table 1.16 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm [a]		Comments
					Mean	Range	
Kim *et al.* (1999) Korea	Personal sampling > 6 hours excluding breaks	Shipyard			GM		
		Mainly spray painting in closed spaces/tanks (high exposure group)	Toluene	18	12.0	ND–154.6	
			Xylene	18	28.2	1.1–249.8	
			Methyl isobutyl ketone	18	4.6	0.03–159.2	
			EGEEA	18	3.0	ND–18.3	
		Spraying and brush painting, wiping, preparation work (low exposure group)	Toluene	12	0.7	0.05–8.6	
			Xylene	12	8.5	1.2–74.0	
			Methyl isobutyl ketone	12	1.4	ND–6.9	
			EGEEA	12	1.8	ND–8.1	
Chang *et al.* (2007) Taiwan, China	Personal dosimeter ≥ 6 hours for 3 days; 15 workers	Shipyard – Spray painting			8h-TWA	SE	
		Outside mask	Ethylbenzene	40	59.2	10.4	CEI >1 for 27.5% of the samples
			Xylene	40	29.4	4.7	
		Inside half mask	Ethylbenzene	33	2.6	0.49	
			Xylene	33	1.2	0.22	
Links *et al.* (2007) Netherlands	Personal	3–7 boatyards – Antifouling paint					
		Rolling	Dichlofluanid	15	0.01 mg/m^3	0.004–0.03	
		Spraying	Copper	12	3.0	0.3–9.0	
		Paint filling	Copper	10	1.0	0.1–2.5	
		Sand blasting	Copper	12	0.8	0.04–1.9	
		Grit filling	Copper	3	1.4	0.10–3.9	

Table 1.16 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm [a]		Comments
					Mean	Range	
Cars							
Husman (1980) Finland	Personal, 1 h; 40 workers	6 garages – Car painting		54	ppm (mg/m^3)	Maximum ppm (mg/m^3)	
			Toluene		30.6 (115)	249 (940)	
			Xylene		5.8 (25)	36 (156)	
			Butylacetate		6.8 (32)	128 (608)	
			White spirits		4.9	150	
			Methyl isobutyl ketone		1.7 (7)	39 (160)	
			Isopropanol		2.9 (7)	85 (209)	
			Ethyl acetate		2.6 (9)	14 (50)	
			Acetone		3.1 (7)	25 (60)	
			Ethanol		2.9 (6)	27 (51)	
Elofsson *et al.* (1980) Sweden	80 workers	Car refinishing workshops – Spray painting	Toluene	106	39 mg/m^3		
			Xylene		14		
			Ethyl acetate		11		
			CEI		0.3		
O'Brien & Hurley (1981) USA	Personal, 15–45 min	Car refinishing			GM	GSD	CEI based on OSHA PELs
			Toluene	7	39 mg/m^3	1.6	
			Xylene	7	10	1.0	
			Petroleum distillates	7	NR	21–63 (range)	
			Other solvents	7	<10		
			CEI	7	0.09	1.5	

Table 1.16 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm [a]		Comments
					Mean	Range	
Takeuchi *et al.* (1982) Japan	Personal ; 13 workers	Car repair painting	8h-TWA		ppm (mg/m^3)	SD ppm (mg/m^3)	
			Toluene		19 (72)	13 (49)	
			Xylene		8 (35)	8 (35)	
			Ethyl acetate		6 (22)	4 (14)	
			Isobutanol		5 (15)	5 (15)	
			CEI		0.38	0.25	
Jayjock & Levin (1984) USA	Personal, short-term exposures	1 small car body repair shop					Levels dependent on fans off/on and winter/summer (open doors) CEI based on STEL
		Lacquer spray painting	Toluene	5	249.4	30–590	
			Xylene	5	7.2	ND–12	
			Benzene	5	0.6	ND–1.1	
			CEI	5	1.9	0.2–4.7	
		Enamel containing 4–9% aliphatic polyisocyanates	Toluene	13		ND–86	
			Xylene	13		15–230	
			Benzene	13		ND–11	
			CEI	13		0.1–3.3	
de Medinilla & Espigares (1988) Spain	Personal, 30 min	11 car repair shops – Painting in booth equipped with local extraction fans	Toluene	11		2.7–467.0 mg/m^3	CEI based on TLV list of ACGIH (1984–85)
			Xylenes	11		1.0–297.2	
			Ethylbenzene	11		0.5–125.0	
			Trimethylbenzene	11		ND–34.1	
			n-Butylacetate	11		ND–180.0	
			n-Hexane	11		ND–15.8	
			Benzene	11		ND–6.0	
			Dichloromethane	11		ND–26.2	
			CEI (STEL)	11		0.06–10.68	

Table 1.16 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm [a]		Comments
					Mean	Range	
Winder & Turner (1992) Australia	Personal, 4–7h; 64 workers	46 car painting shops – Spray painting of acrylic and polyurethane paint, duration 10min–4h	Toluene	66*	43.5 mg/m^3	ND–323 mg/m^3	*Number of positive samples out of 70 samples
			Xylenes	42*	8.7	ND–26	
			Trimethylbenzene	22*	4.1	ND–15	
			Methyl ethyl ketone	20*	12.2	ND–30	
			C5–C7 aliphatics	16*	32.2	ND–71	Means based on samples above detection limit
			Acetone	10*	34.1	ND–77	
			Butanols	9*	4.4	ND–12	
			2-Butoxyetanol	8*	2.0	ND–3	CEI based on composite exposure standard
			High-boiling point hydrocarbons	8*	19.5	ND–85	
			Butylacetate	7*	11.7	ND–23	
			n-Hexane	6*	3.8	ND–10	
			Methyl isobutyl ketone	4*	6.8	ND–13	
			Ethanol	4*	88.3	ND–217	
			Benzene	3*	1.0	ND–1	
			Ethyl acetate	1*	17.0		
			CEI		0.19	0.01–0.99	
Moen & Hollund (2000) Norway	Personal sampling inside mask when in use, 15–282 min; 28 workers	6 car repair shops – Paint mixing and spraying		30		Range of 6 means	
			Toluene		2.6	0.2–11.1	
			Xylene		3.8	0.2–0.8	
			Ethylbenzene		0.1	0.1–0.3	
			Isopropanol		1.7	ND–4.0	
			Acetone		0.9	ND–1.6	
			Butylacetate		0.6	0.3–1.0	

Table 1.16 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm [a]		Comments
					Mean	Range	
Bråtveit *et al.* (2004) Norway	Personal full shift sampling outside mask, over 3 days, for 5–9 h	8 car repair shops – Sanding, cleaning surfaces, masking, paint mixing and spraying, cleaning of equipment Solvent-based paint (6 shops, 17 painters)		51	GM	Range of 6 means	CEI based on Norwegian limit values
			Toluene		0.80	0.02–9.17	
			Xylene		0.34	0.09–1.8	
			Ethylbenzene		0.07	ND–0.36	
			Trimethylbenzene		0.06	ND–0.30	
			Isopropanol		0.29	ND–6.41	
			Acetone		0,09	ND–12.1	
			Butylacetate		0.58	0.13–2.78	
			2-Propylacetate		0.02	ND–0.68	
			CEI		0.15	0.01–1.60	
		Water-based paint (4 shops, 10 painters)		28		Range of 4 means	
			Toluene		0.08	0.03–0.20	
			Xylene		0.25	0.06–0.42	
			Ethylbenzene		0.05	0.02–0.07	
			Trimethylbenzene		0.05	0.02–0.09	
			Isopropanol		0.01	ND–0.04	
			Acetone		0,01	ND–0.07	
			Butylacetate		0.23	0.11–0.37	
			2-Propylacetate		0.02	ND–0.34	
			CEI		0.05	0.01–0.22	
Vitali *et al.* (2006) Italy	personal dosimeters, 236–323 min; 8 painters;	8 small car repair shops – varnishing (preparation, spraying, tool cleaning, etc.)	Toluene	8	17.8 mg/m^3	1.9–93.8 mg/m^3	Masks were not used
			Xylene	8	20.1	1.2–75.0	
			Ethylbenzene	8	7.2	0.4–23.8	
			Butylacetate	8	19.5	<0.1–100.2	
			Benzene	8	9.8	0.4–53.1	

Table 1.16 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm [a]		Comments
					Mean	Range	
Other industries							
Chrostek (1980), USA	Breathing zone; 3 workers	Paint stripping from wood and metal	Dichloromethane (TWA)	7	NR	633–1017 mg/m^3	
Hellquist *et al.* (1983) Sweden		Fireplace production – Spray painters	Toluene Isobutyl acetate			3–18 mg/m^3 2–44	
ISOCYANATES – Aircraft & Cars							
Okawa & Keith (1977) USA	Breathing zone; 17–77 min	Airline maintenance – Spraying of enamel top coat	HDI	15	1.1 mg/m^3	<0.04–3.20 mg/m^3	
O'Brien & Hurley (1981) USA	Breathing zone; 5–13min	Car repainting shop – Spraying	HDI	3		<130 µg/m^3	
	Breathing zone; 7–21min	Light aircraft finishing	HDI	8		<70 (7 samples) – 250 (1 sample)	
Rosenberg & Tuomi (1984) Finland	Personal, 5–10 min samples	4 car paint shops – Spray painting with HDI-based polyurethane paint	TWA HDI HDI-biuret oligomer	 10 10	 49 µg/m^3 1440	SD 22 1130	
Alexandersson *et al.* (1987) Sweden	43 workers	Car repair shops (8h-TWA)	HDI HDI-biuret oligomer		1.0 µg/m^3 115	 10–385 µg/m^3	

Table 1.16 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm [a]		Comments
					Mean	Range	
Pisaniello & Muriale (1989) Australia	Task-based breathing zone samples, 18 min on average	14 car body repair shops – Spray painting			GM		
		Primer undercoat (in open workshop)	NCO	NR	29 μg/m^3	7–180	
		Topcoat (in booth)					
		solid colours	NCO	NR	202	8–3500	
		clearcoat	NCO	NR	70	9–550	
Carlton & England (2000) USA	Task-based breathing zone samples, generally less than 25 min.	4 Aircraft bases – Spray painting with polyurethane enamel in booths or painting inserts	HDI				
			Task	57	15.5 μg/m^3	3.05–53.1	
			8-hr TWA	57	0.67	0.31–3.51	
			HDI Oligomer				
			Task	53	0.33 mg/m^3	<0.01–3.36	
			8-hr TWA	53	0.01	<0.01–0.17	
Sparer *et al.* (2004) USA	Task-based personal sampling	Auto body shop – Spray painting (% NCO in hardener)			Median	25–75th percentile	
		Primer (8%)	NCO	31	66.5 μg/m^3	16.9–165	
		Sealer (11%)	NCO	29	134	48.4–296	
		Clear (10%)	NCO	93	358	157–855	

Table 1.16 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm [a]		Comments
					Mean	Range	
Woskie *et al.* (2004) USA	Task-based sampling (1–493 min) for 2 days; personal samples unless specified	33 auto body shops –			Median	Range or maximum	* % of samples >LOD
		Spraying inside and outside booth	HDI (90%)*	166	1.69 µg/m^3	ND –56.16	Total NCO: total NCO based on HDI monomer, HDI polyisocyanate (biuret and isocyanurate) and isophorone diisocyanate [IPDI] polyisocyanate
			Total NCO	166	205.53	5519	
		Bystander to spraying (area and personal samples)	HDI (54%)*	37	0.03	ND–1.17	
			Total NCO	37	0.93	108.7	
		Background (area samples)	HDI (40%)*	107	0.01	ND–0.24	
			Total NCO	107	0.05	12.6	
		Mixing and cleaning equipment	HDI (38%)*	45	0.04	ND–2.38	
			Total NCO	45	0.17	118.3	
		Sanding or compounding coated surfaces	HDI (28%)*	25	0.05	ND–0.71	
			Total NCO	25	0.27	36.1	
Boutin *et al.* (2006) Canada	Breathing zone, 15 min	Car body shops – Paint removal by thermal degradation					
		Cutting	Total NCO	10		1.07–9.80 µg/m^3	
		Grinding		10		0.63–3.62	
		Sanding		NR		ND–1.29	

Table 1.16 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm [a]		Comments
					Mean	Range	
Pronk *et al.* (2006a) Netherlands	Mainly personal task-based samples, 1–113 min, 1–2 days per company; 109 workers	24 autobody repair workshops		475 total	Median NCO**		*Number of samples >LOD
			HDI factor	256*	8.55 μg/m^3	0.002–1124 μg/m^3	**Median and range for samples >LOD
			TDI factor	111*	0.07	0.001–5.38	
			MDI factor	12*	0.10	0.02–0.54	
			Thermal degradation products	103*	0.12	0.001–4.64	
			Monomers	217*	0.42	0.002–15.5	
			Oligomers	217*	27.92	0.02–1122	
			Total	293*	5.13	0.01–1124	
		5 industrial painting companies – spray painters		36			
			HDI factor	35	6.67	0.01–2643	
			TDI factor	11	0.02	0.004–0.65	
			MDI factor	0	-	-	
			Thermal degradation products	17	0.17	0.01–3.95	
			Monomers	34	0.11	0.01–28.8	
			Oligomers	29	14.21	0.12–2614	
			Total	35	6.68	0.01–2643	

Table 1.16 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm [a]		Comments
					Mean	Range	
Pronk *et al.* (2006b) Netherlands	Personal task-based samples, 1–40 min	6 car body repair shops		95	Median NCO**		* % of the samples >LOD
		Mixing polyurethane lacquer	HDI (20%*)	15	1.0 µg/m^3	0.2–2.7 µg/m^3	**Median and range for samples >LOD
			Oligomers (27%)	15	1.4	0.3–33.1	
		Spraying	HDI (65%)	31	2.1	0.2–6.5	
			Oligomers (87%)	31	116.3	2.5–728.4	Oligomers; uretidine, isocyanurate, biuret, diisocyanurate, unknown oligomer of HDI
		Spray gun cleaning	HDI (0%)	19	-	-	
			Oligomers (32%)	19	11.1	1.6–45.3	
		Welding	HDI (33%)	3	0.04		
			Oligomers (33%)	3	0.1		
	Personal task-based samples, 4–41 min	5 industrial painting companies for ships and harbour equipment					
		Spraying polyurethane lacquer	HDI (100%)	10	3.7	0.03–28.8	
			Oligomers (100%)	10	199.6	6.4–2613.8	
		Rolling/brushing	HDI (100%)	11	0.02	0.01–0.1	
			Oligomers (46%)	11	0.7	0.1–5.3	
		Mixing	HDI (67%)	3	0.5	0.01–1.0	
			Oligomers (67%)	3	10.8	1.6–20.0	
		Assisting spray painter	HDI (100%)	3	0.3	0.09–4.4	
			Oligomers (100%)	3	14.2	6.3–347.7	
OTHER AGENTS							
Larson (1978) USA	Full-shift samples	8 plants. Pipeline coating with coal-tar enamel (heat)	Coal-tar pitch volatiles Benzo[*a*]pyrene (respirable fraction)		133 µg/m^3	Max. 24 mg/m^3	

Table 1.16 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm [a]		Comments
					Mean	Range	
Chrostek & Levine (1981) USA	Personal breathing zone, 3–8 h	Steel structure finishing – spray painting with epoxy paint or oil-based paint	Epichlorohydrin Bisphenol A glycidyl ethers	13 9	64.9 mg/m^3 9.8 μg/m^3	2.4–138.9 mg/m^3 <0.6–28.6 μg/m^3	NIOSH report
Bäck & Saarinen (1986) Finland	Breathing zone ; 1 worker	Spray painting of paper machine and pulp tanks	Diethylene triamine (component of curing agent)	3		0.02–0.07 mg/m^3	
Herrick *et al*. (1988) United Kingdom		Painting of tank and ceiling using epoxy coating	Epoxide functional groups		2.7–12 μEq/ m^3		
Allmaras (2003) USA	Personal samples, 57 min	Powder paint coating Spraying paint line-facility 1 Spraying paint line-facility 2	1,3,5-Triglycidyl isocyanurate	3 1	0.092 mg/m^3 31 mg/m^3 TWA	0.041–0.16 mg/m^3	
Lee *et al*. (2003) Korea	Breathing zone sampling, 6h for 3 days; 25 workers	Shipyard – spraying coal-tar paint	Total PAHs	25	4.82 μg/m^3	0.08–22.49	

Table 1.16 (contd)

Reference Country, year of study	Sampling type and duration; No. of workers	Site/job/task	Agent	No. of samples	Air levels in ppm [a]		Comments
					Mean	Range	
Blomqvist *et al.* (2005) Sweden	Personal + area samples, 5–7h	2 powder paint shops	Trimellitic anhydride				No trimellitic anhydride detected inside breathing protection device
		Shop 1					
		personal samples		5	NR	0.006–0.18 mg/m^3	
		area samples		5	NR	0.015–1.04 mg/m^3	
		Shop 2					
		inside booth		1	0.2 mg/m^3	-	
		outside booth		NR	-	<0.001–0.003	

[a] unless otherwise stated;

CEI, cumulative exposure index; EGEEA, ethylene glycol monoethyl ether acetate; GM, geometric mean; GSD, geometric standard deviation; HDI, 1,6-hexamethylene diisocyanate; MDI, methylene diphenyl diisocyanate; NCO, isocyanates; ND, not detected; NR, not reported; SD, standard deviation; SE, standard error; TDI, toluene diisocyanate.

Shipyards: In Poland, shipyard painters working in small spaces of superstructures and in large holds were exposed to levels of benzene ranging from undetectable to 11 ppm [35 mg/m^3]. Concentrations of toluene and xylene were 7–88 ppm and 23–538 ppm, respectively (Mikulski *et al.*, 1972).

United Kingdom shipyard painters working in ships' accommodation and bilges were exposed to various mean concentrations of organic solvents, depending on their job: 125 mg/m^3 for three painters using a chlorinated rubber paint with white spirits as solvent, 215 mg/m^3 for a worker using paint stripper with dichloromethane as the main solvent, and 577 mg/m^3 for four men using white interior paint with white spirits as the main solvent (Cherry *et al.*, 1985).

In the Republic of Korea, nine of the 18 shipyard painters who were spray painting in closed spaces/tanks were exposed to concentrations of ethylene glycol monoethyl ether acetate that exceeded the threshold limit value (TLV) of the American Conference of Industrial Hygienists (ACGIH) of 5 ppm. Solvents such as toluene and xylene were found at relatively low concentrations (Kim *et al.*, 1999). During spray painting inside the block units of assembled ships in Taiwan, China, 11 of 40 samples had a CEI exceeding 1, based on the TLV-ACGIH (Chang *et al.*, 2007).

Car refinishing: A large study of car refinishing workshops in Sweden was carried out and results showed that toluene and xylene were present at mean concentrations of 39 and 14 mg/m^3, respectively. A reconstitution of working conditions in 1955 indicated that exposure levels to solvents at that time were higher than those in 1975, which were considered to be representative of the 1960s and 1970s. In particular, when benzene was used as a solvent in 1975–77, the CEI reached 0.8 (Elofsson *et al.*, 1980).

In Finland (Husman, 1980) and Japan (Takeuchi *et al.*, 1982), personal exposure measurement of solvents were reported with a highest mean concentration for toluene (30.6 ppm [115 mg/m^3] for 1-hour samples and 19 ppm [72 mg/m^3] for full-shift TWA samples).

Personal samples were taken during short-term spray painting operations in a small autobody repair workshop in the USA (Jayjock & Levin, 1984). In winter, when the spraybooth fan was turned off to conserve heat, maximal concentrations of toluene of 590 ppm were recorded during lacquer spray painting, and of 230 ppm xylene, and 11 ppm benzene during enamel spray painting.

In a study in 11 car paint workshops in Spain, toluene (2.7–467.0 mg/m^3), xylene and ethylbenzene were found in all air samples; benzene was detected in three workshops at 0.6, 1.7, and 6.0 mg/m^3 (de Medinilla & Espigares, 1988). In 46 autobody repair workshops in Australia (Winder & Turner, 1992), toluene was detected in nearly all samples (n = 70), and average concentrations across the workshops ranged up to 323 mg/m^3 (mean 43.5 mg/m^3). Benzene was detected in three workplaces at an exposure level of 1 mg/m^3 in each case.

Exposure to solvents was generally low in two Norwegian studies of spray painters using water-based or solvent-based paint systems in car-repair shops. All shops had spraying booths with downdraft ventilation and enclosed mixing room with air supply and exhaust hoods (Moen & Hollund, 2000; Bråtveit *et al.*, 2004). In Italy, personal exposure of

car painters was measured in eight workshops with ventilated spray booths but not any general mechanical ventilation. The individual levels of toluene, *n*-butylacetate, xylene, and ethylbenzene were low, except for two workshops where concentrations ranging up to 100.2 mg/m^3 were measured. Benzene was detected in all workshops. In two workshops, benzene concentrations were considerably higher (18.8 and 53.1 mg/m^3) than in the others. Exposure to benzene concentrations was mainly due to fuel vapour and to gasoline used for degreasing and dilution of paints (Vitali *et al.*, 2006).

Other industries: In a plant in the USA where paint was stripped from wood and metal, average breathing-zone TWA concentrations of dichloromethane were in the range of 633–1017 mg/m^3 (Chrostek, 1980).

In another plant in the USA where truck bodies and refuse-handling equipment were manufactured, breathing-zone concentrations of xylene during spray painting operations were in the range of 5–140 ppm (22–608 mg/m^3) (Vandervort & Cromer, 1975). Exposure to low solvent concentrations was observed for spray painters in a plant manufacturing fireplaces in Sweden (Hellquist *et al.*, 1983).

In a study in China, the range of mean benzene concentrations determined by grab samples at 18 unspecified paint workplaces was reported as 15–1105 mg/m^3 (Yin *et al.*, 1987).

(ii) *Exposure to isocyanates* (Table 1.16)

Use of polyurethane-type paints can result in exposure to diisocyanate monomers and their oligomers. Concentrations of HDI during the spray application of an enamel top coat at a US airline maintenance facility had a mean of 1.1 mg/m^3 (Okawa & Keith, 1977). Exposure concentrations of HDI during polyurethane enamel spray painting of aircrafts or aircraft components at Air Force bases were low (8h-TWA; 0.67 µg/m^3) compared to the TLV-ACGIH of 34 µg/m^3 (Carlton & England, 2000).

In a US car repainting shop, short-term breathing zone samples taken during spray painting operations were measured for HDI with reported concentrations of <130 µg/m^3. Similar measurements taken during various aircraft finishing operations reported HDI concentrations below 70 µg/m^3, except for one operation with a level of 250 µg/m^3 (O'Brien & Hurley, 1981). In Finland, average HDI and HDI-biuret oligomer concentrations in short-term personal samples during spray painting of cars were 49 µg/m^3 and 1440 µg/m^3, respectively. All spraying chambers were fitted with exhaust ventilation systems (Rosenberg & Tuomi, 1984). In Sweden, 43 car repair painters were exposed to average concentrations of 115 µg/m^3 HDI-biuret oligomer and 1.0 µg/m^3 HDI (Alexandersson *et al.*, 1987).

Spray painting of topcoat (solid colours) resulted in the highest short-term exposure concentrations (mean, 202 µg/m^3 isocyanate (NCO)) compared to spraying of undercoat and clearcoat in a survey of 45 crash repair workshops in Australia (Pisaniello & Muriale, 1989). Sparer *et al.* (2004) characterized isocyanate exposure in the autobody industry as a part of the epidemiological study SPRAY. Personal samples were measured and contained median concentrations of 66.5 µg/m^3 NCO for primer, and 358.5 µg/m^3 NCO for clearcoat.

As part of the same study, Woskie *et al.* (2004) reported an exposure concentration of 206 µg/m^3 NCO for spray operations. In the Netherlands, task-based assessment of isocyanate exposure was carried out as part of an epidemiological study among autobody repair shop workers and industrial spray painters (Pronk *et al.*, 2006a,b). Oligomers of HDI dominated over the monomer during all tasks in both industries. In both branches, exposure was highest during those tasks where paint was aerolised, i.e. when spraying cars (median concentration of HDI oligomers, 116.3 µg/m^3), and ships and harbour equipment (199.6 µg/m^3) (Pronk *et al.*, 2006a).

Airborne isocyanates generated during thermal degradation of car paint in body repair shops were determined in France (Boutin *et al.*, 2006). They found that the concentration of NCO in the breathing zone was in the range of 1.07–9.80 µg/m^3 during cutting, 0.63–3.62 µg/m^3 during grinding, and 0–1.29 µg/m^3 during sanding of painted surfaces.

(iii) *Exposure to paint mists, dusts and specific metals* (Table 1.13)

In a larger study of car refinishing workshops in Sweden, average concentrations of 7 mg/m^3 paint mist, 100 µg/m^3 lead, and 26 µg/m^3 chromium were measured during spraying activities. The conditions were thought to be representative of those in the 1960s and 1970s. Simulation of work conditions in 1955 led to measurements of low concentrations of lead during the use of all colours except for red, when the Swedish exposure limit was exceeded 70-fold (Elofsson *et al.*, 1980).

Substantial but short-term lead exposure was encountered in situations where lead-based pigments were used, such as in painting transportation and heavy equipment (O'Brien & Hurley, 1981). Elevated but brief exposures to chromium were noted during the spraying of aircraft with primer (O'Brien & Hurley, 1981). At a plant in the USA where truck bodies and refuse handling equipment were made, breathing zone concentrations during various spray painting operations were 20–3000 µg/m^3 lead, and 10–400 µg/m^3 chromium (Vandervort & Cromer, 1975). A manufacturer of aero-mechanical systems in the USA reported workers a mean exposure concentration to hexavalent chromium of 606.7 µg/m^3 when spraying aircraft wheels with zinc chromate primer (Kominsky *et al.*, 1978).

Breathing-zone samples were taken during short-term spray painting operations in a small autobody repair workshop in the USA. Only one of eight samples, corresponding to exposure to a red paint formula, contained significant levels of chromium (490 µg/m^3), and lead (210 µg/m^3) (Jayjock & Levin, 1984). At a plant in the USA where buses were manufactured, employees working in and around the paint booth were exposed to hexavalent chromium at mean concentrations of 0.23 mg/m^3 and to lead at mean concentrations of 0.78 mg/m^3 (Zey & Aw, 1984). In a Finnish registry of occupational exposure measurements, average exposure concentration of painters to hexavalent chromium and nickel were reported as 180 µg/m^3 and 100 µg/m^3, respectively (Kiilunen, 1994).

In a recent study of spray painters in automobile body repair shops lacking isolated spraying rooms in Thailand, low full-shift exposure concentrations of lead (0.05–

5.8 µg/m^3), cadmium (nd–5.7 µg/m^3) and chromium (0.25–3.1 µg/m^3) were reported (Vitayavirasuk *et al.*, 2005).

At a coating and painting facility that used products containing hexavalent chromium (1–30% chromates) in the USA, full-shift exposure concentrations of painters and helpers during spray painting and removal of chromate-containing paint were in the range of 2.4 to 55 µg/m^3 (Blade *et al.*, 2007). Spray painting with chromate-containing paint in booths at an aerospace facility in the USA was measured for personal 8h-TWA exposure to hexavalent chromium and was reported in the range of 19–327 µg/m^3 (Sabty-Daily *et al.*, 2005).

The mass median aerodynamic diameters of paint overspray aerosols during spraying of high-solid paint in a down-draft spraying booth ranged from 2.9 to 9.7 µm (D'Arcy & Chan, 1990); that of total chromium particles in the paint aerosol during spraying chromate-containing paint at an aerospace facility was 7.5 µm (Sabty-Daily *et al.*, 2005).

During removal of lead-containing paint at a shipyard in the USA, geometric mean personal exposure to lead was 60.6 µg/m^3 during sanding, and 2.36 µg/m^3 during chipping (Booher, 1988). High airborne mean-TWA lead concentrations were found when lead paint was removed aboard a ship in the USA: during chipping with needle gun, 91.6 µg/m^3, during grinding, 400.5 µg/m^3, and during chipping and/or grinding, 375.2 µg/m^3 (Zedd *et al.*, 1993). During maintenance of a large hammerhead crane on a shipyard in the USA, company data indicated that paint removal by abrasive blasting was associated with high lead exposure for blasters (range 309 to 6522 µg/m^3) and for labourers (578–3852 µg/m^3) within the containment structure (Jarrett, 2003). Personal 8h-TWA exposure to cadmium, lead and hexavalent chromium were up to 250, 6 and 5 times higher than the PELs, respectively, when paint and primer were removed by abrasive blasting from aircraft parts and ground equipment at four US air force facilities (Aizenberg *et al.*, 2000).

(iv) *Other exposures*

Epoxide levels of 2–12 µEq/m^3 epoxide functional group were recorded during the painting of a tank with coal-tar epoxy coatings, and the painting of a metal ceiling using an epoxy architectural coating (Herrick *et al.*, 1988). In a company in the USA where steel products were blasted with steel shot or sand and spray-painted with two-component epoxy paints or oil-based paints, epichlorohydrin and bisphenol A glycidyl ethers were detected in the workers' breathing zone (Chrostek & Levine, 1981).

Diethylene triamine, which is a component of curing agents of epoxy paints, was measured in three samples collected from the breathing zone of a painter during spray painting of paper machine cylinders and pulp tanks at concentrations in the range of 0.02–0.07 mg/m^3 (Bäck & Saarinen, 1986).

In plants where coal-tar enamel protective coating was applied to pipelines with heat, the workers were exposed to high concentrations of coal-tar pitch volatiles (see IARC, 1985) of up to 24 mg/m^3 of benzene-soluble matter (full-shift samples). The overall respirable concentration of benzo[*a*]pyrene in the plants averaged 133 µg/m^3 (Larson, 1978). In a shipyard in Korea, painters using coal-tar paints were exposed to concentrations of total polycyclic aromatic hydrocarbons (PAHs) in the range of 0.08–22.49 µg/m^3 (mean,

4.82 µg/m^3) (Lee *et al.*, 2003). The composition of the total PAHs was 64.1% naphthalene, 11.3% acenaphthene, 6.2% fluorene, 3.9% anthracene, 3.3% pyrene, 2.9% benzo[*a*]anthracene, 2.8% fluoranthene, 2.0% acenaphthylene, 0.7% chrysene, and <0.1% benzo[*a*]pyrene.

During powder paint coating operations in the USA, the occupational exposure to 1,3,5-triglycidyl isocyanurate was high (31 mg/m^3) in one of the facilities visited by OSHA (Allmaras, 2003). In Sweden, two of five personal samples exceeded the Swedish limit value for trimellitic anhydride of 0.04 mg/m^3 during powder coating (Blomqvist *et al.*, 2005).

In an asbestos job exposure matrix, painters (classified as bystanders) were assigned a relative exposure intensity of 3 on a 1–4 scale, where 4 was highest (Rice & Heineman, 2003).

1.4.2 *Dermal exposures*

(a) Introduction

Schneider *et al.* (1999) have provided a generalized conceptual model of dermal exposure processes. They argue that the amount of any hazardous substance in the contamination layer on the surface of the skin is linked to transfer from the air, from contact with surfaces, and from direct transfer from the source. In addition, the air and surface compartments in their model are linked so that contamination on surfaces is in part caused by deposition from the air and vice versa. Clothing may play an important part in protecting the skin from exposure, particularly in the case of solids and non-volatile liquids, and this is incorporated into the model as twin compartments, i.e. inside and outside clothing layers. It is conventional to describe exposure measured on the outside of clothing or protective gloves as “potential” exposure, and measurements made directly on skin as “actual” exposure.

Once the hazardous substance deposits in the skin contamination layer, there are three possible outcomes:

• It may evaporate and be removed from contact with the skin before it passes through the stratum corneum;

• It may be retained in the stratum corneum or skin contamination layer, and be removed at some later time by washing or because of skin cells sloughing off; or

• It may diffuse through the stratum corneum and be available for systemic uptake.

Only in the latter situation is there any contribution to risk of disease, although most exposure measurement methods include at least some contribution from material that will not be taken up through the stratum corneum.

(b) Measurement of exposure

Unlike inhalation exposure assessments, the methods available for measuring dermal exposures are not standardized, and it is therefore more difficult to compare studies that have used different approaches. The available methods include:

• *Interception methods*, where the sampling medium comprises a cotton pad (for solids and non-volatile liquids) or an activated-charcoal-based pad (for volatile liquids);

• *Removal techniques*, where the contaminant is removed from the subjects' skin by wiping, washing or skin stripping;

• *Direct techniques*, where some property of the contaminant, such as its ability to fluoresce under ultraviolet light, is used to determine exposure.

These methods do not have the same sampling efficiencies, but more importantly they do not measure the same aspect of exposure. For example, an interception method using a cotton pad for metal exposure in a painting task will obtain a measure of the total flux of metal-containing particles onto the skin over the duration that the sampler is worn. However, using a removal method such as swabbing the skin with a moist wipe will determine the mass of metal retained on the skin at the time the measurement was made. Both approaches provide measures that may be linked with the mass of metal taken up through the skin, but the numeric value of exposure, in mg or mg per unit area of skin, may be very different. For painting activities, many studies have used interception methods to assess dermal exposure.

The available literature on dermal exposure has been reviewed to assess the magnitude of dermal exposure in terms of total paint formulation or some constituent part of the paint, and whether dermal exposure is associated with inhalation exposure.

(c) Magnitude of exposure

Brouwer *et al.* (2000) measured dermal exposure during airless spray painting of a 36 m^3 container. They used a fluorescent tracer added to the paint to assess the mass of paint deposited onto the skin of the subject and the coverall worn. On average, 72% of the contaminant mass landed on the legs, 13% on the torso, and 13% on the hands and arms. Hughson & Aitken (2004) demonstrated that dermal exposure of spray painters was greatest on the hands and that other body parts were only sporadically affected, while Links *et al.* (2007) corroborated this finding with results for highest exposure for the hands, followed by the front torso, and the lower arms.

Dermal exposure during painting of wood preserve and antifouling paints was described by Garrod *et al.* (2000). They found whole body median potential exposure rates of 5.06 mg/min for brushing wood preserve and 16.4 mg/min for antifouling agents (assuming a body area of 1.8 m^2, the corresponding values are 0.28 and 0.91 $\mu g/cm^2/min$).

Liu *et al.* (2000, 2007) made qualitative assessments of isocyanate contamination on the skin of workers and environmental work surfaces in three autobody workshops. Work surfaces such as painters' work benches, spray equipment and work tools were contaminated with isocyanates. Painters frequently contacted contaminated surfaces with

their hands, often without wearing gloves. Moderate-to-heavy contamination of some skin surfaces was found for painters from two of the three autobody workshops. The use of latex gloves did not protect the painters from dermal exposure.

In a study of potential dermal exposure of vehicle spray painters using an interception method, Delgado *et al.* (2004) found that, during filling of the spray gun, exposure occurred mainly on the hands and ranged from 0.68 to 590 μg paint/cm^2/min with a geometric mean of 24 μg paint/cm^2/min, based on the amount of aluminium measured and the concentration of aluminium in the paint. During spraying, the geometric mean exposure rate was 0.9 μg paint/cm^2/min (range 0.2 to 4.4) for the body and 2.7 (range 0.40 to 13) μg paint/cm^2/min for the hands. While cleaning the spray gun, the hands were again the principal area exposed, with exposure of 17 (range 0.44 to 213) μg paint/cm^2/min. These figures represent the cumulative amount of paint on the skin or clothing over the duration of spraying.

Data from spray painters and their assistants in a naval dockyard applying antifouling paint to the outside of a ship showed the geometric mean dermal exposure rate for the hands during spray painting was 46 μg/cm^2/min, with the corresponding value for the rest of the body of 2.9 μg/cm^2/min (Hughson & Aitken, 2004). The geometric mean for mixing the relatively large quantities of paint used in this workplace (up to about 200 L in two hours) were 520 μg/cm^2/min for the hands and 5.5 μg/cm^2/min for the rest of the body. These data were obtained as potential exposure using an interception method similar to that used by Delgado *et al.* (2004).

Dermal exposure during the filling, loading and brushing of paint products containing 2-(2-butoxyethoxy)ethanol was obtained using cotton interception samplers (Gijsbers *et al.*, 2004). The geometric mean exposure rate for the hands during filling was 11.5 μg/cm^2/min, and whole body exposure during filling was 0.016 μg/cm^2/min. The corresponding exposure rate for hands during brush application was much lower at 1.7 μg/cm^2/min.

Roff *et al.* (2004) studied the exposure of painters using dry powder spray paints containing triglycidyl isocyanurate or other compounds. Workers wore Tyvek suits and some also wore cotton sampling gloves. The samples were then analysed using a portable X-ray fluorescence spectrometer. The geometric mean potential exposure rate was 0.7 μg/cm^2/min for the body, and 16 μg/cm^2/min for the hands (the Pearson correlation coefficient between hands and body was 0.67).

Fent *et al.* (2006) used a tape-stripping method to measure dermal exposure to HDI among autobody shop workers. Samples were collected at the end of a painting task. The workers wore a respirator but no protective gloves or protective clothing. The measured geometric mean concentrations were 5.1, 6.6 and 3.4 pmol/cm^2 HDI for the arms, hands and forehead, respectively.

Flynn *et al.* (2006) presented a simple theoretical model to predict the deposition of paint droplets on the skin and some further measurements of isocyanate skin levels using the tape-stripping method of Fent *et al.* (2006). The model provided a reasonable prediction of exposure for the circumstances for which data were available, although it tended to underestimate exposure at higher levels. The main determinant of dermal exposure in this

model was the air concentration in the vicinity of the painter. The HDI exposure concentration on the hands or forearms of a spray painter ranged from 7.5 to 31.8 pmol/cm^2.

An interception sampling approach to measuring dermal exposure to isocyanates was used by Pronk *et al.* (2006b) for workers in car body shops and industrial painting companies. The samples were collected on nitrile rubber gloves; at the end of the sampling period the gloves were submerged into di-*n*-butylamine in toluene. Analysis for HDI and its oligomers was performed by liquid chromatography-tandem mass spectrometry (LC-MS/MS). For the car body shop workers, between 39% and 47% of the samples had detectable levels of HDI; NCO levels ranged from 0.3 to 20 μg on both hands (equivalent to 0.36 to 24 ng NCO/cm^2, assuming the area of the gloves was 840 cm^2). Exposure of the industrial painters was much lower, with one out of 27 samples having detectable levels of HDI. Exposure to HDI oligomers were higher, with 32–53% of samples from the car body shop workers and about 90% of samples from the industrial painters having detectable levels. The highest geometric mean exposures to oligomers in the car workshop were for mixing (geometric mean, 207 μg NCO on hands or 246 nm NCO/cm^2), then spraying (133 μg NCO or 158 ng NCO/cm^2), and cleaning (34 μg NCO or 40 ng NCO/cm^2). Corresponding data for the industrial painters were: 63 μg NCO for mixing (75 ng NCO/cm^2), 44 μg NCO spraying (52 ng NCO/cm^2) and 16 μg NCO rolling/brushing (19 ng NCO/cm^2). The authors noted that inhalation exposure was strongly associated with tasks during which aerosolization occurred and dermal exposure occurred during tasks that involved direct handling of paint.

Links *et al.* (2007) also presented data from the spraying of antifouling paint using an interception method based on the use of Tyvek suits, cotton gloves, socks, underclothing and outer protective gloves as sampling media. They showed that the geometric mean potential exposure rate was 1075 mg/hour (equivalent to about 1 μg/cm^2/min, assuming that the total body surface area was 1.8 m^2). Corresponding values for mixing of paint and application of paint by roller were slightly higher (equivalent to 3.5 and 2.4 μg/cm^2/min, respectively). The main potential dermal exposure was to the hands (52% for rolling and 78% for spraying). The actual exposures were much lower than the potential exposures, demonstrating the protective effect of a simple Tyvek suit and protective gloves; actual exposure of the hands was 0.42% of the potential exposure for spraying, and 0.01% for rolling and mixing.

Exposure to solvents from painting is difficult to measure because they evaporate rapidly from the sampling medium. Chang *et al.* (2007) measured dermal exposure using an interception sampler with two layers of charcoal cloth fixed to an impervious backing that was attached to the skin of dockyard spray painters. The authors measured exposure to ethyl benzene and xylene for workers inside and outside “spraying blocks” over 2-hour periods. The average whole body exposure was equivalent to 282 and 153 μg/cm^2/min for ethyl benzene and xylene inside blocks, respectively, and 49 and 30 μg/cm^2/min, respectively, outside blocks.

As Cherrie (2008) pointed out, any solvent from paint droplets that land on the skin is likely to evaporate before it is taken up through the skin, with only a small proportion

diffusing through the stratum corneum and being available for systemic distribution. However, solvent in droplets that landed on the charcoal pads used by Chang *et al.* (2007) would have been almost completely adsorbed onto the sampler. This results in an overestimation of actual dermal exposure, which is a reported limitation of this dermal sampling methodology. Based on the data by Chang *et al.* (2007), there would have been about 0.3 kg whole body dermal exposure to xylene, and a similar mass of ethyl benzene.

Some researchers have developed models to estimate dermal exposure (Brouwer *et al.*, 2001a; Semple *et al.*, 2001). The former study presented a model for deposition of paint aerosol that provided a reasonably good rank correlation with measured exposure, although it tended to overpredict the actual level of exposure. The latter study extended the model to calculate the flux of solvent through the stratum corneum and thus the total dermal uptake, and provided a demonstration of the modelling approach for spray painters using a xylene-based paint. The painter was assumed to have been wearing a cotton overall with his sleeves rolled up to the elbows, no gloves or respiratory protective equipment, leaving his forearms, hands, head and face uncovered. The average airborne xylene concentration was assumed to be 100 ppm (441 mg/m^3), and the task to continue for 10 minute. In this example, approximately 12% of the xylene burden was estimated to be received dermally. In a range of work scenarios investigated with this model, the highest dermal contribution to total exposure (58%) occurred in a simulation where the painter wore respiratory protective equipment.

This methodology was applied in an epidemiological study of dockyard painters to estimate both inhalation and dermal exposure to a range of solvents (Semple *et al.*, 2000; Dick *et al.*, 2002). Dermal exposure generally contributed a small fraction of total solvent exposure, with about 75% of subjects having less than 10% of their solvent exposure from skin exposure, and about 95% having less than 20% of their exposure by the dermal route (Semple, 2002).

(d) Comparison of inhalation and dermal exposures

As detailed above, there are good theoretical reasons for believing that inhalation and dermal exposures are correlated. For spray painting the volume of paint sprayed is likely to be the main determinant of the air concentration and the amount of paint aerosol depositing on the worker's skin or clothing (Semple *et al.*, 2001). Similar considerations would apply to brush or roller application although it would be expected that the association between inhalation and dermal exposure would be less strong because the process of aerosolization is less consistent. In all cases, direct contact with paint applied to surfaces or with the paint source will tend to reduce the association between inhalation and dermal exposure.

The relationship between inhalation and potential dermal exposure was investigated by Links *et al.* (2007) during application and removal of antifouling paint. They found that the correlation between dermal exposure and inhalation exposure was relatively high for spraying (Pearson correlation coefficient, 0.46 to 0.80 depending on the body part).

However, it was poorer for roller application of paint (–0.03 to 0.60), and paint filling (–0.13 to 0.77).

Pronk *et al.* (2006b) found that in autobody repair workshops there was an association between airborne concentration and dermal exposure. However, most of the workers wore respiratory protection when spraying and about 50% when mixing so that their actual inhalation uptake would have been much lower than that measured.

In the study mentioned above, Chang *et al.* (2007) also undertook biological monitoring of methyl hippuric acid and mandelic acid in urine. The average increase of methyl hippuric acid over a work shift was 61.4 mg/g creatinine. Jacobson & McLean (2003) calculated that this level of methyl hippuric acid increase would be consistent with airborne exposure to about 4 ppm xylene, which is similar to the levels Chang *et al.* (2007) measured inside the respirators worn by the painters (i.e. average 1.2 ppm). These data suggest that the urinary metabolites may result from exposure by inhalation and that the dermal exposure contributed the equivalent of 2–3 ppm of inhaled vapour for xylene and a similar level for ethyl benzene.

Chang *et al.* (2007) also found a strong correlation between ambient air concentration and dermal exposure to xylene, which is indicative that the dermal samplers were strongly influenced by the air concentrations of the solvents or paint aerosol.

1.5 Biomarkers of exposure

Biological monitoring provides an insight into the exposure received by workers from all routes, including inhalation and skin contact. However, to obtain an insight into the relative contributions from these routes of exposure, it is necessary to have some data on inhalation exposure levels and dermal exposure levels. Biological monitoring can also provide information about the effectiveness of personal protective equipment. Biomonitoring studies generally use one or two analytes to act as markers of exposure to the complex mixture of substances that make up the paint.

1.5.1 *Benzene, toluene and xylene*

In Poland, phenol and hippuric acids were measured in 51 urine samples from shipyard painters working in small spaces within the ship superstructure and in large holds. The average values of phenol in urine were 12.4–66.4 mg/L compared to 7.9 mg/L on average for a control group. Urinary phenol was attributed to benzene: the benzene concentration in air ranged from undetectable to 11 ppm (35 mg/m^3). The average concentrations of hippuric acids in urine (sum of hippuric and methyl hippuric acids) were in the range of 1812–5500 mg/L compared to 790 mg/L in a control group. Concentrations of toluene and xylene in air were 7 to 88 ppm (26–332 mg/m^3) and 23–538 ppm (100–2335 mg/m^3), respectively (Mikulski *et al.*, 1972). Elevated values of hippuric acid (up to 6700 mg/L) and methyl hippuric acid (up to 7100 mg/L) were also measured in the urine of shipyard workers in Japan (Ogata *et al.*, 1971).

Several biomonitoring studies among painters have focused on exposure to toluene. Apostoli *et al.* (1982) measured the exposure of 20 workers employed in painting and hand-finishing in an art furniture factory. Inhalation exposure concentrations of toluene were in the range of 10–200 mg/m^3. Alveolar toluene concentrations were significantly correlated with environmental toluene concentrations (r = 0.62). Duydu *et al.* (1999) studied furniture workers involved with painting. They measured urinary hippuric acid and compared the data with inhalation exposure levels. The 8h-TWA air toluene concentration in the two painting areas were 44 and 66 ppm, and the corresponding urinary hippuric acid concentrations were 0.79 and 1.1 g/g creatinine.

Katsuyama *et al.* (1998) studied the exposure of shipyard painters to toluene and xylene while working in very confined spaces. Air concentrations were high in six of the 14 workplaces where monitoring was undertaken, i.e. the exposure to the total mixture of solvents in air exceeded the combined occupational exposure limit. Urinary excretion of hippuric acid and methyl hippuric acid in the highly exposed painters varied at the end of the shift from 0.07 to 0.92 (geometric mean, 0.22) g/g creatinine and from 0.02 to 0.42 (geometric mean, 0.11) g/g creatinine, respectively. Based on the study by Loizou *et al.* (1999), exposure to 50 ppm xylene would be expected to result in the excretion of about 1.25 g/g creatinine of methyl hippuric acid at the end of the exposure period. Concentrations of toluene and xylene in the end-of-exhale air varied from <0.1 to 5.0 ppm and <0.1 to 10.6 ppm, respectively. The biological monitoring data were lower than that expected from inhaling the high concentrations prevalent in these workplaces, which was because the workers wore either a chemical cartridge respirator or a “body-mounted gas mask” (breathing apparatus).

Krämer *et al.* (1999) measured exposure levels to inhaled xylene plus concentrations of blood xylene and urinary methyl hippuric acid in a group of paint manufacturers and a group of paint sprayers. Average xylene air concentrations for sprayers were 8 ppm (3 to 21 ppm) and the corresponding average concentrations of xylenes in blood were 130 µg/L (49 to 308 µg/L). They also excreted on average 485 mg/L (range 65–1633 mg/L) methyl hippuric acid in their urine.

1.5.2 *Isocyanates*

Several researchers have used biological monitoring to evaluate exposure to isocyanates from spray painting. Williams *et al.* (1999) developed a method for measuring HDI in the urine of exposed workers, based on an analysis of hexamethylene diamine by gas chromatography-mass spectrometry (GC-MS). They measured exposure in 22 workers associated with paint spraying in automobile repair: 11 sprayers who wore respiratory protection, three bystanders and eight unexposed people. Hexamethylene diamine was detected in four sprayers and one bystander. No hexamethylene diamine was detected in the urine of the unexposed subjects. The detectable levels were in the range of 1 to 12 µmol/mol creatinine.

Pronk *et al.* (2006b) also analysed urinary hexamethylene diamine levels in autobody workshop workers and industrial painters. A total of 36% of the autobody workshop workers and 10% of the industrial painters had detectable levels of hexamethylene diamine in their urine. Positive samples were found in all groups of workers present in the autobody workshops, including welders, bystanders and office workers. Workers spraying paint wore respiratory protection but less consistently wore gloves (40% in autobody repair shops and 75% in industrial painting companies). For the autobody workshop workers, wearing gloves significantly decreased the odds ratio for having a urine sample positive for hexamethylene diamine (OR, 0.22; 95% CI: 0.09–0.57).

Creely *et al.* (2006b) measured inhalation exposure and all urinary isocyanate metabolites (methylenedianiline; 2,4-toluene diamine; 2,6-toluene diamine; 1,6-hexamethylene diamine; and isophorone diamine) in a wide range of work situations, including spray painting and roller application of paints. Overall, the geometric mean total isocyanate metabolite level for the data set was 0.29 mmol/mol creatinine (range 0.05–12.64 mmol/mol creatinine). Hexamethylene diamine was the most commonly detected metabolite in the urine samples. The geometric mean total isocyanate metabolite level for roller painting was 0.39 mmol/mol creatinine, and for spray painting, 0.29 mmol/mol creatinine. Inhalation exposure concentrations were low (geometric mean of 1 $\mu g/m^3$ for both painting operations), and the spray painting workers wore respiratory protection and gloves. The authors suggested that dermal exposure, and possibly ingestion, were important contributors to total exposure.

1.5.3 *Other solvents*

Kawai *et al.* (2003) investigated unmetabolized methyl isobutyl ketone and methyl ethyl ketone in the urine of workers in a furniture factory where spray painting and gluing were performed. The correlation between inhalation exposure concentration and the concentration of the corresponding solvent in the end-of-shift urine sample was significant both for methyl isobutyl ketone and for methyl ethyl ketone ($r = 0.98$ and 0.79, respectively). The authors calculated that approximately 0.12% of methyl isobutyl ketone inhaled would be excreted into the urine, and approximately 0.19% of the inhaled methyl ethyl ketone.

Exposure to ethylene glycol monoethyl ether acetate was assessed in two groups of shipyard painters: a “low” exposure group mostly involved with brush painting and other duties ($n = 27$), and a “high” exposure group involved with spraying or assisting with the spraying ($n = 30$), along with an unexposed control group ($n = 41$) (Kim *et al.*, 1999). Workers in the high-exposure group wore half-mask respirators while the other workers only occasionally wore respiratory protection. Urinary ethoxyacetic acid and methyl hippuric acid was measured for all subjects. The mean and range of inhalation ethylene glycol monoethyl ether acetate exposure concentrations were 3.03 ppm (not detectable to 18 ppm) and 1.76 ppm (not detectable to 8.1 ppm) for the high and low groups, respectively. The geometric mean concentrations of methyl hippuric acid in the three

exposure groups were 0.08, 0.03, and 0.01 g/g creatinine; the corresponding values for ethoxyacetic acid were 9.2, 0.6, and 0.1 mg/g creatinine. The authors noted that the levels of ethoxyacetic acid that they had measured were lower than in another study of shipyard painters, which they suggested may be due to the wearing of respiratory protection and percutaneous absorption.

Laitinen & Pulkkinen (2005) measured the inhalation exposure to 2-(2-alkoxy)ethoxy ethanols and urinary 2-(2-alkoxyethoxy)acetic acids in a group of floor lacquerers ($n = 22$). The 8-hour average inhalation exposures of floor lacquerers to 2-(2-methoxyethoxy)ethanol, 2-(2-ethoxyethoxy)ethanol and 2-(2-butoxyethoxy)ethanol were on average 0.23 ppm, 0.08 ppm, and 0.05 ppm, respectively. The excretion levels of the corresponding metabolites 2-(2-methoxyethoxy)acetic acid, 2-(2-ethoxyethoxy)acetic acid and 2-(2-butoxyethoxy)acetic acid were on average 4.9 mmol/mol creatinine, 9.3 mmol/mol creatinine, and 9.2 mmol/mol creatinine, respectively. A linear relationship was found between the urinary 2-(2-alkoxyethoxy)acetic acid concentrations and the inhalation exposure to 2-(2-alkoxyethoxy)ethanol.

1.5.4 *Polycyclic aromatic hydrocarbons*

Paints containing coal tar are used in shipyards, for example in South Korea, and they account for 13% of all shipyard paints used. Lee *et al.* (2003) used urinary 1-hydroxypyrene glucuronide as a marker of exposure to polycyclic aromatic hydrocarbons (PAHs) in three groups: 111 painters using coal-tar paints, 70 painters using general paints, and 27 on-site controls who used no paint. Average urinary 1-hydroxypyrene glucuronide levels for the group exposed to coal-tar paints was 2.24 μmol/mol creatinine, for general painters 1.38 μmol/mol creatinine, and for the controls 0.62 μmol/mol creatinine. The elevated 1-hydroxypyrene glucuronide in general painters was attributed to bystander exposure from working alongside coal-tar painters and from low levels of PAHs in general paints.

1.5.5 *Metals*

Higher blood lead levels have been measured in painters involved in paint removal using sand blasting or other mechanical means (Jarrett, 2003). Blood lead levels in 21 workers in two autobody workshops were in the range of 2–38 μg/dL (Enander *et al.*, 2004). The highest levels were found in workers who were involved in sanding painted surfaces and who ate, drank or smoked cigarettes in areas contaminated with lead dust.

Saito *et al.* (2006) reported results of blood lead monitoring carried out between 1990 and 2000 from more than 7500 workers in 259 lead-handling facilities in Japan. The mean concentration for 82 people painting or baking was 5.4 μg/dL (range 1.4–21.1 μg/dL), which was one of the lowest for the groups of workers studied.

Kiilunen (1994) reported the results from a large database of urinary metal concentrations made by the Finnish Institute of Occupational Health between 1980 and 1989; 9377 urinary chromium and 3172 urinary nickel analyses were made. The mean end-

shift urinary chromium level among the 265 painters in the database was 0.04 μmol/L with 95% of the results being less than 0.12 μmol/L. The corresponding values for urinary nickel were 0.3 and 0.61 μmol/L, although in this case there were only 10 workers for whom data were available.

1.6 Personal protective equipment

Wearing of clothing and gloves protects the skin from paint, and the use of respiratory protection may reduce inhalation exposure. Normal work clothing or gloves will substantially reduce contact of the skin with solid components in paints and can reduce contact of liquids with the skin. However, volatile liquids will permeate through some relatively impervious materials such as rubber, and to obtain effective protection, it is important to carefully select the protecting material according to the chemical properties of the paint ingredients.

Respiratory protection is generally not widely used by painters. The main exceptions have been situations where painters have used solvent-based paints in confined spaces, e.g. in some shipyard applications, or where relative hazardous compounds are used in the paint formulation. The appropriate respiratory protection must be carefully selected to ensure that the filter/adsorbent removes all contaminants present in each work situation.

The Assigned Protection Factor for respirators and protective clothing is a measure of the reduction in exposure that might be expected from properly wearing a personal protective device (Brouwer *et al.*, 2001b). For example, a device with an Assigned Protection Factor of 4 would reduce exposure by 4 times, e.g. to 25% of what it otherwise might have been. For respiratory protection, the authorities in the United Kingdom recommend Assigned Protection Factors from 4 to 40 for different designs of respiratory protection, with the lower factors for half-mask respirators, and the higher values for power-assisted full-face devices. Other authorities recommend higher protection factors based on the results from laboratory tests. Studies of the effectiveness of personal protective equipment in real work situations have shown that protection is lower than achieved under laboratory conditions. This is explained by the workers either not wearing the equipment sufficiently carefully or for the whole period of exposure. Similarly, biological monitoring studies that have assessed the potential reduction in exposure from wearing respirators or protective gloves have shown that, in general, the protection factors are lower than expected. This may in part be due to exposure by skin contact or because the workers do not wear the respirators for all tasks.

1.6.1 *Respiratory protection*

Liu *et al.* (2006) investigated 36 autobody repair workshops to assess the quality of their respiratory protection, and to investigate the protection factors for the respirators in use. Only about a third of workshops had a written respiratory protection programme. For 22 painters, air samples were obtained from inside and outside air-purifying half-facepiece

respirators with organic vapour cartridges and paint prefilters to assess the Workplace Protection Factor during spray-painting and priming activities. The samples were analysed for isocyanate concentration as NCO. The geometric mean Workplace Protection Factor of total NCO was 319 (geometric standard deviation (GSD), 4) and the 5th percentile was 54. The Workplace Protection Factor was positively correlated with the duration of painting task.

Bolsover *et al.* (2006) assessed the Workplace Protection Factor for air-fed visors, which are commonly used for protection against exposure to airborne isocyanates during paint spraying. They did not consistently measure any contamination inside the mask, but the external contaminant concentrations were generally quite low, making an accurate determination of the protection difficult. The median Workplace Protection Factor was between about 100 and 200 depending on the assumption of detection limit for the measurement method.

Vitayavirasuk *et al.* (2005) measured inhalation exposures and biological monitoring of lead, cadmium and chromium levels in automobile spray painters. The workers were divided into two groups, those who wore an aerosol-removing respirator while spraying and those who did not (Table 1.13). On-site observations revealed that improper use of the respirator, lack of an isolated spraying room, and poor personal hygiene habits, i.e. resulting in inadvertent ingestion exposure, resulted in the respirators being ineffective.

Vincent *et al.* (1994) measured the exposure of painters to ethylene glycol mono ethyl ether acetate during the painting of an aircraft. The workers wore gloves, boots and an apron, and a charcoal-based filtering respirator while spraying. The inhalation exposure to ethylene glycol monoethyl ether acetate was measured along with an assessment of internal exposure to ethylene glycol monoethyl ether acetate by measuring its urinary metabolite, ethoxy acetic acid. Ethylene glycol monoethyl ether acetate concentrations were in the range of 29–150 mg/m^3. The average urinary ethoxy acetic acid concentrations were 108 mg/g creatinine in pre-shift and 139 mg/g creatinine in post-shift samples. Despite the workers wearing respiratory protective equipment during paint spraying, the ethoxy acetic acid urinary concentrations were high and the authors suggested that dermal uptake was the main route of exposure for ethylene glycol monoethyl ether acetate.

1.6.2 *Gloves and clothing*

Some measure of the protection afforded by gloves that is often used is the "breakthrough time," i.e. the time from initial use until the contaminant is detected inside the glove. For example, Liu *et al.* (2007) demonstrated that latex gloves worn while using polyurethane paints in autobody workshops were ineffective at preventing dermal exposure to isocyanates, although a nylon coverall was. Pronk *et al.* (2006b) showed that by selecting the appropriate type of gloves, the chance of spray painters having a positive urinary sample for isocyanate was substantially reduced.

Chang *et al.* (2004) defined a Protective Effectiveness Index (PEI) as a measure of the protection afforded by gloves. The authors used the urinary and plasma metabolite levels

from workers who wore gloves (cotton and butyl rubber) compared with the levels from those who did not to assess the protective effectiveness in workers exposed to 2-methoxyethanol. Cherrie (2004) calculated that the protection factor for these butyl rubber gloves would be about 4 (PEI of 74%); for the cotton gloves, 1.1 (PEI of 11%) for "special" workers who had high 2-methoxyethanol exposure, and 0.85 (PEI of –17%) for "regular" workers. The protection factor for butyl rubber gloves appeared to be particularly low in comparison with what might have been expected, suggesting that other factors were reducing the effectiveness of these gloves. Zellers *et al.* (1992) found that this type of glove from the same manufacturer provided up to 4 hours' protection against 2-methoxyethanol without any breakthrough.

For most volatile agents, uptake through the skin from the vapour phase is negligible. However, Shih *et al.* (2000) investigated uptake of 2-methoxyethanol from vapour. Volunteers were exposed to 300 ppm or 25 ppm 2-methoxyethanol. Uptakes during a 4-hour period were 65 mg and 7 mg, respectively, with corresponding uptake rates of 13.2 $\mu g/cm^2/hr$ and 1.36 $\mu g/cm^2/hr$. The authors concluded that vapour absorption through skin is a significant contributor to overall glycol ether exposure, which is substantiated by other studies (WHO, 2006).

1.7 Regulations

Regulations concerning the work environment for the painters, which include the national OELs for specific agents in paint, are not covered in this monograph. These limits usually take into account not only health issues, but also economic concerns, and technological feasibility to control exposure.

Product regulations deal with restrictions on hazardous materials. In 1998, The Federal Environmental Protection Agency (EPA) in the USA developed final rules for national VOC emission standards for architectural coatings and for automobile refinish coatings (EPA, 1998a,b). These rules set limits to the VOC content of 61 architectural and seven automobile-coating categories. The regulations do not apply to coatings supplied in nonrefillable aerosol containers. Further, the regulations do not apply to architectural paints sold in containers less than 1 litre, or to automobile topcoats or their components. In southern California, an analogous regulation set more stringent limits to the VOC content of architectural coatings than that of the Federal standards (Rule 1113 on architectural and maintenance coatings).

Legislation that limits the VOC content of decorative paint or restrict the use of high-VOC paints exist in Denmark, Sweden, and the Netherlands (European Community, 2000). In the Netherlands, a legal ban on high-VOC paint for interior use by professional painters came into force in 2000. The maximum VOC content for interior paint is 60 g/L for wall paints, and 100 g/L for other paints (European Community, 2000).

In April 2004, the European Union published the Directive 2004/42/CE of the European Parliament and of the Council on the limitation of the emissions of VOCs due to the use of organic solvents in certain paints and varnishes and vehicle refinishing products (European Union, 2004). These were to come in over two phases commencing January

2007 and January 2010. Maximum VOC content limit values are set for 12 subcategories of both water-based and solvent-based paints and varnishes. They are coatings applied to buildings, their trim and fittings, and associated structures for decorative, functional and protective purpose. Maximum VOC content limit values for vehicle-refinishing products are set for five subcategories of products used for the coating of road vehicles carried out as part of vehicle repair, conservation or decoration outside of manufacturing installations. VOC means any organic compound having an initial boiling point below or equal to 250°C measured at a standard pressure of 101,3 kPA.

The EC Regulation No 1907/2006 (Annex XVII) (European Union, 2006) relates to restrictions on the marketing and use of certain dangerous substances and preparations. Several of the agents listed are of relevance for paint products:

• Benzene shall not be used in concentrations equal to, or greater than, 0.1% by mass in substances or preparations placed on the market.

• Lead carbons and lead sulfates shall not be used as substances and constituents of preparations intended for use as paints, except for the restoration and maintenance of works of art and historic buildings.

• Mercury and arsenic compounds shall not be used as substances and constituents of preparations intended for use to prevent the fouling by microorganisms, plants or animals of the hull of boats, equipment used for fish farming and on any totally or partly submerged appliances or equipment.

• Organostannic compounds shall not be placed on the market for use as substances and constituents of preparations when acting as biocides in free association paint or to prevent the fouling by microorganisms, plants or animals.

• Cadmium shall not be used to give colour to paint. In any case, the cadmium content may not exceed 0.01% by mass. However, if the paint has a high zinc content its residual concentration of cadmium shall be as low as possible and at all events not exceed 0.1% by mass.

• Metallic coating; deposit or coating of metallic cadmium on a metallic surface are prohibited in some specific sectors such as equipment and machinery for food production and agriculture.

• Substances which appear in Annex I to Directive 67/548/EEC classified as carcinogen, mutagen or toxic to reproduction in categories 1 or 2 shall not be used in substances and preparations placed on the market for sale to the general public in individual concentration equal to or greater than specified in Council Directives. The provision does not apply to artists' paint covered by Council Directive 1999/45/EC.

The US Consumer Product Safety Commission has declared that paint and similar surface-coating materials for consumer use that contain lead or lead compounds and in which the lead content is in excess of 0.06 percent of the weight of the total nonvolatile content of the paint or the weight of the dried paint film are banned hazardous products (16 CFR Part 1303). In addition to those products which are sold directly to consumers, the ban applies to products which are used or enjoyed by consumers after sale, such as paints used in residences, schools, hospitals, parks, playgrounds, and public buildings or other areas

where consumers will have direct access to the painted surface. Paints and coatings for motor vehicles are not covered by the ban. Artists' paints are also exempt from the regulation (US CPSC, 2001).

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2. Studies of Cancer in Humans

2.1 Cohort, record linkage and proportionate mortality studies

2.1.1 *Background*

In 1989, the International Agency for Research on Cancer (IARC) classified painting as an occupation as *carcinogenic to humans* (Group 1) (IARC, 1989, Volume 47). At the time, the epidemiological evidence for the evaluation was primarily based on a total of eight studies (five record linkage and three cohort studies), listed in Table 23 of that volume. The primary findings in these data were relatively consistent excesses for all cancers (standardized mortality ratio [SMR] 1.21, 9100 cases), and for cancer of the lung (SMR 1.41, 468 cases). The lung cancer excess was noted to be above what could reasonably be expected to be due to confounding by smoking. Other findings which drew comment in Volume 47 were excesses for cancers of the oesophagus, stomach, and bladder, although these excesses were smaller than for cancer of the lung and were less consistent across studies. It was noted that results from a few studies showed excesses of leukaemia, and cancers of the buccal cavity, and of the larynx.

Cohort studies generally represent a stronger study design than record linkage studies. In the latter, the exposure is often taken from census employment data, is typically less accurate than the employment records upon which cohort studies are usually based, and does not usually take into account duration of employment. However, in the case of the cohort and record linkage studies listed in Table 23 by IARC in 1989, findings from both types of studies were reasonably consistent.

2.1.2 *Cohort studies since IARC Monograph Volume 47* (Table 2.1)

Yin *et al.* (1987) studied workers who were employed at least 6 months within different factories in the People's Republic of China. They compared 13 604 benzene-exposed painters to 28 257 production workers without occupational benzene exposure with a similar sex and age distribution. Mortality follow-up occurred from 1972–1981, and the authors presented the leukaemia mortality rates separately for painters (15.9/100 000 person–years) and the comparison cohort (2.01/100 000 person–years). [The painters, not including paint-production workers, had a mortality rate ratio of [7.9] (14 leukaemia deaths) compared to workers in other production jobs without benzene exposure (four leukaemia deaths). This high rate ratio is presumably due to the selection of these painters for specifically benzene exposure.] No other cancer outcomes were presented.

Hrubec *et al.* (1995) followed a cohort assembled from a roster of approximately 300 000 caucasian, male WWI and WWII veterans for mortality from 1954–1980. These

men served in the US Armed Forces at some time during 1917–1940, and held active government life insurance policies. Personal data on usual occupation and smoking habits were obtained by mailed questionnaire in the 1950s. SMRs were calculated using Poisson regression, using all other occupations as the reference. After adjustment for smoking, age and calendar time, 1178 construction and maintenance painters had an SMR for all cancers of 1.0 (90% CI: 0.84–1.11, based on 140 cancer deaths). Cancer mortality was not remarkable for most anatomical sites. For anatomical sites with more than five deaths, the SMRs were 0.8 (90% CI: 0.42–1.61; six deaths) for cancer of the stomach, 1.0 (90% CI: 0.69–1.51; 18 deaths) for cancer of the colon, 1.6 (90% CI: 0.89–2.86; eight deaths) for cancer of the rectum, 1.1 (90% CI: 0.84–1.47; 36 deaths) for cancer of the respiratory system, 0.5 (90% CI: 0.27–0.78; ten deaths) for cancer of the prostate, 0.9 (90% CI: 0.48–1.67; seven deaths) for lymphoma, and 1.2 (90% CI: 0.69–2.10; nine deaths) for leukaemia. A smaller number of non-construction painters (n = 140) provided little extra information on cancer mortality owing to the small numbers involved.

Alexander *et al.* (1996) conducted a cohort study of 2429 chromate-exposed workers in the aerospace industry, of whom 62% had ever worked as a painter. A total of 15 cases of lung cancer were observed among the entire cohort, which was less than expected based on incidence data (SIR, 0.8; 95% CI: 0.4–1.3). No exposure–response trends with hexavalent chromium was seen, although the number of cases of lung cancer were too small to draw any meaningful conclusions. There was an inverse trend of lung cancer with duration of employment for painters, although sanders and polishers (exposed to dusts rather than mists) had a somewhat positive trend with duration. None of these results were statistically significant.

van Loon *et al.* (1997) conducted a population-based cohort study in the Netherlands that prospectively followed 58 279 men, aged 55–69 years, for cancer incidence from 1986–1990. Rate ratios were estimated by a case–cohort analysis (524 cases, 1630 non-cases in the subcohort). Self-reported lifetime job history, reviewed by experts on a case by case basis, was used to create a job exposure matrix (JEM) for exposure to paint dust (none, low, high). Positive non-significant increases in lung cancer were found for the 'low' exposed group (RR, 2.29; 95% CI: 0.61–8.63) and the 'high' exposed group (RR, 2.48; 95% CI: 0.88–6.97) compared to the unexposed group, after adjustment for age, smoking, diet, and other occupational exposures; although the test for trend was significant ($P < 0.01$). [This study was limited owing to the small sample size (14 'high' and '4' low exposed lung cancer deaths) and the use of a JEM to assign exposure level based on self-reported employment information.]

Boice *et al.* (1999) conducted a retrospective cohort study among 77 965 aircraft industry employees in California (1216 painters), employed for at least one year on or after 1960, with registry-linked mortality follow-up through 1996. There was little detail available on the type of painting done, except that the paints contained chromates. There were 101 cancer deaths among painters (all cancer SMR, 0.87; 95% CI: 0.71–1.06). The SMR for cancer of the lung was 1.11 (95% CI: 0.80–1.51; 41 deaths).

Table 2.1. Cohort, linkage and proportionate mortality studies of painters published since Monograph Volume 47, 1989

Reference, location, time period	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95% CI)	Adjustment for potential confounders	Comments
Yin *et al.* (1987) China	13 604 benzene-exposed workers in China employed in factories ≥ 0.5 yrs during 1972-81; leukaemia mortality follow-up 1972-81; controls were 28 257 workers not occupationally exposed to benzene	Information on occupational history, history of benzene poisoning, working conditions and workplace atmospheric benzene concentrations were collected from factory records.	Leukaemia			Mortality rate ratio = 7.9	None; controls had similar age and sex distributions	Compared to benzene-unexposed workers
				Painters (not including paint producers)	14	Mortality rate: 15.9/100 000 person-years		
				Benzene-unexposed workers	4	Mortality rate: 2.01/100 000 person-years		
Hrubec *et al.* (1995) USA 1954–80	1178 painters were followed during 1954–80 within a cohort assembled from a roster of approximately 300 000 white male WWI veterans who served in the US Armed Forces some time during 1917–40 and who held active government life insurance policies	Mailed questionnaire that inquired about tobacco use, usual industry of employment and occupation, coded using 1950 Census Occupation and Industry codes		Construction and maintenance painters		**SMR (90% CI)**	Smoking, age, calendar time	Usual occupation was recorded
			Respiratory system		36	1.1 (0.84–1.47)		
			Stomach		6	0.8 (0.42–1.61)		
			Colon		18	1.0 (0.69–1.51)		
			Rectum		8	1.6 (0.89–2.86)		
			Prostate		10	0.5 (0.27–0.78)		
			Lymphoma		7	0.9 (0.48–1.67)		
			Leukaemia		9	1.2 (0.69–2.10)		

Table 2.1 (contd)

Reference, location, time period	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95% CI)	Adjustment for potential confounders	Comments
Alexander *et al.* (1996) Seattle, WA, USA 1974–94	2429 chromate exposed workers employed ≥6 months in the aerospace industry during 1974–94 were assembled from company work-history records; 62% had ever worked as a painter; incidence follow-up 1974–94 with linkage to the SEER registry; median 42 yrs of age	Exposure to chromium [VI] was estimated from industrial hygiene measurements and work-history records; cumulative exposure to chromium [VI] = years in each job x TWA for each exposure category	Lung			**SIR (95% CI)**	Standardized by age, race, gender and calendar time using the Puget Sound population during 1974–94 as reference	No information on smoking; no trend with cumulative exposure to chromium (VI) but slightly positive trend with duration of employment as a sander/polisher; small numbers preclude conclusions
				Entire cohort	15	0.8 (0.4–1.3)		
				Years worked as a painter				
				0	9	1.1 (0.5–2.0)		
				<5	3	0.8 (0.2–2.4)		
				≥5	3	0.4 (0.1–1.2)		
van Loon *et al.* (1997) the Netherlands 1986–90 Europe	58 729 men, aged 55–69 yrs, enrolled from the general Dutch population and followed for lung cancer incidence from 1986–90 by linkage to national and regional registries	Paint exposure was obtained from job history as part of a self-administered questionnaire and case by case expert assessment	Lung	Low exposure to paint dust	4	2.29 (0.61–8.63)	Age, other occupational exposures, smoking habits and dietary intake of vitamin C, beta-carotene and retinol	No paint exposure was the reference; cumulative probability of exposure = probability x duration of exposure
				High exposure to paint dust	14	2.48 (0.88–6.97)		
				P value for trend		<0.01		

Table 2.1. (contd)

Reference, location, time period	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95% CI)	Adjustment for potential confounders	Comments
Boice *et al.* (1999) Lockheed Martin Plant Burbank, Los Angeles county, California, USA 1960–96	1216 painters (1139 men, 77 women) employed ≥1yr in the aircraft industry, followed-up retrospectively for mortality	Detailed job history was obtained from work-history records		Painter		**SMR (95% CI)**	Age, sex, race, calendar year	Other cancer causes non-informative due to small numbers of deaths; painting not described in detail except that paints contained chromates
			Lung		41	1.11 (0.80–1.51)		
			Oesophagus		21	0.61 (0.07–2.20)		
			Liver		1	0.36 (0.01–2.03)		
			Non-Hodgkin lymphoma		3	0.72 (0.15–2.12)		
			Multiple myeloma		4	1.70 (0.46–4.35)		
			Leukaemia		3	0.74 (0.15–2.16)		
Steenland & Palu (1999) California, Missouri, New York, Texas, USA 1975–94	42 170 painters and 14 316 non-painters with ≥1 yr union membership were identified from union records and followed from 1975–94 by linkage to national and local registers; Restricted to white men (98% of the cohort).	Job titles were inferred from union membership records which identified the specialty affiliation and trade of the local union for all members		Painter		**SMR (95% CI)**	Restricted to caucasian men (98% of the cohort). Stratification by age and calendar time	No information on trade of individual members; SMRs compared painters to the general US population; SRRs compared painters to non-painters
			All cancers		4674	1.12 (1.09–1.15)		
			Lung		1746	1.23 (1.17–1.29)		
			Bladder		166	1.23 (1.05–1.43)		
			Stomach		197	1.39 (1.20–1.59)		
			Liver		119	1.25 (1.03–1.50)		
			Pharynx		49	1.15 (0.85–1.52)		
			Oesophagus		110	1.12 (0.92–1.35)		
			Larynx		48	0.97 (0.71–1.29)		
			Non-Hodgkin lymphoma		137	1.06 (0.89–1.25)		
			Hodgkin disease		16	1.30 (0.74–2.11)		
			Multiple myeloma		64	0.97 (0.75–1.24)		
			Leukaemia		138	0.92 (0.78–1.11)		

Table 2.1. (contd)

Reference, location, time period	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95% CI)	Adjustment for potential confounders	Comments
Zeegers *et al*. (2001) Netherlands 1986–92	58 729 men, aged 55–69 yrs, were enrolled from the general Dutch population and followed for bladder cancer incidence from 1986–92 by linkage to national and regional registries	Paint exposure was obtained from job history as part of a self-administered questionnaire and case by case expert assessment	Bladder	No paint exposure Low Medium High	483 8 20 19	1.00 (reference) 0.75 (0.33–1.72) 1.78 (0.94–3.37) 1.31 (0.72–2.40)	Age, other occupational exposures, and cigarette smoking amount and duration	Same Dutch cohort as that described in van Loon *et al*. (1997)
Zeegers *et al*. (2004) Netherlands 1986–92	58 729 men, aged 55–69 yrs, were enrolled from the general Dutch population and followed for bladder cancer incidence from 1986–92 by linkage to national and regional registries	Paint exposure data obtained from job history as part of a self-administered questionnaire, and job titles were coded using the Dutch Occupation Classification system	Prostate	Ever painter Painter as one's usual occupation	12 7	1.10 (0.39–3.08) 1.28 (0.31–5.30)	Age, diet, cigarette and alcohol use, family history of prostate cancer, education and physical activity	Same Dutch cohort as that described in van Loon *et al*. (1997)
Linkage studies								
Malker *et al*. (1987) Sweden 1961–79	1960 Swedish census linked to the Swedish Cancer Registy to follow-up for bladder cancer incidence from 1961–79	Occupations and industries obtained from the 1960 census and coded using ILO standards.	Bladder	Painter as one's specific occupation Artistic painter	186 42	**SIR (*P*-value)** 1.0 (not given) 1.7 ($P<0.01$)	Age, sex, region	No adjustment for smoking. The census code not given for 'artistic painters' and thus may correspond to the Swedish 'pictorial artists' studied in Brown *et al*. (2002)

Table 2.1. (contd)

Reference, location, time period	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95% CI)	Adjustment for potential confounders	Comments
Carstensen *et al.* (1988) Sweden 1961–79 Scandinavia	1 622 547 Swedish men in the 1960 national census, aged 30–64 years and gainfully employed, were linked to the Swedish Cancer Registry and followed for cancer incidence from 1961–79	Occupations and industries were obtained from the 1960 census and coded using ILO standards. Smoking data were obtained from a large survey among an age-stratified random sample of the Swedish population in 1963	Lung	Painters and paperhangers	425	**SIR (95% CI)** 1.01 (0.88–1.16)	Indirect smoking adjustment. SIRs were standardized using the age and residential distribution in the total population	It is likely that paperhangers work in the same job environment as painters or may also paint, and it is reasonable to consider this category as a whole as ‘painters’. This study population overlaps with that of Malker *et al.* (1987)
Lynge & Thygesen (1988) Denmark	Persons aged 20–64 years in the 1970 Danish census linked to the national cancer registry and followed for cancer incidence through 1980	Data on industry and occupation captured in the 1970 census. Industry coded using ISIC codes and occupation coded using a special Danish code.	Pharynx	All painters (n = 19163)	10	2.27 (1.09-4.18)	RRs (SIRs) were age-standardized according to the age distribution of the subcohort	
				Skilled workers, painter in paint workshop (n = 9703)	6	3.30 (1.21-7.18)		
				Self-employed, painter in paint workshop (n = 5150)	3	1.73 (0.34-5.07)		
				Skilled workers, painter in metal industry (n = 2564)	1	1.95 (0.05-10.92)		
				Skilled workers, painter/other industries (n = 1746)	0	NG		

Table 2.1. (contd)

Reference, location, time period	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95% CI)	Adjustment for potential confounders	Comments
Gubéran *et al.* (1989) Switzerland 1971–84	1916 male painters from the 1970 Geneva census were linked to the Geneva Cancer Registry and followed for cancer incidence during 1971–84	Occupational classifications were obtained from the 1970 census				**SIR (90% CI)**	Standardized by sex-, age- and matrimonial status-specific incidence rates of the Geneva population	Regarding non-cancer outcomes, painters showed a significant excess mortality from alcoholism (SMR, 6.25; 90%CI: 2.46–13.14; 5 deaths) and a borderline significant excess mortality from cirrhosis (SMR, 1.59; 90%CI: 0.96–2.49; 14 deaths), suggesting excess alcohol consumption among painters
			All cancers	Painters	159	1.20 (1.05–1.37)		
			Lung		40	1.47 (1.11–1.91)		
			Bladder		13	1.71 (1.01–2.72)		
			Buccal cavity, pharynx (ICD-8, 140-149)		13	1.49 (0.88–2.38)		
			Oesophagus (ICD-8, 150)		2	0.67 (0.12–2.10)		
			Liver		5	1.39 (0.55–2.92)		
			Gallbladder		3	3.75 (1.02–9.69)		
			Larynx (ICD-8, 161)		5	1.14 (0.45–2.39)		
			Testis		5	3.13 (1.23–6.57)		
			Non-Hodgkin lymphoma (ICD-8, 200, 202)		2	0.80 (0.14–2.52)		
			Leukaemia (ICD-8, 204-207)		1	0.43 (0.02–2.06)		
Carstensen *et al.* (1990) Sweden 1961–79	2.1 million men and 820 000 women aged 20–69 years and gainfully employed obtained from the 1960 Swedish population census and linked to the Swedish Cancer Registry to follow for cancer incidence from 1961–79	Occupations and industries obtained from the 1960 census and coded using ISIC and ILO standards	Thyroid			**SIR (*P*-value)**	Indirect standardization by year of birth, year of follow-up, region of residence	The whole population used as the reference. Nearly the same design as used in Carstensen *et al.* (1988) but did not adjust for smoking. This study population overlaps with that of Malker *et al.* (1987)
				Male painters (occupation)	11	0.67 (NG)		
				Male painters (construction industry)	5	0.36 (P<0.05)		

Table 2.1. (contd)

Reference, location, time period	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95% CI)	Adjustment for potential confounders	Comments
Dolin & Cook-Mozaffari (1992) England and Wales 1965–80	Male British painters, aged 25–64, who died from bladder cancer during 1965–80	Information on occupation and industry of usual employment was extracted from death certificates and coded according to British standards	Bladder			**SMR (95% CI)**	Indirect standardization by age and urbanization	Degree of urbanization used as a proxy for smoking data that were unavailable
				All painters	65	1.27 (0.99–1.61)		
				Coach painter	5	7.03 (2.28–16.38)		
				Painter, decorator	57	1.20 (0.93–1.56)		
				Spray painter	3	0.92 (0.19–2.70)		
Firth *et al.* (1993) New Zealand	Male cancer deaths during 1973–86 obtained from the New Zealand Cancer Registry and linked to census data from 1976, 1981, and 1986	Occupation obtained from census data and coded using the New Zealand Standard Classification of Occupations	Multiple myeloma	Painter	NG	**SMR (95%CI)** 3.52 (1.40–7.29)	Standardized by age and social class	Only select findings reported
Skov *et al.* (1993) Denmark 1970–80, Finland 1971–80, Norway 1961–84, Sweden 1961–79 Scandinavia	87 004 economically active, male painters and lacquerers included in the national census of 4 Scandinavian countries were followed-up for cancer incidence by linking individual records with national cancer registries	Painters were identified by combining census codes for occupation and industry		Painter		**SIR (95%CI)**	Standardized by birth cohort, site and sex	Entire census population used as a reference
			Lung		1043	[1.30][1.22–1.38]		
			Mouth (ICD-7, 143-144)		48	[1.51][1.12–2.01]		
			Pharynx (ICD-7, 145-148)		64	[1.43][1.10–1.83]		
			Oesophagus (ICD-7, 150)		98	[1.29][1.05–1.57]		
			Liver		122	[1.11][0.92–1.32]		
			Larynx (ICD-7, 161)		95	[1.05][0.85–1.28]		
			Bladder		380	[1.05][0.95–1.16]		

Table 2.1. (contd)

Reference, location, time period	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95% CI)	Adjustment for potential confounders	Comments
OPCS (1995) England and Wales	29 689 male painters and decorators, aged 20–74 years, who died during 1979–80 or 1982–90, linked to census denominators	Last full-time occupation obtained from death certificates		Painters and decorators		**PMR (95%CI)**	Age, social class	
			Lung		4110	1.12 (1.09–1.16)		
			Oral cavity		75	1.33 (1.03–1.70)		
			Kidney		130	0.77 (0.64–0.91)		
Andersen *et al.* (1999) Denmark 1971–87, Finland 1971–90, Norway 1971–91, Sweden 1971–89 Scandinavia	65 868 male and 2121 female painters and wallpaper hangers, aged 25–64 years at 1970 censuses, were followed-up for cancer incidence during 1987–91 by linkage to national cancer registries	Occupation was obtained from census data and coded according to national adaptations of the Nordic Occupational Classification or according to a special Danish nomenclature		Male painters and wall paper hangers		**SIR (95%CI)**	Standardization by age, gender and time period	National populations as the reference. The Swedish component partly overlaps Brown *et al.* (2002) who also included painters from the 1960 Swedish census. Also overlaps the 4-country study by Skov *et al.* (1993), who reported on fewer cancer sites with shorter follow-up
			All cancers		7070	1.06 (1.03–1.08)		
			Lung		1450	1.22 (1.16–1.28)		
			Pleura		47	1.70 (1.25–2.26)		
			Bladder		566	1.10 (1.01–1.20)		
			Mouth (ICD-7, 143-144)		48	1.21 (0.89–1.60)		
			Pharynx (ICD-7, 145-148)		72	1.31 (1.02–1.64)		
			Oesophagus (ICD-7, 150)		95	1.11 (0.90–1.36)		
			Larynx (ICD-7, 161)		116	1.03 (0.86–1.24)		
			Rectum (ICD-7, 154)		406	1.14 (1.04–1.26)		
			Hodgkin disease (ICD-7, 201)		48	1.04 (0.76–1.37)		
			Non-Hodgkin lymphoma (ICD-7, 200,202)		184	0.97 (0.84–1.12)		
			Multiple myeloma (ICD-7, 203)		103	0.98 (0.81–1.19)		
			Acute leukaemia (ICD-7, 204.3)		67	0.98 (0.76–1.24)		
			Other leukaemia (ICD-7,204.0-2,4)		108	0.96 (0.79–1.16)		

Table 2.1. (contd)

Reference, location, time period	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95% CI)	Adjustment for potential confounders	Comments
Andersen *et al.* (1999) (contd)			Lung	Female painters and wallpaper hangers	13	1.55 (0.83–2.65)		
			Bladder		5	1.46 (0.47–3.41)		
			Tongue		3	6.53 (1.35–19.08)		
			Uterine cervix		15	2.01 (1.13–3.32)		
Aronson *et al.* (1999) Canada	242 196 women and 457 224 men employed during 1965–71 and who completed employment surveys linked to the Canadian mortality database for follow-up during 1965–91	Occupation (≥1 year) obtained from employment surveys and coded using standardized Canadian codes	Brain	Male painters, except construction and maintenance	6	**SMR (95%CI)** 3.79 (1.70–8.48)	Age, calendar period; stratification by gender and white- or blue-collar jobs	
Brown *et al.* (2002) Sweden 1971–89 Scandinavia	People in the painting trades or painting industry (42 433 male painters and 6662 male and 2136 female pictorial artists) obtained from 1960 and 1970 Swedish census data were linked to the Cancer Environment Register to follow-up for cancer incidence from 1971–89	Job title and industry were obtained from census data and coded using Swedish occupational codes.		Male painters (classified either in 1960 or 1970)		**SIR (95%CI)**	Standardized by gender, age and calendar year	Bladder cancer risk was significantly increased by about the same magnitude in male and female artists, although this association was not significant in women. Female artists were at increased risk of cancer of the uterus. Lung cancer risk was not increased among artists
			Lung		548	1.2 (1.1–1.3)		
			Bladder		344	1.1 (1.0–1.2)		
			Pleura		19	1.6 (0.9–2.4)		
			Oral cavity		122	1.0 (0.8–1.1)		
			Oesophagus		63	1.1 (0.9–1.4)		
			Stomach		276	1.0 (0.9–1.1)		
			Rectum		267	1.2 (1.0–1.3)		
			Liver		36	0.8 (0.6–1.1)		
			Extra hepatic bile ducts		22	1.5 (1.0–2.3)		
			Larynx		62	1.2 (0.9–1.6)		
			Non-Hodgkin lymphoma		123	1.0 (0.8–1.2)		
			Hodgkin disease		25	1.0 (0.6–1.4)		
			Multiple myeloma		71	1.0 (0.8–1.3)		
			Leukaemia		115	0.9 (0.8–1.1)		

Table 2.1. (contd)

Reference, location, time period	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95% CI)	Adjustment for potential confounders	Comments
Proportionate mortality studies								
Miller *et al.* (1986) USA United States of America	630 caucasian male painters were identified from a registry of death certificates of 1757 artists deceased during 1940–69	Artists identified from obituaries	Bladder Leukaemia	Painters	14 10	**PCMR (95%CI)** 3.5 (2.1–5.7) 3.1 (1.8–5.6)	Race, sex, age, calendar time	Total number of cancer deaths for all sites combined was used as the comparison group. The PMR for lung cancer was not significantly elevated
OPCS (1995), no. 10 England, 1981–87	Men, aged 20–74 years, England 1981–87	Occupation recorded at the time of cancer registration/death	Lung, bronchus, trachea (ICD9 162)	Painters & decorators Other spray painters	1664 213	**PRR (95% CI)** 1.08 (1.03–1.14) 1.11 [0.97–1.27]	Age, social class, region of registration	
OPCS (1995), no. 10 England & Wales 1979–80, 1982–90	29 689 male painters and decorators, aged 20–74 years, who died during 1979–80 or 1982–90, linked to census denominators	Last full-time occupation was obtained from death certificates	Lung, bronchus, trachea (ICD9 162)	Other spray painters Painters & decorators Coach painters	557 4110 69	**PMR (95% CI)** 1.26 (1.16–1.37) 1.12 (1.09–1.16) 0.87 [0.68–1.10]	Age, social class	Data for 1981 were omitted because of questionable quality

Table 2.1. (contd)

Reference, location, time period	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95% CI)	Adjustment for potential confounders	Comments
Peto *et al.* (1995) England, Wales, Scotland 1979–80, 1982–90	British painters, aged 16–74 years, who died during 1979–80 and 1982–90 were obtained from a UK register	Last full-time occupation obtained from death certificates	Mesothelioma	Male painters and decorators	100	**PMR (*P*-value)** 1.31 ($P<0.05$)	Age, calendar year	This study partially overlaps with the Registrar General's report (1996)
Terstegge *et al.* (1995) Netherlands 1980–92	9812 Dutch male painters identified from a registry and deceased during 1980–92	Painters obtained from a registry with which nearly all commercial painters are affiliated	All cancers Lung Bladder Non-Hodgkin lymphoma	Commercial painters	3266 1480 132 65	**PMR (95%CI)** 1.07 (1.03–1.11) 1.20 (1.14–1.26) 1.19 (1.00–1.41) 1.28 (0.99–1.64)	Age, time period	Total Dutch male population during 1980–1992 used as a comparison
Wang *et al.* (1999) North Carolina, USA	All male construction workers who lived and died in North Carolina during 1988–94	Usual occupation obtained from coded death certificates	Lung Pharynx	Painters, wallpaper hangers, plasterers	NG NG	**PMR** 1.18 1.78	Gender and race	No confidence intervals or number of deaths provided

CI, confidence interval; ILO, International Labor Office and the United Nations Statistical Office; ISIC, International Standard Industrial Classification; NG, not given; PCMR, proportionate cancer mortality ratio; RR, rate ratio or relative risk; SIR, standardized incidence ratio; SMR, standardized mortality ratio; TWA, time-weighted average

Other cancer categories had very few deaths and provided little information. More detail can be found in Table 2.1.

Steenland & Palu (1999) updated a previous large cohort study of US painters by Matanoski *et al.* (1986): 42 170 painters and 14 316 non-painters were assembled from union records and followed for mortality through local and national registries from 1975–1994. The update added 15 years of follow-up during which time the number of deaths increased from 5313 to 23 458. When painters were compared to the general US population, the updated data showed significant but modest excesses for all cancers (SMR, 1.12; 95% CI: 1.09–1.15; 4674 deaths), cancers of the lung (SMR, 1.23; 95% CI: 1.17–1.29; 1746 deaths), of the bladder (SMR, 1.23; 95% CI: 1.05–1.43; 166 deaths), of the stomach (SMR, 1.39; 95% CI: 1.20–1.59; 197 deaths), and of the liver (SMR, 1.25; 95% CI: 1.03–1.50; 119 deaths). In an additional analysis comparing painters and non-painters directly at other anatomical sites, the standardized rate ratios (SRRs) were 1.23 (95% CI: 1.11–1.35) for cancer of the lung, 1.77 (95% CI: 1.13–2.77) for cancer of the bladder, 0.92 (95% CI: 0.68–1.25) for cancer of the stomach, and 1.36 (95% CI: 0.87–2.11) for cancer of the liver. Further analyses restricted to painters with at least 20 years of membership in the union, showed reductions in the SRRs for cancers of the bladder, stomach, and liver while the SRR for cancer of the lung increased slightly (to 1.32). Both painters and non-painters showed significant excesses of cirrhosis compared to the US population (SMRs, 1.21; 95% CI: 1.07–1.35, and 1.26; 95% CI: 1.03–1.51, respectively), suggesting an excess of alcohol consumption compared to the US population; nonetheless, as noted above, the excess of liver cancer persisted in a direct comparison of painters to non-painters.

The data were also adjusted indirectly for smoking using detailed information on smoking in the general population from two large US surveys (see Axelson & Steenland (1988) for the description of methods). The authors found that confounding by smoking when comparing painters to the US population would have resulted in a rate ratio of 1.14 for lung cancer and 1.05 for bladder cancer, compared to the observed SMRs of 1.23 and 1.23, respectively. While this suggested that confounding by smoking may have accounted for some of the lung cancer excess, the case for an occupational etiology was strengthened by the finding of an SRR of 1.23 (95% CI: 1.11–1.35) through a direct comparison painters to non-painters in the same union as both these groups were expected to have similar smoking habits.

The same Dutch cohort described by van Loon *et al.* (1997) was studied for incident cancers of the bladder (532 cases, 1630 subcohort members) and of the prostate (830 cases, 1525 subcohort members), using the same case–cohort design (Zeegers *et al.*, 2001, 2004). Using a case by case expert assessment, and adjustment for age, other occupational exposures as well as the amount and duration of cigarettes consumed, a positive trend for exposure to paint components was observed, with incident rate ratios of 1.00, 0.75 (95% CI: 0.33–1.72), 1.78 (95% CI: 0.94–3.37), and 1.31 (95% CI: 0.72–2.40) for increasing levels of estimated exposure (none, low, medium and high, respectively; *P*-value for trend, 0.09), based on 483, 8, 20, and 19 bladder cancer cases, respectively

(Zeegers *et al.*, 2001). For the 765 prostate cancer cases that reported occupational history, job titles were coded using the Dutch Occupational Classification system. Incident rate ratios were presented for ever being a painter (RR, 1.10; 95% CI: 0.39–3.08; 12 cases), and for being a painter as one's usual occupation (RR, 1.28; 95% CI: 0.31–5.30; seven cases), after adjustment for age, diet, cigarette and alcohol use, family history of prostate cancer, education and physical activity (Zeegers *et al.*, 2004).

2.1.3 *Record Linkage studies since IARC volume 47* (Table 2.1)

Malker *et al.* (1987) conducted a record linkage study of bladder cancer in Sweden, linking the 1960 census with the Swedish National Cancer Registry to follow up for cancer incidence from 1961–1979. Age- and sex-specific bladder cancer incidence rates for painters were compared to the general Swedish population cancer incidence rates. They found no excess of bladder cancer in painters (SIR, 1.00; 186 cases; adjusted for age and region), but an elevated risk in artistic painters (SIR, 1.70; $P < 0.01$; 42 cases). [The census code corresponding to 'artistic painters' is not given and thus it is not clear if this corresponds to Swedish 'pictorial artists' (census code 081) as in the study by Brown *et al.* (2002). The results were not adjusted for smoking.]

The Swedish Cancer-Environment Registry was used to evaluate occupational risks of renal cancer (McLaughlin *et al.*, 1987). This is a record linkage study involving the Swedish Cancer Registry with employment data from the national census. For this study employment data came from the 1960 census and cancers were diagnosed between 1960 and 1979. Among Swedish men there were 7405 cases of renal cell cancer and 821 renal pelvis cancer. Standardized incidence ratios (SIR) were calculated based on national cancer incidence rates. The SIR from painting and paperhanging, adjusted for age and geographic region, was 0.94 for renal cell cancer, and 0.69 for renal pelvis cancer.

Carstensen *et al.* (1988) conducted a record linkage study in Sweden focusing on male lung cancer. Census records from 1960 were linked to the Swedish Cancer registry to follow-up for cancer incidence from 1961–1979. SIRs were standardized using the age and residential distribution in the Swedish general population as the comparison group. Indirect adjustment for smoking was done using a 1963 large survey of smoking habits in Sweden. Painters and paperhangers as a combined group had a smoking-adjusted SIR for lung cancer of 1.01 (95% CI: 0.88–1.16; 425 exposed cases). [It is likely that paperhangers work in the same job environment as painters or may also paint, and it is reasonable to consider this category as a whole as "painters."]

Lynge & Thygesen (1988) studied painters, obtained from the 1970 Danish census, who were linked to the national cancer registry to follow-up for cancer incidence through 1980, and compared them to the economically active Danish population. Only selective findings were reported. Painters had a relative risk of 3.30 (95% CI: 1.21–7.18; six exposed cases) for incident cancer of the pharynx.

Gubéran *et al.* (1989) studied 1916 painters in the 1970 Geneva census who were linked to the Geneva Cancer Registry and followed for cancer incidence during 1971–1984. Regional incidence rates, standardized by age, sex, and marital status were used as

a comparison. Painters had significant excess incident cancers for all anatomical sites (SIR, 1.20; 90% CI: 1.05–1.37, 159 cases), lung (SIR, 1.47; 90%CI: 1.11–1.91, 40 cases), urinary bladder (SIR, 1.71; 90%CI: 1.01–2.72, 13 cases), gall bladder (SIR, 3.75; 90%CI: 1.02–9.69; three cases), and testis (SIR, 3.13; 90%CI: 1.23–6.57, five cases). More detail can be found in Table 2.1. Regarding non-cancer outcomes, painters showed a significant excess mortality from alcoholism (SMR, 6.25; 90%CI, 2.46–13.14; five deaths) and a borderline significant excess mortality from cirrhosis (SMR, 1.59; 90%CI: 0.96–2.49; 14 deaths), suggesting excess alcohol consumption among painters.

Malker *et al.* (1990) provided some evidence of an increase in mesothelioma incidence among Swedish painters followed from 1961–1979, although largely without quantified data. [A more detailed article on the same subject by Malker *et al.* (1985), cited in Monograph 47, predates Malker *et al.* (1990).]

Carstensen *et al.* (1990) obtained information on occupation and industry on gainfully employed individuals (2.1 million men and 820 000 women aged 20–69 years) from the 1960 Swedish population census, and linked them to the Swedish Cancer Registry to follow-up for thyroid cancer incidence from 1961–1979. [They used nearly the same design as in Carstensen *et al.* (1988).] Painters had a reduced risk of cancer of the thyroid (SIR, 0.67; 11 cases).

Dolin & Cook-Mozaffari (1992) linked 2457 death certificates for English and Welsh men age 25–64 who died of bladder cancer from 1965–1980. They determined that painters had an SMR of 1.27 (95% CI: 0.99–1.61, 65 deaths).

Firth *et al.* (1993) used death certificates in New Zealand from 1973–1986, for men aged 15–64 years, considering all different types of cancer and occupations. Denominator data came from the 1976, 1981 and 1986 censuses. Only selective positive findings were reported, including an SMR of 3.52 (95% CI: 1.40–7.29) for multiple myeloma among painters.

Skov *et al.* (1993) studied cancer incidence among painters for selected sites in four Scandavian countries by linking census data (1960 for Norway and Sweden, 1970 for Finland and Denmark) for those who were economically active (generally under age 70) to cancer incidence registries for follow-up extending to 1984 and 1979 in Norway and Sweden respectively, and to 1980 in Finland and Denmark. The study included 87 004 painters and lacquerers, grouped together. The SIRs were significantly elevated for cancers of the lung [SIR, 1.30, 95% CI: 1.22–1.38, 1043 cases], oral cavity [SIR, 1.51; 95% CI: 1.12–2.01, 48 cases], pharynx [SIR, 1.43, 95% CI: 1.10–1.83, 64 cases], and oesophagus [SIR, 1.29, 95% CI: 1.05–1.57, 98 cases]. SIRs were not significantly elevated for cancers of the liver, larynx, and bladder with SIRs of [1.11; 95% CI: 0.92–1.32], [1.05, 95% CI: 0.85–1.28], and [1.05, 95% CI: 0.95–1.16] respectively, based on 122, 95, and 380 cases, respectively.

The Registrar General in England and Wales (OPCS, 1995) considered 29 689 male painters and decorators, aged 20–74 years, who died during 1979–80 and 1982–1990. They published selective findings which were statistically significant at the 0.05 level. PMRs were calculated for cancers of the lung, oral cavity, and kidney and were reported

as 1.12 (1.09–1.16), 1.27 (1.00–1.59), and 0.77 (0.64–0.91) respectively, based on 4110, 75, and 130 deaths, respectively.

Andersen *et al.* (1999) linked people aged 25–64 years from the 1970 census in four Scandinavian countries to cancer incidence registries in those countries through approximately 1990 (range 1987–1991). This study included 65 868 male painters and 2121 female painters. Data for all cancer sites were reported. For males, the SIR for all cancer was 1.06 (95% CI: 1.03–1.08; 7070 cases), and significant elevations were found for cancers of the lung (SIR, 1.22; 95% CI: 1.16–1.28; 1450 cases), pleura (SIR, 1.70; 95% CI: 1.25–2.26; 47 cases; [presumably mesothelioma]), bladder (SIR, 1.10; 95% CI: 1.01–1.20; 566 cases), pharynx (SIR, 1.31; 95% CI: 1.02–1.64; 72 cases), and rectum (SIR, 1.14; 95% CI: 1.04–1.26; 406 cases). More detail can be found in Table 2.1. Subsequent work with the Norwegian component of this study by Haldorsen *et al.* (2004) showed that indirect adjustment for smoking increased the lung cancer SIR from 1.38 to 1.52 (95% CI: 1.3–1.7, 260 cases). The Swedish component of this study partly overlaps with Brown *et al.* (2002) who also included painters from the 1960 Swedish census. It also overlaps the four country study by Skov *et al.* (1993), who reported on fewer cancer sites with shorter follow-up, and also overlaps Scandanavian record linkage studies by Malker *et al.* (1987), Carstensen *et al.* (1988, 1990), and Lynge & Thygesen (1988).

Aronson *et al.* (1999) conducted a record linkage study of 457 224 Canadian men and 242 196 Canadian women employed during 1965–1971, with follow-up for mortality from 1965–1991. Only selected positive findings were reported. A significant excess of brain cancer (SMR, 3.79; 95% CI: 1.70–8.48) was observed for male painters, based on only six deaths.

Brown *et al.* (2002) linked Swedish census data from 1960 and 1970 (for those employmed as a painter) to cancer incidence and mortality data from 1971–1989. This study focused specifically on male painters, male paint-manufacturing workers, as well as male and female pictorial artists (see section below for results). There were 42 433 male painters in the study, and although significant excesses for cancers of the lung and bladder were observed, these were very modest (lung SIR, 1.2; 95% CI: 1.1–1.3, 548 cases; bladder SIR, 1.1; 95% CI: 1.0–1.2, 344 cases). The SIR for mesothelioma was 1.6 (95% CI: 0.9–2.4, 19 cases). Incident cancer of the extrahepatic bile ducts was also increased (SIR, 1.5; 95% CI: 1.0–2.3, 22 cases), but liver cancer itself was not (SIR, 0.8; 95% CI: 0.6–1.1; 36 cases). More detail can be found in Table 2.1. The authors also studied 6662 male pictorial artists and found significantly elevated cancer incidence was found for cancers of the oral cavity (SIR, 1.5; 95% CI: 1.0–2.1, 29 cases), and of the bladder (SIR, 1.5; 95% CI: 1.2–1.9, 71 cases). Non-significant elevations were found for the incidence of cancers of the oesophagus (SIR, 1.4; 95% CI: 0.7–2.4, 11 cases), and of the liver and biliary tract (SIR, 1.4; 95% CI: 0.8–2.2, 18 cases). The incidence of lung cancer was not elevated (SIR, 1.0; 95% CI: 0.80–1.3, 69 cases). Among 2136 female pictorial artists there was a significant excess incidence of cancer of the uterus (SIR, 1.6; 95% CI: 1.10–2.3, 31 cases). [The Working Group noted that the percentage of pictorial artists who

were painters was not known, although presumably a significant proportion were likely to also be painters.]

2.1.4 *Proportionate mortality studies since IARC Monograph volume 47* (Table 2.1)

Miller *et al.* (1986), in the United States, conducted a proportionate mortality study of deaths among 1746 caucasian pictorial artists who died during 1940–1969. Proportionate cancer mortality ratios (PCMR) were significantly elevated for bladder cancer (PCMR, 2.6; 95% CI: 1.5–4.4, 14 deaths), and leukaemia (PCMR 2.3; 95% CI: 1.2–4.5, ten deaths). Terstegge *et al.* (1995) conducted a proportionate mortality study of Dutch painters among whom 9812 deaths were observed during 1980–1992. These authors found significant excesses of mortality from cancer of the lung (PMR, 1.20; 95% CI: 1.14–1.26, 1480 deaths), and all cancers (PMR, 1.07; 95% CI: 1.03–1.11, 3266 deaths). Mortality from bladder cancer was borderline significant (PMR, 1.19; 95% CI: 1.00–1.41, 132 deaths) as was mortality from non-Hodgkin lymphoma (PMR, 1.28; 95% CI: 0.99–1.64, 65 deaths). Results for most sites were provided but were generally unremarkable.

Peto *et al.* (1995) studied mesothelioma mortality among men aged 16–74 in England, Scotland and Wales during the years 1979–1980 and 1982–1990. The PMR for mesothelioma in painters was reported as 1.31 ($P < 0.05$, 100 deaths).

Wang *et al.* (1999) studied American construction workers, which included a group of painters, paperhangers, plasterers, and supervisors, who died during 1988–1994. [As noted previously with regard to Carstensen *et al.* (1988), this grouping may be relevant for paint exposures as these workers are all likely to work together and to be exposed to paint fumes.] Significantly excess mortality was seen for cancers of the of the lung (PMR, 1.18), and of the pharynx (PMR, 1.78) with significantly decreased mortality seen for cancers of the kidney, brain, colon, and leukaemia. No confidence intervals or number of cause-specific deaths were given. [This was a proportionate mortality study and the elevation of some cancer PMRs may have been artificial and due to the observed low heart disease among healthy workers in this occupation (PMR, 0.87). No correction was made via use of PCMRs.]

2.1.5 *Study of paint-manufacturing workers since 1989*

Paint-manufacturing workers have different exposures than painters, and were judged separately by IARC in 1989. IARC concluded in 1989 that occupation as a paint-manufacturing worker is *not classifiable as to its carcinogenicity to humans* (Group 3).

Lundberg & Milatou-Smith (1998) studied cancer incidence among 411 workers in paint manufacturing that had been exposed to organic solvents for at least 5 years during 1955–1975. This was an update of an earlier study that included follow-up from 1961–1992. A total of 83 incident cancers were observed, versus 80 expected (SIR, 1.0; 95% CI: 0.8–1.3). There were no notable cancer excesses with the exception of a borderline increased risk for multiple myeloma (SIR, 3.2; 95% CI: 0.9–8.3), and cancer of the prostate (SIR, 1.5; 95% CI: 1.0–2.2).

Brown *et al.* (2002) studied 5741 male paint- and lacquer-manufacturing workers in a record linkage study in Sweden (see description above), and found significant elevations of incident cancers of the lung (SIR, 1.5; 95% CI: 1.2–1.9, 87 cases), of the small intestine (SIR, 2.6; 95% CI: 1.0–5.4, seven cases), of the colon (SIR, 1.3; 95% CI: 1.0–1.7, 52 cases), of the pancreas (SIR, 1.7; 95% CI: 1.1–2.4, 30 cases), and non-lymphocytic leukaemia (SIR, 2.1; 95% CI: 1.1–3.6, 13 cases). [The relevance of these findings for paint-manufacturing workers specifically is difficult to judge as they are combined with lacquer-manufacturing workers, who may have had different exposures].

2.2 Case–control studies

2.2.1 *Cancer of the lung* (Table 2.2)

In 1989 (Monograph 47), nine case–control studies of lung cancer and two multisite case–control studies, which included lung cancer, were evaluated. These studies are summarized in Table 24 of Monograph 47 (IARC, 1989).

(a) Europe

Jahn *et al.* (1999) carried out a pooled analysis of the two case–control studies on lung cancer conducted in Germany: the Bremen Institute for Prevention Research and Social Medicine (BIPS) study in the Bremen and Frankfurt/Main areas, during 1988–1993, and the GSF-National Research Center for Environment and Health (GSF) study in Nordrhein-Westfalen, Rheinland-Pfalz and Bayern, Saarland, Thuringen, and Sachsen, during 1990–1996. The results from the BIPS study had been reported earlier by Jöckel *et al.* (1992, 1998) for both sexes combined. The Jahn *et al.* (1999) analysis was restricted to women, and included 686 cases aged 75 or less at diagnosis, of German nationality, residing in the study regions. All cases were confirmed by histology or cytology. Population controls, 712 individuals, were randomly selected from population registries or by random digit dialling, and were individually (BIPS study) or frequency- (GSF study) matched to cases by age, and region. A standardized questionnaire, with full occupational history and supplementary job-specific modules, was administered during face-to-face interviews. The response rate was 73% among cases, and 45% in controls. An odds ratio (OR) of 3.00 (95% CI: 0.73–12.33) was found after adjustment for smoking and asbestos exposure (age and region of residence were strata-defining variables in the conditional logistic regression models) for the occupation of ‘ever’ painter. [A major strength of this study was exposure definitions, based on complete and accurate occupational histories, and expert-based quantitative exposure assessment for a series of carcinogens. However, the low response rate among controls might have led to selection bias].

Brüske-Hohlfeld *et al.* (2000) also carried out a pooled analysis of the two case-control studies described above (the BIPS and GSF studies). The results from the BIPS study had been reported earlier by Jöckel *et al.* (1992, 1998) for both sexes combined. This analysis was restricted to men, and included 3498 cases aged 76 or less at diagnosis

who lived in Germany for at least 25 years and resided in the study regions. All cases were confirmed by histology or cytology. Population controls, 3541 individuals, were randomly selected from population registries or by random digit dialling, and were individually (BIPS study) or frequency- (GSF study) matched to cases by age and region. A standardized questionnaire, with full occupational history and supplementary job-specific modules, was administered during face-to-face interviews. The response rate was 77% among cases, 41% in controls. An OR of 1.42 (95% CI: 1.05–1.92) was found after adjustment for smoking and asbestos exposure (age class and region of residence were strata-defining variables in the conditional logistic regression modelling) for the occupation of "ever painter/lacquerer." [A major strength of this study was the exposure definition, based on complete and accurate occupational histories, aiming to expert-based quantitative exposure assessment to a series of carcinogens. However, the low response rate among controls might have led to selection bias].

Pohlabeln *et al.* (2000) conducted a case–control study among non-smokers in 12 European study centres in Germany, Italy, Portugal, Sweden, United Kingdom, France and Spain to evaluate the role of occupational risk factors among non-smokers. Non-smoking cases and controls were defined as subjects who smoked fewer than 400 cigarettes during their lifetime. Lifetime occupational histories in face-to-face interviews were obtained from 650 non-smoking cases (509 females, 141 males) and 1542 non-smoking controls (1011 females, 141 males). Community-based controls were selected in six centres, hospital-based controls in five centres, and both community and hospital-based controls in one centre. Hospital controls were selected from diseases not related to tobacco smoking. Painting was among the three occupations where an excess risk was identified in males (OR, 1.84; 95% CI: 0.59–5.74; based on six cases). Numbers of females involved were too small to produce reliable estimates of effect. [This is the only case–control study of non-smokers, sufficiently large to study occupational exposures.]

Bouchardy *et al.* (2002) identified 58 134 incident cancer cases in men from five cantonal Swiss Cancer Registries (Basel, Geneva, St Gall, Vaud, and Zurich), 1980–9193. The overall proportion with histological or cytological confirmation of diagnosis was 95.1%. The study was restricted to cases aged 25 years or more at registration (and less than 65 year in St Gall and Vaud). The longest, current or most recent occupation at registration was recorded (the main or most accurately specified occupation was used in the Zurich Registry). Subjects with unknown occupation were not reported separately. The association between different cancer sites and work in a pre-defined set of industries and occupation was studied by estimating ORs adjusted for age, registry, civil status, period of diagnosis, nationality, urban/rural residence, and socioeconomic status. For each neoplasm, registrants for the other cancer sites were used as reference. Overall, 9106 lung cancer cases were registered, 273 of those were plasterers and painters in the construction industry. A total of 49 028 non-lung cancer cases were registered, 867 of whom were painters. The OR for cancer of the lung among painters was 1.1 (95% CI: 1.0–1.3),

adjusted for all variables. The OR when adjusted for all variables except socioeconomic status was 1.4 (95% CI: 1.2–1.6). [ORs could not be adjusted for smoking.]

Richiardi *et al.* (2004) carried out a population-based case-control study in two industrialized areas of Northern Italy (city of Turin and Eastern Veneto) in 1990–1992, including 1132 lung cancer cases and 1553 controls less than 75 years of age. Histologically or cytologically confirmed cases were identified through weekly monitoring of all hospitals in the study areas. Population controls were frequency-matched with cases by sex, study area and 5-year age groups. Response proportions for Turin and Eastern Veneto were, respectively, 86% and 72% among cases, and, respectively, 85% and 74% among controls. A face-to-face interview was used to collect information on each subject's occupation lasting >6 months, record the job title and industry and the time period of employment. Occupational histories were coded according to international classifications and evaluated for employment in occupations known (list A) or suspected (list B) to determine any exposure to lung carcinogens. This was done using a previously suggested translation of lists A and B into combinations of codes for job titles and industries (Ahrens & Merletti, 1998). Analyses on specific list A occupations, including painters, was limited to men (956 cases and 1253 controls). Compared to men who were never employed in occupations in lists A or B, painters had an OR for cancer of the lung of 2.0 (95% CI: 1.4–3.3) after adjusting for matching variables, smoking and number of job periods, and of 1.7 (95% CI: 1.1–3.0) if additionally adjusting for educational level.

Baccarelli *et al.* (2005) conducted a study in the Leningrad province (the Russian Federation), during 1993–1998 on lung cancer cases diagnosed at autopsy: 540 cases (474 men, 66 women) diagnosed at postmortem examination at the St Petersburg central pathology laboratory, serving 88 state hospitals in the study area, were included along with 582 (453 men, 129 women) individuals with diagnoses of non-cancer, non-tobacco related conditions, frequency-matched by sex, age, area, year of death. Postmortem examinations were conducted in about 95% of decedents in the state hospitals involved. Full occupational records were retrieved for all cases and all controls. Information on smoking was abstracted from medical records at local health centres; however the proportion of success for data abstraction and data quality are not stated. An OR of 0.6 (95% CI: 0.3–1.4) was found for occupation as 'ever painter', 0.5 (95% CI: 0.2–1.5) for < 10 years of employment as a painter, and 0.8 (95% CI: 0.2–3.0) for ≥ 10 years of employment as a painter, adjusted for age, sex, and smoking.

Zeka *et al.* (2006) conducted a multicentre case–control study of lung cancer in several European countries between 1998–2002. A total of 223 'never' smoking cases (48 men, 175 women) and 1039 non-smoking controls (534 men, 505 women) were included in the analysis. In-person interviews were conducted to obtain lifetime occupational histories for jobs held ≥1 year. Occupation as a painter was associated with a non-significant increased risk of lung cancer among women (OR, 1.8; 95% CI: 0.53–6.0, based on six cases and six controls), adjusted for age and study centre.

Table 2.2. Case-control studies of lung cancer among persons with occupation as a painter

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Europe *Studies since Vol. 47*								
Jahn *et al.* (1999); Brüske-Hohlfeld *et al.* (2000) BIPS study in Bremen area and Frankfurt/Main area (Germany) 1988–93 GSF study in Nordrhein-Westfalen, Rheinland-Pfalz and Bayern, Saarland, Thuringen, and Sachsen (Germany) 1990–96	686 women, ≤75 yrs of age at diagnosis, of German nationality 3498 men, ≤76 yrs of age at diagnosis, living in Germany for at least 25 years, resident in the study region 100% confirmed by histology or cytology. Response rate 63% BIPS, 77% GSF [73% overall]	712 female and 3541 male population controls randomly selected from population registries or by random-digit dialling, individually (BIPS study) or frequency (GSF study) matched to cases by sex, age, and region. Response rate 60% BIPS, 41% GSF [45% overall]	Standardized questionnaire with full occupational history and supplementary job-specific modules, administered during a face to face interview; jobs coded according to the classification of the German Statistical Office (Statistiches Bundesamt)	Ever painters (women) Ever painters/ lacquerers (men) Ever painters/ lacquerers (men and women)	13 147 [160]	3.0 (0.73–12.33) 1.42 (1.05–1.92) [1.47 (1.09–1.97)]*	Smoking, asbestos, education, age, region of residence	Low response rate among controls with potential for selection bias; frequency matched cases and controls of the GSF-study were post-hoc stratified according to the matching variables age, region; *fixed effects model used to calculate a weighted average; these studies have substantial overlap with Kreuzer *et al.* (2001) that presented results for painters in lifetime non-smoking men [2.31 (0.57–9.47)] and women (OR=1.2), respectively. BIPS study overlaps with Jöckel *et al.* (1998)

Table 2.2 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Pohlabeln *et al.* (2000) 12 centres in Germany, Italy, Portugal, Sweden, UK, France and Spain 1988–94	650 non-smoking cases (509 women, 141 men)	1542 non-smoking controls (1011 females, 531 males); community based controls in 6 centres, hospital controls (diseases not related to tobacco smoking) in 5 centres and both community and hospital-based controls in 1 centre	In-person interview for lifetime occupational history, coded using ISCO and ISIC classification; non-smokers = subjects who smoked <400 cigarettes during their lifetime	Ever painters (men)	6	1.84 (0.59–5.74)	Age, centre	This is the only case-control study of non-smokers sufficiently large to study occupational exposures. Controlling for other confounders (occasional smoking, residence in urban/rural area, dietary habits, ETS) did not change the estimate. There is a small overlap with Jahn *et al.* (1999), Brüske-Hohlfeld *et al.* (2000), Richiardi *et al.* (2004)

Table 2.2 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Bouchardy *et al.* (2002) Cantons of Basel, Geneva, St Gall, Vaud and Zurich, Switzerland 1980–93	9106 men from cantonal Cancer Registries, aged 25 or more (and 65 or less in St Gall and Vaud)	49 028 male non-lung cancer registrants from the same registries and period	Longest, current or most recent occupation as recorded at the time of registration (main or best specified occupation in Zurich Registry), coded using the ASCR Classification of Occupations	Plasterers and painters (in the construction industry)	273	1.1 (1.0–1.3)	Age, registry, civil status, period of diagnosis, nationality, urban/rural residence, socio-economic status, histological confirmation, information from death certificate only (cases)	OR adjusted for all variables except socioeconomic status was 1.4 (95% CI 1.2–1.6). Adjusting for SES may over-adjust for occupational risk factors but serve as a surrogate for smoking. Overall 95.1% microscopic confirmation for all sites
Richiardi *et al.* (2004) Turin and Eastern Veneto, Italy 1990–92	956 men from active search in all hospitals of the study areas; aged less than 75; response rate: 86% in Turin, 72% in Eastern Veneto; all cases histologically or cytologically confirmed	1253 male population-based controls, matched by study area, 5-year age groups; response rate: 85% in Turin, 74% in Eastern Veneto	Lifetime occupational history obtained from interviewer-administered questionnaire, coded using ISCO and ISIC codes	*Ever painters* Small cell carcinoma Construction painters Painters, n.e.c.	62 4 42 20	1.7 (1.1–2.8) 5.2 (1.2–23) 1.7 (1.0–3.0) 1.7 (0.8–3.7)	Age, study area, smoking (never, ex-, active smokers), number of job periods, education	OR adjusted for all variables but education 2.0 (1.4–3.3)

Table 2.2 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Baccarelli *et al.* (2005) Leningrad province (Russia) 1993–98	540 (474 men, 66 women) autopsy cases from the St Petersburg central pathology laboratory, serving 88 state hospitals in the study area. Occupational records retrieved for all cases	582 (453 men, 129 women) individuals with autopsy-based diagnoses of non-cancer and non-tobacco related conditions, frequency matched by sex, age, area, year of death (20 painters). Occupational records retrieved for all controls	Lifetime occupational histories were obtained from personal records (“Green Book”), coded based on ISCO and ISIC classification	Ever painters *<10 years* *≥10 years*	10 6 4	0.6 (0.3–1.4) 0.5 (0.2–1.5) 0.8 (0.2–3.0)	Age, sex, smoking	Post-mortem examinations were conducted in about 95% of decedents. Information on smoking was abstracted from medical records at local health centres, but neither the proportion of success nor the quality of data assessed were stated. Occupational histories from the “Green Books” are reported to be complete

Table 2.2 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Zeka *et al.* (2006) Czech Republic, Hungary, Poland, Romania, Russia, Slovakia, UK 1998–2002	223 never smoking cases (48 men, 175 women) diagnosed at participating centers; 20–74 years; lived in the study area for ≥1 year; 100% confirmed by histology or cytology; 86% participation rate	1039 non-smoking controls (534 men, 505 women); selected from patients that did not have malignant neoplasms, respiratory diseases, or other smoking related disorders or selected from healthy individuals in the general population (Warsaw, Liverpool only); 85% participation rate	In-person interview to obtain lifetime occupational histories for jobs held ≥1 year; jobs coded by ISCO or NACE	*Painters* Men Women	6 0 6	[1.81 (0.72–4.59)] NG 1.8 (0.53–6.0)	None None Sex, age, study centre	Never smokers = smoked <100 cigarettes in lifetime; painters were classified as working in construction, automotive industry and other users

Table 2.2 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Studies in Vol. 47								
Coggon *et al.* (1986) Cleveland, Humberside, Cheshire counties, UK 1975–80	738 male bronchial cancer cases, aged 18–54 yrs, identified from hospital and cancer registry records	1221 other cancers	Occupation from mailed questionnaire	Painters and decorators	20	1.3 [0.62–2.72]	Age, smoking, residence, respondent	52.1% overall response rate; the variance was doubled to approximate an adjusted 95%CI. The unadjusted 95%CI was 0.78–2.18. *Included in the analysis restricted to case-control studies but excluded from the combined meta-analysis because of possible overlap with OPCS (1986)*

Table 2.2 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Kjuus *et al*. (1986) Norway 1979–83 Scandinavia	176 male incident lung cancer cases (ICD 162-163), <80 years; 99% response rate	176 age-matched hospital controls excluding those with physical or mental handicaps, poor general health, or diagnosed with chronic obstructive lung disease; 99% response rate	Interview and worksite records for longest job held; coded using Nordic Classification of Occupations; Exposed if worked ≥3 years	Painting, paper-hanging (occupation)	5	1.7 (0.4–7.3)	Age, smoking	
				Paints, glues, lacquer (exposure)	17	1.2 (0.6–2.6)		

Table 2.2 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Ronco *et al.* (1988) Italy 1976–80	126 men who died from lung cancer; 77% participation rate	Random sample of 384 men who died from causes other than from smoking-related or chronic lung diseases; matched by year of death and age (± 10 yrs); 78% participation rate	Lifetime occupational history from interview with next of kin; coded using ILO classification	Painter	5	1.33 (0.43–4.11)	Age, year of death, smoking, other employment in suspect high-risk occupations	

Table 2.2 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
North America *Studies since Vol. 47*								
Vineis *et al.* (1988) Analysis of 5 case-control studies in Louisiana, Florida, Pennsylvania, Virginia and New Jersey, USA, 1970s and 1980s	2973 men from cancer registries, co-operating hospitals or death certificates, resident in selected areas of the states; response rate range: 70%–93%.	3210 men from hospital records, decedents, death certificate, licensed drivers, matched by characteristics varying from study to study, with age always included; response rate range: 63%–89%	Life-time occupational history obtained during interviews with subjects or next of kin, coded using SIC and 1970 Census Classification	Painters	201	1.1 (0.9–1.4)	Age, birth cohort, smoking	Unexposed group: selected occupations and industries without a well-established or suspected carcinogenic exposure; studies analyzed: Correa *et al*. (1984), Blot *et al*. (1980, 1982, 1983), Schoenberg *et al.* (1987)

Table 2.2 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Zahm *et al.* (1989) Missouri, USA 1980–85	4431 white male cases with histological type and grade recorded at Missouri Cancer Registry, residing in Missouri	11 326 white male non-lung cancer registrants from the same Registry and period, excluding cancers of lip, oral cavity, esophagus, lung, bladder, ill-defined or unknown sites	Occupation at the time of diagnosis abstracted from medical records, coded using US Bureau of Census classification	*Painters, paper hangers, plasterers*	37	2.0 (1.2–3.3)	Age, smoking	
				<60 yrs of age	NG	3.2 (1.1–10.0)		

Table 2.2 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Burns & Swanson (1991) Detroit metropolitan area, USA Recruitment period not specified, probably 1984–87, as in Swanson *et al*., (1993)	5935 (3918 males, 2017 females; 77% white, 23% black) from Occupational Cancer Incidence Surveillance System/Metro-politan Detroit Cancer Surveillance System, aged 40–84 years; response rates: 94% for cases and 95% for controls	3956 (1981 males, 1975 females) with colon and rectum cancer, registry-based	Life-time occupational history obtained during telephone interviews to the subjects or to their surrogates, coded using US Bureau of Census classification	Painters (usual occupation, grouped)	97	1.96 (1.23–3.13)	Age at diagnosis, race, smoking, gender	Interviews to surrogates: 53.7% for cases, 27.5 % for controls. Unexposed group: selected occupations and industries with little or no exposure to carcinogens. Proportion of histologic confirmation not given; 93.4% overall response rate
				Painting & spray painting machine operators (male, usual occupation, detailed occupational code)	37	4.5 (1.7–11.8)	Age at diagnosis, race, smoking	

Table 2.2 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Swanson *et al*. (1993) Detroit metropolitan area, USA 1984–87	3792 males (2866 white, 926 black) from Occupational Cancer Incidence Surveillance System/Metro-politan Detroit Cancer Surveillance System (participant in SEER), aged 40–84 years; 100% histolo-gically confirmed	1966 males (1596 white, 370 black) with colon and rectal cancer, registry-based; 100% histolo-gically confirmed	Life-time occupational and smoking history obtained during telephone interviews with subjects or their surrogates. Jobs coded using US Bureau of Census classification	**Painting machine operators**			Age at diagnosis, pack-years of cigarette smoking	Interviews with surrogates: 56.1% for cases, 29.5 % for controls; unexposed group: selected occupations and industries with little or no exposure to carcinogens. >90% overall response rate; *this paper does not represent an independent set of cases and controls, but is a re-analysis of a sub-group reported in the study of Burns & Swanson (1991). Therefore it was omitted from the overall meta-analysis but kept for the analysis by duration.* **Calculated using a fixed effects model*
				White males				
				Employment (years)				
				0	88	1.0		
				1–9	23	1.1 (0.5–2.4)		
				10–19	6	0.6 (0.2–2.2)		
				20+	17	3.9 (1.2–13.0)		
				Black males				
				Employment (years)				
				0	12	1.0		
				1–9	17	1.5 (0.4–5.6)		
				10–19	7	9.9 (0.9–109.2)		
				20+	10	8.7 (0.9–89.3)		
				p for trend		≤0.05		
				Black and White				
				<10 yrs	40	[1.19 (0.61–2.34)]*		
				≥10 yrs	40	[2.23 (1.05–4.73)]*		
				<20 yrs	53	[1.15 (0.65–2.04)]*		
				≥20 yrs	27	[4.62 (1.61–13.31)]*		

Table 2.2 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Morabia *et al.* (1992) Detroit, Chicago, Philadelphia, Pittsburgh, New York, Long Island, San Francisco, Birmingham, USA 1980–89 American Health Foundation study	1793 male cases from 24 hospitals; 100% confirmed by histology; response rate not given. Number of cases that were painters not given	3228 controls not hospi-talized for lung cancer but including tobacco related conditions; matched by age, race, hospital, smoking history, admission date; response rate not given	Standardized questionnaire, administered during a face to face interview. Only "usual" occupation recorded, plus exposure circumstances to up to 2 agents out of a list of 44 (study period 1980–4), or up to 6 agents (study period 1985–9); Jobs coded using US Bureau of Census classification	Painters	[13]	0.8 [0.32–2.03]	Age, geographic area, race, smoking, study period	The variance was doubled to approximate an adjusted 95%CI. The unadjusted 95%CI was 0.41–1.54

Table 2.2 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Muscat *et al.* (1998) New York City, Long Island, Philadelphia, Washington D.C., Detroit, and Chicago, USA 1978–96	365 black men and 185 black women with histologically confirmed lung carcinomas recruited from teaching hospitals	251 male and 135 female black patients admitted to teaching hospitals for conditions unrelated to tobacco use, matched by race, gender, 5 years age groups, month of diagnosis	Interviewer-administered questionnaire. Only "usual" occupation and whether the job entailed regular exposure to an occupational exposure (for a minimum of 8 hours a week) was obtained from interviews with subjects or their next of kin or death certificates	*Ever painters* Men Men (no overlap) Women	[24] 30 [19] 5	[1.32 (1.30–1.35)]* 0.7 (0.3–1.1) [0.68 (0.29–1.59)] 1.8 (0.3–12.3)	Age, education, smoking	Response rate: over 90 % overall (no specific rate by gender or case-control status given); the study partially overlaps with Morabia *et al.* (1992) and thus some estimations were used to eliminate the overlap in men and the estimated variance was doubled to approximate an adjusted CI; *fixed effects model used to calculate a weighted average
Finkelstein *et al.* (1995) Hamilton and Sault Ste-Marie, Ontario, Canada 1979–88	967 men who died of lung cancer, aged 45–75 yrs, residing in the study areas	2821 men who died of any cause other than lung cancer, matched by age, year of death, and city of residence	Occupation (job and industry) as reported on the death certificate	Painters & plasterers	16	1.25 (0.63–2.36)	Age, year of death, city of residence	No information was available on smoking

Table 2.2 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Studies in Vol. 47								
Wynder & Graham (1951) St. Louis, MO, USA NG	Subset of 200 cases from a Hospital Chest Service from a total of 709 US male cases of confirmed cases with epidermoid, undifferentiated or unclassified lung cancer	200 controls with a chest disease other than lung cancer from the Hospital Chest Service	Lifetime occupational history from interview	Painter ≥5 years within the last 40 years	11	[5.76 (1.41–23.44)]	None	The chest diseases were not specified. Only 2 painters were nonsmokers (smoked <1 cigarette/day for >20 years). Cases and controls were of similar age and economic status
Breslow *et al.* (1954) California, USA 1949–52	518 patients with histologically confirmed lung cancer from 11 hospitals	518 hospital controls matched by hospital, age, sex, race; excluded admission of lung cancer or a chest disease	Interview	Construction and maintenance painters for ≥5years	22	[1.87 (0.93–3.77)]	Hospital, age, sex, race	The gender distribution is not presented
				Painters, except construction and maintenance for ≥5 years	3	[0.50 (0.14–1.82)]		

Table 2.2 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Viadana *et al*. (1976); Decouflé *et al.* (1977); Houten *et al.* (1977) Buffalo, NY, USA 1956–65 United States of America	Lung cancer cases (ICD7 162, 163) from 11591 white male cancer cases at a treatment center, age ≥14 years	Non-cancer admissions from the same cancer treatment center	Lifetime occupation recorded during interview before diagnosis, coded using the Standard Industrial Classification Manual	**Painter**				Unexposed = clerical occupations
				Ever	42	1.71 [1.08–2.77]	Age	
				Ever (smoking adj)	42	1.90 [1.32–2.48]	smoking, age	
				<60 yrs old	21	2.12 [1.08–4.18]	Age	
				≥60 yrs old	21	1.42 [0.74–2.73]		
				Worked ≥5 yrs	29	1.31 [0.73–2.26]		
				<60 yrs old	14	1.76 [0.75–4.16]		
				≥60 yrs old	15	1.03 [0.49–2.18]		
Williams *et al.* (1977) Atlanta, Birmingham, Colorado, Dallas-Ft.Worth, Detroit, Minneapolis-St.Paul, Pittsburgh, San Franciso-Oakland, USA 1969–1971 Third National Cancer Survey	432 lung cancer cases that reported an occupation, 95% histologically confirmed	2173 patients with cancers other than lung, larynx, oral cavity, esophagus, bladder that reported an occupation	Main lifetime employment from survey questionnaire, coded using the 1970 census classification	Painting (men)	12	4.21 [1.40–12.65] (p <0.01)	Age, race, education, education, tobacco, alcohol, geographic location	Painting included construction workers, paper-hangers, and pattern & model makers; The CI was estimated by doubling the variance

Table 2.2 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Milne *et al*. (1983) Alameda County, CA, USA 1958–62	925 lung cancer deaths (747 men, 178 women)	4880 deaths from other cancers (except pancreas, bladder, nasal, kidney, haema-topoietic) that are not known to be strongly associated with occupational risk factors (reported as the "reduced control group")	Occupation from death certificates, coded using the Bureau of Census Industrial and Occupational Classification System	Painter (men)	24	1.80 [1.09–2.98]	Age	The gender distribution was not presented for the "reduced control group", used to reduce potential exposure bias; the CI was estimated by applying the ratio of reduced/ total controls to the observed cell counts reported for the total control group
Lerchen *et al*. (1987) New Mexico, USA 1980–82	771 cases (333 men, 173 women) identified from a SEER tumor registry; Hispanic whites and whites ages 25–84 years; 89% response rate	771 controls (499 men, 272 women) from randomly selected phone numbers and Medicare rosters; frequency matched by sex, ethnicity, 10-year age category; 83% response rate	Interview for lifetime occupational history; jobs coded using the SIC or SOC	Ever construction painters (males)	9	2.7 (0.8–8.9)	Age, ethnicity, smoking	Exposed = ever employed at least 1 year in an industry/occupation

Table 2.2 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Siemiatycki *et al.* (1987) Montreal, Canada, 1979–85	857 male cases (159 oat-cell, 359 squamous-cell, 162 adeno-carcinoma, 177 other types)	Other cancers	Interview to obtain lifetime occupational history; painters coded using Canadian occupation classification	*Mineral spirit exposure*		**OR (90% CI)**	Age, socio-economic status, ethnicity, cigarette smoking, blue/white collar	Of those exposed to mineral spirits, 21% were in construction trades (mostly painters) *Excluded from meta-analysis because risk associated with occupation as a painter is not presented*
				Oat-cell	36	1.1 (0.8–1.4)		
				Squamous cell	92	1.2 (1.0–1.5)		
				Long duration, high exposure	44	1.7 (1.2–2.3)		
				Adenocarcinoma	37	1.0 (0.7–1.3)		
				Other types	32	0.8 (0.6–1.1)		
				Construction workers (mainly painters)	NG	1.4 (NG)		
Siemiatycki (1991) Montreal, Canada, 1979–85	857 incident male cases; aged 35–70 yrs; histologically confirmed; 79% response rate	533 population controls, 1360 cancer controls; 72% response rate	Interview to obtain lifetime occupational history; painters coded using Canadian occupation classification	*Construction painter*			Age, family income, ethnicity, respondent type, cigarette & alcohol index	The ORs were higher and the 90% CIs were narrower when restricted to lung squamous cell cancers
				Any exposure	26	1.4 [0.77–2.17] (90% CI, 0.8–2.3)		
						OR (90% CI)		
				Substantial exposure	14	1.7 (0.8–3.4)		

Table 2.2 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
South America								
De Stefani *et al.* (1996) Montevideo, Uruguay, 1993–94	270 male patients from five major hospitals in Montevideo, aged 30–75 years	383 male hospital-based controls: other cancer sites except oral cavity, pharynx, oesophagus, stomach, larynx and bladder	Interviewer-administered questionnaire with life-time occupational history	**Ever painters** *Employment (years)* 1–20 21+ Squamous cell Small cell Adenocarcinoma	18 12 4 2	1.2 (0.6–2.4) 0.9 (0.2–3.0) 1.4 (0.6–3.1) 1.5 (0.6–3.4) 2.8 (0.8–9.9) 0.5 (0.1–2.5)	Age, residence, education, tobacco smoking (pack-years), alcohol consumption	Descriptive characteristics and separate response rates for cases and controls were not given; overall response rate for all cancer sites 97.4%
Wünsch-Filho *et al.* (1998) Sao Paulo, Brazil 1990–91	398 cases (307 men, 91 women) from 14 hospitals, living in the metropolitan area of Sao Paulo; 100% confirmed by histology or cytology	860 controls (546 men, 314 women) hospitalized for non-tobacco related conditions, matched by age, sex, hospital	Standardized questionnaire with full occupational history, administered during a face to face interview	**Ever painters (men)** *Employed* ≥10 years ≥10 years and latency ≥40 years	128 82 70	0.77 (0.56–1.08) 1.29 (0.79–2.11) 1.28 (0.77–2.15)	Age, sex, hospital, smoking, cancer in family, migration history, socio-economic status	

Table 2.2 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Pezzotto & Poletto (1999) Rosario City, Argentina 1992–98	367 male newly diagnosed primary lung cancer patients from three medical institutions of Rosario City; mean age 60.3 ± 9.5; 100% histologically confirmed	586 hospital based males controls admitted for a non-smoking related disease at the same hospitals for traumatic conditions, urological diseases, acute surgical conditions, and other illnesses, matched by age (± 3 years); mean age 60.1 ± 10.2 yrs	Standardized questionnaire with lifetime occupational history for each job held >1 year	*House painters* Squamous cell Adenocarcinoma	4 2 1	2.4 (0.4–19.4) 3.3 (0.4–52.9) 1.3 (0.1–30.7)	Age, smoking habit, lifelong cigarette consumption	Unexposed group: never employed in occupations involving exposure to agents classified in group 1, 2A or 2B of the IARC Monographs. Individuals who had more than two jobs were excluded from the study

Table 2.2 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Matos *et al.* (2000) Buenos Aires, Argentina 1994–96	200 male cases from four hospitals in Buenos Aires, residing in the town or province of Buenos Aires; 94.5% confirmed by histology or cytology; response rate 93%	397 male controls hospitalized for non-tobacco related conditions, residing in the town or province of Buenos Aires, matched by hospital and age; response rate 99%	Face to face interview using standardized questionnaire for full occupational history, coded using ISCO/ISIC; Further details requested for occupations held >1 year	*Ever painters* General Blowtorch	16 8	1.2 (0.5–2.4) 1.4 (0.5–4.4)	Age, hospital, smoking (pack-years), other occupations with significant ORs (p <0.05)	
De Stefani *et al.* (2005) Montevideo, Uruguay, 1994–2000	338 male patients from four major hospitals in Montevideo, aged 30–89 years; response rate 96.8% (338 subjects); 100% histologically confirmed; restricted to lung adeno-carcinomas	1014 males hospitalized for conditions not related to tobacco smoking, matched by age, residence and urban/rural status; response rate 95.7%	Interviewer-administered questionnaire with life-time occupational history	**Ever painter** *Employment (years)* 1–20 21+ p for trend	26	1.8 (1.0–3.1) 9.6 (2.6–36.0) 1.2 (0.6–2.2) 0.07	Age, residence, urban/rural status, education, smoking status and years since quitting and age at start, number of cigarettes per day	Hospital controls: 20.3% eye disorders, 18.3% fractures, 17.9% abdominal hernias, 11.0% injuries, 7.9% acute appendicitis, 7.2% diseases of the skin, 5.8% varicose veins, 3.9% hydatid cyst, 2.9% blood disorders, 2.6% urinary stones and 2.2% osteoarticular disorders

Table 2.2 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Other Regions								
Bethwaite *et al.* (1990) New Zealand 1980–84	4224 male cases had known occupation among 5031 cases identified from the New Zealand Cancer Registry, aged 20 or more at registration; % microscopic confirmation not given	15 680 male non-lung cancer registrants with known occupation, [out of 19 731 identified] from the same Registry and period, aged 20 or more at registration; % microscopic confirmation not given	Current/ most recent occupation as recorded at the time of registration and smoking history obtained through telephone interview, coded using NZSCO	Painter decorators, steel and other construction painters, car painters, spray painters, signwriters, other unclassified painters	88	1.12 (0.93–1.52)	Age	

Table 2.2 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Notani *et al.* (1993) Bombay, India 1986–90	246 male patients from Tata Memorial Hospital in Bombay; age not given; 98% histologically confirmed	212 male hospital-based controls diagnosed with cancers of the mouth (n = 160) and oro- or hypo-pharynx (n = 27), and non-cancerous oral disease (n = 25), frequency matched by age and community; age not given	Interviewer-administered questionnaire with life-time occupational history	Ever painters	6	1.62 (0.4–7.0)	Age, community, smoking (two groups)	Descriptive characteristics and response rate for cases and controls not given. Further analysis for painters using a “not-exposed” group of watchmen, policemen, semi-skilled/unskilled workers, office workers, teachers, salesmen, small business employees resulted in an OR of 1.84 (95% CI, 0.4–8.5)

Table 2.2 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Studies in Vol. 47								
Levin *et al.* (1988) China 1984–85	733 incident male cases, aged 35–64, identified through the Shanghai Cancer Registry	760 age-matched population controls	Lifetime occupational history from interview, classified according to the Chinese population census	**Ever painter**	15	1.4 (0.5–3.5)	Age, smoking	* The variance was doubled to approximate an adjusted 95%CI. #calculated using a fixed effects model
				Duration (yrs)				
				0	718	1.0 (ref)		
				<10	7	1.9 [0.36–16.60]*		
				10–19	2	2.8 [0.07–62.47]*		
				20–29	5	2.2 [0.26–26.67]*		
				≥30	1	0.3 [0.01–5.81]*		
				>10	8	[1.34 (0.26–6.92)]#		
				<20	9	[2.35(0.44–12.47)]#		
				>20	6	[1.18 (0.18–7.64)]#		

ETS, environmental tobacco smoke; NG, not given; OR, odds ratio; CI, confidence interval; ASCR, Association of Swiss Cancer Registries; SIC, Standard Industrial Classification; SOC, Standard Occupational Classification; ISCO, International Standard Classification of Occupations; ISIC, International Standard Industrial Classification; NZSCO, New Zealand Standard Classification of Occupations; NACE, Nomenclature Générale des Activités Économiques dans les Communautés Européennes

(b) North America

Vineis *et al.* (1988) analysed data from five case–control studies of lung cancer conducted during 1970–1980 in the States of Louisiana, Florida, Pennsylvania, Virginia, and New Jersey, USA (Blot *et al.*, 1980, 1982 and 1983; Correa *et al.*, 1984, Schoenberg *et al.*, 1987). Subjects with a diagnosis of lung cancer resident in selected geographic areas of the respective states were identified from existing cancer registries, from cooperating hospitals or from death certificates. Information was collected by interview, with the enrolled subject or with the next-of-kin, for each job held for 6 months or more. Unexposed subjects were those with an occupation/industry without a well established or suspected carcinogenic exposure (Simonato & Saracci, 1983). Overall, 2973 male cases (201 painters) and 3210 controls (193 painters) were included in the analysis. For painters, the OR for cancer of the lung adjusted by age, birth cohort, and usual cigarette use was 1.1 (95% CI: 0.9–1.4). [The results of the studies included in the analysis had been previously published without focusing on painters only, and therefore were not evaluated in Monograph 47.]

From the Missouri Cancer Registry, 1980–1985, Zahm *et al.* (1989) identified 4431 caucasian male cases with lung cancer (histological type and grade recorded), residing in Missouri. Controls were 11326 caucasian male non-lung-cancer registrants from the same registry and period, excluding cancers of lip, oral cavity, oesophagus, lung, bladder, ill-defined or unknown sites. Occupation at the time of diagnosis was abstracted from the registry records. There were 37 painters, wallpaper hangers, and plasterers among cases, and 39 among controls. Painters, wallpaper hangers, and plasterers had an age- and smoking-adjusted OR of 2.0 (95% CI: 1.2–3.3). Restricting the analysis to cases aged <60 years, an OR of 3.2 (95% CI: 1.1–10.0) was found. [Absence of life-long occupational history may have led to non-differential misclassification of exposure.]

Among residents of the Detroit metropolitan area, Burns & Swanson (1991) examined incident cancer cases selected through the Metropolitan Detroit Cancer Surveillance System (MDCSS), a population-based cancer reporting system in the context of the Occupational Cancer Incidence Surveillance System (OCISS) study. The study enrolled 5935 (3918 males, 2017 females) lung cancer cases and 3956 (1981 males, 1975 females) colorectal cancer cases as control group, all aged 40–84 years, over a non-specified period. Subjects or their surrogates were interviewed by telephone (response rates of 94% for cases, and 95% for controls), and complete lifetime occupational and smoking histories were obtained. Usual occupation was defined by summing up the total number of months a person was employed in a specific occupation over their entire work history, and then selecting the occupation for which the person had accumulated the largest number of months of exposure. Occupations and industries categorized as ’unexposed’ were those considered to have the least potential for exposure to carcinogenic agents. For the occupational group of painters (97 cases, 35 controls), the OR was 1.96 (95% CI: 1.23–3.13) after adjusting for age at diagnosis, race, smoking, and gender. When detailed occupation codes (specific occupation) were analysed among males, the elevated risk among painters was found to be concentrated among painting

machine operators working in an industrial setting (OR, 4.50; 95% CI: 1.71–11.82; adjusted for age at diagnosis, race, and smoking; based on 37 cases), rather than among house painters (the cancer sites included in the OCISS study are: salivary glands, oesophagus, stomach, colon, rectum, liver, lung and bronchus, pleura [mesothelioma], urinary bladder, melanoma of the skin, and eye).

Again in the context of the OCISS study, Swanson *et al.* (1993) studied possible differences by race in the relationship between length of employment in specific occupations and the risk of lung cancer. The study included 3792 males (2866 caucasian, 926 black) aged 40–84 years, with incident lung cancer cases from the MDCSS in the period 1984–1987; 1966 males (1596 caucasian, 370 black) with cancers of the colon and of the rectum constituted the referent group. Exposure was collected and coded as per the study of Burns & Swanson (1991). The ORs and corresponding 95% CIs (adjusted for age at diagnosis and pack–years of cigarette smoking) according to number of years employed in the specific occupation of 'painting machine operators' among caucasian males were as follows: 1–9 years, 1.1 (0.5–2.4); 10–19 years, 0.6 (0.2–2.2); ≥ 20 years, 3.9 (1.2–13.0), with a non-significant trend. The same figures among black men were: 1–9 years, 1.5 (0.4–5.6); 10–19 years, 9.9 (0.9–109.2); ≥ 20 years, 8.7 (0.9–89.3), with a significant trend. [Although not clearly stated in the published reports, this paper does not represent an independent set of cases and controls, but is a re-analysis of a subgroup reported in the study of Burns & Swanson (1991).]

Morabia *et al.* (1992) conducted the American Health Foundation study in the US (Detroit, Chicago, Philadelphia, Pittsburgh, New York, Long Island, San Francisco, Birmingham, and Atlanta), during 1980–1989: 1793 male cases from 24 hospitals diagnosed with lung cancer (all confirmed by histology) were included, with 3228 controls hospitalized for diagnoses other than lung cancer but including tobacco-related conditions, matched by age, race, hospital, smoking history, and admission date. A standardized questionnaire was administered during face-to-face interviews. Only the 'usual' occupation was recorded, along with exposure to up to two agents out of a list of 44 (during the study period 1980–1984), or up to six agents (during the study period 1985–1989). The response rate was not reported. An OR of 0.8 was found for occupation as 'ever painter', adjusted for age, geographic area, race, smoking, and study period. Neither the number of cases that ever worked as a painter nor the confidence interval were given, but a 0.33 power to detect an OR of 1.5 was reported. [Full occupational histories were not collected, as only the 'usual' occupation was recorded, so random misclassification of exposure is likely.]

Muscat *et al.* (1998) reported results during 1978–1996 of an on-going hospital-based case–control study in teaching hospitals in New York City, Long Island, Philadelphia, Washington DC, Detroit, and Chicago. The analysis included black subjects only and was "similar to an analysis of occupational factors and lung cancer risk previously performed for white subjects" (Morabia *et al.*, 1992). The case series were 365 black men and 185 black women with histologically confirmed lung carcinomas. Controls were 251 male and 135 female black patients admitted to teaching hospitals for conditions

unrelated to tobacco use, matched by race, gender, 5-years age groups, and month of diagnosis. Over 90% of eligible participants who were approached were interviewed by interviewer-administered questionnaire (no specific rates for gender or case–control status were given). Subjects were asked to provide their usual adult occupation and whether the job entailed regular exposure to an occupational agent (a minimum of 8 hours a week). A list of over 40 occupational exposures was provided. Compared to men who were 'never' painters, the OR for male painters for cancer of the lung was 0.7 (95% CI: 0.3–1.1; based on 30 cases after adjusting for age, education, and pack–years of smoking). Females painters compared to female 'never' painters had an OR of 1.8 (95% CI: 0.3–12.3, based on five cases and one control after adjusting for age, education, and pack–years of smoking). [It was not possible to assess the overlap between Morabia *et al.* (1992) and Muscat *et al.* (1998).]

In two Ontario (Canada) cities, Hamilton and Sault Ste-Marie, Finkelstein (1995) identified 967 men aged 45–75, residing in the study areas, who died from lung cancer during 1979–1988. Decedents (n = 2821) of any cause other than lung cancer, matched on age, year of death, and city of residence, were used as reference. The analysis was based on occupation (job and industry) as reported on the death certificate. Painters and plasterers had an OR of 1.25 (95% CI: 0.63–2.36; based on 16 cases, after adjustment for age, year of death, and city of residence). [No information was available on smoking.]

(c) South America

De Stefani *et al.* (1996) conducted a study of 270 male incident lung cancer cases, aged 30–75 years, admitted to five major hospitals in Montevideo, Uruguay, during 1993–1994, as part of a multisite case-referent study. Controls (n = 383) were patients with cancer diagnoses other than the lung, oral cavity, pharynx, oesophagus, stomach, larynx, and bladder. Occupational histories and tobacco smoking were collected through face-to-face interviews. The subjects employed in each occupation for at least one year were compared with subjects never employed in the corresponding occupations. The OR for painters (job title) was 1.2 (95% CI: 0.6–2.4; 18 cases), adjusted for age, residence, education, tobacco smoking (pack–years), and alcohol consumption. The adjusted ORs (95% CI) according to length of exposure were: 1–20 years, 0.9 (0.2–3.0); ≥ 21 years, 1.4 (0.6–3.1). The adjusted ORs (95% CI) of lung cancer stratified by cell type were as follows: squamous cell, 1.5 (0.6–3.4); small cell, 2.8 (0.8–9.9); and adenocarcinoma, 0.5 (0.1–2.5).

In the same area of Uruguay, De Stefani *et al.* (2005) examined occupations associated with adenocarcinoma of the lung. During 1994–2000, 349 histologically verified adenocarcinomas of the lung occurring in male patients admitted to four major hospitals in Montevideo, Uruguay, were identified, and 338 were included in the study (response rate 96.8%, 26 painters). During the same period and in the same hospitals, 1060 men were hospitalized for conditions not related to tobacco smoking, and 1014 of them constituted the control series (response rate 95.7%, 38 painters). Controls were frequency-matched on age, residence, and urban/rural status. Complete occupational and

tobacco smoking histories were obtained through face-to-face interviews. 'Ever' versus 'never' having worked as a painter was associated with an OR of 1.8 (95% CI: 1.0–3.1), adjusted for age, residence, urban/rural status, education, smoking status, number of cigarettes per day, years since quitting, and age at start of smoking. The adjusted ORs (95% CI) according to length of exposure were: 1–20 years, 9.6 (2.6–36.0), ≥ 21 years, 1.2 (0.6–2.2), *P* for trend = 0.07.

Wünsch Filho *et al.* (1998) conducted a hospital-based case–control study in Sao Paulo, Brazil, during 1990–1991: 398 cases (307 men, 91 women) living in the metropolitan area of Sao Paulo and diagnosed with lung cancer (all confirmed by histology or cytology) in 14 hospitals were included, as well as 860 controls (546 men, 314 women) hospitalized for non-tobacco-related conditions, matched by age, sex, and hospital. A standardized questionnaire, with full occupational histories, was administered through face-to-face interviews. Response rates were not given. Among men, 'ever' painters with duration ≥ 10 years and latency ≥ 40 years had an OR of 1.28 (95% CI: 0.77–2.15), after adjustement for age, smoking, cancer in family, migration history, and socioeconomic status.

Pezzotto & Poletto (1999) identified 367 newly diagnosed primary lung cancer male patients from three medical institutions of Rosario City, Argentina, admitted during the period 1992–1998. A total of 586 age-matched controls were selected from patients admitted to the same hospitals as cases for a non-smoking-related disease. Lifetime occupational history was collected through standardized questionnaires, and subjects never employed in occupations involving exposure to agents listed in the IARC Monographs in groups 1, 2A or 2B were considered as the reference group. The OR for house painters for cancer of the lung was 2.4 (95% CI: 0.4–19.4; four cases, five controls) after adjusting for age, smoking habit, and lifelong cigarette consumption. An analysis stratified by cell type was also performed (see Table 2.2).

Matos *et al.* (2000) conducted a hospital-based case–control study in Buenos Aires, Argentina during 1994–1996. A total 216 men residing in the town or province of Buenos Aires diagnosed with lung cancer (94.5% confirmed by histology or cytology) were identified in four hospitals, along with 402 controls hospitalised for non-tobacco related conditions, matched by hospital and age. A standardized questionnaire, with full occupational history, was administered through face-to-face interviews, with a response rate of 93% among cases, and 99% among controls resulting in the inclusion of 200 cases and 397 controls. ORs, adjusted for age, hospital, smoking (pack–years), and other occupations with significantly increased ORs, were 1.2 (95% CI: 0.5–2.4; based on 16 cases) for 'ever' painters (general), and 1.4 (95% CI: 0.5–4.4; based on eight cases) for painters who used a blowtorch. Only occupations lasting at least 1 year were considered for the analysis.

(d) Other regions

Bethwaite *et al.* (1990) identified 24 762 incident cancer cases in men from the New Zealand Cancer Registry, 1980–1984. The proportion with histological or cytological

confirmation of diagnosis was not stated. The study was restricted to cases aged 20 years or more at registration, and for 19 904 of their total,the current or most recent occupation at registration was recorded. The association between different cancer sites and work as a painter was studied by conducting a series of case–control studies. For each neoplasm, registrants for the other cancer sites were used as reference. Overall, 5031 lung cancer cases were registered, 4224 (84%) with known occupation – 88 of those were painters. Corresponding figures among controls were: 19 731 registered, 15 680 with known occupation, of which 265 painters. An age-adjusted OR of 1.12 (95% CI: 0.93–1.52) was calculated by the Mantel-Haenszel method. [ORs could not be adjusted for smoking. Absence of life-long occupational history may have led to non-differential misclassification of exposure. The Working Group noted that an excess risk was found for cancers of the kidney, of the bladder, and for multiple myeloma. For multiple myeloma, the risk was higher for car, spray, and signwriter painters (OR: 2.81; 95% CI: 0.73–10.7) than for construction and general painters (OR,1.80; 95% CI: 0.89–3.64).]

Notani *et al.* (1993) identified 246 male lung cancer cases resident in the State of Maharashtra who were admitted to the Tata Memorial Hospital of Bombay, India, and interviewed during 1986–1990. A total of 212 controls were selected from male patients admitted to the same hospital for other cancers (mouth, pharynx, $n = 187$) or non-cancerous oral disease ($n = 25$). The case and control groups had similar age distributions. Occupational history and tobacco use were obtained by interviews conducted in the hospital. The OR for ‘ever‘ painters compared to ‘never’ painters, adjusted for age and smoking was 1.62 (95% CI: 0.4–7.0; based on six cases). The risk was also not significantly increased when using a reference category of ‘unexposed’ subjects who had exclusively worked in occupations with little possibility of exposure to any occupational carcinogen (OR, 1.84; 95% CI: 0.4–8.5). [The Working Group noted that the study could be limited by the lack of statistical power, as cited by the authors. The study examined also the association between occupations and 153 cases of bladder cancer.]

2.2.2 *Mesothelioma*

There were two case–control studies on mesothelioma that showed an increased risk (OR, 4.5; 95% CI: 1.0–23.7; 6 exposed cases; Teschke *et al.*, 1997a) and (OR, 2.6; 95% CI: 1.3–5.3; 31 exposed cases; Pan *et al.*, 2005) for persons ever employed as painters.

2.2.3 *Bladder cancer* (Table 2.3)

(a) Europe

González *et al.* (1989) conducted a multicentre case–control study of bladder cancer in four regions of Spain. The study included 497 cases (438 males and 59 females), 583 hospital controls and 530 population-based controls. Employment as a painter was only associated with a slightly increased risk of bladder cancer among males (OR, 1.16; 95% CI: 0.7–2.0; 17 cases).

Table 2.3. Case-control studies of lower urinary tract cancer among persons exposed in painting

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Europe *Studies since Vol.47*								
González *et al*. (1989) Barcelona, Madrid, Cadiz, Guipuzcoa and Vizcaya, Spain 1985–86	497 (438 men, 59 women) from 12 hospitals; below age of 79 years; response rate 71.9%; 100% histologically confirmed	583 hospital-based controls from the same hospitals, 530 population-based controls selected from census or municipal registers; matched by age and sex; response rate 70.5% for hospital controls and 65.7% for population controls	Interviewer-administered standardized questionnaire. All interviews were conducted at the subjects' home and occupational history included any job lasting more than six months	Male Painters	17	1.16 (0.7–2.0)	Exposure to other high risk occupations and cigarette smoking (included in the model in three categories: smokers, ex-smokers and never-smokers)	The hospital controls were selected from hospital patients. Patients with the following diagnoses were excluded from the control selection: chronic respiratory diseases, coronary heart disease, infections of the urinary tract, haematuria and cancer of the respiratory tract. *Excluded from the meta-analysis because of inclusion in Kogevinas et al. (2003)*

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
La Vecchia *et al.* (1990) Milan, Italy 1985–88	263 (219 men, 44 women) from major teaching and general hospitals; below the age of 75 years; response rate greater than 97%; 100% histologically confirmed	287 (210 men, 77 women) hospital-based controls from the same hospitals; response rate greater than 97%; controls were admitted for acute, non-neoplastic or urinary tract diseases	Interviewer-administered standardized questionnaire to collect information on age at starting and stopping work in 19 industries or occupations, on subjects' role in the industry in terms of direct involvement in production aspects, and on exposure to 14 selected occupational agents or groups of agents	Painting (including spraying) *Dyes/paint exposure* ≤10 years >10 years *p* for trend	NG	1.8 [0.72–4.48] 1.6 [0.70–3.65] 4.8 [1.37–16.78] 0.04	Age, sex, smoking	

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Myslak *et al*. (1991) Dortmund, Germany 1984–87	403 men from three major hospitals; 82% response rate; 100% histologically confirmed	426 hospital-based controls with benign prostate diseases from the same hospitals; 84% response rate	Mailed standardized questionnaire was used to collect information on occupational history and smoking habits	Painters	21	2.8 (1.21–6.28)	None	While smoking information was collected, there was no indication that the study controlled for any confounding effect from smoking. *Excluded from meta-analysis because of overlap with Golka (1999)*

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Kunze *et al.* (1992) Southern Lower Saxony, Germany 1977–85	675 (531 men, 144 women) cases admitted to hospitals for lower urinary tract cancers; 100% histologically confirmed	675 controls admitted to the same hospitals as cases for non-neoplastic diseases of the urinary tract; matched by age (± 5 years) and sex at a 1:1 ratio	Interviewer-administered standardized questionnaire to collect occupational exposure information. Participants were asked to give a chronologic account of all jobs held at least 6 months and the duration of the employment. Length of employment in a certain occupation was computed from all jobs included in that occupation category	Painters	15	1.3 (0.6–2.7)	Smoking status, lifetime cigarette consumption	63.7% male controls had hyperplasia of the prostate, 72.9% female controls had infection of the lower urinary tract. Cases were diagnosed with benign or malignant epithelial tumors of the urinary bladder, ureters, renal pelvis and urethra. *Excluded from the meta-analysis because included in Kogevinas et al. (2003)*
				Dyestuffs and paints				
				Duration (years)				
				1–9	6	1.2 (NG)		
				10–19	4	1.0 (NG)		
				20+	24	2.5 (p <0.05)		
				p for trend		0.03		
				Lacquer and paint	78	1.5 (1.1–2.2)		
				Spray paints				
				Ever	52	2.9 (1.7–4.9)		
				Duration (years)				
				1–9	13	4.7 (NG)		
				10–19	8	8.4 (NG)		
				20–29	14	2.0 (NG)		
				30+	17	2.4 (NG)		
				p for trend		0.004		

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Cordier *et al.* (1993) Paris, Strasbourg, Clermont-Ferrand, Lille, France 1984–87	765 (658 men, 107 women) from seven hospitals, aged under 80 years; 100% histologically confirmed	765 hospital-based controls (no respiratory disease or symptoms suggestive of bladder cancer); matched at a 1:1 ratio by sex, age, ethnic origin and place of residence	Interviewer-administered standardized questionnaire to collect lifelong occupational history for each paid or unpaid job held for at least 6 months	Male painters Male spray painters	19 8	0.97 (0.50–1.88) 6.41 (0.79–51.9)	Hospital, place of residence, and smoking status	*Excluded from the meta-analysis because of inclusion in Kogevinas (2003)*
Barbone *et al.* (1994) Northeast Italy 1986–90	273 (236 men, 37 women) from clinic centres; 97.5% histologically confirmed	573 (390 men, 183 women) hospital-based controls from the same clinic centers.	Interviewer-administered structured questionnaire to collect usual occupation and employment in any of 18 industries and 13 occupational agents	Painting (Males)	6	3.1 (0.7–13)	Age, cigarette smoking, coffee consumption, and area of residence	Controls were patients without bladder cancer, but admitted for trauma, non-traumatic musculoskeletal conditions, acute surgical conditions, eye diseases, and other conditions such as diseases of ears, nose, throat or mouth

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Hours *et al.* (1994) Lyon, France 1984–87	116 cases (97 male, 19 female)	232 hospital-based controls matched by gender, hospital, age, nationality	Job history from in-person interview	Painting (regular leisure-time activity)	12	1.56 (0.56–4.58)	Gender, hospital, age, nationality	*Excluded from the meta-analysis because of inclusion in Kogevinas et al., (2003)*
Porru *et al.* (1996) Brescia, Italy 1992–93	355 (275 men, 80 women) from the General Hospital of Brescia; men aged 24–84 years, women aged 26–87 years; response rate 98.6%; 100% histologically confirmed	579 (397 men, 182 women) hospital-based controls, selected from three hospitals; men aged 19–89 years, women aged 21–86 years; males matched by age; response rate 99.1%	Interviewer-administered structured questionnaire to collect information on lifetime occupation history for each job lasting for at least six months	Male Painters	12	1.4 (0.6–3.5)	Age, residence, education, smoking, and coffee and alcohol consumption	Controls were patients with urological non-neoplastic diseases. If these diseases are also associated with paint exposure, use of the patients with these diseases may cause an underestimation of the association of interest. *Excluded from the meta-analysis because of inclusion in Kogevinas (2003)*

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Golka *et al.* (1999) Dortmund, Germany 1984–88	412 male cases from urology departments of 3 hospitals in Dortmund, Germany, 1984–88. Response rate 82%	414 male controls with benign prostatic hyperplasia, Response rate 84%	Complete occupational history for jobs held >1 year and at least 10 years before interview	Painters & lacquerers	21	2.24 (1.07–5.13)	Smoking	
Pohlabeln *et al.* (1999) Hessen, West Germany 1989–1992	300 cases (239 male, 61 female) of histologically confirmed cancer of the lower urinary tract (LUT); malignant tumours of the urinary bladder (89.6% ICD9: 188), ureter (1.0%), renal pelvis (3.7%), urethra (1.7%), multiple localizations (4.0%); 92.6% participation rate	300 controls with non-neoplastic diseases of the lower urinary tract individually matched to cases from the same hospitals with respect to sex, age & area of residence; 98% participation rate	Job history from in-person interview			No specific info on painters other than 3-fold increased risk	Age, sex, area of residence	Ex-smokers = stopped smoking ≥1 year before the interview. *Excluded from the meta-analysis because of inclusion in Kogevinas et al., (2003)*

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Pesch *et al.* (2000a, b) West Berlin, Bremen, Leverkusen, Halle and Jena, Germany 1991–95	1035 cases (704 men, 331 women) of cancers of the urinary bladder, ureter, renal pelvis from hospitals; response rate 84%; 100% histologically confirmed	4298 population-based controls (2650 men, 1648 women) selected from local residency registries, matched by region, age and sex; response rate 71%	Interviewer-administered structured questionnaire to collect information on lifetime occupational history. Two job–exposure matrices and one job task–exposure matrix were used to assess exposure to occupational agents	**Male Painters**		No summary OR	Age, study centre, smoking	90.2% of the male cases and 84.3% of the female cases had urinary bladder cancer
				Duration				
				Medium	12	1.3 (0.6–2.6)		
				Long	6	0.7 (0.3–1.6)		
				Very long	5	1.6 (0.5–4.7)		
				Paints and Pigments				
				Male				Categories for exposure duration (short, medium, long and very long) and level of exposure to paints and pigments (low, medium, high and substantial) were defined based on the 30th, 60th, 90th percentile in exposed controls. *Excluded from the meta-analysis because of inclusion in Kogevinas et al. (2003)*
				Medium	97	1.0 (0.8–1.3)		
				High	75	1.0 (0.8–1.3)		
				Substantial	35	1.3 (0.9–2.0)		
				Female				
				Medium	9	1.7 (0.7–3.8)		
				High	5	0.6 (0.2–1.8)		
				Substantial	1	0.3 (0.03–2.5)		
				Paints				
				Male				
				Medium	57	1.0 (0.8–1.3)		
				High	181	1.2 (1.0–1.5)		
				Substantial	67	1.2 (0.9–1.7)		
				Female				
				Medium	25	0.8 (0.5–1.3)		
				High	31	0.9 (0.6–1.4)		
				Substantial	9	0.9 (0.4–1.9)		
				Use or production of paints				
				Male				
				Medium	29	0.6 (0.4–0.9)		
				High	60	1.0 (0.7–1.3)		
				Substantial	24	1.4 (0.8–2.3)		

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Pesch *et al*. (2000a, b) (contd)				*Female*				
				Medium	5	1.0 (0.4–2.8)		
				High	51	1.3 (0.9–1/8)		
				Substantial	22	1.3 (0.8–2.3)		
Bouchardy *et al*. (2002) Cantons of Basel, Geneva, St Gall, Vaud and Zurich, Switzerland 1980–93	3014 male cases from cantonal Cancer Registries, aged 25 or more (and 65 or less in St Gall and Vaud)	55 120 male non-bladder cancer registrants from the same registries and period	Longest, current or most recent occupation as recorded at the time of registration (main or best specified occupation in Zurich Registry), coded using the ASCR Classification of Occupations	Plasterers and painters (in the construction industry)	73	1.1 (0.8–1.4)	Age, registry, civil status, period of diagnosis, nationality, urban/rural residence, SES, histological confirmation, information from death certificate only (cases)	Adjusting for SES may over-adjust for occupational risk factors but serve as a surrogate for smoking. Overall 95.1% histologic confirmation for all sites

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Pelucchi *et al.* (2002) Milan area and Pordenone, Italy 1985–92	110 women from major teaching and general hospitals; aged 30–79 years; response rate greater than 97%; 100% histologically confirmed	298 hospital-based controls from the same hospitals, aged 26–79; response rate greater than 97%	Interviewer-administered standardized questionnaire to collect information on occupation history and selected occupational exposures as well as other potential confounders	Dyestuff and painting industry	3	1.4 (0.3–6.8)	Age, study centre, education, BMI, cigarette smoking, coffee and alcohol consumption	Controls were patients diagnosed with acute, non-neoplastic, non-urinary or genital tract diseases. The study reported dyestuff and painting industry as one exposed group, and dyes have also been linked to bladder cancer

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Kogevinas *et al*. (2003) Germany, France, Italy, Spain, Greece, Denmark 1976–1996 Pooled analysis of 11 case-control studies	3346 male cases aged 30–79 yrs	6840 male hospital-based and population-based controls aged 30–79 yrs; individually or frequency matched on age & geographic area	Lifetime occupational history (for jobs held ≥6 months) or longest job held; coded using ISCO 1968 and ISIC rev2 codes	*Painters* *Automobile painters* Employed ≥25 yrs	116 19 NG	1.17 (0.91–1.50) 1.95 (1.01–3.75) 2.1 (0.6–7.1)	Age, smoking, study centre	Data were pooled from Claude *et al.* (1998), Pohlabeln *et al.* (1999), Pesch *et al.* (2000), Cordier *et al.* (1993), Hours *et al.* (1994), Vineis & Magnani (1985), Porru *et al.* (1996), González *et al.* (1989), Serra *et al.* (2000), Rebelakos *et al.* (1985), Jensen *et al.* (1987); unexposed group excludes subjects who worked in high-risk occupations; 93% cases & 78% controls had ever smoked

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Reulen *et al.* (2007) Limburg, Belgium 2003–05	202 cases (174 men, 28 women), ages 40–96, diagnosed with histologically confirmed transitional cell carcinoma of the bladder; 9% participation rate	390 controls (231 men, 159 women); selected from the general population of the province of Limburg by simple random sampling; >50 years old, Caucasian, with no previous diagnosis of bladder cancer; 26% participation rate	lifetime occupational history (jobs held ≥6 months) from in-person interview coded using ISCO codes	Painters & varnishers	10	2.2 (0.7–7.2)	Sex, age, years of cigarette smoking, number of cigarettes smoked per day, current smoking status, education	

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Golka *et al.* (2008) North Rhine-Westphalia, Germany 1992–95	156 male bladder cancer cases; 63% response rate	336 male controls diagnosed with prostate cancer; 72% response rate	Occupational history (for jobs held ≥6 mo) from mailed questionnaire; coded using a German classification scheme (Statistisches Bundesamt, 1992)	Painter/varnisher	7	1.98 (0.64–6.11)	Age, smoking	The variable smoking pertains to the smoking status 10 yr ago; hence individuals who had quit smoking for more than 10 yr before first diagnosis were included in the nonsmoking group. Proportion of never smokers: 13% for bladder cancer, 26% for prostate cancer

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Studies in Vol. 47								
Vineis & Magnani (1985) Italy 1978–83	512 men	Hospital; other urological and surgical	Interview	Painter in building industry Car painter ≥5 years Carpentry painter Spray painter in different industries	12 7 1 2	1.0 (0.40–2.2) 2.0 (0.60–7.0) 0.6 (0.04–8.4) 1.2 (0.20–5.8)	Age, smoking	*Excluded from the meta-analysis because of inclusion in Kogevinas et al. (2003)*
Jensen *et al*. (1987) Denmark 1979–81	371	Population	Interview	Different painting industries Painter 10 years	13	2.5 (1.1–5.7) 1.4 (1.0–1.9)	Age, sex, smoking	*Excluded from the meta-analysis because of inclusion in Kogevinas et al. (2003)*

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Schifflers *et al*. (1987) Belgium 1984–85	74	Population	Interview	Painter in high-risk occupation	NG	NG	NG	[A group of 16 jobs, including painting, were defined as hazardous and associated with a high risk for bladder cancer, but exposure to painting as a specific job did not show a significant excess]. No increased risk reported
Claude *et al*. (1988) Germany NG	531 men	Hospital urological and homes for elderly	Interview	Ever painter Lacquer and paint Spray paints	15 78 52	1.3 (0.59–2.7) 1.5 (1.1–2.2) 2.9 (1.7–4.9)		Trend, $p = 0.04$ for exposure to spray paints. *Excluded from the meta-analysis because of inclusion in Kogevinas et al. (2003)*

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Morrison *et al*. (1985) USA, UK, Japan, 1976–78	UK, 399	Population	Interview	Paint and paint manufacture	23	0.7 [0.42–1.18]	Age, smoking	
Coggon *et al*. (1986) Cleveland, Humberside, Cheshire counties, UK 1975–80	179 male cases of cancer and the bladder and renal pelvis, aged 18–54 yrs, identified from hospital and cancer registry records	1221 other cancers	Occupation from mailed questionnaire	Painters and decorators	10	0.7 [0.27–1.81]	Age, smoking, residence, respondent	52.1% overall response rate; the variance was doubled to approximate an adjusted 95%CI. The unadjusted 95%CI was 0.78–2.18. *Possible overlap with OPCS (1986)*

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
North America								
Studies since Vol. 47								
Miller *et al.* (1986) USA 1977–78	2331 white cases; aged 21–84 years; 100% histologically confirmed	4525 white population-based controls; matched by age and sex	Interviewer-administered standardized questionnaire. A list of materials the subjects reported using in each job held for ≥6 months was evaluated to determine exposure to paint	Painter (Artistic)	15	2.5 (1.1–5.7)	Smoking	Subjects were considered to be exposed if they were ever employed as an artist and had worked with paint. *Excluded from meta-analysis because artistic painters could have different exposures than other occupationally exposed painters*
				Duration (years)				
				<10 years	4	1.7 (NG)		
				10+ years	11	3.0 (NG)		
				p for trend		0.01		

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Silverman *et al.* (1989a) New Jersey, Connecticut, Iowa, New Mexico and Utah, plus Atlanta, Detroit, New Orleans, San Francisco, and Seattle, USA 1977–78	2100 white men from registry; aged 21–84 years; response rate 75%; 100% histologically confirmed	3874 white male population-based controls, selected by random digit dialing for those 21–64 years, stratified sampling from the Health Care Financing Administration's lists for those aged 65–84 years; matched by age and geographic area; response rate 84% for aged 21–64 years, and 83% for aged 65–84 years	Interviewer-administered standardized questionnaire to collect detailed information on every job a subject had held for at least 6 months since the age of 12 years	Construction and maintenance painter	76	1.5 (1.1–2.2)	Age, smoking	Workers within each industry were grouped by occupational code, and occupational codes were grouped by potential for similar exposure. The study transformed 417 census codes into 163 occupational categories that were meaningful for analysis. *The variance was doubled to approximate and adjusted confidence interval; **calculated using a fixed effects model
				Manufactured articles painter	25	1.3 (0.8–2.3)		
				Sign painter	NG	1.1 (0.3–3.7)		
				Artistic painter	13	1.8 (0.8–4.3)		
				All painters	116	1.5 (1.2–2.0)		
				Duration (years)				
				<5	50	1.7 [0.97–2.90]*		
				5–9	14	0.9 [0.38–2.34]*		
				10–24	26	1.6 [0.82–3.74]*		
				25+	22	1.9 [0.75–4.09]*		
				p for trend		0.001		
				<10 yrs	64	[1.44 (0.90–2.29)]**		
				≥10 yrs	48	[1.73 (0.98–3.04)]**		

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Silverman *et al.* (1989a) (contd)				*Duration (years) by initial year of employment as a painter*				
				<1930				
				<5	10	1.2 (NG)		
				5–9	5	1.3 (NG)		
				10+	18	3.0 (NG)		
				1930–1939				
				<5	8	1.5 (NG)		
				5–9	2	0.4 (NG)		
				10+	9	1.5 (NG)		
				≥1940				
				<5	32	2.0 (NG)		
				5–9	7	1.0 (NG)		
				10+	21	1.4 (NG)		

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Silverman *et al.* (1989b) New Jersey, Connecticut, Iowa, New Mexico, and Utah, plus Atlanta, Detroit, New Orleans, San Francisco, and Seattle,USA, 1977–78	126 non-white men from Cancer Registry; aged 21–84 years; response rate 75%; 100% histologically confirmed	383 population-based controls, selected by random digit dialling for those 21–64 years, stratified sampling from the Health Care Financing Administration's lists for those aged 65–84 years; matched by age and geographic area; response rate 84% for aged 21–64 years, and 83% for aged 65–84 years	Interviewer-administered standardized questionnaire	All Painters Painter, construction and maintenance	5 4	1.2 (0.4–3.7) 1.4 (0.4–5.4)	All ORs were adjusted for smoking	Non-white men, 70% cases and 75% controls were black
Silverman *et al.* (1989a,b) See above	See above	See above	See above	All painters (white & non-white)	121	[1.48 (1.16–1.90)]*	See above	*calculated using a fixed effects model

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Burns & Swanson (1991) Michigan, USA, Time period not stated Recruitment period not specified, probably 1984–87, as in Swanson *et al.*, (1993)	2160 (1571 men, 589 women) from the Metropolitan Detroit Cancer Surveillance System; aged 40–84; response rate 94%; 100% histologically confirmed	3979 (1997 men, 1982 women) with cancer of the colon or rectum from the Metropolitan Detroit Cancer Surveillance System; response rate 95%	Life-time occupational history obtained during telephone interviews to the subjects or to their surrogates, coded using US Bureau of Census classification.	Painters	30	1.1 (0.7–1.9)	Cigarette smoking, race, gender, and age at diagnosis	It is unclear about the validity of occupational data from telephone-based surrogate interviews

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Zheng *et al.* (2002) Iowa, USA, 1986–89	1452 (1135 men, 317 women) from the State Health Registry; aged 40–85; response rate 85%; 100% histologically confirmed	2434 (1601 men, 833 women) population-based controls randomly selected from computerized state driver's license records for aged under 65; aged 65 years and older were selected from US Health Care Financing Administration listings; matched by gender and age; response rate 82% for aged under 65 and 80% for aged 65 and older	A standardized questionnaire was mailed to all participants to inquire about history of each job held for 5 years or longer since the age of 16; a telephone interview was done with those who did not complete the mailed questionnaire.	**Male painters (construction and maintenance)** *All* Duration (years) <10 ≥10 **Male painting and paper-hanging** *All* Duration (years) ≥10	 11 5 6 9 6	 2.7 (1.0–7.7) not possible 1.4 (0.4–4.7) 2.9 (0.9–9.1) 1.9 (0.5–6.5)	Age, lifetime pack-years of cigarette smoking, and first-degree relative with bladder cancer	For each job recorded, detailed information was collected on job title, industry, the year the job began and ended, activities associated with the job; 5 cases and 0 controls male construction & maintenance painters exposed <10 years

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Colt *et al*. (2004) New Hampshire, USA 1994–98	424 (331 men, 93 women) from the New Hampshire State Cancer Registry; aged 25–74; participation rate 74.3%; 100% histologically confirmed	645 (407 men, 238 women) population-based controls selected by using population lists from the New Hampshire Department of Transportation for less than 65 years of age, and from the Centres for Medicare and Medicaid Services of New Hampshire for those age 65 years and more; matched by age and gender; participation rate 67.2%	Subjects completed a mailed questionnaire describing detailed lifetime occupational history and responses were reviewed by interviewers during an in-person interview	Male painters Male painters, construction and maintenance	12 7	[0.98(0.45–2.13)] [0.78(0.30–2.03)]	Smoking, age	The risk for painters was listed in a table for jobs with odds ratios less than 1.3. No confidence interval or *p* value was provided. Questionnaire included information on job title and place of work for each job held

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Siemiatycki (1991) Montreal, Canada, 1979–85	484 incident male cases; aged 35–70 yrs; histologically confirmed	533 population controls, 1879 cancer controls	Interview to obtain lifetime occupational history; painters coded using Canadian occupation classification			**OR (90% CI)**	Age, family income, ethnicity, respondent type, cigarette & alcohol index	*Excluded from the meta-analysis and replaced by Ramanakumar et al. (2008) analysis*
				Construction painter				
				Any exposure	13	1.3 (0.8–2.4)		
				Substantial exposure	8	1.7 (0.8–3.4)		
				Other painter				
				Any exposure	9	1.1 (0.6–2.1)		
				Substantial exposure	4	0.8 (0.3–2.2)		

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Siemiatycki *et al.* (1994) Montreal, Canada 1979–86	484 male cases from all large hospitals in the Montreal area; aged 35–70 years; response rate 84%; 100% histologically confirmed	533 population-based controls selected from electoral lists and by random digit dialing; response rate 72%; 1879 cancer controls (except lung or kidney cancer) from the same hospitals; response rate 84%	Interviewer-administered semi-structured questionnaire to collect detailed lifetime job history. Experts translated each job into a list of potential exposures by means of a checklist that included 294 substances	**Construction painters**			Age, ethnicity, socio-economic status, smoking, coffee consumption, and the status (self/proxy) of the respondents	The results presented in the paper were based on pooled controls (cancer and population controls). There was rather little difference between results based on cancer controls and those based on population controls when analyses were carried out separately with cancer controls, population controls, or the pooled controls. *Used only for the duration-response analysis*
				Duration (years)				
				<10	5	1.2(0.4–3.2)		
				≥10	8	1.5(0.7–3.4)		
				Other painters				
				Duration (years)				
				<10	5	1.1(0.4–3.0)		
				≥10	4	0.9(0.3–2.7)		

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Ramanakumar *et al.* (2008) Montreal, Canada 1979–1986	478 male bladder cancer cases from 18 hospitals in Montreal; aged 35–70 years; 100% histologically confirmed; 82% response rate.	1066 pooled age-matched controls (533 population controls from electoral lists and by random-digit-dialing, 533 controls from other cancers); response rate 72% and 84%	Detailed job history (including specific tasks and protective devices) obtained from in-person interviews and reviewed by a team of chemists and industrial hygienists who translated each job into a list of potential exposures by means of a checklist that included 294 substances	**Ever worked as a painter**	17	1.0 (0.3–2.7)	Age, ethnicity, years of school attendance, median family income, the status (self/proxy) of the respondents, smoking and occupational exposure to asbestos, silica, cadmium compounds	No other cancer sites showed any evidence of an association with type of paint or stain. Overlaps with Parent *et al.* (2000); this study population is the same as that of Siemiatycki *et al.* (1994) and therefore used for the overall analysis
				Substantial exposure				
				Any paint product	37	1.3 (0.7–2.2)		
				Metal coatings	13	1.7 (0.7–4.4)		
				Wood varnishes, stains	18	1.7 (0.9–3.6)		
				Wood and gypsum paints	25	1.0 (0.5–2.0)		

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Teschke *et al*. (1997a) British Columbia, Canada 1990–91	105 (88 men, 17 women) from British Columbia Cancer Registry; aged 19–75 years; response rate 88.2%; 100% histologically confirmed	159 (112 men, 47 women) population-based controls selected from provincial voters list, frequency matched to the age and sex distribution of cases of all three types of cancers included in this study (bladder cancer, cancers of the nasal cavity and sinuses); response rate 80.3%	Subjects were interviewed either in person or by telephone using a standardized questionnaire to collect information on occupational history	Ever employed as a painter Employed as a painter with most recent 20 years removed	4 2	2.8 (0.4–21.3) 2.0 (0.1–33.0)	Cigarette smoking, sex, age	Latency analyses were conducted for all occupational groups with the most recent 20 years of employment removed

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Gaertner *et al.* (2004) Newfoundland, Prince Edward Island, Nova Scotia, Manitoba, Alberta, Saskatchewan, and British Columbia, Canada, 1994–97	887 (535 men, 352 women) from 7 Canadian provincial cancer registries; aged 20–74 years; response rate 58% for males, 61% for females, respectively; 100% histologically confirmed	2847 population-based controls matched by age and sex; selected by random digit dialling for controls in Newfoundland and Alberta; others randomly sampled from the provincial health insurance plan database; response rate 59% for males, 65% for females	Information on occupational history was collected through mailed questionnaire	Male painters Female painters	12 3	0.74 (0.36–1.53) 1.08 (0.27–4.37)	Province, age, race, smoking, ex-smoking, and consumption of fruit, fried food, coffee and employment in other suspect occupations	Two to five months after diagnosis, questionnaires were mailed to participants to obtain information on occupational history, smoking and other exposure information. Up to 12 occupations per person were recorded by the type of industry, service, company name, main job duties and job title

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Band *et al.* (2005) British Columbia, Canada, 1983–90	1125 males from the British Columbia Cancer Registry; aged 20 years or older; response rate 64.7%; 100% histologically confirmed	8492 males from the British Columbia Cancer Registry; aged 20 years or older; matched by exact age and year of diagnosis; response rate 60.1%	Self-administered questionnaire (or completed by a proxy respondent) to collect detailed lifetime occupational history	Painters/Paper-hangers related *Ever* *Usual*	 22 10	 1.53 [0.95–2.47] 1.4 [0.71–2.76]	Tobacco smoking (age started smoking, average number of cigarettes, pipe or cigars smoked per day, total years smoked), alcohol drinking, marital status, education, respondent type (self or proxy)	Registry based, used patients with other cancers as controls excluding lung cancer and cancers of unknown primary site
Studies in Vol. 47								
Wynder *et al.* (1963) USA, 1957–61	300	Hospital, without smoking-related disease	Interview	Ever painter	18	[2.2] [1.0–4.5]	None	

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Cole *et al*. (1972) USA, 1967–68	461	General population	Interview	Painter (men)	28	1.2 (0.71–1.9)	Age, smoking	
Decouflé *et al*. (1977); Houten *et al*. (1977) Buffalo, NY, USA 1956–65	Bladder cancer cases (ICD7 181) from 11591 white male cancer cases at a treatment center, age ≥14 years	Non-cancer admissions from the same cancer treatment center	Lifetime occupation recorded during interview before diagnosis, coded using the Standard Industrial Classification Manual	*Painter*				Unexposed = clerical occupations
				Ever	16	1.62 [0.92–3.38]	Age	
				<60 yrs old	3	1.68 [0.46–6.29]		
				≥60 yrs old	13	1.61 [0.75–3.48]		
				Ever (smoking adj)		1.72 (p >0.05)	Smoking, age	
				Worked ≥5 yrs	12	1.51 [0.78–3.69]	age	
				<60 yrs old	1	1.04 [0.15–7.76]		
				≥60 yrs old	11	1.59 [0.67–3.79]		

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Williams *et al*. (1977) Atlanta, Birmingham, Colorado, Dallas-Ft.Worth, Detroit, Minneapolis-St.Paul, Pittsburgh, San Franciso-Oakland, USA 1969–71 Third National Cancer Survey	169 bladder cancer cases that reported an occupation, 95% histologically confirmed	2173 patients with cancers other than lung, larynx, oral cavity, esophagus, bladder that reported an occupation	Main lifetime employment from survey questionnaire, coded using the 1970 census classification	Painting (men)	1	0.42 [0.02–7.14]	Age, race, education, education, tobacco, alcohol, geographic location	Painting included construction workers, paper-hangers, and pattern & model makers; the CI was estimated by doubling the variance
Silverman *et al*. (1983) USA, 1977–78	303 men	Population	Interview	Ever painter Car painter	15 3	1.0 (0.5–2.2) 0.5 (0.1–2.1)	None	
Schoenberg *et al*. (1984) USA, 1978–79	658 men	Population	Interview	Ever painter Paint exposure	34 111	1.4 (0.85–2.3) 1.6 (1.2–2.1)	Age, smoking, other employment	

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Morrison *et al*. (1985) USA, UK, Japan 1976–78	USA, 430	Population	Interview	Paint and paint manufacture	35	1.5 [0.84–2.69]	Age, smoking	
Howe *et al*. (1980) Canada, 1974–76	480 men	Neighbourhood	Interview	Commercial painting Ever spray painting	≥24 ≥16	1.0 (0.6–2.3) 1.8 (0.7–46)	None	After correction for exposure to other suspect 'high-risk' industry, RR for spray painter, 1.0
Siemiatycki *et al*. (1987) Canada, 1979–85	486	Other cancers	Interview	Listed as white spirits, but in exposed group construction is 21% of total, mostly painters	91	1.0 (90% CI, 0.8–1.2)	Age, socioeconomic status, ethnicity, cigarette smoking, blue/white collar work	*Excluded from meta-analysis because the exposure was not specific to painters*
Risch *et al*. (1988) Canada, 1979–82	781	Population	Interview; exposed to paints in full-time job at least 6 months, 8–28 years before diagnosis	*Commercial painting* Men Women *Spray painting* Men Women	 204 14 49 67	 1.1 (0.77–1.6) 3.9 (0.9–26.7) 0.90 (0.39–2.1) 0.91 (0.48–1.7)	Smoking	

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Other Regions								
Studies since Vol. 47								
Bethwaite *et al.* (1990) New Zealand, 1980–84	912 male bladder cancer cases (ICD9 188) had known occupation among 1259 cases identified from New Zealand Cancer Registry; aged 20 or older ; % histologic confirmation not given	18 992 males with cancers other than bladder cancer from New Zealand Cancer Registry; with known occupation, [out of 23 503 identified] from the same Registry and period, aged 20 or more at registration; % histologic confirmation not given	Data were collected through cancer registration, death certification and incidental necropsy findings	**Painters**			Age	Potential selection bias for using other cancers to form the control group. Information on exposure was largely based on cancer registration
				Ever	24	1.52 (1.00–2.31)		
				Age (years)				
				20–59	9	2.3 (1.2–4.5)		
				≥60	15	1.3 (0.8–2.2)		

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Dryson *et al.* (2008) New Zealand, 2003–2004	213 incident cases of bladder cancer (165 men, 48 women); age 25–70 years; notified to the New Zealand Cancer Registry; ~64% participation rate	471 population controls (221 men, 250 women) randomly selected from the 2003 New Zealand Electoral Roll; frequency matched by age according to the 1999 age distribution of cancer registrations for NHL, bladder cancer & leukemia; ~48% participation rate	Full occupational history from in-person interview	**Painters & paperhangers**	11	1.42 (0.56–3.60)	Gender, age group, smoking status, Maori ethnicity, occupational status	Numbers were too small (less than 10 cases 1 controls) for spray painters; *information on duration obtained by contacting authors; **calculated using a fixed effects model
				Men	10	1.28 (0.50–3.30)		
				Women	1	NG		
				Duration (yrs)*				
				0	205	1.0 (ref)		
				1–2	1	0.22 (0.02–2.35)		
				2–10	4	2.20 (0.37–13.08)		
				>10	3	0.98 (0.23–4.24)		
				<10	5	[0.96 (0.23–4.01)]**		
				Painter, decorator and/or paperhanger	7	1.35 (0.42–4.39)		
				Men	7	1.41 (0.44–4.56)		
				Painting and decorating services industry	7	1.13 (0.39–3.29)		
				Men	6	1.11 (0.34–3.56)		
				Women	1	1.38 (0.10–19.76)		

Table 2.3 (contd)

Reference, Location, Time period	Characteristics of cases	Characteristics of controls	Exposure Assessment	Exposure	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Studies in Vol. 47								
Morrison *et al*. (1985) USA, UK, Japan, 1976–78	Japan, 226	Population	Interview	Paint and paint manufacture	5	0.7 [0.25–1.97]	Age, smoking	
Iscovich *et al*. (1987) Argentina, 1983–85	117	Neighbourhood and hospital	Interview	Ever painter	3	0.55 [0.12–2.5]	Age, tobacco smoke	Adjusted for age and tobacco smoke, pooling the two control groups

OR, odds ratio; CI, confidence interval; ASCR, Association of Swiss Cancer Registries; SIC, Standard Industrial Classification; ISCO, International Standard Classification of Occupations; ISIC, International Standard Industrial Classification; NG, not given

La Vecchia *et al.* (1990) conducted a hospital-based case–control study of bladder cancer in the greater Milan area, Italy. The study included 263 cases and 287 controls. While patients diagnosed with acute, non-neoplastic or urinary tract diseases were used as controls, a relative risk of 1.8 (90% CI: 0.8–3.7) was observed for those who worked in the painting (including spraying) industry. Those who had been occupationally exposed to dyes/paints for more than 10 years had an almost 5-fold increased risk of bladder cancer (RR, 4.8; 90% CI: 1.7–13.9), and this risk increased significantly with increasing duration of exposure to dyes/paints (*P* for trend = 0.04).

Myslak *et al.* (1991) conducted a hospital-based case–control study in the East Ruhr area, a major industrial area of Germany. The cases included in the study were 403 male bladder cancer patients, and the controls were 426 patients diagnosed with benign prostate disease from the same hospital. The study authors reported an increased RR of bladder cancer of 2.76 (95% CI: 1.21–6.28; 21 cases) for painters. [It should be noted, however, that, while smoking information was collected in this study, there was no indication that the study actually controlled for potential confounding effect from smoking.]

In Volume 47 (IARC, 1989), Claude *et al.* (1986, 1988) reported results from a hospital-based case–control study for cancer of the lower urinary tract in northern Germany. Their results showed a significantly increased risk of lower urinary tract cancers associated with exposure to lacquer, paint, and spray paints. With additional cases and controls, Kunze *et al.* (1992) reported an OR of 2.9 (95% CI: 1.7–4.9; adjusted for tobacco consumption) for having ever been exposed to spray paints. The risk of bladder cancer increased significantly with increasing duration of exposure to spray paints in this study (*P* for trend = 0.004).

Cordier *et al.* (1993) conducted a hospital-based case–control study in five regions of France. This study involved 765 cases (658 men and 107 women), and the same number of controls. Controls were patients admitted to the same hospital as the cases for causes other than cancer, respiratory disease or symptoms suggestive of bladder cancer. Controls were matched 1:1 to cases by sex, age, ethnic origin, and place of residence. This study did not find any association between employment as a painter and a risk of bladder cancer (RR, 0.97; 95% CI: 0.50–1.88; 19 cases). An OR of 6.41 (95% CI: 0.79–51.85), however, was observed for spray painters, based on eight cases and one control.

Barbone *et al.* (1994) conducted a hospital-based case–control study of bladder cancer in northeastern Italy. The study included 273 bladder cancer cases and 573 controls. Controls were patients without bladder cancer, but admitted for trauma, non-traumatic musculoskeletal conditions, acute surgical conditions, eye diseases, and other conditions such as diseases of the ears, nose, throat or mouth. Cases and controls were interviewed at hospitals. A non-significantly increased risk of bladder cancer was found for men employed in the painting industry (RR, 3.1; 95% CI: 0.7–13; six cases) after controlling for major potential confounders, including cigarette smoking.

Hours *et al.* (1994) conducted a case–control study of bladder cancer in Lyon, France between 1984–1987 involving 116 cases (97 male, 19 female) and 232 hospital-based controls matched by gender, hospital, age, nationality. Job history was obtained from in-

person interviews. Painting (regular leisure-time activity) was associated with a non-significantly increased risk of bladder cancer (OR, 1.56; 95% CI: 0.56–4.58; 12 exposed cases) after adjusting for the matching variables.

Porru *et al.* (1996) conducted another hospital-based case–control study in northern Italy. A total of 355 (275 men, 80 women; aged 24–87) bladder cancer cases from the General Hospital of Brescia were included in the study. Controls were patients with urological non-neoplastic diseases. A non-significantly increased risk of bladder cancer was observed for male painters (RR, 1.4; 95% CI: 0.6–3.5; 12 cases), after adjusting for smoking and other major confounders. [Use of patients with urological non-neoplastic diseases as controls may pose an issue for interpreting the results because if there is indeed an association between paint exposure and risk of urological non-neoplastic diseases, use of these patients as controls would cause an underestimation of the association between painting and bladder cancer risk in this study.]

Golka *et al.* (1999) conducted a case–control study of bladder cancer involving 412 male cases from urology departments of 3 hospitals in Dortmund, Germany, and 414 male controls with benign prostatic hyperplasia. Complete occupational history were obtained for jobs held >1 year and at least 10 years before the interview. The smoking-adjusted OR for painters & lacquerers for cancer fo the bladder was 2.24 (95% CI, 1.07–5.13; 21 exposed cases).

Pohlabeln *et al.* (1999) performed a case–control study involving 300 cases (239 male, 61 female) of histologically confirmed cancer of the lower urinary tract (including malignant tumours of the urinary bladder [89.6%, ICD9: 188], ureter [1.0%], renal pelvis [3.7%], urethra [1.7%], multiple localizations [4.0%]), and 300 controls with non-neoplastic diseases of the lower urinary tract individually matched to cases from the same hospitals with respect to sex, age & area of residence. Job history was obtained from in-person interviews. The authors did not provide an OR for cancer of the lower urinary tract but reported a 3-fold increased risk after adjusting for age, sex and area of residence.

Pesch *et al.* (2000a) conducted a multicentre population-based case–control study of urothelial cancers in Germany. Among the 1035 incident urothelial cancer cases (704 men, 331 women), 90.2% of the male patients and 84.3% of the female patients were diagnosed with cancer of the urinary bladder. Job–exposure matrices and a job-task–exposure matrix were used to assess the relationship between exposure to occupational agents and risk of urothelial cancers. An OR of 1.6 (95% CI: 0.5–4.7; five cases) was reported for males who had a very long period of employment as a painter. A borderline significantly increased risk of urothelial cancers was also observed for males who reported to have had high (OR, 1.2; 95% CI: 1.0–1.5; 181 cases) or substantial (OR, 1.2; 95% CI: 0.9–1.7; 67 cases) occupational exposure to paints. [The study, however, did not give a clear definition for exposure duration (medium, long, and very long) and intensity of exposure to paints and pigments (medium, high, and substantial).]

Bouchardy *et al.* (2002) conducted a case–control study based on a cancer registry in Switzerland. The cases in the study were patients diagnosed with cancer of the urinary bladder, and the controls, patients with all other types of cancer. No association was

observed between male plasterers and painters and the risk of cancer of the urinary bladder (RR, 1.1; 95% CI: 0.8–1.4; 73 exposed cases), after adjusting for age, registry, civil status, period of diagnosis, nationality, urban/rural residence, socioeconomic status histological confirmation, and information from death certificate only (cases). [Use of patients with all other types of cancer as controls in this study could complicate the interpretation of the observed association since some of the cancer types may well be linked to exposure to paints, and use of patients with all other types of cancer as controls would cause an underestimation of the association between painting and bladder cancer risk.]

Pelucchi *et al.* (2002) conducted a hospital-based case–control study in Italy that involved 110 histologically confirmed female bladder cancer patients, and 298 sex-matched controls. The controls were patients admitted for acute, non-neoplastic, non-urinary or genital tract diseases. The study found that women who had ever worked in the dyestuff and painting industry had a non-significantly increased risk of bladder cancer (OR, 1.44; 95% CI: 0.30–6.84; three cases). [It is difficult to interpret the study result since the study treated the dyestuff and painting industry as one exposed group, and dyes have also been linked to bladder cancer.]

Kogevinas *et al.* (2003) performed an analysis of pooled data from 11 case–control studies of bladder cancer that were conducted in six European countries during 1976–1996. A total of 3346 male incident bladder cancer cases and 6840 controls, aged 30–79 years, were included in the pooled analyses which adjusted for age, smoking, and study centre. The results showed that men who had ever worked in the manufacture of paints, varnishes and lacquers had nearly three times the risk of bladder cancer (OR, 2.94; 95% CI: 1.48–5.84; 22 cases) compared to those who were not exposed. Painters had an approximately 20% increased risk of bladder cancer compared to non-painters, although this was not statistically significant (OR, 1.2; 95% CI: 0.91–1.50; 116 cases).

Reulen *et al.* (2007) enrolled 202 bladder cancer cases (174 men, 28 women) and 390 controls (231 men, 159 women) selected from the general population of the province of Limburg, Belgium by simple random sampling. Lifetime occupational history for jobs held >6 months was obtained from in-person interviews. Painters and varnishers showed an increased risk of bladder cancer (OR, 2.2; 95% CI: 0.7–7.2; based on ten cases) after adjusting for sex, age, years of cigarette smoking, number of cigarettes smoked per day, current smoking status, and education.

(b) North America

Miller *et al.* (1986) conducted a case–control study to examine the association between employment as an artistic painter and the risk of bladder cancer in the United States. The analysis was restricted to caucasian artists because of the small number of non-caucasian artists. For the case–control study involving 2331 bladder cancer cases and 4525 population-based controls, artistic painters had a significantly increased risk of cancer of the bladder (OR, 2.5, 95% CI: 1.1–5.7; 15 cases), and this increased with prolonged duration of employment as a painter (P for trend = 0.01).

The US National Bladder Cancer Study by Silverman *et al.* (1989a) included 2100 caucasian male bladder cancer cases, and 3874 population-based controls recruited in ten areas of the United States. Among caucasian men, a 50% increased risk of cancer of the bladder was observed in painters (OR: 1.5; 95% CI: 1.2–2.0; 116 cases). For caucasian painters who had started working before 1930, a significant trend in risk with increasing duration of employment as a painter was apparent with a relative risk of 3.0 was observed for those employed 10 or more years as a painter. With 126 non-caucasian cases and 383 non-caucasian controls, Silverman *et al.* (1989b), however, did not find a significantly increased risk of bladder cancer among painters (RR, 1.2; 95% CI: 0.4–3.7; five cases).

Burns & Swanson (1991) conducted a case–control study in Michigan, the United States, based on the Occupational Cancer Incidence Surveillance Study (OCISS). The OCISS is a population-based study of occupational risk factors for cancers diagnosed among residents of the metropolitan Detroit area. Cases were 2160 patients diagnosed with bladder, and controls 3979 patients diagnosed with cancers of the colon or rectum from the OCISS study. Lifetime occupational history was collected through telephone interviews of the subjects or their surrogates (spouse or first-degree relative of the subject). The study did not find any association between work as a painter and risk of bladder cancer (RR, 1.1; 95% CI: 0.7–1.9; adjusted for cigarette smoking, race, gender, and age at diagnosis; 30 cases). [The Working Group noted that controls in this study were patients diagnosed with cancers of the colon or rectum. While the authors pointed out that persons diagnosed with cancers of the colon or rectum constitute the most appropriate comparison group within OCISS because their cigarette smoking patterns were similar to those of the general population, it is unclear whether these patients also represent the population which produced the cases with regards to the exposure itself (paint exposure). Also, no information was given about the quality and the comparability of lifetime occupational history collected through telephone interviews with the subjects themselves or their surrogates.]

Zheng *et al.* (2002) conducted a population-based case–control study in Iowa, USA. The study included 1452 incident bladder cancer cases (1135 men, 317 women) and 2434 population-based controls (1601 men, 833 women). The study used mailed questionnaires to collect detailed information on occupational history for each job held for 5 years or longer since the age of 16: detailed information was collected on job title, industry, the year the job began and ended, and activities associated with the job. Telephone interviews were conducted with a small number of subjects who did not complete the mailed questionnaires. The study reported a borderline significantly increased risk of bladder cancer among male construction and maintenance painters (OR, 2.7; 95% CI: 1.0–7.7; 11 cases). Men who worked in the painting and wallpaper-hanging industry had a nearly 3-fold increased risk of bladder cancer (OR, 2.9; 95% CI: 0.9–9.1; nine cases).

Colt *et al.* (2004) conducted a population-based case–control study of bladder cancer in New Hampshire, USA. The study included 424 cases and 645 controls. To collect information on occupational exposures, the study mailed a work history calendar to the

participants two weeks before the interview date, and the participants were asked to complete information on job title and place of work for each job held. The study interviewers reviewed the responses on the day of the interview for completeness. Information on exposure to other risk factors was collected through in-person interviews. The study did not find an association between employment as a painter and risk of bladder cancer for men (OR < 1.3, adjusted for age and smoking; 12 cases). There were no women employed as painters in this study. [The risk for painters was listed in a table for jobs with odds ratios less than 1.3. No confidence interval or *P* value was provided.]

Siemiatycki *et al.* (1994) conducted a population-based case–control study in Montreal, Canada during 1979–1986. The study involved 484 bladder cancer cases, 1879 cancer controls, and 533 population-based controls. The job histories of these subjects were evaluated by a team of chemists/hygienists for evidence of exposure to a list of 294 workplace chemicals. A non-significant increased risk was observed for those who had worked as construction painters for 10 or more years (RR, 1.5; 95% CI: 0.7–3.4). No increased risk of bladder cancer was observed for other painters either as a group or stratified by duration of working as a painter.

Ramanakumar *et al.* (2008) reanalysed the data from the population-based case–control study in Montreal by Siemiatycki *et al.* (1994). Risks were estimated for exposure to each of the paint-related agents (metal coatings, wood varnishes and stains, and wood and gypsum paints) and development of bladder cancer, adjusting for several potential confounders, including smoking. While 'ever' work as a painter was not associated with bladder cancer risk in this study (OR, 1.0; 95% CI: 0.3–2.7; 17 cases), a non-significantly increased risk was reported for subjects who had had substantial exposure to metal coatings (OR, 1.7; 95% CI: 0.7–4.4; 13 cases), and for wood varnishes and stains (OR, 1.7; 95% CI: 0.9–3.6; 18 cases).

Teschke *et al.* (1997a) conducted a case–control study in British Columbia, Canada, to study the relationship between occupational exposures and risk of nasal and bladder cancers. The study included 105 cases (88 men and 17 women) and 139 population-based controls (112 men, 27 women) selected from provincial voting lists. Subjects were interviewed either in person or by telephone using a standardized questionnaire to collect information on occupational history and other potential risk factors for these cancers. A non-significantly increased risk of bladder cancer was observed for those who had ever worked as painters (OR, 2.8; 95% CI: 0.4–21.3; four cases). Removal of the most recent 20 years of employment from the analyses made the results even less stable (OR, 2.0; 95% CI: 0.1–33.0; two cases).

A population-based case–control study was conducted in seven Canadian provinces (Gaertner *et al.*, 2004). The study included 887 incident, histologically confirmed bladder cancer cases, and 2847 controls. Approximately 2–5 months after diagnosis, questionnaires were mailed to participants to obtain information on occupational history, smoking and other exposure information. Up to 12 occupations per person were recorded by type of industry, service, company name, main job duties, and job title. Employment as a painter was not found to be associated with an increased risk of bladder cancer

among males (OR, 0.74; 95% CI: 0.36–1.53; 12 cases) or females (OR, 1.08; 95% CI: 0.27–4.37; three cases), after adjusting for province, age, race, smoking, ex-smoking, employment in other suspect occupations, and consumption of fruit, fried food and coffee.

Band *et al.* (2005) conducted a case-control study based on the British Columbia Cancer Registry to assess the association between lifetime occupational histories and risk of bladder cancer. The cases in this study were 1125 male incident bladder cancer cases reported to the registry during 1983–1990. Controls were 8492 male incident cancer patients diagnosed with all other types of cancer (excluding lung, and of unknown primary site) reported to the registry during the same time period. A self-administered questionnaire was mailed to male cancer patients to collect lifetime occupational history, including job descriptions, job and industry titles, duration and period of work, etc. A significantly increased risk of bladder cancer was observed for those who had ever worked as painters/wallpaper hangers (OR, 1.53; 95% CI: 1.02–2.28; 22 cases). [Caution must be exercised in interpreting the results because patients with other types of cancer were used as controls (excluding lung cancer and cancers of unknown primary site). If some of the cancer sites were associated with paint exposure, inclusion of these cancer sites in the control group would cause an underestimation of the association of interest. Also, the questionnaires were completed by either the subject himself or by a proxy respondent for information on lifetime occupational history.]

(c) Other Regions

Bethwaite *et al.* (1990) conducted a case–control study based on a cancer registry in New Zealand to investigate the association between employment as a painter and risk of various cancers. A total of 912 male bladder cancer cases who reported an occupation were included in this study as well as 18 992 male control patients of all other types of cancer. Painters were found to be associated with an increased of bladder cancer (OR, 1.52; 95% CI: 1.00–2.31; 24 cases), especially those painters aged 20–59 years (OR, 2.27; 95% CI: 1.15–4.48; nine cases). The risk was not significantly increased for those aged 60 and over (OR, 1.27; 95% CI: 0.75–2.15; 15 cases).

2.2.4 *Lymphatic and haematopoietic cancer*

The Working Group for Volume 47 evaluated five case–control studies of leukaemia among persons exposed to paint and its manufacture.(two with significant excesses). Two small studies on Hodgkin disease and three studies on multiple myeloma also showed excesses (IARC, 1989).

A summary of studies of painters and paint exposures and lymphatic and haematopoietic cancer is presented in Table 2.4.

(a) Europe

Lindquist *et al.* (1987) conducted a study of 125 acute leukaemia cases (76 men and 49 women aged 16–84, diagnosed between 1980–1983), and 125 age- and sex-matched population controls in Sweden. Participants were interviewed in person to obtain information on a variety of factors including detailed lifetime occupational history.

Table 2.4 Case–control studies of lymphohaematopoietic cancer among painters

Reference, location, time period	Characteristics of cases and controls	Organ site	Exposure categories	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Europe							
Lindquist *et al*. (1987) Sweden 1980–83	125 cases (76 men, 49 women), aged 15 to 84 years, from 5 Swedish hospitals that captured most leukemia cases 125 controls, obtained from the population register of the taxation authorities, matched 1:1 by sex and age (± 4 years)	Acute leukaemia	Painters	13	13 (2.0–554)	NG	Lifetime work history from in-person interview; 42% of cases and 48% controls were smokers
Persson *et al*. (1989) Orebro, Sweden 1964–86	54 HD cases (35 men and 19 women) and 106 NHL cases (66 men and 40 women), aged 20 to 79 years. 275 population controls (157 men and 118 women), aged 20 to 77 years	HD NHL	Painters	2 3	Could not be calculated Could not be calculated	Not applicable	Selected occupational exposures, including painting, obtained through a mailed questionnaire. Odds ratios could not be calculated because there were no exposed controls

Table 2.4 (contd)

Reference, location, time period	Characteristics of cases and controls	Organ site	Exposure categories	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
LaVecchia *et al*. (1989) Milan, Italy 1983–1988	69 incident cases of HD (44 men, 25 women), 153 NHL (93 men, 60 women), 110 MM (56 men, 54 women), aged 15 to 74 years. 396 hospital-based controls (269 males, 127 women) admitted for acute conditions to the same hospital network as cases, aged 15 to 74 years.	HD NHL MM	Painting (including spray)	3 6 5	Not presented for painters but there was no significant association with painting for any site	Age, sex, smoking and area of residence	Information on 16 occupations and 13 agents, including painting, obtained by a trained interviewer
Heineman *et al*. (1992) Denmark 1970–1984	835 male cases identified from the Danish Cancer Registry who were ≥18 years at diagnosis 2979 male population controls identified from the Danish Central Population Registry; matched on year of birth; not previously diagnosed with a malignancy	MM	Painter	11	1.0 (0.5–2.1)	Age	Employment history from pension files

Table 2.4 (contd)

Reference, location, time period	Characteristics of cases and controls	Organ site	Exposure categories	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Persson *et al*. (1993) Linkoping, Sweden 1975–84	124 male cases (31 HD; 93 NHL), ≥20 years old, born in Sweden and residing in the hospital catchment area at time of diagnosis, were obtained from the Regional Cancer Registry. 204 male controls randomly drawn from population registers and residing in the same area as cases	HD NHL	Painters	2 NG	**OR (90% CI)** 2.3 (0.4–11) NG	Age, other exposures with a crude OR ≥2.0 or significantly <1	Occupational exposures from a mailed questionnaire
Persson & Fredrikson (1999) Sweden Orebro, 1964–86 Linkoping, 1975–84	199 male cases, ≥20 years old, born in Sweden and residing in the hospital catchment area at time of diagnosis, were obtained from the Regional Cancer Registry. 479 male population controls randomly drawn from population registers and residing in the same area as cases.	NHL	Painters	5	2.5 (0.5–9.6)	Age, other exposures with a crude OR ≥2.0 or significantly <1	Pooled data from two Persson studies (1989 & 1993)

Table 2.4 (contd)

Reference, location, time period	Characteristics of cases and controls	Organ site	Exposure categories	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Mele *et al*. (1994) Rome, Bologna, Pavia, Italy 1986–90	619 cases (252 AML, 100 ALL, 111 RAEB, 156 CML). 1161 controls with nonneoplastic disorders were obtained from the same hematology departments as cases, ≥15 yrs old	AML ALL RAEB CML	Male painter	10 26 9 19	3.2 (0.5–20.8) 4.7 (0.6–34.2) 5.4 (0.5–61) 7.6 (1.5–39.8)	Age, education, residence, other listed occupations	Occupational exposures obtained from in-person interview
Nordström *et al*. (1997) Sweden 1987–92	111 male cases obtained from the Swedish Cancer Registry 400 male controls obtained from the National Population Registry; matched by age and county	HCL	Painter (building)	6	5.7 (1.6–20.8)	Age	Lifetime job history for jobs held 1 year or more obtained through a mailed questionnaire

Table 2.4 (contd)

Reference, location, time period	Characteristics of cases and controls	Organ site	Exposure categories	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Clavel *et al*. (1998) France 1980–90	226 living male cases obtained from 18 French hospitals. 465 male controls selected from the admission lists of inpatients for the same 10 year period as for cases; matched by residential area, date of birth and hospital admission	HCL	Painters Spray painters Artists & designers	6 5 1	1.0 (0.3–3.0) 2.0 (0.5–8.0) 1.3 (0.1–16.7)	Smoking, farming	Lifetime work history through self-administered questionnaires
Costantini *et al*. (2001) 12 areas in Italy 1991–93	1520 male cases (811 NHL+CLL, 383 leukaemia, 193 HD, 133 myeloma) aged 20-74 years, enrolled through periodic surveys of hospitals or the Varese Cancer Registry Age and sex stratified random sample of 918 controls from the general population of the study area	NHL+CLL Leukaemia	Painters	20 10	1.2 (0.6–2.4) 1.7 (0.8–3.8)	Age	Lifetime work history and occupational exposures from in-person interview

Table 2.4 (contd)

Reference, location, time period	Characteristics of cases and controls	Organ site	Exposure categories	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Dryver *et al*. (2004) South Sweden 1990–98	859 cases identified from the South Swedish Tumor Registry; ≥18 years of age 1310 controls identified using Swedish unique personal identification numbers; matched by sex, age and parish	NHL	Painting	46	1.77 (1.13–2.76)	NG	Mailed questionnaire with list of jobs querried including painters and the FINJEM exposure matrix
North America							
Scherr *et al*. (1992) Boston, USA 1980–82	303 cases (152 males, 151 females), median age 65 years. 303 controls identified from a population register; matched on sex, age, town and precinct of residence	NHL	Painter, plasterer, housepainter	3	6.0 (0.9–38)	NG	Occupations held included most recent, 15 years ago, major, second major, and those linked to an exposure list obtained from in-person interviews or mailed questionnaires

Table 2.4 (contd)

Reference, location, time period	Characteristics of cases and controls	Organ site	Exposure categories	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Blair *et al.* (1993) Iowa/Minnesota, USA 1980–83	622 white male cases obtained from state registries. 1245 white male population controls without a hematopoietic or lymphatic malignancy were obtained through random digit dialing (<65 years), Medicare files (≥65 years) or state vital records (for those matched to deceased cases); frequency matched by state, age, year of death (for deceased cases).	NHL	Painting/paper-hanging Painting/plastering/cementing *<10 years* *≥10 years*	16 NG NG	1.9 (0.9–3.8) 0.6 (0.1–2.0) 2.7 (1.1–6.6)	Age, state, smoking, family history of lympho-proliferative malignancies, agricultural pesticide exposure, hairy dye use, direct or proxy respondent	Detailed work history for all jobs held ≥ 1 year since the age of 18
Demers *et al.* (1993) Utah, Washington state, Atlanta, Detroit, USA 1977–81	692 cases identified from SEER registries, <80 years of age. 1683 population controls, aged 40–79 years, identified through random digit dialing and door-to-door sampling	MM	Painters *All respondents* *Self-responders* *With solvent exposure* *<10 years* *≥10 years*	 31 22 14 15 16	 2.1 (1.2–3.6) 2.5 (1.3–4.7) 3.1(1.5–7.5) 1.4 (0.6–2.8) 4.1 (1.8–10.4)	Sex, race, age, study area	Lifetime work history from in-person interview

Table 2.4 (contd)

Reference, location, time period	Characteristics of cases and controls	Organ site	Exposure categories	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Blair *et al*. (2001) Iowa and Minnesota, USA 1980–83	513 white male leukemia cases, ≥30 years old, identified from the Iowa Cancer Registry and Minnesota hospital surveillance network 1087 population controls identified from RDD (<65 years), Medicare Lists (≥65 years), death certificates; frequency matched by 5-year age group, vital status and state of residence	AML CML ALL CLL Myelodyplasia Leukaemia	Painting, plastering, waterproofing, and related occupations ≥10 years employment	4 0 2 7 1	1.9 (0.6–5.9) NG 8.4 (1.4–51.3) 1.3 (0.5–3.2) 1.1 (0.1–8.9) 1.7 (0.7–4.2)	Age, state of residence, proxy interview, post-secondary education, with a lymphatic or hematopoietic tumour	Occupational history for all jobs held 1 year or more and JEM obtained during in-person interview
Kato *et al*. (2005) Upstate New York, USA 1995–98	376 female cases, aged 20–79, were identified from the New York Cancer Registry 463 female, age-matched, population-based controls were obtained through New York State DMV records (<65 years) or Medicare files (≥65 years)	NHL	Paint/varnish exposure	23	0.79 (0.40–1.58)	Age, year of interview, pesticide exposure, use of pain-relieving drugs, use of antibiotics, family history of hematologic cancer, college education, surrogate status, BMI	Paint exposure obtained through telephone interview

Table 2.4 (contd)

Reference, location, time period	Characteristics of cases and controls	Organ site	Exposure categories	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Colt *et al*. (2007) USA (4 SEER areas) 1998–2000	551 cases, aged 20–74 years, identified from the SEER registry. 462 population controls, aged 20-74 years, identified using RDD (<65 years) or Medicare files (≥65 years); frequency matched on age, sex, race, study centre.	NHL	Hobby painting *Ever* *Lifetime hours* 0.5–104 105–520 521–1800 ≥1801	 144 43 39 23 32	 0.9 (0.6–1.2) 1.0 (0.6–1.6) 1.0 (0.6–1.8) 0.6 (0.3–1.1) 0.9 (0.5–1.6)	Age, race, education, sex, SEER study area	Hobby painting/-silkscreening/artwork exposure was obtained during in-person interviews
Ramanakumar *et al*. (2008) Montreal, Canada 1979–86	215 male cases, aged 35–70 years, from all large hospitals in the Montreal area. 1066 pooled controls (533 population controls and 533 other cancer controls) selected from electoral lists, RDD or from the same hospitals as cases	NHL	Ever worked as a painter *Substantial exposure* Any paint product Metal coatings Wood varnishes, stains Wood and gypsum paints	3 16 3 4 11	0.9 (0.2–4.1) 1.2 (0.6–2.6) 2.2 (0.6–8.1) 0.3 (0.1–2.3) 1.0 (0.4–2.6)	Age, ethnicity, years of school attendance, median family income, the status (self/-proxy) of the respondents, smoking and occupational exposure to asbestos, silica, cadmium compounds	Paint exposure from lifetime job history and an extensive checklist of potential exposures during an in-person interview

Table 2.4 (contd)

Reference, location, time period	Characteristics of cases and controls	Organ site	Exposure categories	No. of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Other Regions							
Bethwaite *et al*. (1990) New Zealand 1980–84	Male cases of 23 different cancers (535 NHL, 170 HD, 295 MM, 534 leukaemia), aged 20 years or older, were obtained from New Zealand Cancer Registry.	NHL	Ever painters	9	0.97 (0.50–1.90)	Age	Occupational data were collected through the cancer registry and death certificates
		HD		1	0.38 (0.06–2.54)		
		MM		10	1.95 (1.05–3.65)		
		Leukaemia		5	0.54 (0.23–1.30)		
		MM	*Age (years)*				
			20–59	5	4.23 (1.80–9.91)		
			≥60	5	1.27 (0.52–3.10)		
	18 992 males with other cancers were obtained from the New Zealand Cancer Registry.						
Adegoke *et al*. (2003) Shanghai, China 1987–89	486 cases (81 ALL, 21 CLL, 236 AML, 79 CML) selected from the Shanghai cancer registry; aged ≥15 years.	Leukaemia	Paint exposure			Age, gender, income	Lifetime history for jobs held 3 years or more
			Men	32	0.9 (0.5–1.5)		
			Women	25	1.7 (0.9–3.4)		
			<15 years	30	0.8 (0.5–1.3)		
			≥15 years	27	2.3 (1.2–4.7)		
		ALL	*≥15 years*	6	3.4 (1.2–9.5)		
		AML	*≥15 years*	10	1.8 (0.7–4.2)		
		CML	*≥15 years*	7	3.7 (1.4–9.9)		
	502 randomly selected general population controls listed in the resident registry, matched by age and sex.						

ALL, acute lymphocytic leukaemia; AML, acute myeloid leukaemia; BMI, body mass index; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; DMV, Department of Motor Vehicles; HCL, Hairy-cell leukaemia; HD, Hodgkin disease; JEM, job-exposure matrix; NG, not given; NHL, non-Hodgkin lymphoma; MM, multiple myeloma; RAEB, refractory anaemia with excess blasts; RDD, random-digit dialling

The OR for employment as a painter was 13 (95% CI: 2.0–554; 13 cases and one control). Tobacco use was not associated with leukaemia.

Persson *et al.* (1989) assembled cases of lymphoma (Hodgkin disease and non-Hodgkin lymphoma) from the Orebro Medical Centre Hospital in Sweden during 1964–1986 for a study of occupational exposures. There were 54 Hodgkin disease cases (35 men and 19 women), and 106 non-Hodgkin lymphoma cases (66 men and 40 women), aged 20–79. A total of 275 controls (157 men and 118 women) who had originally been drawn from population registries for previous studies were included. A mailed questionnaire was used to gather information on chemical exposures on the job, and during leisure time. Two Hodgkin disease cases and two non-Hodgkin lymphoma cases reported jobs as painters, while no controls were painters.

La Vecchia *et al.* (1989) evaluated occupational exposure and risk of lymphoid neoplasms in a case–control study in Milan, Italy. Study subjects, aged 15–74 years, were assembled from hospitals in the area during 1983–1988. Results reported were 69 cases of Hodgkin disease (44 men and 25 women), 153 cases of non-Hodgkin lymphoma (93 men and 60 women), and 110 cases of multiple myelomas (56 men and 54 women). A total of 396 controls (269 men and 127 women) diagnosed with acute conditions were selected from hospitals providing cases. Trained interviewers obtained information on 16 occupations, 13 occupational exposures, and other potential risk factors. ORs were adjusted for age, sex, area of residence and smoking. Although ORs were not presented, the authors reported no significant association with painting.

Heineman *et al.* (1992) used the Danish Cancer Registry and the Danish Central Population Registry to evaluate occupational exposures and risk of multiple myeloma among men. A total of 1098 cases (diagnosed during 1970–1984) and 4169 age-matched population controls with occupational information were included in the analysis. Only the most recent occupation was available from recent pension records. Industries where the men were employed were available from 1964 to diagnosis. Possible exposures based on occupation and industry were assessed by Danish industrial hygienists. ORs were calculated adjusted for age. The OR for men employed in the paint industry was 2.3 (95% CI: 0.4–11.1; three cases), while occupational painters had an OR of 1.0 (95% CI: 0.5–2.1; 11 cases). Exposure to paints and lacquers classed as ‘possible’ had an OR of 1.0 (95% CI: 0.8–1.4; 69 cases), and exposure classed as ‘probable’ had an OR of 0.8 (95% CI: 0.6–1.2; 39 cases).

Cases diagnosed during 1975–1984 from the University Hospital in Linköping, Sweden were assembled for a case–control study of occupational exposures and malignant lymphoma among men (Persson *et al.*, 1993). A total of 31 cases of Hodgkin disease, 93 cases of non-Hodgkin lymphoma, and 204 controls were available for study. Controls were population-based and had been selected for other studies. A mailed questionnaire was used to gather information on occupational exposures, leisure time exposures, and other factors. The OR for Hodgkin disease among painters was 2.3 (90% CI: 0.4–11; two cases).

Persson & Fredrikson (1999) pooled data from two case–controls studies to evaluate the role of occupational exposures in the development of non-Hodgkin lymphoma. The data came from Swedish studies located in Orebro (Persson *et al.*, 1989), and Linköping (Persson *et al.*, 1993). Described previously, both were population-based studies that used mailed questionnaires to gather information on occupational exposures. The OR for non-Hodgkin lymphoma among painters was 2.5 (95% CI: 0.5–9.6).

Mele *et al.* (1994) conducted a large case–control study (619 cases and 1161 controls) in Italy to study leukaemia, and refractory anaemia with excess blasts. Cases were identified in Rome, Bologna, and Pavia during 1986–1990. Controls with non-neoplastic disorders were obtained from the same haematology departments as cases. Cases and controls were interviewed while in the hospital. ORs were adjusted for age, sex, education, residence outside the study town, and occupations other than painters. Among male painters, the ORs were 3.2 (95% CI: 0.5–20.8; ten cases) for acute myeloid leukaemia, 4.7 (95% CI: 0.6–34.2; 26 cases) for acute lymphocytic leukaemia, 7.6 (95% CI: 1.5–39.8; 19 cases) for chronic myeloid leukaemia, and 5.4 (95% CI: 0.5–61.0; nine cases) for refractory anaemia with excess blasts.

Nordström *et al.* (1997) conducted a case–control study of hairy cell leukaemia in Sweden that included 111 male cases, identified from the Swedish Cancer Registry during 1987–1992, and 400 male controls, drawn from the National Population Registry and matched to cases on age and county. Information, including a complete working history, was obtained by mailed questionnaire. Occupations with more than ten cases and controls combined were analysed, controlling for age. Construction painters had an OR of 5.7 (95% CI: 1.6–20.8; six cases).

Hairy cell leukaemia and occupational exposures was studied among men in a case–control study in France (Clavel *et al.*, 1998). Cases ($n = 226$) diagnosed during 1980–1990 were identified in 18 hospitals around the country. Controls ($n = 425$) were selected from patients from the same hospitals and matched to cases on residence, date of birth, and hospital admission. Mailed self-administered questionnaires were used to gather information on a variety of factors including lifetime occupation. A telephone interview was conducted with subjects who were suspected to have had occupational solvent exposure. Matched analyses were performed and ORs were adjusted for smoking and farming. Painters had no excess of hairy cell leukaemia (OR, 1.0; 95% CI: 0.3–3.0; six cases).

Costantini *et al.* (2001) conducted a case–control study to evaluate occupational risk factors in relation to haematolymphopoietic cancers in Italy. A total of 2737 cases (811 non-Hodgkin lymphoma/chronic lymphocytic leukaemia, 383 leukaemia, 193 Hodgkin disease, and 133 myelomas) among men aged 20–74 years were identified from 12 areas in Italy during 1991–1993. Controls were a random sample of the population matched to the cases by age, sex, and study area. In-person interviews were conducted to gather information on many potential risk factors including a detailed occupational history. Age-adjusted ORs were presented separately for men and women. ORs among male painters were 1.2 (95% CI: 0.6–2.4; 20 cases) for non-Hodgkin lymphoma/chronic lymphocytic

leukaemia, and 1.7 (95% CI: 0.8–3.8; 10 cases) for leukaemia. Results were not presented for Hodgkin disease or multiple myeloma.

Dryver *et al.* (2004) conducted a case–control study of non-Hodgkin lymphoma in southern Sweden. A total of 859 cases were enrolled during 1990–1998, and 1310 controls. Controls were matched to cases by age, gender, and parish and were identified using the unique Swedish personal identification number. Mailed questionnaires were used to gather information on demographics, smoking, education, occupations (up to eight), and occupational exposures. The questionnaire specifically enquired whether individuals had held a set of specific occupations that included occupation as a painter. The OR for occupation as a painter was 1.77 (95% CI: 1.13–2.76; 46 cases).

(b) North America

Scherr *et al.* (1992) conducted a population-based case–control study of occupational exposure in relation to non-Hodgkin lymphoma in the Boston area. A total of 152 men and 151 women were diagnosed with non-Hodgkin lymphoma during 1980–1982 and interviewed at nine participating hospitals. Controls were matched to cases by sex, age, town and precinct of residence. The participation rate was 80% for cases and 72% for controls. Participants provided information on a variety of possible risk factors including job held 15 years prior to interview, major occupation, second most major occupation, and up to two occupations. Analyses done to evaluate potential confounding indicated that no covariates needed to be included in the models. From the subjects, 1% were painters (n = 3) resulting in an OR of 6.0 (95% CI: 0.9–38).

Blair *et al.* (1993) conducted a case–control study of non-Hodgkin lymphoma among caucasian men in Iowa and Minnesota. Cases were identified from the Iowa State Health Registry during 1981–1983, and a surveillance network of hospitals in Minnesota during 1980–1982. Of 715 cases identified, 622 (87%) were interviewed. A total of 1245 caucasian male population controls – frequency-matched by state, age and by year of death for deceased cases – were selected from random-digit dialling (< 65 years), Medicare files (≥ 65 years), and death certificates (for those matched to deceased cases). Information on all jobs held for more than one year and other potential risk factors were obtained during an interview with subjects or their next-of-kin. ORs were adjusted for age, state of residence, agricultural use of pesticides, hair-dye use, family history of cancer, smoking, and direct or proxy respondent. The OR for employment in the painting/wallpaper-hanging industry was 1.9 (95% CI: 0.9–3.8; 16 cases). ORs for painting, plastering and cementing by duration were 0.6 (95% CI: 0.1–2.0) for < 10 years, and 2.7 (95% CI: 1.1–6.6) for 10 or more years.

Demers *et al.* (1993) conducted a case–control study of occupational exposures in relation to multiple myeloma (682 cases and 1683 controls) using four cancer registries in the Surveillance, Epidemiology and End Results (SEER) of the National Cancer Institute (NCI) located in Washington state, Utah, Atlanta, and Detroit. Population controls, obtained through door-to-door sampling and random digit dialling, had a similar age and sex distribution as the cases but were otherwise representative of the general population.

Lifetime occupational histories were collected during in-person interviews. Analyses were performed separately for self and surrogate respondents, adjusted for age, sex, race, and geographic location. ORs for multiple myeloma were 2.1 (95% CI: 1.2–3.6; 31 cases) for painters overall, and 2.5 (95% CI: 1.3–4.7; 22 cases) among self-respondents. Risks by duration of employment as a painter were 1.4 (95% CI: 0.6–2.8; 15 cases) for < 10 years, and 4.1 (95% CI: 1.8–10.4; 16 cases) for 10 or more years. Risks were greatest among self-responding painters who reported high exposure to paints or solvents (OR: 3.1; 95% CI: 1.5–7.5; 14 cases).

Blair *et al.* (2001) conducted a population-based case–control study of leukaemia among caucasian men in Iowa and Minnesota. Cases (n = 513) were assembled from the cancer registry in Iowa during 1981–1983, and from a surveillance network of hospitals in Minnesota during 1980–1982. Population controls (n = 1087) were selected by random-digit dialling for those aged under 65 years, Medicare files for those aged 65 years or older, and death certificates. Controls were frequency-matched by age, vital status, and state of residence. Information was obtained (including all jobs held more than one year) by in-person interviews. ORs were adjusted for age, state of residence, proxy interview, education, pesticide use, hair-dye use, smoking, and first degree relative with a cancer. Persons employed for 10 or more years in painting, plastering, waterproofing, and related occupations had an OR of 1.7 (95% CI: 0.7–4.2).

Kato *et al.* (2005) conducted a case–control study of non-Hodgkin lymphoma among women from upstate New York. Cases (n = 376) were identified from the New York State Cancer Registry during 1995–1998. Population-based controls (n = 463) were matched to cases by age and selected from the New York state driver's licence files for women aged under 65 years, and from Medicare files for women 65 years or older. Telephone interviews were conducted to obtain information on a variety of factors including exposure to paints and varnishes. ORs were calculated and adjusted for age, year of interview, pesticide exposure, use of pain-relieving drugs, use of antibiotics, family history of haematological cancer, college education, surrogate status, and body mass index (BMI). The OR for non-Hodgkin lymphoma from exposure to paints/varnishes was 0.79 (95% CI: 0.40–1.58; 23 cases). ORs by number of uses of paints/varnishes/lacquers (compared to no use) were 1.00 (95% CI: 0.60–1.68; 55 cases) for one to eight uses, 0.84 (95% CI: 0.50–1.40; 59 cases) for nine to 20 uses, 1.26 (95% CI: 0.77–2.07; 77 cases) for 21 to 59 uses, and 1.17 (95% CI: 0.70–1.97; 85 cases) for 60 or more uses (P for trend, 0.30).

Colt *et al.* (2007) evaluated the risk of non-hodgkin lymphoma in relation to exposures in hobby activities. Cases (n = 551) were men and women from four SEER areas (Iowa, Los Angeles county, Detroit and Atlanta) diagnosed during 1998–2000. Population-based controls (n = 462) were matched to cases by age, sex, race, and study centre, and selected from Medicare files (≥ 65 years) or from random digit dialling (< 65 years). In-person interviews were held to gather information on several potential risk factors including lifetime participation in hobbies involving painting, silk screening, and artwork. ORs were estimated by logistic or polychotomous regression while adjusting for

age at interview, SEER area, sex, race, and education. Potential confounding from other exposures and factors was evaluated, but did not need to be included in the model. ORs for categories of lifetime hours of painting as a hobby compared to non-painters were 1.0 (95% CI: 0.6–1.6; 43 cases) for 0.5–104 hours, 1.0 (95% CI: 0.6–1.8; 39 cases) for 105–520 hours, 0.6 (95% CI: 0.3–1.1; 23 cases) for 521–1800 hours, and 0.9 (95% CI: 0.5–1.6; 32 cases) for 1801 or more hours.

Ramanakumar *et al.* (2008) evaluated painting-related occupations and the risk of non-Hodgkin lymphoma, along with cancers of the oesophagus, stomach, colon, rectum, prostate, bladder, and kidney, in a re-analysis of Siemiatycki *et al.* (1994) data from a large case–control study from Montreal, Canada. The study included 215 non-Hodgkin lymphoma cases, a pooled control group of 533 population and 533 cancer controls, and a detailed assessment of exposures by a team of chemists and industrial hygienists. ORs were adjusted for age, family history, ethnicity, respondent status, education, and smoking. The OR for non-Hodgkin lymphoma among painters was 0.9 (95% CI: 0.2–4.1; 3 cases). ORs for persons exposed to wood and gypsum paints were 0.9 (95% CI: 0.5–1.7; 27 cases) for any level of exposure, and 1.0 (95% CI: 0.4–2.6; 11 cases) for substantial exposure.

(c) Other Regions

Bethwaite *et al.* (1990) conducted a case-control study based on a cancer registry in New Zealand during 1980–1984 to investigate the association between employment as a painter and risk of various cancers, including haematopoetic cancers. Cases (535 non-Hodgkin leukaemia, 170 Hodgkin disease, 295 multiple myeloma, 534 leukaemia) who reported an occupation were included in this study as well as male control patients of all other types of cancer. Painters were found to be associated with an increased risk of multiple myeloma (OR, 1.95; 95% CI: 1.05–3.65; ten cases), especially those painters aged 20–59 years (OR, 4.23; 95% CI: 1.80–9.91; five cases). The risk was not significantly increased for those aged 60 years and over (OR, 1.27; 95% CI: 0.52–3.10; five cases). For multiple myeloma, the risk was higher for car, spray, and signwriter painters (OR, 2.81; 95% CI: 0.73–10.7) than for construction and general painters (OR, 1.80; 95% CI: 0.89–3.64).

Adegoke *et al.* (2003) evaluated occupational exposures and risk of leukaemia in a case–control study from Shanghai, China. A total of 486 cases identified from the Shanghai Cancer Registry during 1987–1989 were interviewed. Controls (n = 502) were randomly selected from the urban Shanghai population and matched to cases on age and sex. In-person interviews were held to gather information on a variety of potential risk factors, including all jobs held for at least three years. Self-reported information was also gathered on a variety of specific exposures, including paints. ORs were adjusted for age, gender, and income. Among those ever exposed to paints, ORs were 1.2 (95% CI: 0.8–1.7; 57 cases) for all leukaemia, 1.1 (95% CI: 0.5–2.4; 10 cases) for acute lymphocytic leukaemia, 0.8 (95% CI: 0.5–1.4; 20 cases) for acute myeloid leukaemia, and 1.7 (95% CI: 0.9–3.2; 13 cases) for chronic myeloid leukaemia. For those exposed for 15 years or

greater, ORs were reported as: 2.3 (95% CI: 1.2–4.7; 27 cases) for all leukaemia, 3.4 (95% CI: 1.2–9.5; six cases) for acute lymphocytic leukaemia, 1.8 (95% CI: 0.7–4.2; ten cases) for acute myeloid leukaemia, and 3.7 (95% CI: 1.4–9.9; seven cases) for chronic myeloid leukaemia. Those were larger than ORs reported for those exposed for shorter time periods: 0.8 (95% CI: 0.5–1.3; 30 cases) for all leukaemia, 0.5 (95% CI: 0.2–1.6; four cases) for acute lymphocytic leukaemia, 0.5 (95% CI: 0.2–1.1; ten cases) for acute myeloid leukaemia, and 1.0 (95% CI: 0.4–2.5; six cases) for chronic myeloid leukaemia. ORs for all leukaemia from potential exposure to paints differed between men (OR, 0.9; 95% CI: 0.5–1.5; 32 cases) and women (OR, 1.7; 95% CI: 0.9–3.4; 25 cases).

2.2.5 *Solid tumours*

(a) Multiple cancer sites

Case–control studies of solid tumours among persons potentially exposed to paints are listed in Table 2.5.

Bethwaite *et al.* (1990) conducted a case–control study of multiple cancers using data from the New Zealand Cancer Registry. Age-adjusted ORs were calculated comparing painters with a particular cancer against painters without that cancer (and cancers that could be caused by the same exposures as that particular cancer). Occupational information (current or recent jobs) was obtained from the cancer registry. A total of 23 types of cancer were evaluated including buccal cavity, oesophagus, stomach, colon, rectum, liver, gallbladder, pancreas, larynx, lung, soft tissue sarcoma, malignant melanoma, prostate, testis, bladder, kidney, brain/nervous system, non-Hodgkin lymphoma, Hodgkin disease, leukaemia, and others. There were no significant increases in risk except for bladder cancer, and multiple myeloma.

In case–control study, Bouchardy *et al.* (2002) identified 58134 incident cancer cases in men from five cantonal Swiss Cancer Registries (Basel, Geneva, St Gall, Vaud, and Zurich) during 1980–1993. The overall proportion with histological or cytological confirmation of diagnosis was 95.1%. The study was restricted to cases aged 25 years or more at registration (and less than 65 years in St Gall and Vaud). The longest, current or most recent occupation at registration was recorded (the main or most accurately specified occupation was used in the Zurich Registry). Subjects with unknown occupation were not reported separately. The association between different cancer sites and work in a pre-defined set of industries and occupation was studied by estimating ORs adjusted for age, registry, civil status, period of diagnosis, nationality, urban/rural residence and socioeconomic status. For each neoplasm, registrants for the other cancer sites were used as the reference. The results for all sites with at least five exposed cases (excluding cancers of the lung, bladder and haematopoietic system because they are mentioned below) are reported in Table 2.5. There were no notable increases in risk except for cancers of the renal pelvis (OR, 2.2; 95% CI: 1.1–4.2; 14 cases) and liver (OR, 1.4; 95% CI: 1.0–2.0; 39 cases). [Use of patients with all other types of cancers as controls in this study could complicate the interpretation of the observed association since some of the

cancer types may well be linked to exposure to paints, and use of patients with all other types of cancers as controls would cause an underestimation of the association between painting and bladder cancer risk.]

Ramanakumar *et al.* (2008) evaluated painting-related occupations and the risk of several different cancers including cancers of the oesophagus (n = 97), stomach (n = 248), colon and rectum (n = 754), prostate (n = 438), bladder (n = 478), and kidney (n = 174), in a re-analysis of data from a large case–control study from Montreal, Canada [Siemiatycki *et al.* (1994)]. A pooled control group of 533 population and 533 cancer controls was used along with a detailed assessment of exposures by a team of chemists and industrial hygienists. ORs were adjusted for age, family history, ethnicity, respondent status, education, and smoking. The results for all cancer sites (excluding bladder cancer and non-Hodgkin lymphoma) are reported in Table 2.5. The OR for oesophageal cancer among persons who ever worked as painters was 1.8 (95% CI: 0.3–15.0; four cases). ORs for persons exposed to wood and gypsum paints were 1.7 (95% CI: 0.8–3.6; 18 cases) for any level of exposure, and 0.7 (95% CI: 0.2–2.8; five cases) for substantial exposure. No other cancer sites showed any association with exposures to paint.

(b) Upper respiratory tract

Huebner *et al.* (1992) conducted a population-based case–control study of incident oral and pharyngeal cancer in the USA (Los Angeles, Santa Clara, San Francisco, and Atlanta). Cases (n = 1114) were identified from population-based cancer registries during 1984–1985. Population-based controls (n = 1268), frequency-matched to cases by sex, race, age, and study area, were selected by random digit dialling (aged 18–64 years), and from medicare files (aged 65–79 years). Interviews were conducted in person or with next-of-kin if necessary, and covered information on tobacco and alcohol use, oral hygiene, medical and dental history, demographic characteristics, and a detailed history of all jobs held 6 months or more since the age of 12 years. Potential confounding was evaluated for several factors but only age, race, smoking, alcohol, and study location were included in the final model. The OR for painters was 1.18 (95% CI: 0.58–2.39; 22 cases) for men and 1.12 (95% CI: 0.37–3.36; seven cases) for women. ORs for cancers by anatomical site among male painters were 0.97 (95% CI: 0.33–2.84; five cases) for tongue, 0.71 (95% CI: 0.22–2.34; five cases) for mouth, and 2.03 (95% CI: 0.87–4.71; 12 cases) for the pharynx.

Maier & Tisch (1997) and Maier *et al.* (1997) conducted a hospital-based case–control study of cancers of the upper aerodigestive tract at the University of Heidelberg in Germany. A total of 369 male cancer patients aged 40–85 years (100 cancers of oral cavity, 105 cancers of the pharynx, and 164 cancers of the larynx) and 1476 non-cancer controls matched by age and residence were recruited between 1988–1991. In questionnaire-based interviews, information on tobacco smoking, alcohol drinking, and occupational exposures was collected. For statistical analyses, exposures to paint, lacquer, and solvents were combined, and exposure was defined as being at least once per week and for a duration of at least 10 years. Using this exposure definition, 4.5%, 5.8%, and

12.6% of the matched control groups were considered exposed. The average exposure duration of cases was between 19.9–21.4 years. The ORs, adjusted for smoking and alcohol drinking, for cancer of the oral cavity was 3.6 (95% CI: 1.4–9.3), and for cancer of the larynx 2.3 (95% CI: 1.1–4.5). [Results were not reported for cancer of the pharynx associated with exposures to paint, lacquer, and solvents were combined, although the authors mentioned that risk was not increased.]

Armstrong *et al.* (2000) evaluated occupational exposures and the risk of nasopharyngeal cancer in the Malaysian Chinese population. Cases ($n = 282$) were identified between 1990–1992 from four centres in the Selangor and the Federal Territory. Controls were selected from among the general Chinese population in the study area by randomly sampling individual houses. Participants provided information on smoking, diet, education, occupation, and housing type during an in-person interview. The OR for a 10-fold increase in exposure to paints or varnishes was 1.08 (95% CI: 0.91–1.29; 16 cases), adjusted for diet and smoking.

Boffetta *et al.* (2003) evaluated occupational exposures and cancer of the larynx and hypopharynx among men from selected areas in France, Italy, Switzerland, and Spain. Cases ($n = 1010$) were identified from cancer registries between 1980–1983. Population controls ($n = 2176$) were selected from census lists, electoral rolls, or population registries. Information on tobacco, alcohol, other risk factors, and all jobs held for at least one year since 1945 was obtained by in-person interviews. ORs were adjusted for age, study area, tobacco, and alcohol use. Construction painters had an OR of 1.36 (95% CI: 0.67–2.74; 18 cases).

Luce *et al.* (1993) indentified cases of cancers of the nasal cavity and paranasal sinuses ($n = 207$) diagnosed between 1986–1988 from 27 hospitals in France for a study of occupational exposures. A total of 409 controls were selected in two ways and pooled for analysis: one set of controls were patients with cancers other than those of the nasal cavity or sinus ($n = 323$), and the second set were individuals named by the cases ($n = 86$). Controls were matched to cases by age, sex and residence (friend controls only). Subjects were interviewed in person about socio-demographic characteristics, smoking habits, alcohol consumption, and a complete job history. Industrial hygienists assessed potential occupational exposures. ORs for specific histological types of nasal cancer were adjusted for multiple factors where appropriate. ORs for histological types of nasal cancer among men with probable or definite medium-to-high level exposure to paints, lacquers or varnishes were 0.9 (95% CI: 0.3–2.7; four cases) for squamous cell carcinoma, 12.2 (95% CI: 6.9–21.6; 35 cases) for adenocarcinoma, and 3.5 (95% CI: 1.3–9.3; six cases) for others.

Teschke *et al.* (1997a) conducted a population-based case–control study of nasal cancer in British Columbia, Canada. Cases ($n = 48$) were registered at the British Columbia Cancer Agency between 1990–1992. Controls ($n = 159$) were identified from provincial voters' lists and matched to cases by age and sex. Subjects, or next-of-kin if necessary, were interviewed in person or by telephone to obtain information on a variety of factors including occupational, residential, smoking, and medical histories.

Table 2.5 Case–control studies of solid cancers among painters grouped by major organ sites

Reference, study location and period	Characteristics of cases and controls	Exposure assessment	Organ Site (ICD-9)	Exposure categories	No.of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Multiple organ sites								
Bethwaite *et al*. (1990) New Zealand 1980–84	4224 male cases with known occupation among 5031 cases identified from the New Zealand Cancer Registry, aged 20 or more at registration; % microscopic confirmation not given	Current/most recent occupation as recorded at the time of registration and smoking history obtained through telephone interview	Buccal Cavity (140–149)	Painter decorators, steel and other construction painters, car painters, spray painters, signwriters, other unclassified painters	10	0.78 (0.41–1.47)	Age	See Table 2.2 for results on lung cancer. See Table 2.3 for results on bladder cancer
			Oesophagus (150)		5	0.70 (0.29–1.71)		
			Stomach		19	1.04 (0.65–1.67)		
			Colon		28	0.74 (0.50–1.09)		
			Rectum		25	0.99 (0.66–1.50)		
			Liver		2	0.61 (0.15–2.41)		
			Gallbladder		3	1.41 (0.45–4.44)		
			Pancreas		6	0.57 (0.26–1.27)		
			Larynx(161)		6	1.06 (0.47–2.41)		
			Soft tissue sarcoma		1	0.43 (0.06–2.88)		
			Melanoma		14	0.73 (0.43–1.25)		
			Prostate		43	1.02 (0.73–1.41)		
	All (15 680) male non-lung cancer registrants with known occupation, (out of 19 731 identified) from the same Registry and period, aged 20 or more at registration; % microscopic confirmation not given		Testis		5	0.99 (0.37–2.66)		
			Bladder		24	1.52 (1.00-2.31)		
			Kidney		14	1.45 (0.85–2.50)		
			Brain, nervous system		10	1.29 (0.68–2.46)		

Table 2.5 (contd)

Reference, study location and period	Characteristics of cases and controls	Exposure assessment	Organ Site (ICD-9)	Exposure categories	No.of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Bouchardy *et al*. (2002) Five cantons in Switzerland 1980–93	58 134 male incident cases from cantonal Cancer Registries, aged 25 or more (and 65 or less in St Gall and Vaud).	Longest, current or most recent occupation as recorded at the time of registration (main or best specified occupation in Zurich Registry)	Oral cavity/ oropharynx (141, 143–6)	Painters/plasterers	40	1.2 (0.8–1.6)	Age, registry, civil status, period of diagnosis, nationality, urban/rural residence, socio-economic status	The Working Group only presented cancers with at least 5 exposed cases
			Other pharynx (148–9)		14	1.1 (0.6–1.9)		
			Oesophagus		21	0.9 (0.6–1.4)		
			Stomach		61	1.0 (0.7–1.3)		
			Cardia		11	0.7 (0.4–1.4)		
	Male patients with cancers other than the site studied from the same registries and period served as controls and therefore the number varies		Small intestine		6	1.0 (0.4–2.3)		
			Colon		75	1.0 (0.8–1.3)		
			Rectum		51	0.9 (0.7–1.2)		
			Liver		39	1.4 (1.0–2.0)		
			Gallbladder/ biliary tract		10	1.3 (0.7–2.4)		
			Pancreas		33	1.2 (0.8–1.7)		
			Larynx		24	1.2 (0.8–1.9)		
			Pleura mesothelioma		8	1.3 (0.6–2.8)		
			Soft tissue		5	0.8 (0.3–1.9)		
			Melanoma of skin		19	0.7 (0.5–1.2)		
			SCC		35	0.7 (0.5–1.0)		
			Basal cel carcinoma		100	1.0 (0.8–1.2)		
			Prostate		186	0.9 (0.7–1.0)		
			Testis		15	0.9 (0.5–1.5)		
			Other male genital		7	1.3 (0.6–2.9)		
			Kidney		26	1.0 (0.6–1.4)		
			Renal pelvis		14	2.2 (1.1–4.2)		
			Brain		21	1.0 (0.7–1.6)		
			Thyroid gland		6	0.8 (0.3–1.8)		

Table 2.5 (contd)

Reference, study location and period	Characteristics of cases and controls	Exposure assessment	Organ Site (ICD-9)	Exposure categories	No.of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Ramanakumar *et al.* (2008) Montreal, Canada 1979–86	Male cases from 18 hospitals in Montreal (97 esophagus, 248 stomach, 754 colorectal, 438 prostate, 478 bladder, 174 kidney, 215 NHL); aged 35–70 years; 100% histologically confirmed; 82% response rate. 1066 pooled age-matched controls (533 population controls from electoral lists and by random-digit-dialing, 533 controls from other cancers); response rate 72% and 84%	Detailed job history (including specific tasks and protective devices) obtained from in-person interviews and reviewed by a team of chemists and industrial hygienists who translated each job into a list of potential exposures by means of a checklist that included 294 substances	Stomach Colon and rectum Prostate Kidney Oesophagus	Painter	7 19 17 6 4	0.8 (0.2–2.8) 1.2 (0.6–2.9) 1.1 (0.3–3.4) 1.0 (0.2–4.3) 1.8 (0.3–15.0)	Age, family income, ethnicity, respondent status, years of schooling, smoking	No other cancer sites showed any evidence of an association with type of paint or stain. Overlaps with Parent *et al.* (2000)
			Oesophagus	*Wood/gypsum paints*				
				Any level of exposure	18	1.7 (0.8–3.6)		
				Substantial exposure	5	0.7 (0.2–2.8)		
				Any paint product				
				Any level of exposure	21	1.4 (0.7–2.8)		
				Substantial exposure	10	1.8 (0.8–4.3)		

Table 2.5 (contd)

Reference, study location and period	Characteristics of cases and controls	Exposure assessment	Organ Site (ICD-9)	Exposure categories	No.of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Upper aerodigestive tract								
Huebner *et al.* (1992) USA (Los Angeles, Santa Clara, San Francisco, Oakland, Atlanta, New Jersey) 1984–85	1114 white and black cases (762 men, 352 women) from population-based cancer registries; aged 18–79 years; 100% histologically confirmed; 75% participation rate 1268 population controls (837 men, 431 women) obtained by RDD (aged 18–64 years) and from Medicare files (aged 65–79 years); frequency matched by age, race, sex, study area; 76% participation rate	Detailed occupational history for all jobs held ≥ 6 months since the age of 12 years obtained from in-person interview	Oral cavity, pharynx (141, 143-146, 148, 149)	Paints/varnish use/ manufacturing			Study location, age, race, sex, smoking, alcohol	
				Males	125	0.99 (0.71–1.38)		
				Females	13	0.89 (0.37-2.14)		
				Painter:				
				Women	7	1.12 (0.37–3.36)		
				Men	22	1.18 (0.58–2.39)		
				by subsite:				
			Tongue (141)		5	0.97 (0.33–2.84)		
			Mouth (143-145)		5	0.71 (0.22–2.34)		
			Pharynx (146, 148, 149)		12	2.03 (0.87–4.71)		

Table 2.5 (contd)

Reference, study location and period	Characteristics of cases and controls	Exposure assessment	Organ Site (ICD-9)	Exposure categories	No.of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Maier & Tisch (1997); Maier *et al.* (1997) Germany 1988–91	369 male cases (100 oral cavity, 105 pharynx, 164 larynx) from the Otorhino-laryngology Department at the University of Heidelberg, Germany 1476 male noncancer hospital controls matched to cases on age and residence	Information on occupational exposures by questionnaire	Oral cavity Larynx	Exposed to paint, lacquer, or solvents ≥ once per week for ≥ 10 years	12 20	3.6 (1.4–9.3) 2.3 (1.1–4.5)	Smoking, alcohol use	

Table 2.5 (contd)

Reference, study location and period	Characteristics of cases and controls	Exposure assessment	Organ Site (ICD-9)	Exposure categories	No.of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Armstrong *et al.* (2000) Malaysia (Selangor and Federal Territory) 1990–92	282 Chinese cases (195 men, 87 women) from 4 centres with radiotherapy; aged 19–74 years; 100% histologically confirmed SCC; 53% participation rate. 282 randomly selected Chinese population controls; matched by age and sex; 90% overall participation rate	Detailed lifetime occupational history obtained from an in-person interview	Nasopharynx	Tenfold increase in exposure to paints and varnishes	16	1.08 (0.91–1.29)	Smoking and diet	42% prevalent cases and 58% incident cases

Table 2.5 (contd)

Reference, study location and period	Characteristics of cases and controls	Exposure assessment	Organ Site (ICD-9)	Exposure categories	No.of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Boffetta *et al.* (2003) France, Italy, Switzerland, Spain 1980–83	1010 male cases from cancer registries; 100% histological confirmed 2176 male population controls from census lists, electoral rolls or population registries; same age distribution as cases	Occupational history for all jobs held one year obtained from in-person interviews	Larynx and hypopharynx (146.4, 146.5, 148, 149.8, 161)	Construction painters	18	1.36 (0.67–2.74)	Age, centre, alcohol, tobacco	

Table 2.5 (contd)

Reference, study location and period	Characteristics of cases and controls	Exposure assessment	Organ Site (ICD-9)	Exposure categories	No.of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Luce *et al.* (1993) France 1986–88	207 cases; (167 men, 40 women) from 27 French hospitals; 99.5% histologically confirmed; 68.3% participation rate 409 pooled cancer and friend controls (320 men and 89 women); frequency matched by age, sex, residence (friend controls only); participation rates of 95% (cancer controls) and 83.5% (friend controls)	Detailed occupational history and exposures obtained from in-person interview; industrial hygienist exposure assessment	Nasal cavity and paranasal sinuses	Paints, lacquers, varnishes (men only)			Age	Men only for paint exposure analysis
			SCC	*low*	8	1.0 (0.4–2.3)		
				med/high	4	0.9 (0.3–2.7)		
			Adenocarcinoma	*low*	20	3.9 (2.7–7.2)		
				med/high	35	12.2 (6.9–21.6)		
			Other	*low*	3	1.0 (0.3–3.6)		
				med/high	6	3.5 (1.3–9.3)		

Table 2.5 (contd)

Reference, study location and period	Characteristics of cases and controls	Exposure assessment	Organ Site (ICD-9)	Exposure categories	No.of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Teschke *et al*. (1997a), British Columbia, Canada 1990–92	48 cases (33 men, 15 women) selected from from the British Columbia Cancer Agency, aged 19–75 years; response rate 88.9%; 100% histologically confirmed 159 population-based controls (128 men, 31 women) selected from provincial voter lists, frequency matched to the age and sex distribution of cases; response rate 81.5%	Occupational history obtained by in-person or telephone interview	Nasal cavity and sinuses	Ever painter Employed as a painter with most recent 20 years removed	2 2	2.2 (0.2–17.9) 2.6 (0.2–24.8)	Cigarette smoking, sex, age	

Table 2.5 (contd)

Reference, study location and period	Characteristics of cases and controls	Exposure assessment	Organ Site (ICD-9)	Exposure categories	No.of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Brown *et al.* (1988) Texas, USA 1975–80	183 white male SCC cases (136 alive, 47 dead) from hospital records and tumor registries; aged 30–79 years; 100% histologically confirmed; participation rates of 69.5% (living cases) and 67.5% (dead) 250 white male population controls (179 alive, 71 dead) from mortality tapes, driver's license records (< 65 years) and Medicare files (≥ 65 years); frequency matched by age, vital status, ethnicity and county of residence; participation rates of 62.8% (dead), 60.9% (< 65 years), 85.7% (≥ 65 years)	Detailed lifetime occupational history for all jobs held 6 months from in-person interview	Larynx (161, 231.0)	Painter Paints	11 32	2.30 (0.84–6.31) 1.79 (1.00–3.22)	Smoking, alcohol	

Table 2.5 (contd)

Reference, study location and period	Characteristics of cases and controls	Exposure assessment	Organ Site (ICD-9)	Exposure categories	No.of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Wortley *et al.* (1992) Seattle, WA, USA 1983–87	235 cases from the SEER registry; aged 20–74 years; 100% histologically confirmed; 80.8% participation rate 547 population controls RDD; matched by age and sex; 80% participation rate	Detailed lifetime occupational history for jobs held, ≥ 6 months, obtained from in-person interview	Larynx (161.0-161.9)	Painters *10 year lag* Spray paint machine operators Construction painters	14 14 NG NG	2.8 (1.1–6.9) 2.3 (0.9–5.7) 2.4 (0.5–11.2) 1.6 (0.4–6.6)	Alcohol, smoking, age, education	

Table 2.5 (contd)

Reference, study location and period	Characteristics of cases and controls	Exposure assessment	Organ Site (ICD-9)	Exposure categories	No.of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Gastrointestinal tract								
Parent *et al.* (2000) Montreal, Canada 1979–85	99 male cases who were Montreal residents; aged 35–70; 100% histologically confirmed (63 SCC); 75% response rate. 533 age-matched population controls selected from electoral lists by RDD; 71% response rate	Lifetime work history obtained from in-person interview and exposures were assessed by industrial hygienists	Oesophagus *All subtypes* *SCC*	Other paints/ varnishes *Any exposure* *Non-substantial* *Substantial* *Any exposure* *Non-substantial* *Substantial*	 18 12 6 16 10 6	 1.5 (0.8–2.6) 2.0 (1.0–4.1) 1.0 (0.4–2.4) 2.3 (1.2–4.4) 2.8 (1.2–6.3) 1.8 (0.7–4.7)	Age, birthplace, education, respondent type, smoking, alcohol, β-carotene intake	Overlaps with Ramanakumar *et al.* (2008)
Jedrychowski *et al.* (1990) Poland 1986–90	562 male adenocarcinoma cases; aged < 75 years; 100% histologically confirmed 572 male age-matched non cancer hospital controls	Occupational histories obtained during in-person interviews	Stomach	Painters/tanners	12	4.0 (1.3–12.7) 3.4 (1.1–11.1)	Age, education, residency, occupational status Above factors, diet, vodka drinking	

Table 2.5 (contd)

Reference, study location and period	Characteristics of cases and controls	Exposure assessment	Organ Site (ICD-9)	Exposure categories	No.of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Cocco *et al.* (1998) 24 States in USA 1984–92	1056 male cases (1023 whites, 33 blacks) from death certificates; aged ≥ 20 years 5280 persons who died from non-malignant disease; matched to cases on geographic region, race, gender, and 5-year age group	Usual occupation and industry from death certificate	Gastric cardia	Painters, construction and maintenance	6	0.6 (0.2–1.4)	Age, marital status, urban versus rural, marital status, socio-economic status	

Table 2.5 (contd)

Reference, study location and period	Characteristics of cases and controls	Exposure assessment	Organ Site (ICD-9)	Exposure categories	No.of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Ji *et al.* (1999) Shanghai, China 1990–93	446 cases (260 men, 186 women) from the Shanghai Cancer Registry; aged 30–74 years; 100% histologically confirmed; 78.2% response rate 1551 population controls (845 men, 696 women) randomly selected from Shanghai residents; frequency matched by age, gender	Lifetime work history from in-person interview	Pancreas	Glass manufacturer, potter, painter, construction worker		:	Age, education income, smoking, other occupations	
				Men	10	2.6 (1.1–6.3)		
				<35 years	7	2.5 (0.9–6.8)		
				35+ years	3	3.0 (0.7–13.8)		
				Women	4	0.6 (0.2–1.9)		
Alguacil *et al.* (2000) eastern Spain 1992–95	164 cases (96 men, 68 women); 89% participation rate 238 hospital controls (167 men, 71 women); 90% participation rate	Job history and list of 10 activities, other activities performed ≥ 6 years obtained from in-person interview	Pancreas	Male painters, varnishes, related workers			Age, hospital, smoking, coffee, alcohol, tobacco	
				Years worked				
				< 20 years	0	0.1 (0.0–2.0)[a]		
				20+ years	3	5.3 (0.5–61.2)		
				Exposure window before diagnosis				
				5-15 years	2	1.6 (0.2–14)		
				>15 years	0	0.3 (0.0–7.1)[a]		

Table 2.5 (contd)

Reference, study location and period	Characteristics of cases and controls	Exposure assessment	Organ Site (ICD-9)	Exposure categories	No.of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Kaerlev *et al.* (2002) Denmark, Sweden, France, Germany, Italy 1995–97	84 cases (51 men, 33 women); aged 35–69; 85% participation rate 2070 controls (1447 men, 623 women) from population registers; matched by age, sex, residence; 62% participation rate	Detailed history of all jobs held 6 months or more obtained from in-person and/or telephone interview	Small bowel carcoid tumor	Construction painters *No lag* *10 year lag* *25 year lag*	 3 3 3	 3.3 (0.9–12.0) 3.5 (1.0–12.8) 3.6 (1.0–13.1)	Sex, country, birth year	
Reproductive and genitourinary organs								
Habel *et al.* (1995) Washington state, USA 1988–90	537 white female cases from the SEER registry; aged 50–64 years; 100% histologically confirmed; 81.4% participation rate 492 white female population controls selected by RDD; aged 50–64 years; 73% participation rate	Detailed history of the 3 longest jobs held since age 17 obtained from in-person interview	Breast	Painters/sculptors/ printmakers *Any* *5 year duration* *10+ years latency*	 5 3 4	 1.7 (0.4–7.4) 1.0 (0.2–4.9) 1.4 (0.3–6.2)	Age, parity, education, alcohol, BMI	

Table 2.5 (contd)

Reference, study location and period	Characteristics of cases and controls	Exposure assessment	Organ Site (ICD-9)	Exposure categories	No.of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Shu *et al.* (1989) Shanghai, China 1984–86	229 cases; aged 18–70 years; 94.3% histologically confirmed; 88.8% participation rate	Occupation obtained through in-person interview	Ovary	Painters, chemical processors and related workers, rubber and plastic products makers, leather workers			Education, number of livebirths, ovarian cyst, age at menarche	
			Epithelial		6	2.7 (0.6–13.9)		
			Non-epithelial		4	1.0 (0.2-3.8)		
	229 age-matched population controls		*Epithelial*	Occupational exposure to paint	18	2.2 (0.8–5.9)		
			Non-epithelial		4	3.7 (0.4–34.2)		
Brownson *et al.* (1988) Missouri, USA 1984–86	1239 white male cases selected from the Missouri cancer registry.	Usual occupation and industry from registry records	Prostate	Paint/varnish manufacturing	5	5.7 (1.4–24.3)	Age	
	3717 white male cancer controls selected from the Missouri cancer registry							

Table 2.5 (contd)

Reference, study location and period	Characteristics of cases and controls	Exposure assessment	Organ Site (ICD-9)	Exposure categories	No.of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Sharpe *et al.* (2001) Montreal, Canada 1979–85	400 male cases; aged 47–70 years; 97% histologically confirmed; 80.6% participation rate 476 male population controls selected from electoral lists or by RDD; aged 45–70 years; matched by age and residence; 64.3% participation rate	Lifetime work history and leisure activities were obtained during in-person interviews to estimate exposures	Prostate	Often painting, stripping or varnishing furniture for leisure Leisure exposure to paints, lacquers, or stains	10 50	2.1 (0.7–6.7); 1.0 (0.6–1.5)	Age, ethnicity, respondent type, family income, BMI, smoking and alcohol use	
Asal *et al.* (1988) Oklahoma, USA 1981–84	315 cases from 29 hospitals in Oklahoma. 313 hospital controls matched to cases on sex, race, age, hospital and date of admission; 336 population controls selected by RDD and matched to cases on sex and age	Longest job held more than one year and industrial exposures obtained during an interview	Renal cell	Painting/paint manufacturing (men only)	22	1.3 (0.7–2.6)	Age	[There was no information on conditions of the hospital controls.]

Table 2.5 (contd)

Reference, study location and period	Characteristics of cases and controls	Exposure assessment	Organ Site (ICD-9)	Exposure categories	No.of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Delahunt *et al.* (1995) New Zealand 1978–86	914 cases (710 men, 204 women) from the New Zealand Cancer Registry with an active occupational code; age > 20 years 12 756 male cancer controls with non-urinary tract tumours	Current or most recent occupation at the time of registration	Renal cell	Male painters	NG NG	1.59 (1.00–2.43) 1.79 (1.31–3.44)	Age only Age and smoking	

Table 2.5 (contd)

Reference, study location and period	Characteristics of cases and controls	Exposure assessment	Organ Site (ICD-9)	Exposure categories	No.of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Pesch *et al.* (2000b) Germany 1991–95	935 cases (570 men, 365 women) from hospitals; 88.5% response rate; 100% histologically confirmed 4,298 population-based controls (2650 men, 1648 women) selected by RDD, matched by region, age and sex; response rate 71%	Lifetime occupational history obtained from in-person interview. Two JEMs and 1 JTEM were used to assess exposure to occupational agents	Renal cell	Painters,tanner,dyers and related occupations			Age, study centre and smoking	It is not clear if the "painters, dyers" for the duration analyses are the same as the "painters, tanners, dyers, and related occupations" for the ever/never analyses. Also for the duration analysis, the sum of exposed cases for "painters, dyers" is 26, while the number for the ever/never analysis is 19
				Women	1	0.6 (0.1–5.2)		
				Men	19	1.9 (1.1–3.3)		
				Duration				
				Medium	12	1.6 (0.8–3.0)		
				Long	10	1.4 (0.7–2.8)		
				Very long	5	2.3 (0.8–6.8)		

Table 2.5 (contd)

Reference, study location and period	Characteristics of cases and controls	Exposure assessment	Organ Site (ICD-9)	Exposure categories	No.of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Mattioli *et al.* (2002) Bologna and surrounding Province, Italy 1987–94	249 cases from the University Hospital in Bologna; 100% histologically confirmed; 76.9% response rate 238 hospital controls without renal cell carcinoma matched on gender, age, birthplace, district, same cluster of small towns, and in plains or hill; 73.5% response rate	Written questionnaire obtained occupational history; occupational exposures coded by an industrial hygienist	Renal cell	Male painters	5	0.31 (0.06–1.56)	Adjustment factors not clear. Used conditional logistic regression thus matching factors should already be adjusted for	No data for women

Table 2.5 (contd)

Reference, study location and period	Characteristics of cases and controls	Exposure assessment	Organ Site (ICD-9)	Exposure categories	No.of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Brüning *et al.* (2003) Germany, 1992–2000	134 cases who had undergone a nephrectomy at a hospital in Arnsberg; no age restriction; 100% histologically confirmed; 82.7% response rate 401 hospital controls selected without dementia or cancer; matched to cases by sex and 5-year age category	In-person interviews obtained every job held at least one year; Specific exposures estimated using a British JEM	Renal cell	Paints and Pigments *Low exposure (below median)* *High exposure (above median)*	 10 9	 2.35 (0.94–5.87) 2.14 (0.86–5.31)	Age, gender, smoking	18 out of 19 substances evaluated resulted in elevated ORs
Brain tumours								
Krishnan *et al.* (2003) USA 1991–94 and 1997–99	879 adult cases from the Northern California Cancer Center SEER registry 864 controls from RDD; matched to cases by age, race, and gender	Lifetime job history for all jobs longer than 3 months (1991-1994) or longer than 1 year (1997-1999) from in-person interview	Brain (Gliomas) Astrocytoma Nonastrocytoma	Painters *Ever* *Longest job* *Men* *Women* Painters	 17 6 4 2 5 1	 1.04 (0.52–2.07) 1.02 (0.33–3.17) 0.78 (0.21–2.93) 2.16 (0.19–24.0) 1.20 (0.36–4.00) 0.59 (0.07–5.14)	Age, ethnicity, gender	Overlaps with study by Corozza *et al.* (2000) (see text)

Table 2.5 (contd)

Reference, study location and period	Characteristics of cases and controls	Exposure assessment	Organ Site (ICD-9)	Exposure categories	No.of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Rajaraman *et al.* (2004) Phoenix, Boston, Pittsburgh, USA 1994–98	293 cases (197 meningioma, 96 acoustic neuromas); ≥ 18 years old; > 93% participation rate 799 hospital controls; frequency matched by hospital, sex, race, age, residence; 86% participation rate	Detailed history of all jobs held 6 months or more obtained from in-person interview	Brain (Meningioma)	Painters *Ever worked* *Worked ≥5 years*	 2 1	 0.5 (0.1–2.2) 0.9 (0.1–7.2)	Hospital, sex, race, age, residence	No cases of acoustic neuroma had ever worked as a painter
Other sites								
Serraino *et al.* (1992) Northeastern Italy 1985–91	93 cases (53 men, 40 women); aged 16–79 years; 100% histologically confirmed 721 hospital controls (371 men, 350 women); aged 17-79 years	Employment in 17 industries and exposure to 15 occupation al agents obtained through interview	Soft-tissue sarcoma	Dyes/paints *≤10 years* *>10 years*	 4 4	 0.9 (0.3–2.9) 0.9 (0.2–2.7)	Age, sex	

Table 2.5 (contd)

Reference, study location and period	Characteristics of cases and controls	Exposure assessment	Organ Site (ICD-9)	Exposure categories	No.of exposed cases	OR (95% CI)	Adjustment for potential confounders	Comments
Fritschi & Siemiatycki (1996) Montreal, Canada 1979–85	103 male cases; aged 35–70 years; 100% confirmed histologically; 83% response rate. 1066 pooled male controls (533 population controls and 533 other cancer controls) selected from electoral lists, RDD or from the same hospitals as cases; 71% response rate	Detailed lifetime job history obtained through in-person interviews. Responses reviewed by chemists and industrial hygienists	Melanoma	Paint and varnish *Insubstantial* *Substantial* *Any*	 14 2 16	 3.0 (1.5–6.0) 0.4 (0.1–1.9) 1.7 (0.9–3.1)	Age, ethnicity, education	
Teschke *et al.* (1997b) British Columbia, Canada 1990–92	51 histologically confirmed cases selected from the British Columbia Cancer Agency; aged ≥ 19 years. 154 age-and sex-matched population controls selected from electoral lists	Occupational history obtained by in-person or telephone interview	Pleural mesothelioma	Painters *Ever employed* *Last 20 years removed*	 6 5	 4.5 (1.0–23.7) 5.4 (0.9–39.3)	Age, sex	

[a] Crude or computed using the Woolf-Haldane correction

Self-reported exposure information associated with these cancers was also.collected. ORs were adjusted for age, sex, and cigarette smoking. Some analyses were sex-specific. The ORs for persons ever employed as a painter was 2.2 (95% CI: 0.2–17.9; two cases), and 2.6 (95% CI: 0.2–24.8; two cases) with most recent 20 years of exposure removed.

Brown *et al.* (1988) conducted a population-based case–control study of cancer of the larynx among caucasian male residents of the Texas Gulf Coast to assess occupational risk factors. A total of 183 laryngeal cancer cases (136 alive, 47 dead) were identified from hospitals in a six-county area of the Gulf Coast between 1975–1980, and the alive cases interviewed. Controls (n = 250) from the area were matched to cases by age, vital status, ethnicity and county of residence, and were selected from Texas mortality files, driver's licence records for those under age 65, and Medicare files for those over age 65. Interviews were conducted with subjects, or next-of-kin, to obtain information on alcohol and tobacco use, diet, demographic factors, and lifetime occupational and residential histories. Tobacco and alcohol use was included in all models. Vital status, age, education, county of residence and certain dietary factors were evaluated as potential confounders but were not included in the final models. The adjusted OR for painters for cancer of the larynx was 2.30 (95% CI: 0.84–6.31; 11 cases). Workers with potential exposure to paints had an adjusted OR of 1.79 (95% CI: 1.00–3.22; 32 cases). ORs by years of exposure were 1.7 (95% CI: 0.7–3.8) for < 5 years, 2.3 (95% CI: 0.7–7.4) for 5 to 14 years, and 1.6 (95% CI: 0.5–4.8) for 15 or more years.

Wortley *et al.* (1992) conducted a case–control study of cancer of the larynx in western Washington state, USA. A total of 291 cases were identified between 1983–1987 through the cancer surveillance system of the the Fred Hutchinson Cancer Research Centre in Seattle, WA, of which, 235 were interviewed. Controls (n = 547), identified by random-digit dialling, were matched to the age and sex distribution of cases. In-person interviews were held to gather information on a variety of factors, including lifetime occupational histories, and tobacco and alcohol use. ORs for cancer of the larynx were adjusted for age, tobacco, alcohol, and education. ORs for painters and sculptors were 1.0 (95% CI: 0.2–6.3; three cases) for those ever employed as a painter or sculptor, and 1.2 (95% CI: 0.2–7.7; three cases) excluding the most recent 10 years of exposure. ORs for painters were 2.8 (95% CI: 1.1–6.9; 14 cases) for those ever employed as a painter, and 2.3 (95% CI: 0.9–5.7; 14 exposed cases) excluding the most recent 10 years of exposure. Among the painters, the ORs for spray paint machine operators was 2.4 (95% CI: 0.5–11.2), and 1.6 (95% CI: 0.4–6.6) for construction painters. [The definition of 'painters, sculptors' and 'painters' is not clear.] No trend by years of employment or exposure was evident.

(c) Gastrointestinal cancers

In a study to evaluate gastrointestinal cancer among workers exposed to asbestos, Kang *et al.* (1997) also provided PMRs for various occupations, including construction painters. The study included over four million deaths in 28 states in the USA during 1979–1990. The proportion of deaths from gastrointestinal cancer in occupations of

specific interest were compared to the proportion in all other occupations, adjusted for age, and stratified by race and sex. There were 89 deaths from gastrointestinal cancer among construction painters. PMRs among construction painters were 89 (95% CI: 81–124) for gastrointestinal cancer, 132 (95% CI: 75–214) for oesophageal cancer, 113 (95% CI: 67–178) for gastric cancer, and 91 (95% CI: 68–118) for colorectal cancer.

Parent *et al.* (2000) reported on a population-based case–control study of oesophageal cancer among men in Montreal which was part of a study of many cancers in the Montreal area (Siemiatycki, 1991). A total of 99 histologically confirmed cases of oesophageal cancer recorded during 1979–1985 were included. A control group of patients with other cancers ($n = 2299$) and population controls ($n = 533$) selected from electoral lists by random digit dialling were included. A pooled group ($n = 1066$) of 533 population controls and 533 cancer controls were included in the analysis. Information was obtained by questionnaire on a variety of factors including age, birth place, education, tobacco and alcohol use, and a detailed lifetime occupational history. 'Other paints and varnishes' was one of the exposure categories based on evaluation of occupational histories by a team of chemists and industrial hygienists. ORs for any exposure to 'other paints and varnishes' were 1.5 (95% CI: 0.8–2.6; 18 cases) for all histological types, and 2.3 (95% CI: 1.2–4.4; 16 cases) for squamous cell carcinoma. ORs for non-substantial exposure were 2.0 (95% CI: 1.0–4.1; 12 cases) for all histological types, and 2.8 (95% CI: 1.2–6.3; ten cases) for squamous cell carcinoma. ORs for substantial exposure were 1.0 (95% CI: 0.4–2.4; six cases) for all histological types, and 1.8 (95% CI: 0.7–4.7; six cases) for squamous cell carcinoma.

A hospital-based case–control study of stomach cancer drew cases from nine university hospitals in Poland during 1986–1990 (Jedrychowski *et al.*, 1990). A total of 562 adenocarcinoma cases were identified among men. Male controls ($n = 572$) were surgical patients admitted for various conditions, such as accidents or orthopaedic problems. Patients were interviewed in the hospital before surgery to obtain information on demographic characteristics, food preparation, alcohol use, and occupation. ORs were adjusted for age, education, residency, and occupational status. The OR for cancer of the stomach among painters and tanners was 4.0 (95% CI: 1.3–12.7; 12 cases), and 3.43 (95% CI: 1.07–11.08), respectively, when further adjusted for dietary habits, and vodka drinking.

Cocco *et al.* (1998) conducted a case–control study of gastric cardia between 1984–1992 using data from a mortality file from 24 states in the USA. Deaths from gastric cardia cancer ($n = 1056$) were matched to five control subjects ($n = 5280$) who died from non-malignant disease by geographic region, race, gender, and age. Usual occupation and industry were abstracted from death certificates. The OR was calculated by logistic regression, and adjusted for age, marital status, rural versus urban residence, and socioeconomic status (based on occupation). It was reported as 0.6 (95% CI: 0.2–1.4) for caucasian male construction and maintenance painters.

Ji *et al.* (1999) conducted a population-based case–control study of pancreatic cancer in Shanghai between 1990–1993. Cases ($n = 451$) were identified from the Shanghai

Cancer Registry. Control ($n = 1541$) were selected from the resident population of Shanghai and matched to the cases by age and gender. Subjects were interviewed in person to obtain information on demographic and residential characteristics, diet, tobacco and alcohol use, medical and family history, and lifetime occupational history. ORs were calculated and were adjusted for age, education, income, smoking, and other high risk occupations. Other potential confounders were evaluated and found not to affect ORs. ORs for the grouping of glass manufacturer, potter, construction worker, and painter were 2.6 (95% CI: 1.1–6.3; ten cases) among men, and 0.6 (95% CI: 0.2–1.9; four cases) among women. ORs by years of working in this occupational grouping among men were 2.5 (95% CI: 0.9–6.8; seven cases) for employment of < 35 years, and 3.0 (95% CI: 0.7–13.8; three cases) for those employed 35 years or longer, compared to individuals never employed in these jobs.

Alguacil *et al.* (2000) conducted a case–control study of occupation and pancreatic cancer in five hospitals in eastern Spain during 1992–1995. A total of 164 cases, and 238 hospital controls were included. Controls were patients without pancreatic cancer who were initially admitted to the hospital with a suspicion of chronic pancreatitis or pancreatic or biliary cancer. Subjects were interviewed in the hospital to obtain information on occupation and lifestyle. ORs were calculated and were adjusted for age, smoking, coffee consumption, and alcohol use. Among male painters, varnishers, and related workers, compared to no employment in these jobs, the ORs were 0.1 (95% CI: 0.0–2.0; no cases; crude OR computed with the Woolf-Haldane correction) for those employed less than 20 years, 5.3 (95% CI: 0.5–61.2; three cases) for those employed 20 or more years, and 1.6 (95% CI: 0.2–14; two cases) for those exposed 5–15 years before diagnosis.

Kaerlev *et al.* (2002) conducted a population-based case–control study of small intestine carcinoid tumours in Sweden, Denmark, France, Germany, and Italy. A total of 84 cases and 2070 controls, matched to the cases by age, sex, and residence, were selected from population registries and interviewed. Interviewers obtained information on a variety of lifestyle factors and all jobs held for at least 6 months. ORs were calculated and were adjusted for sex, country and year of birth. ORs for construction painters were 3.3 (95% CI: 0.9–12.0; three cases) for no exposure lag, 3.5 (95% CI: 1.0–12.8; three cases) for a 10-year lag, and 3.6 (95% CI: 1.0–13.1; three cases) for a 25-year lag. ORs for specific occupational activities among painters were 5.6 (95% CI: 0.7–43.3; three cases) for sandblasting, 7.6 (95% CI: 0.9–66.3; five cases) for paint stripping with a blowtorch, 2.1 (95% CI: 0.2–26.6; six cases) using a solvent-based paint, 6.0 (95% CI: 0.5–74.7; six cases) using a rust-preventive paint, and 9.1 (95% CI: 0.8–107; six cases) using of a rust-preventive paint containing lead.

(d) Reproductive and genitourinary organs

Habel *et al.* (1995) evaluated occupational risks for breast cancer among caucasian women in a population-based case–control study in Washington state, USA. A total of 537 cases were identified from a cancer registry covering western Washington during

1988–1990. Population controls (*n* = 492) were selected by random digit dialling and matched to cases by age. In-person interviews were held to gather information on a variety of risk factors including a detailed history of the three occupations held for the longest period of time since the age of 17 years. ORs were adjusted for age, parity, BMI, education, and alcohol consumption. The OR for employment as a painter, sculptor or printmaker was 1.7 (95% CI: 0.4–7.4; five cases). Employment in these occupations by duration of employment were 1.0 (95% CI: 0.2–4.9; three cases) for 5 or more years, and 1.4 (95% CI: 0.3–6.2; four cases) for 10 or more years.

Shu *et al.* (1989) conducted a population-based case–control study of ovarian cancer in Shanghai. Cases (*n* = 229) were identified from the Shanghai Cancer Registry during 1984–1986. Controls were selected from the Shanghai general population and matched to cases by age. Participants were interviewed to obtain information on demographic characteristics, reproductive history, medical history, familial cancer history, personal habits, diet and occupation. ORs were adjusted for education, reproductive history, ovarian cysts, and age at menarche. ORs for occupational exposure to paint was 2.2 (95% CI: 0.8–5.9; 18 cases) for epithelial ovarian cancer, and 3.7 (95% CI: 0.4–34.2; four cases) for non-epithelial ovarian cancer.

Brownson *et al.* (1988) evaluated occupational risks for cancer of the prostate in cases (*n* = 1239) selected from the Missouri Cancer Registry during 1984–1986.. Age-matched controls were selected from other cancer cases (*n* = 3717). Information on smoking and alcohol use as well as occupation (occupation held for the longest period of time) were available from registry files. ORs were calculated using two control groups: all-controls and all-controls except for lung and bladder cancer. The OR among persons employed in the manufacture of paints and varnishes using all-controls was 5.7 (95% CI: 1.4–24.3; five cases). No controls in the second control group were employed in this industry.

Sharpe *et al.* (2001) reported on occupational exposures and prostate cancer in a case–control study among men from Montreal. Cases (*n* = 400) were identified during 1979– 1985. Population controls (*n* = 476) were selected from electoral lists or by random-digit dialling. Subjects were interviewed at home or in the hospital. Information on a variety of risk factors and a detailed history on occupations and occupational exposures as well as non-occupational exposures was gathered. Specific occupational exposures were assessed by chemists and industrial hygienists. ORs were adjusted for age, ethnicity, respondent status, income, BMI, and tobacco and alcohol consumption. The OR among individuals reporting painting, stripping or varnishing furniture often during leisure time was 2.1 (95% CI: 0.7–6.7; ten cases). The OR for self-reported exposure to paints, lacquers, or stains was 1.0 (95% CI: 0.6–1.5; 50 cases).

Asal *et al.* (1988) evaluated occupational risk factors renal cell cancer in case–control study (cases, *n* = 315) recorded during 1981–1984 from 29 hospitals in Oklahoma, USA. Hospital (*n* = 313) controls were matched to cases on age, sex, race, hospital and date of admission. Population controls (*n* = 336) selected by random digit dialling were matched to cases by age and sex. Information gathered was analysed to identify occupations held

for longet than 1 or more years. The OR for men employed in painting or paint manufacturing was 1.3 (95% CI: 0.7–2.6; 22 cases).

Delahunt *et al.* (1995) conducted a case–control study of occupational risk factors for renal cell carcinoma within the New Zealand Cancer Registry (NZCR) during 1978–1986. The NZCR captures and codes the current and most recent occupation at the time of registration. A total of 914 cases (710 men, 204 women) with an active occupation coded were identified as well as 12 756 male controls with non-urinary tract tumours. Women were excluded from the analysis due to a low representation of female cases with "at-risk" occupations. Among painters, the OR for renal cell carcinoma was 1.59 (95% CI: 1.00–2.43) when adjusted for age only, and 1.79 (95% CI: 1.31–3.44) when stratified by age and smoking history.

Pesch *et al.* (2000b) conducted a population-based case–control study of renal cell carcinoma in Germany. Cases (570 men and 365 women) were recorded during 1991–1995 from five regions (West Berlin, Bremen, Leverkusen, Halle, and Jena). Population controls (2650 men and 1648 women) were selected from local residency registries and matched to cases by region, age, and sex. Occupational histories covered all occupations held for at least one year. Job exposure matrices (JEMs) developed in Germany and Great Britain were used to assess specific exposures. Conditional logistic regression was used to calculate ORs, adjusting for smoking as a potential confounder. The ORs for painters, tanners, dyers, and related occupations were 1.9 (95% CI: 1.1–3.3; 19 cases) for men, and 0.6 (95% CI: 0.1–5.2; one case) for women. The ORs for male painters and dyers by duration of employment were 1.6 (95% CI: 0.8–3.0; 12 cases) for the 30th percentile, 1.4 (95% CI: 0.7–2.8; ten cases) for the 31st to 60th percentile, and 2.3 (95% CI: 0.8–6.8; five cases) for the 60th percentile or greater. [It is not clear if the "painters/dyers" for the duration analyses were the same as the "painters, tanners, dyers, and related occupations" for the ever/never analyses. Also, in the duration analysis, the sum of exposed cases for "painters/dyers" was 26, while the number for the ever/never analysis was 19.] ORs from the British JEMs on paints were for "paints and pigments" (0.9, 1.1, and 1.6 for medium, high, and substantial exposure among men, and 1.8, 1.1, and not calculable for the same categories among women). The German JEM for paints produced ORs of 1.1, 1.3, and 1.1 for medium, high and substantial exposure to paints among men, and 1.2, 1.2, and 0.6 for the same categories among women.

Mattioli *et al.* (2002) evaluated risk for renal cell cancer in a hospital-based case–control study in northern Italy. A total of 324 cases were identified at the University Hospital of Bologna during 1987–1994. Controls (n = 324) were individuals admitted to the hospital for anything other than renal cell cancer and residing in the same geographic area. Controls were matched to cases by age, gender, place of birth, same urban area, same cluster of small towns, and plains or hills. The OR for male painters was 0.31 (95% CI: 0.06–1.56; five cases). ORs were calculated by matched analysis and additionally adjusted for BMI, smoking, alcohol consumption, use of phenacetin and diuretics, meat consumption, coffee consumption, occupation titles and related exposures.

Brüning *et al.* (2003) conducted a case–control study of renal cell carcinoma in Arnsberg and surroundings, Germany. Interviews were completed with 134 cases identified during 1992–2000. Controls (n = 401) without dementia and with no diagnosis of cancer were selected from the same hospitals and matched to cases by age and sex. Information was obtained on all occupations held for longer than 1 year. A British JEM was used to classify jobs by exposure. Conditional regression was used to calculate ORs, adjusted for gender, age, and smoking. The OR for individuals potentially exposed to paints/pigments at low levels was 2.35 (95% CI: 0.94–5.87; ten cases), and 2.14 (95% CI: 0.86–5.31; nine cases) for high levels.

(e) Other solid tumours

Carozza *et al.* (2000) assessed occupational risk factors for gliomas in a population-based case–control study. Histologically confirmed glioma cases (n = 476), aged 20 years and older, were identified from the Northern California Cancer SEER registry and interviewed. Controls (n = 462) were identified by random digit dialling and frequency-matched to cases by 5-year age groups, gender, and race/ethnicity. Lifetime job histories were obtained through in-person interviews. ORs for those who had ever worked as painters, adjusted for age, gender, years of education and race, were 1.6 (95% CI: 0.5–4.9; ten cases) for all gliomas, and 1.8 (95% CI: 0.5–5.8; eight cases) for astrocytic tumours.

Krishnan *et al.* (2003) updated the study by Carozza *et al.* (2000) to assess occupational risk factors for adult glioma. A total of 879 cases from the Northern California Cancer SEER registry and 864 population controls, matched to cases by age, gender and race, were interviewed. The OR for 'ever' working as a painter was 1.04 (95% CI: 0.52–2.07; 17 cases).

Rajaraman *et al.* (2004) conducted a hospital-based case–control study of brain tumours in Arizona, Massachusetts, and Pennsylvania, USA. Cases (197 meningiomas, and 96 acoustic neuromas) were identified during 1994–1998. Controls (n = 799) were admitted to the same hospitals for a variety of non-neoplastic diseases and matched to cases by hospital, sex, race, age, and proximity of their residence to the hospital. In-person interviews were held to gather information on a variety of risk factors including every occupation held for 6 months or more since the age of 16 years. In addition, job-specific questions developed by an industrial hygienist were used to assess the probability, frequency, duration and intensity of specific chemical occupational exposures. ORs were adjusted for hospital, sex, race, age, and proximity of the residence to the hospital. ORs for meningioma were 0.5 (95% CI: 0.1–2.2; two cases) for having 'ever' worked as a painter, and 0.9 (95% CI: 0.1–7.2; one case) for 5 or more years' employment as a painter. No cases of acoustic neuroma had ever been employed as a painter.

Serraino *et al.* (1992) conducted a hospital-based case–control study of soft-tissue sarcoma and occupational exposures. Cases (n = 93) were obtained from hospitals in north-eastern Italy. Controls (n = 721) were patients admitted to the hospital for a variety of conditions, except cancer and diseases associated with tobacco consumption or diet modification. A questionnaire was designed to gather information on a variety of factors

including age at start and stop of employment in 17 industries or occupations, and exposure to 15 occupational agents. ORs were adjusted for age and sex. ORs for exposure to dyes and paints were 0.9 (95% CI: 0.3–2.9; four cases) for a duration of 10 years or less, and 0.9 (95% CI: 0.2–2.7; four cases) for a duration of more than 1 years.

Fritschi & Siemiatycki (1996) evaluated occupational exposures and the risk of melanoma among men in a population-based case–control study in Montreal, Canada. A total of 103 cases, identified during 1979–1985, were interviewed. A pooled group of 1066 controls was used: population controls ($n = 533$) selected from electoral lists and by random digit dialling, and also other cancers patients ($n = 533$). The interviews held gathered information on a variety of risk factors including detailed information on all occupations. A team of chemists and industrial hygienists translated interviews into specific occupational exposures. ORs were adjusted for age, education, and ethnicity. The OR for potential exposure to some paints and varnishes were 1.7 (95% CI: 0.9–3.1; 16 cases) for any exposure, 0.4 (95% CI: 0.1–1.9; two cases) for substantial exposure, and 3.0 (95% CI: 1.5–6.0; 14 cases) for non-substantial exposure.

Teschke *et al.* (1997b) conducted a population-based case–control study of mesothelioma in British Columbia, Canada. This study also included nasal and bladder cancers, which have already been previously discussed (Teschke *et al.*, 1997a). Cases ($n = 51$) were registered at the British Columbia Cancer Agency during 1990–1992. Controls ($n = 154$) were identified from provincial voters' lists and matched to cases by age and sex. Subjects, or next-of-kin if required, were interviewed in person or by telephone to obtain information on a variety of factors including occupational, residential, smoking and medical histories. The OR for persons 'ever' employed as a painter was 4.5 (95% CI: 1.0–23.7; six cases), and 5.4 (95% CI: 0.9–39.3; five cases) with the most recent 20 years of exposure removed.

2.2.6 *Review articles and meta-analyses since 1989*

There have been several review articles on cancer risk associated with occupation as a painter in addition to the individual post-Monograph (IARC, 1989) studies cited above. Lynge *et al.* (1997) presented a brief review of seven painter studies after the 1989 IARC Monograph 47, but their review is primarily oriented toward the effects of solvents in general.

Yamaguchi *et al.* (1991) conducted a meta-analysis to investigate employment as a painter and the risk of bladder cancer. The meta-analysis included 27 case–control studies of occupational exposures and the risk of bladder cancer published during 1972–1989. A summary relative risk was calculated from extracted ORs for each occupation as a geometric mean weighted by the numbers of bladder cancer cases in the case–control studies. Employment as a painter was found to be associated with a 50% increased risk of bladder cancer in this pooled study (RR, 1.48; 95% CI: 1.06–2.08).

In a meta-analysis of occupational cohort studies, Chen & Seaton (1998) found significant excess mortality for cancers of the oesophagus (SMR, 1.70; 95% CI: 1.22–2.37, 35 deaths), stomach (SMR, 1.27; 95% CI: 1.01–1.60, 79 deaths), colon (SMR, 1.18;

95% CI: 1.00–1.38, 152 deaths), rectum (SMR, 1.20; 95% CI: 1.01–1.44, 124 deaths), liver (SMR, 1.76; 95% CI: 1.37–2.26, 63 deaths), with borderline significance for cancers of the lung (SMR, 1.21; 95% CI: 1.12–1.31, 640 deaths), bladder (SMR, 1.26; 95% CI: 0.98–1.62, 63 deaths), larynx (SMR, 1.40; 95% CI: 0.94–2.09, 24 deaths), and leukaemia (SMR, 2.21; 95% CI: 0.95–5.13, 72 deaths). Heterogeneity between studies was significant only for leukaemia ($P < 0.001$).

Bosetti *et al.* (2005) systematically reviewed bladder cancer among painters, looking at post-1989 evidence (after IARC volume 47) through to 2004. They included four cohort studies on the incidence of bladder cancer among painters, and calculated a meta-RR of 1.10 (95% CI: 1.03–1.18; 893 cases). The corresponding meta-RR from four cohort studies on mortality was 1.23 (95% CI: 1.11–1.37; 370 deaths). The meta-RR from 14 case–control studies and a pooled-analysis of another 11 case–control studies was 1.35 (95% CI: 1.19–1.53; 465 exposed cases). Overall, the meta-RR from all epidemiological studies was 1.17 (95% CI: 1.11–1.27).

2.2.7 *Comprehensive meta-analyses of studies on painters and cancers of the lung and of the bladder*

The Working Group conducted a meta-analysis with studies that reported the risk of lung and bladder cancer among painters.

(a) Selection criteria

All epidemiological studies included in the previous IARC Monographs were considered (IARC, 1989). Reports in any language describing lung or bladder cancer in painters referenced in or published after the previous IARC monograph (IARC monograph volume 47 published in 1989) (IARC, 1989) until October 2007 were searched for in PubMed using the search terms "(paint*[tw] OR varnish*[tw] OR lacquer*[tw]) AND (cancer OR neoplasms[mh]) AND (case-control study[mesh] OR cohort study[mesh] OR meta-analysis[mh] OR review[pt] OR risk factors[mh] OR neoplasms/epidemiology OR neoplasms/etiology OR neoplasms/CI OR occupational diseases/etiology OR occupational diseases/epidemiology OR occupational diseases/CI OR occupational diseases/MO OR occupational exposure/adverse effects OR death certificates[mh] OR epidemiologic methods[mh]) AND bladder AND lung." The search was restricted to studies in humans. Certain studies were excluded from the PubMed search because they were either not an epidemiological study, did not include original data (review articles), did not assess occupation as a painter, overlapped with another population already included in the meta-analysis, or lung or bladder cancers were not the outcomes. The reference lists of pertinent articles were also reviewed to capture relevant publications that may not have been identified with the search criteria.

To be included in this meta-analysis, studies had to report estimates of the relative risk (RR, OR, SIR, SMR) with corresponding 95% confidence intervals (CIs) for 'ever' versus 'never' occupation as a painter or have provided enough information that allowed for their computation. For studies that did not report the 'ever' versus 'never' painter

category, the risk estimates and 95% CIs for these categories were estimated (see statistical analysis section). For studies that reported only point estimates without corresponding CIs, *P*-values or standard errors, or did not report the distribution of data to allow for computation of relative risks and CIs, conservative assumptions were made to estimate relative risks and 95% CIs from the data provided on a study-by-study basis. These conservative assumptions underestimated the relative risk (towards the null) and overestimated the width of the CI (i.e. by doubling the variance to approximate a 95% CI adjusted for multiple factors). Studies were excluded if estimation was impossible. Square brackets indicate the relative risks and 95% CIs calculated by the Working Group (Tables 2.1, 2.2, 2.3, 2.6). For studies with overlapping populations, only the publication with the most complete study population was included.

(b) Data abstraction

All articles were assessed independently by three reviewers who extracted data that included authors, publication date, country of origin, characteristics of the study population including gender and any details on the definition of painters, incidence versus mortality, lung or bladder cancer histology, observed and expected cancer cases (for cohort and proportionate mortality studies), number of exposed cases and controls (for case-control studies), yes/no adjustment for smoking or other occupational carcinogens, relative risks with corresponding 95% confidence intervals and results on exposure-response (Tables 2.1, 2.2, 2.3, 2.6). If adjusted and unadjusted results were reported, the most valid point estimate (i.e. adjusted for smoking and other variables) was abstracted. Any discrepancies in data collection were resolved by two other reviewers.

(c) Summary statistics calculated for inclusion in the meta-analysis

For cohort and record linkage studies, risk estimates (SIR, SMR) were computed by dividing the observed number of cases by the expected number, based on an external reference population. The corresponding 95% CIs were estimated using the PAMCOMP program (Taeger *et al.*, 2000). If only subgroup results (e.g. by gender, race, or duration of exposure) were reported, fixed effects models were used to combine stratum specific data into one summary estimate.

Subgroup analyses were conducted by further restricting to studies with stronger methodologies, such as those studies that adjusted for smoking, other occupational risk factors or population-based case–control studies that adjusted for smoking. Only two of the cohort and record linkage studies provided information on smoking status.

To allow for inclusion in the meta-analysis, 95% CIs were calculated if they were not presented in the original paper. If a 90% CI was presented and if the upper (UL) and lower limit (LL) were proportionally symmetric around the risk ratio (for RR and OR; i.e. if UL/RR = RR/LL), an estimate of the standard error (SE) was calculated by SE = (ln UL – ln LL/3.29), where 3.29 = 2 * 1.645 for 90% CIs. If only a *P*-value for the null hypothesis was presented, then a "test-based" SE was estimated using SE = (ln RR)/Z_p, where Z_p is the value of the standard-normal test statistic corresponding to the *P*-value

using a two-tailed test. The UL and LL of the 95% CI were estimated by exp[ln(RR) ± 1.96(SE)], where $Z_p = 1.96$ if $P = 0.05$ using a two-tailed test (Rothman & Greenland, 1998). A 95% CI corresponding to an unadjusted RR was used in the meta-analysis if a paper did not present enough data to allow for estimation of the adjusted CI.

(d) Statistical analysis

For cohort and record linkage studies, incidence and mortality data were compared. Because cancer incidence data are often more accurate than mortality data, SIRs were used in the combined analyses instead of SMRs whenever both were presented. Assuming that the different effect estimates (e.g. SMR, SIR, RR, OR) represent the relative risk, the data were combined for all of the cohort, record linkage and case–control studies. Separate meta-analyses were also done by study design.

Many of the cohort and record linkage studies used an external reference population to calculate the expected cases. When the external reference rates that are used to calculate the expected cases were usually assumed to be known without error, an estimate of the exposure coefficient in a regression could be obtained by a weighted linear regression of the natural log of the adjusted SMR on exposure (Sutton *et al.*, 2000). The risk estimates from nested case–control studies were included with the analysis of cohort studies because, essentially, this design can represent a more efficient way to analyse cohort studies and does not suffer from the problems associated with control selection in a case–control study. Summary odds ratios (meta-OR) were obtained separately from the meta-analysis of case–control studies. Subgroup analyses were performed stratified by gender, study region, study design, types of adjustment, and by duration of employment.

The I^2 statistic quantified the extent of inconsistency among the studies (Higgins & Thompson, 2002). I2 values of 25–50% indicate moderate inconsistency, while values larger than 50% reflect large inconsistencies among studies. The I2 values were presented instead of the Cochran's Q-statistic because the Q-statistic only informs about the presence or absence of heterogeneity but does not quantify the extent (Huedo-Medina *et al.*, 2006). Both random- and fixed-effect models, with weights equal to the inverse of the variance, were used to calculate a summary risk estimate (DerSimonian & Laird, 1986). Results from random-effect models, which account for heterogeneity among studies, are presented.

Influence analyses were conducted by dropping one study at a time and examining its influence on the summary effect estimates. Forest plots were used to graphically display the data (Lewis & Clarke, 2001). In the forest plot, the risk estimate for each study is represented by a black square that is proportional to the sample size, the horizontal line shows the corresponding 95% CI, a dashed line marks the summary estimate, while the vertical solid line represents the null result. Publication bias was visually assessed using Funnel plots (Deeks *et al.*, 2005). All statistical analyses were performed by using STATA (version 10.0; StataCorp, College Station, TX), employing the "metan" command for the meta-analyses (Bradburn, 2004).

Table 2.6. Proportionate mortality studies of painting and lung cancer, organized by geographical region and publication date.

Reference, location	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	PMR (95% CI)	Adjustment for potential confounders	Comments
Terstegge *et al* (1995) Netherlands 1980–92	9812 Dutch male painters deceased during 1980–92, identified from a registry	Painters were obtained from a registry with which nearly all commercial painters are affiliated	Lung, trachea, bronchus, pleura, thymus, heart, mediastinum, less defined parts of respiratory tract (ICD 162–165)	Commercial painters	1480	1.20 (1.14–1.26)	Age, time period	Reference = proportion of lung cancers among all deaths within the Dutch male population during 1980–1992
OPCS (1958) England & Wales 1949–53 UK	Registered deaths of men and women aged ≥65 yrs in the broad occupational category of painters and decorators	Occupation at time of death or last occupation from death certificates; Occupations coded according to the Census 1951, Classification of Occupations	Lung, bronchus, trachea, primary cancer (ICD6 162)	Other painters & decorators Men Aerographers, paint sprayers	 461 5	 1.30 [1.18–1.42] 1.67 [0.54–3.90]	Age, sex	Reference = mortality rates of painters taken from the 1951 national census
OPCS (1971) England & Wales 1959–63 UK	Registered deaths of men and women aged 65–74 in England and Wales	Last occupation recorded on the death certificate	Lung, bronchus & trachea (ICD7 162, 163)	Painters & decorators Men (15–64 yrs) Men (65–74 yrs) Single women Aerographers, paint sprayers Men (15–64 yrs)	 728 849 1 98	 1.22 [1.13–1.31] 1.31 [1.22–1.40] 1.81 [0.05–10.08] 1.48 [1.20–1.80]	Age, sex	

Table 2.6 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	PMR (95% CI)	Adjustment for potential confounders	Comments
OPCS (1978), no.1 England & Wales 1970–72 UK	Registered deaths of 277,168 men, aged 15–64	Last occupation recorded on the death certificate, as coded by the *1970 Classification of Occupations*	Lung, bronchus, trachea (ICD8, 162)	Painters & decorators	847	1.25 [1.17–1.34]	Age	Reference = proportions of all deaths in the population of England & Wales during 1970–1972; The occupation unit of ‘painters and decorators’ was comprised of aerographers, paint sprayers; painters, decorators n.e.c.; coach painters
				Painters, decorators nec	728	1.22 [1.13–1.31]		

Table 2.6 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	PMR (95% CI)	Adjustment for potential confounders	Comments
OPCS (1986), no.6 UK (Scotland, England & Wales) 1979–80, 1982–83	Men aged 20–64 and married women aged 20–59 in Great Britain during 1979–80 and 1982–83	Last full-time occupation recorded on the death certificate	Lung, bronchus, trachea (ICD9,162)	Painters, decorators, French polishers				Female mortality was from England & Wales only
				Men	779	1.21 [1.13– 1.30]		
				Women	128	1.33 [1.11–1.58]		PRR indicates the differences in the proportions of all cancer registrations for a given occupation attributable to particular sites
						PRR (95% CI)		
UK	Men aged 15–74 in England & Wales in 1981			Other spray painters, males	34	1.56 [1.08–2.18]		
				Painters & decorators nec French polishers	226	1.25 [1.09–1.42]		
	Women aged 15–74 in 1981 or aged 20–74 in England & Wales during 1979–80 and 1982–83			Painting, assembling, & related occupations nec (women)				
				15–74 yrs of age	21	1.79 [1.11–2.74]		
						PCMR (95% CI)		
				20–74 yrs of age	39	1.01 [0.72–1.38]		

Table 2.6 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	PMR (95% CI)	Adjustment for potential confounders	Comments
OPCS (1995), no. 10 Roman & Carpenter (1995) England, 1981–87 UK	Men, aged 20–74 years, England 1981–87	Occupation recorded at the time of cancer registration/death	Lung, bronchus, trachea (ICD9 162)			**PRR (95% CI)**	Age, social class, region of registration	
				Painters & decorators	1664	1.08 (1.03–1.14)		
				Other spray painters	213	1.11 [0.97–1.27]		
OPCS (1995), no. 10 Winter (1995), Coggon (1995) England & Wales 1979–80, 1982–90 UK	29 689 male painters and decorators, aged 20–74 years, who died during 1979–80 or 1982–90, linked to census denominators	Last full-time occupation was obtained from death certificates	Lung, bronchus, trachea (ICD9 162)			**PMR (95% CI)**	Age, social class	Data for 1981 were omitted because of questionable quality
				Other spray painters	557	1.26 (1.16–1.37)		
				Painters & decorators	4110	1.12 (1.09–1.16)		
				Coach painters	69	0.87 [0.68–1.10]		

Table 2.6 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	PMR (95% CI)	Adjustment for potential confounders	Comments
Peto *et al* (1995) England, Wales, Scotland 1979–80, 1982–90 UK	British painters, aged 16–74 years, who died during 1979–80 and 1982–90 were obtained from a UK register	Last full-time occupation was obtained from death certificates	Mesothelioma	Male painters and decorators	100	**PMR (95% CI)** 1.31 [1.07–1.59]	Age, calendar year	This study partially overlaps with the Registrar General's report (1996); *Mesotheliioma excluded from the meta-analysis*
Enterline & McKiever (1963) USA								Overlaps with Guralnick (1963)

Table 2.6 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	PMR (95% CI)	Adjustment for potential confounders	Comments
Chiazze *et al*. (1980) 1970–76 USA	226 deceased white male spray painters from a cohort of workers in 10 automobile assembly plants Nested case–control study using 263 lung cancer deaths among white males and 1001 controls deceased from circulatory system disease or accidents, matched by age (± 2 years) and plant	Complete work history from plant records	Lung, bronchus, trachea (ICD8, 162)	Spray painter	21	**PMR (95% CI)** 1.41 [0.87–2.15]	Race, sex, age, cause of death	Reference was general population where each plant is located
				Ever	21	**OR (95% CI)** 1.43 [NG]		
				≥1 year	16	1.36 [NG]		
				≥3 years	13	1.29 [NG]		
				≥5 years	11	1.15 [NG]		

Table 2.6 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	PMR (95% CI)	Adjustment for potential confounders	Comments
Dalager (1980) 1959–77 USA	202 deaths in white male spray painters among 977 male painters employed ≥3 months and terminated employment at one of 2 large aircraft maintenance plants between 1949–59; followed up for mortality through 1977 (deaths certificates 90% complete)	Occupation	Respiratory organs (ICD7, 160–164)			**PCMR (95% CI)**	Age, time	Primer paints used were primarily chromium base compounds, especially zinc chromate, but epoxy paints were also used; Reference calculated using cancer mortality for US white males. *Calculated using a fixed effects model
				Painters	21	1.84 [0.90–2.23]		
				Years employed				
				<5	9	1.25 [0.57–2.37]		
				5–9	6	1.50 [0.55–3.26]		
				≥10	6	1.88 [0.69–4.08]		
				<10	15	[1.34 (0.77–2.34)]*		

Table 2.6 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	PMR (95% CI)	Adjustment for potential confounders	Comments
Milham (1983) 1950–79 USA	Death records of 429,926 men and 25,066 women in Washington state. Deaths of 5287 painters, 832 paperhangers and decorators (painters), 428 body/fender repairmen and auto painters	Occupation from death certificate	Lung, bronchus, trachea (ICD6-8 162)			**PMR (95% CI)**	Age, calendar time	Findings presented for white males (95% of study population).
				Painters, mainly construction and maintenance	251	1.21 [1.06–1.37]		
				Age 20–64 years	103	1.12 [0.91–1.36]		Expected: The age-adjusted number of deaths that would have occurred in a specific occupation and cause-of-death group, if that occupation had the same mortality experience as the entire cohort
			Bronchus and lung (ICD6-8 162.1, 163)	Auto painters & body/fender repairmen	39	1.48 [1.05–2.02]		
				Age 20–64 years	29	1.84 [1.23–2.64]		
				Paperhangers and decorators (painters)	50	1.40 [1.04–1.85]		
				Age 20–64 years	21	1.39 [0.86–2.12]		
Miller *et al.* (1986) USA	630 white male painters were identified from a registry of death certificates of 1757 artists deceased during 1940–69	Artists were identified from obituaries	Lung	Artistic painters	17	**PCMR (95%CI)** 0.8 (0.4–1.7)	Race, sex, age, calendar time	Total number of cancer deaths for all sites combined was used as the comparison group. The PMR for lung cancer was not significantly elevated

Table 2.6 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	PMR (95% CI)	Adjustment for potential confounders	Comments
Wang *et al.* (1999) North Carolina, USA	All male construction workers who lived and died in North Carolina during 1988–94	Usual occupation was obtained from coded death certificates	Lung	Painters, paperhangers, plasterers	NG	**PMR** 1.18 [1.01–1.35] ($p<0.05$)	Gender and race	No confidence intervals or number of deaths provided.

OPCS, Office of Population Censuses and Surveys; nec, not elsewhere classified; NG, not given; SPIR, standardized proportional incidence ratio; CI, confidence interval; ILO, International Labor Office and the United Nations Statistical Office; ISCO, International Standard Classification of Occupations; ISIC, International Standard Industrial Classification; NG, not given; PCMR, proportionate cancer mortality ratio; RR, rate ratio or relative risk; SIC, Standard Industrial Classification; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SMSA, Standard Metropolitan Statistical Area; TWA, time-weighted average; PRR, proportional registration ratio

2.2.8 *Results of the meta-analysis of lung cancer risk in painters*

The combined analysis of 17 cohort and linkage studies (meta-RR, 1.36; 95% CI: 1.28–1.44; I2 = 74.4%, *P* = 0) and 29 case–control studies (meta-OR: 1.35; 95% CI: 1.22–1.51; I2 = 48.4%, *P* = 0.002) demonstrated a significantly increased risk overall in persons who had ever reported occupation as a painter (meta-RR, 1.34; 95% CI: 1.28–1.41; I2 = 62.2%, *P* = 0) (Fig. 2.1). A total of 13 proportionate mortality studies, although not included in the combined analysis, also demonstrated a significantly increased risk of lung cancer in painters (Table 2.6). An influence analysis showed that dropping individual studies did not significantly alter the results (data not shown).

Stratification by study region showed that risks where highest in Asia (meta-RR, 1.47; 95% CI: 0.66–3.28; I2 = 0%, *P* = 0.87), similar in Europe (meta-RR, 1.37 95% CI: 1.28–1.47; I2 = 69.3%, *P* = 0) and North America (meta-RR, 1.35; 95% CI: 1.26–1.45; I2 = 56.4%, *P* = 0.001), and lower in South America (meta-RR, 1.17; 95% CI: 0.77–1.76; I2 = 48.8%, *P* = 0.10). Stratification by gender showed higher odds ratios in women (meta-RR, 2.05; 95% CI: 1.35–3.10; six studies) (Muscat *et al.*, 1998; Jahn *et al.*, 1999; OPCS, 1958; OPCS, 1971; Zeka *et al.*, 2006; Andersen *et al.*, 1999) than in men (meta-RR, 1.35; 95% CI: 1.27–1.42; 39 studies). Of the few studies that reported results for specific histologies (De Stefani *et al.*, 1996; De Stefani *et al.*, 2005; Pezzotto & Poletto, 1999; Richiardi *et al.*, 2004; Siemiatycki *et al.*, 1987), risks were generally highest among those diagnosed with small cell cancer, though the confidence intervals were wide due to the small number of cases and results for the different histological entities were not reported consistently.

Visual inspection of the funnel plot for 29 independent case–control studies demonstrated some evidence of publication bias: the plot was slightly skewed with a deficit of smaller non-positive studies (represented by large standard errors) (Fig. 2.2). When restricting the analysis to the larger case–control studies that showed both positive and negative results, the meta-OR remained significantly elevated (meta-OR, 1.31; 95% CI: 1.18–1.45; I2 = 51.6%, *P* = 0.003). There was little difference in the results of case–control studies stratified by hospital-based controls (meta-OR, 1.37; 95% CI: 1.09–1.74; I2 = 59.3%, *P* = 0.002) or population-based (meta-OR, 1.34; 95% CI: 1.18–1.51; I2 = 25.9%, *P* = 0.16), though the population-based studies were less heterogeneous.

Restricting to population-based case–control studies that adjusted for smoking demonstrated less heterogeneity between studies and strengthened the results (meta-OR, 1.41; 95% CI: 1.23–1.61; I^2 = 0%, *P* = 0.45). Three cohort studies reported smoking-adjusted results (Dunn & Weir 1965; Hrubec *et al.*, 1995; van Loon *et al.*, 1997) with a meta-RR of 1.16 (95% CI: 0.96–1.40; I2 = 9.3%, *P* = 0.33) which was slightly lower than the meta-RR for cohort studies that did not adjust for smoking (meta-RR, 1.38; 95% CI: 1.30–1.46; I2 = 77.3%, *P* = 0). An analysis restricting to never-smokers (meta-RR, 2.00; 95% CI: 0.80–5.02; I2 = 0%, *P* = 0.79) (Kreuzer *et al.*, 2001; Zeka *et al.*, 2006) and never- and non-smokers (meta-RR, 1.94; 95% CI: 0.95–3.96; I2 = 0%, *P* = 0.96) (Pohlabeln *et al.*, 2000) demonstrated a 2-fold increased risk of lung cancer among painters.

Figure 2.1. Forest plot of studies assessing lung cancer in painters, stratified by study design

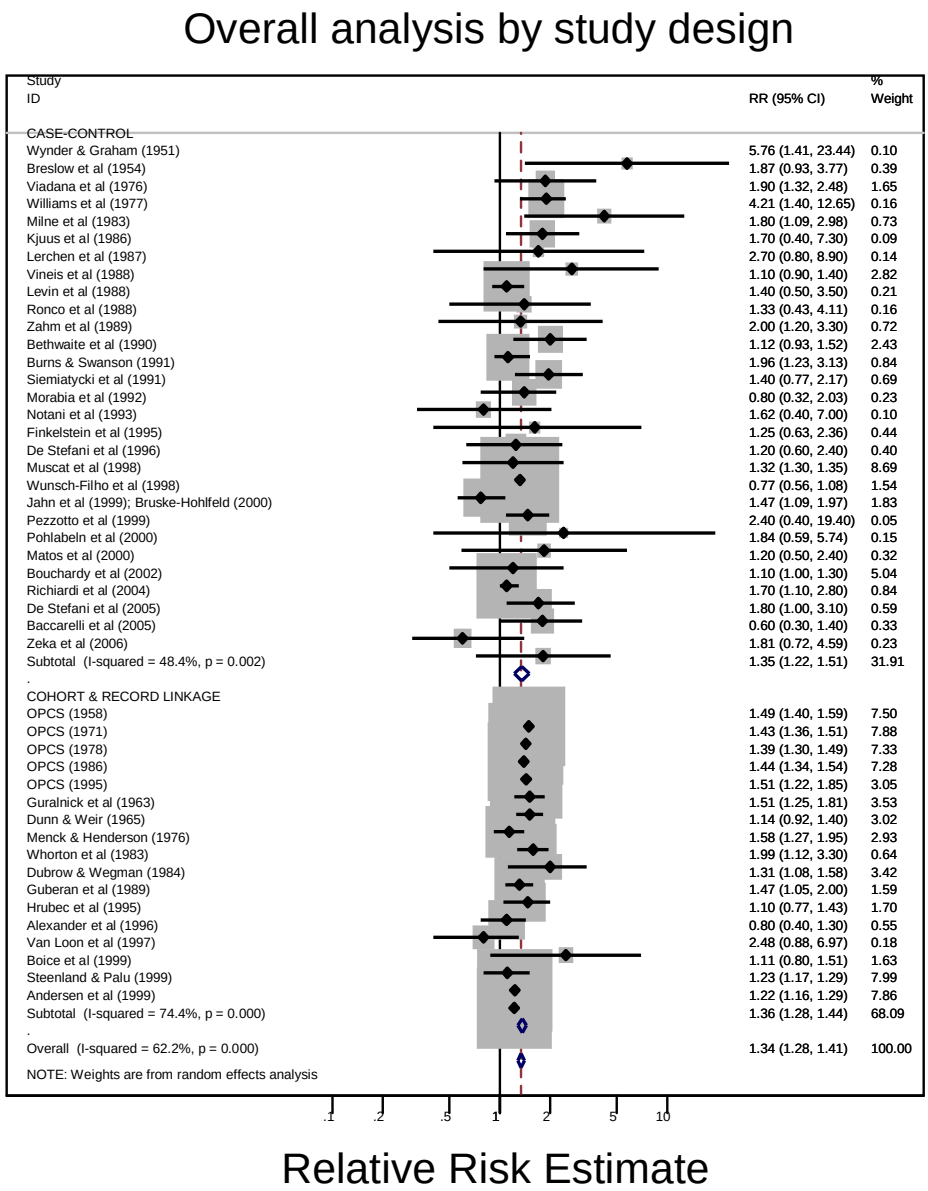
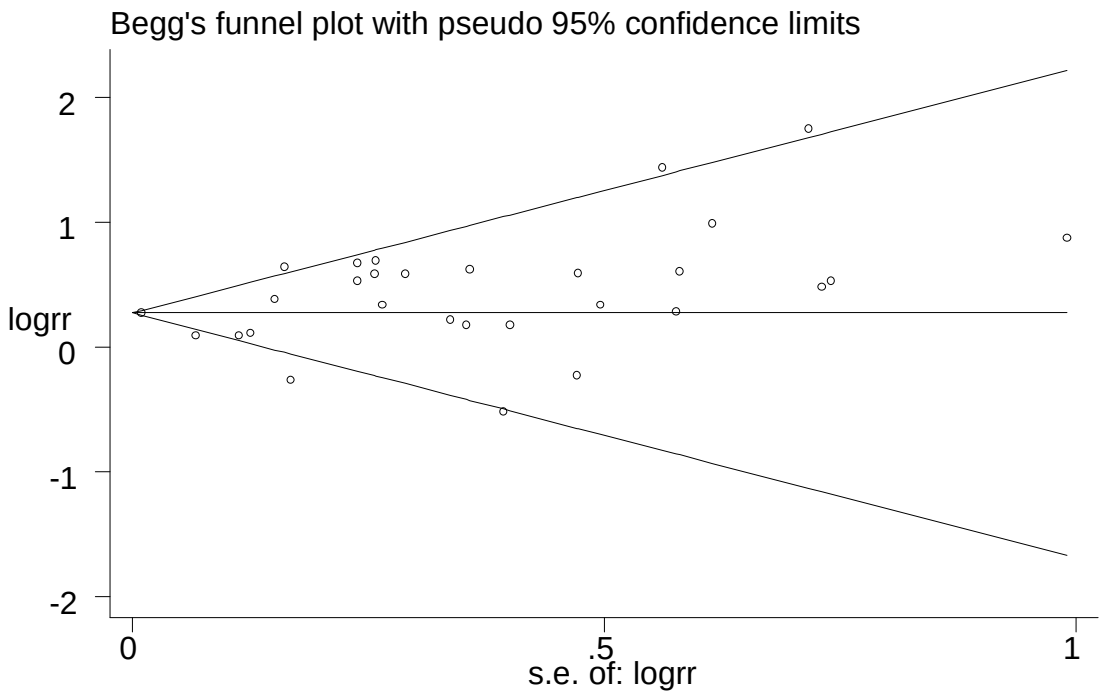


Figure 2.2. Funnel plot to assess publication bias in case-control studies of lung cancer in painters



Regardless of study design, those studies that adjusted for other occupational exposures as well as smoking further strengthened the results (meta-RR, 1.57; 95% CI: 1.21–2.04; I2 = 0%, *P* = 0.68). Analysis by duration of exposure (< 10 years versus ≥ 10 years, < 20 years versus ≥ 20 years) (Baccarelli *et al.*, 2005; Dalager *et al.*, 1980; Levin *et al.*, 1988; Swanson *et al.*, 1993) showed that those exposed ≥ 10 years (meta-RR, 1.75; 95% CI: 1.06–2.89; I2 = 0%, *P* = 0.61) or ≥ 20 years (meta-RR, 2.10; 95% CI: 0.88–5.02; I2 = 16.4%, *P* = 0.18) had a higher risk than those exposed < 10 years (meta-RR, 1.13; 95% CI: 0.73–1.74; I2 = 14.7%, *P* = 0.32) or < 20 years (meta-RR, 1.19; 95% CI: 0.72–1.96; I2 = 0%, *P* = 0.67) (reference category was 0 years exposure), respectively.

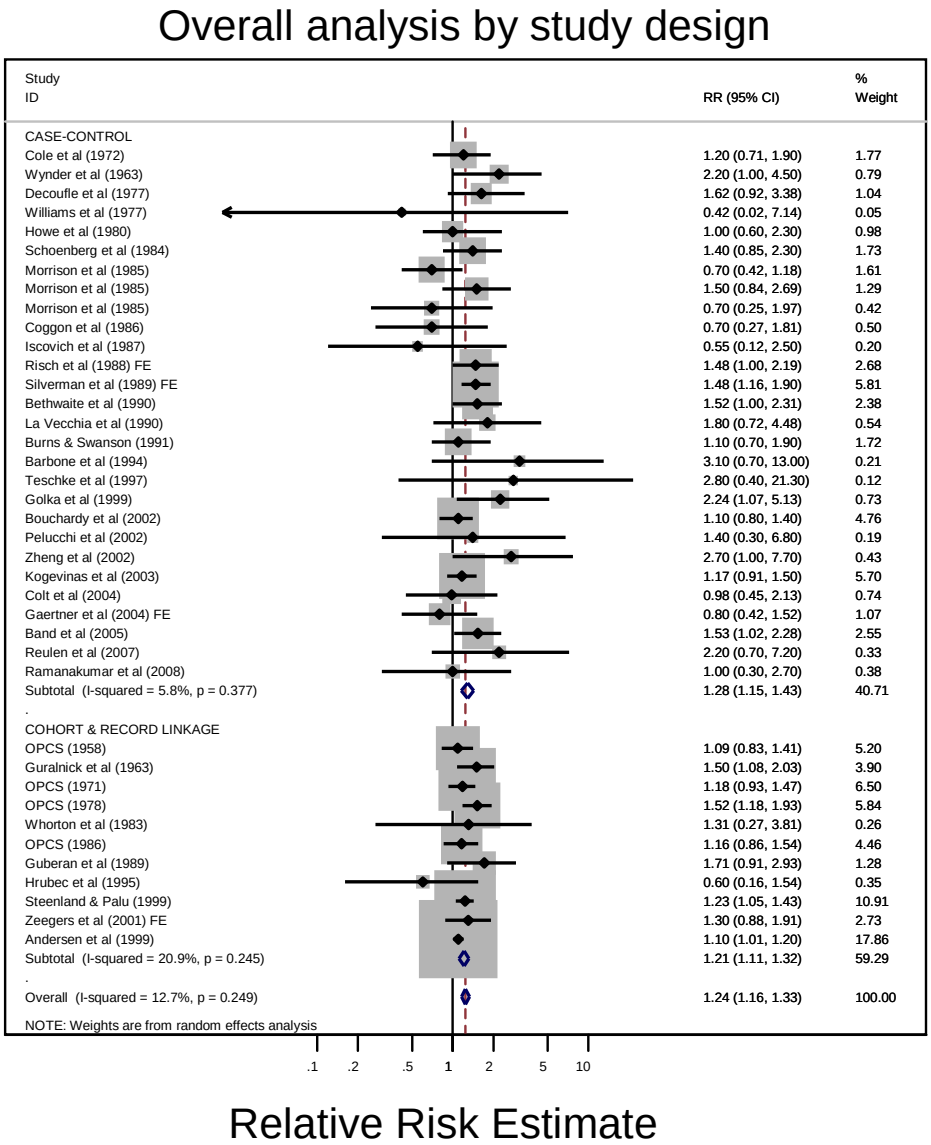
2.2.9 *Results of the meta-analysis of bladder cancer risk in painters*

The combined analysis of 11 cohort and record linkage studies (meta-RR, 1.21; 95% CI: 1.11–1.32; I2 = 20.9%, *P* = 0.25) and 28 case–control studies (meta-OR, 1.28; 95% CI: 1.16–1.43; I2 = 0.8%, *P* = 0.38), demonstrated a significantly increased risk overall in persons who had ever reported occupation as a painter (meta-RR, 1.24; 95% CI: 1.16–1.33; I2 = 12.7%, *P* = 0.25) (Fig. 2.3). An influence analysis showed that dropping individual studies did not significantly alter the results (data not shown).

Risks were higher in female painters (meta-RR, 1.54; 95% CI: 1.03–2.31) (Gaertner *et al.*, 2004; Pelucchi *et al.*, 2002; Risch *et al.*, 1988) than in males (meta-RR, 1.27; 95% CI: 1.18–1.36). It is notable that although there were only three studies among female painters, the meta-RR was statistically significant. Stratification by study region showed that risks were elevated in North America (meta-RR, 1.32; 95% CI: 1.20–1.46; I2 = 0%, *P* = 0.73) and Europe (meta-RR, 1.19; 95% CI: 1.08–1.31; I2 = 24.1%, *P* = 0.18).

Additional analyses were performed to examine the summary risk estimates when restricted to population-based case–control studies or studies with stronger design or analytical methods (adjusting for smoking or other occupational exposures). Restricting to studies that adjusted for smoking (meta-OR, 1.27; 95% CI: 1.13–1.43; $I^2 = 6.3\%$, *P* = 0.37), population-based case–control studies that adjusted for smoking (meta-OR, 1.26; 95% CI: 1.09–1.45; I2 = 16.9%, *P* = 0.25), or studies that adjusted for other occupational exposures as well as smoking (meta-RR, 1.27; 95% CI: 0.99–1.63; I2 = 0.1%, *P* = 0.39) did not significantly change the results from the overall estimate. Only two cohort studies reported smoking-adjusted results (Zeegers *et al.*, 2001; Hrubec *et al.*, 1995) with a meta-RR of 1.07 (95% CI: 0.55–2.07; I2 = 37.6%, *P* = 0.21). One of the two cohort studies was based on only four exposed cases (SMR, 0.60; 95% CI: 0.16–1.54; Hrubec *et al.*, 1995) while a second study was based on 47 exposed cases [RR, 1.30; 95% CI: 0.88–1.91] (Zeegers *et al.*, 2001), with higher risks in the medium- and high-exposure categories. Analysis by duration of exposure (la Vecchia *et al.*, 1990; Silverman *et al.*, 1989a; Zheng *et al.*, 2002; Siemiatycki *et al.*, 1994) showed that those exposed > 10 years (meta-RR, 1.92; 95% CI: 1.21–3.05; I2 = 18.3%, *P* = 0.30) had a higher risk than those exposed < 10 years (meta-RR, 1.45; 95% CI: 1.01–2.08; I2 = 0%, *P* = 0.91) (reference category was 0 years exposure).

Figure 2.3. Forest plot of studies assessing bladder cancer in painters, stratified by study design



There appeared to be no evidence of publication bias overall or among the case–control studies, as assessed by visual inspection of the funnel plot (Fig. 2.4). The meta-OR was higher in the seven studies using hospital-based controls (meta-OR, 1.54; 95% CI: 1.15–2.07; I2 = 0%, $P = 0.62$) than in the 21 studies using population-based controls (meta-OR, 1.25; 95% CI: 1.11–1.41; I2 = 11.6%, $P = 0.31$), though the hospital-based studies were less heterogeneous.

2.3 Childhood cancer (Table 2.7)

Studies providing information on childhood cancer and parental occupation as painters or paints are listed in Table 2.7.

Reviews by Savitz & Chen (1990), Colt & Blair (1998), and McBride (1998) of childhood cancer and parental occupation and environmental exposures provide excellent overviews of the literature. They note that occupations with potential exposure to paints have been associated with increased risk for leukaemia, lymphoma, cancer of the nervous system, hepatoblastoma, and rhabdomyosarcoma.

2.3.1 *Chilhood leukaemia*

The Children's Cancer Study Group (CCSG), a cooperative of clinical trials involving approximately 100 members in the USA and Canada, conducted a case–control study of parental occupational exposure and the risk of acute non-lymphocytic leukaemia (ANLL) among children (Buckley *et al.*, 1989a). A total of 262 cases were identified during 1980–1984, and both mothers ($n = 204$) and fathers ($n = 154$) of the cases were interviewed. Controls were selected by random-digit dialling using the area code and first five digits of the case's telephone number, and were matched to cases by date of birth and race. If the selected control family would not participate, a second control was selected. Second controls were used for 23 cases. Interviews gathered information on a variety of potential risk factors, including lifetime occupational history for each job held for 6 months or more, and self-reported exposures. The OR for paternal occupation as a painter was 7.00 ($P = 0.02$). The ORs for maternal exposure to paints and pigments as inferred from the job titles were 1.5 (95% CI: 0.6–3.3; 15 cases) for durations of up to 1000 days, and 2.2 (95% CI: 0.9–5.4; 15 cases) for durations of more than 1000 days (P for trend, 0.05). The timing of maternal exposure to paints and pigments resulted in ORs of 2.3 ($P < 0.05$) before the pregnancy, 1.5 during the pregnancy, and 0.9 after the pregnancy. In a multivariate stepwise regression analysis, self-reported paint and pigment exposure did not reach statistical significance for entry, but was the most significant of the remaining unselected variables ($P = 0.06$).

Shu *et al.* (1999) conducted a case–control study of childhood acute lymphocytic leukaemia (ALL) and parental occupational exposure. Cases ($n = 1842$) were diagnosed during 1989–1993 by a member of the Children's Cancer Group in the USA. Controls ($n = 1987$) were selected by random-digit dialling and individually matched to cases by age, race, and telephone area code and exchange.

Figure 2.4. Funnel plot to assess publication bias in case-control studies of bladder cancer in painters

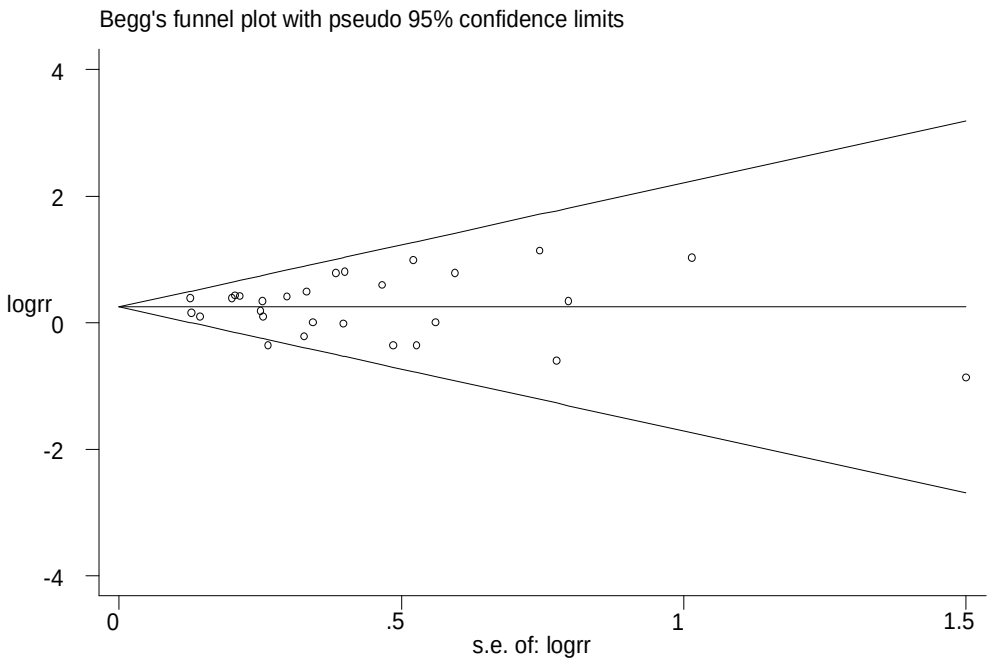


Table 2.7 Studies of childhood cancers and parental occupational exposure to paints

Reference, study location, period, study design	Characteristics of the cohort or of cases and controls	Exposure assessment	Organ Site	Exposure categories	No.of exposed cases	RR (95% CI)	Adjustment for potential confounders	Comments
Childhood leukaemia								
Buckley *et al*. (1989a) 100 institutions in USA and Canada, 1980–84 Case–control study	204 cases aged <18 years from the CCSG cooperative clinical trial group 262 population controls selected by RDD, matched by date of birth and race	Parental lifetime work history obtained through interviews with each parent	ANLL	Father painters	7	7.0 (P=0.02)	Unclear	
				Maternal paint and pigment exposure				
				Duration (days)				
				1 to 1000	15	1.5 (0.6–3.3)		
				>1000	15	2.2 (0.9–5.4)		
				P for trend		0.05		
				Period of use in relation to pregnancy				
				Before	NG	2.3 (P<0.05)		
				During	NG	1.5		
				After	NG	0.9		
				Maternal use of spray paints (prolonged exposure)	NG	3.0 (P<0.03)		

Table 2.7 (contd)

Reference, study location, period, study design	Characteristics of the cohort or of cases and controls	Exposure assessment	Organ Site	Exposure categories	No.of exposed cases	RR (95% CI)	Adjustment for potential confounders	Comments
Shu *et al*. (1999) 100 institutions in USA, 1989–93 Case–control study	1842 cases from CCG hospitals; aged <15 years 1987 population controls selected by RDD, individually matched by age, race, telephone area code and exchange	Detailed lifetime parental occupa-tional history from telephone interview: all jobs held 6 months (father since age 18; mother for two years prior to pregnancy); assessment of specific exposures by an industrial hygenist	ALL	Maternal occupational exposure *Spray paints (time period)* Anytime Preconception During pregnancy Postnatal	 53 27 27 38	 1.0 (0.7–1.5) 1.3 (0.7–2.3) 1.4 (0.8–2.6) 1.2 (0.7–1.9)	Maternal education, race and family income	Evaluation of maternal exposures to paints and thinners by duration found a slightly larger OR for the shorter duration category.

Table 2.7 (contd)

Reference, study location, period, study design	Characteristics of the cohort or of cases and controls	Exposure assessment	Organ Site	Exposure categories	No.of exposed cases	RR (95% CI)	Adjustment for potential confounders	Comments
Shu *et al*. (1999) (contd)				*Other paints (time period)*				
				Anytime	87	1.3 (0.9–1.7)		
				Preconception	44	1.9 (1.2–3.1)		
				During pregnancy	37	2.0 (1.2–3.5)		
				Postnatal	51	1.3 (0.9–2.0)		
				Paternal occupational exposure			Paternal education, race, family income, age and sex of index child	
				Spray paints (time period)				
				Anytime	364	0.9 (0.7–1.1)		
				Preconception	272	1.0 (0.8–1.3)		
				During pregnancy	157	1.0 (0.8–1.3)		
				Postnatal	208	1.0 (0.8–1.2)		
				Other paints (time period)				
				Anytime	315	0.9 (0.7–1.1)		
				Preconception	226	0.9 (0.7–1.1)		
				During pregnancy	117	1.0 (0.7–1.3)		
				Postnatal	163	0.9 (0.7–1.2)		

Table 2.7 (contd)

Reference, study location, period, study design	Characteristics of the cohort or of cases and controls	Exposure assessment	Organ Site	Exposure categories	No.of exposed cases	RR (95% CI)	Adjustment for potential confounders	Comments
Schüz *et al*. (2000) Germany, LSP Study 1992–96; NIP and WGP 1993–97 Pooled analysis of three case–control studies	1138 cases from the German Childhood Cancer Registry; age <15 years. 2962 population controls from population registration files; matched on gender, year of birth and community (NIP study)	Self-reported parental occupational chemical exposures	ALL	Paints or lacquers			Age, gender, year of birth, urbanization, and SES	
				Fathers				
				Any time	157	1.1 (0.9–1.4)		
				Preconception	147	1.1 (0.9–1.4)		
				During pregnancy	129	1.1 (0.9–1.4)		
				Postnatal	115	1.0 (0.8–1.3)		
				Mothers				
				Any time	54	1.8 (1.2–2.6)		
				Preconception	45	1.6 (1.1–2.4)		
				During pregnancy	32	2.0 (1.2–3.3)		
				Postnatal	18	1.0 (0.6–1.8)		

Table 2.7 (contd)

Reference, study location, period, study design	Characteristics of the cohort or of cases and controls	Exposure assessment	Organ Site	Exposure categories	No.of exposed cases	RR (95% CI)	Adjustment for potential confounders	Comments
Freedman *et al*. (2001) USA (9 midwestern and mid-Atlantic states), 1989–93 Case–control study	640 cases from CCG hospitals; age <15 years. 640 population controls selected by RDD; individually matched by age, race, first 8 digits of telephone number	Household exposures of mothers During the interview mothers provided information on household activities that could result in chemical exposure, including painting	ALL	Ever Painted *Mother painted* *Other people painted* *Number of rooms painted* 1–2 3–4 ≤4 *P* for trend In homes painted after birth: >4 rooms painted >5 times painted	289 160 128 161 62 64 NG NG	1.2 (0.9–1.5) 1.1 (0.9–1.5) 1.3 (0.9–1.7) 1.0 (0.8–1.3) 1.4 (0.9–2.1) 1.7 (1.1–2.7) 0.01 1.6 (1.2–2.2) 1.8 (1.1–2.8)	Age, income, sex, maternal education, painting during other periods	
McKinney *et al*. (2003) England, Scotland, Wales 1991–96	1737 leukaemia cases (1461 ALL); age ≤14 years 2 controls per case randomly selected from population registries; individually matched by sex, age, geographic area	Complete occupational history from in-person interview	Leukaemia ALL	Paternal occupational exposure to paint Leukaemia ALL	 25 21	 1.22 (0.76–1.85) 1.22 (0.73–1.91)	Age, sex, region of residence	

Table 2.7 (contd)

Reference, study location, period, study design	Characteristics of the cohort or of cases and controls	Exposure assessment	Organ Site	Exposure categories	No.of exposed cases	RR (95% CI)	Adjustment for potential confounders	Comments
Central nervous system tumours								
Peters *et al.* (1981) Los Angeles, USA, 1972–77 Case–control study	92 cases from the Los Angeles County Surveillance Program; <10 years of age. 92 friend and neighbour controls individually matched by sex, race, year of birth and social class	Detailed parental occupational history before conception, during pregnancy and at the time of diagnosis was obtained through telephone interview	Brain tumours	Father exposed occupationally to paints	7	7.0 (*P*=0.04)	Matching factors were accounted for in a matched-pairs analysis	

Table 2.7 (contd)

Reference, study location, period, study design	Characteristics of the cohort or of cases and controls	Exposure assessment	Organ Site	Exposure categories	No.of exposed cases	RR (95% CI)	Adjustment for potential confounders	Comments
Olshan *et al*. (1999) USA and Canada, 1992–96 Case–control study	504 cases under the age of 19 from 139 hospitals in the CCG and POG collaborative clinical trials 504 controls selected by RDD; individually matched to cases on date of birth	Telephone interviews obtained all maternal and paternal occupations held since age 18 until the reference date	Neuro-blastoma	Paternal painters	18	2.1 (0.9–4.8)	Mother's race, age, and education; household income in year of birth	No OR for maternal painters. 18 discordant pairs with case exposed and control unexposed.

Table 2.7 (contd)

Reference, study location, period, study design	Characteristics of the cohort or of cases and controls	Exposure assessment	Organ Site	Exposure categories	No.of exposed cases	RR (95% CI)	Adjustment for potential confounders	Comments
De Roos *et al.* (2001) 139 hospitals in USA and Canada, 1992–94 Case–control study	538 cases aged <19 years from 139 hospitals in the CCG and POG collaborative clinical trials 504 population controls selected by RDD and individually matched to cases on date of birth	Telephone interviews obtained parental occupational history. For the 2 years before child's birth, parents were asked about occupational exposure to 65 specific chemicals and responses were reviewed by an industrial hygienist.	Neuro-blastoma	Maternal			Child's age, maternal race, maternal age, maternal education	
				Paints, inks, pigments				
				Self-reported	21	1.0 (0.5–1.9)		
				IH-based	7	0.6 (0.2–1.4)		
				Oil-based paints				
				Self-reported	15	1.1 (0.5–2.4)		
				IH-based	2	0.2 (0.1–1.1)		
				Water-based paints				
				Self-reported	13	1.2 (0.5–2.7)		
				IH-based	5	1.2 (0.3–4.7)		

Table 2.7 (contd)

Reference, study location, period, study design	Characteristics of the cohort or of cases and controls	Exposure assessment	Organ Site	Exposure categories	No.of exposed cases	RR (95% CI)	Adjustment for potential confounders	Comments
De Roos *et al.* (2001) (contd)				Paternal				
				Paints, inks, pigments				
				Self-reported	52	0.8 (0.5–1.3)		
				IH-based	35	0.9 (0.5–1.6):		
				Oil-based paints				
				Self-reported	40	1.0 (0.6–1.7)		
				IH-based	27	1.4 (0.7–2.8);		
				Water-based paints				
				Self-reported	34	0.9 (0.5–1.5)		
				IH-based	24	1.1 (0.6–2.2)		

Table 2.7 (contd)

Reference, study location, period, study design	Characteristics of the cohort or of cases and controls	Exposure assessment	Organ Site	Exposure categories	No.of exposed cases	RR (95% CI)	Adjustment for potential confounders	Comments
Feychting *et al*. (2001) Sweden, 1976–93 Cohort study	Cohort of 235,635 children, born to married couples in 1976–1977 and 1981–1982, followed from birth until the age of 15 or 1993 through linkage with the Swedish Death and Cancer Registries. 522 childhood cancer cases (162 nervous system, 161 leukaemia, 40 lymphoma) observed	Occupational hygienists used a JEM to assess exposure through the 1975 or 1980 census reports of paternal occupation and industry	Nervous system cancers	Paternal occupation as a painter before conception	7	3.65 (1.71–7.80)	Census year, gender, maternal age, and SES (for 1981–1982 birth cohort)	

Table 2.7 (contd)

Reference, study location, period, study design	Characteristics of the cohort or of cases and controls	Exposure assessment	Organ Site	Exposure categories	No.of exposed cases	RR (95% CI)	Adjustment for potential confounders	Comments
Tsai *et al*. (2006) USA (6 states), 1992–95 Case–control study	303 cases that were <9 years of age 575 population controls selected by RDD; frequency-matched by age and race	Telephone interview to obtain maternal occupational history 2 years before child's birth and abbreviated information on paternal occupational history	Wilms' tumour	Paints and paint strippers *During pregnancy* *2 year study period*	 16 17	**OR (90% CI)** 1.09 (0.64–1.86) 1.04 (0.62–1.74)	SES, parental occupation and hobbies	
Other cancers								
Buckley *et al*. (1989b) USA (100 institutions) and Canada 1980–83 Case–control study	75 cases registered with the CCSG. 75 age-matched population controls identified through RDD	Lifetime work history and a list of specific exposures for mothers and fathers obtained from interview	Hepato-blastoma	Paints or pigments: *Father* *Mother* *Mother*	 34 11 NG	 1.5 (P>0.10) 3.7 (P<0.05) 2.8 (P=0.11)	 Age-matched Age-matched Age-matched and adjusted for metal exposure	Multivariate models unclear but likely to be adjusted for exposure to oil and petroleum products and metal

ALL, Acute lymphocytic leukaemia; ANLL, Acute non-lymphocytic leukaemia; CCG, Children's Cancer Group; CCSG, Children's Cancer Study Group; IH, industrial hygienist; JEM, job–exposure matrix; NG, not given; POG, Pediatric Oncology Group; RDD, random-digit dialling; SES, socioeconomic status

Questionnaires were administered by telephone to obtain information on a variety of risk factors, including occupational histories, and potential environmental exposures. Specific exposures were assessed by industrial hygenists. ORs were estimated by logistic regression, adjusted for maternal education, race, and family income or paternal education, race, family income, age and sex of index child. ORs for ALL from maternal exposure to spray paints were 1.0 (95% CI: 0.7–1.5; 53 cases) for any exposure, 1.3 (95% CI: 0.7–2.3; 27 cases) at preconception, 1.4 (95% CI: 0.8–2.6; 27 cases) during pregnancy, and 1.2 (95% CI: 0.7–1.9; 38 cases) postnatally. ORs from maternal exposure to other paints were 1.3 (95% CI: 0.9–1.7; 87 cases) for any exposure, 1.9 (95% CI: 1.2–3.1; 44 cases) at preconception, 2.0 (95% CI: 1.2–3.5; 37 cases) during pregnancy, and 1.3 (95% CI: 0.9–2.0; 51 cases) postnatally. ORs for maternal exposure to paints or thinners with a cut-off at the median duration of time of exposure were 1.3 (95% CI: 0.9–1.8; 74 cases) below the median and 1.4 (95% CI: 1.0–1.9; 83 cases, *P* for trend = 0.04) above the median for any exposure, 1.8 (95% CI; 1.2–2.9; 54 cases) below the median and 1.4 (95% CI; 0.9–2.2; 43 cases; *P* for trend = 0.02) above the median at preconception, 1.8 (95% CI; 1.1–3.0; 45 cases) below the median and 1.5 (95% CI; 0.9–2.4; 43 cases; *P* for trend = 0.01) above the median during pregnancy, and 1.2 (95% CI; 0.8–1.8; 53 cases) below the median and 1.1 (95% CI; 0.7–1.6; 52 cases; *P* for trend = 0.56) above the median postnatally. ORs for paternal exposure to spray paints were 0.9 (95% CI: 0.7–1.1; 364 cases) for any exposure, 1.0 (95% CI: 0.8–1.2; 272 cases) at preconception, 1.0 (95% CI: 0.8–1.3; 157 cases) during pregnancy, and 1.0 (95% CI: 0.8–1.2; 208 cases) postnatally. ORs for paternal exposure to other paints were 0.9 (95% CI: 0.7–1.1; 315 cases) for any exposure, 0.9 (95% CI: 0.7–1.1; 226 cases) at preconception, 1.0 (95% CI: 0.7–1.3; 117 cases) during pregnancy, and 0.9 (95% CI: 0.7–1.2; 163 cases) postnatally. None of the ORs from the fathers' exposures to paints or thinners by duration of exposure exceeded 1.0.

Schüz *et al.* (2000) pooled data from three case–control studies of childhood leukaemia in Germany to evaluate risks from parental occupational exposures. The three studies were from north-western Germany (LSP study), near German nuclear installations (NIP study), and in west Germany (WGP only). All studies included childhood cases of leukaemia diagnosis before the age of 15 years. The time periods varied for each study, but overall ranged from 1992 up to 1997. Controls were drawn from population files and matched on gender, date of birth within one year and community (NIP study only). Self-administered questionnaires gathered information on potential occupational exposures among the parents. ORs were adjusted for gender, age, year of birth, urbanization and socioeconomic status. ORs for paternal exposure to paints or lacquers were 1.1 (95% CI: 0.9–1.4; 157 cases) for any exposure, 1.1 (95% CI: 0.9–1.4; 147 cases) at preconception, 1.1 (95% CI: 0.9–1.4; 129 cases) during pregnancy, and 1.0 (95% CI: 0.8–1.3; 115 cases) postnatally. ORs for maternal exposure to paints or lacquers were 1.8 (95% CI: 1.2–2.6; 54 cases) for any exposure, 1.6 (95% CI: 1.1–2.4; 45 cases) at preconception, 2.0 (95% CI: 1.2–3.3; 32 cases) during pregnancy, and 1.0 (95% CI: 0.6–1.8; 18 cases) postnatally.

Freedman *et al.* (2001) conducted a case–control study of children < 15 years old with ALL and potential exposure to household chemicals. Cases ($n = 640$) were diagnosed during 1989–1993 and enrolled in the Children's Cancer Group in the USA. [Data from this study were used in the papers by Buckley *et al.* (1989a) and Shu *et al.* (1999) on parental occupational exposures.] Population controls ($n = 640$) were selected by random-digit dialling and matched to cases by age, race, first 8 digits of telephone number. During the interview, mothers provided information on household activities that could result in chemical exposure, including painting. ORs were adjusted for age, income, sex, maternal education, painting during other periods. ORs from engaging in artwork (using solvents) were 1.3 (95% CI: 0.9–1.8; 73 cases) for 'ever' use, 1.1 (95% CI: 0.7–1.8; 34 cases) for low exposure, 1.2 (95% CI: 0.7–2.0; 28 cases) for medium exposure, and 4.1 (95% CI: 1.1–15.1; 11 cases) for high exposure. ORs from painting in the house were 1.2 (95% CI: 0.9–1.5; 289 cases) for 'ever' painting, 1.0 (95% CI: 0.8–1.3; 161 cases) for painting 1 to 2 rooms, 1.4 (95% CI: 0.9–2.1; 62 cases) for 3 to 4 rooms, and 1.7 (95% CI: 1.1–2.7; 64 cases) for more than 4 rooms (P for trend, 0.01).

McKinney *et al.* (2003) conducted a case–control study among children < 14 years old; 1737 leukaemia cases ($n = 1461$ ALL cases) were enrolled along with two controls per case randomly selected from population registries and individually matched by sex, age, and geographic area. Complete occupational histories were obtained from in-person interviews. Paternal occupational exposure to paint was associated with an increased risk of childhood leukaemia in the offspring overall with ORs of 1.22 (95% CI, 0.76–1.85; 25 cases), and when restricted to ALL cases, 1.22 (95% CI, 0.73-1.91; 21 cases).

2.3.2 *Central nervous system tumours*

Peters *et al.* (1981) conducted a case–control study of brain tumours among children < 10 years old. Cases ($n = 92$) were identified from the Los Angeles County Cancer Surveillance Program during 1972–1977. Controls ($n = 92$) were matched to cases by sex, race, and year of birth, and selected from among friends or neighbours of the cases. Telephone interviews obtained information on occupational histories of fathers and mothers and other factors, including tobacco, alcohol, hair dyes, foods, and drugs. The OR from paternal occupational exposure to paints was 7.0 ($P = 0.04$).

Olshan *et al.* (1999) conducted a population-based case–control study of neuroblastoma and parental occupation. Cases ($n = 504$) were selected from 139 hospitals participating in the Children's Cancer Group or the Paediatric Oncology Group in 1992 and 1996 in the United States and Canada. Controls ($n = 504$) were selected by random-digit dialling and individually matched to cases by date of birth. Telephone interviews were conducted with mothers and fathers to obtain information on a variety of potential risk factors, including an occupational history on each parent since the age of 18 until the reference. Risk of neuroblastoma was 2.1 (95% CI: 0.9–4.8; 18 cases) among children whose fathers were painters. ORs were adjusted for the mothers' race, age and education and household income in the birth year. [No information was presented on risk among children whose mothers were painters.]

DeRoos *et al.* (2001) evaluated the risk of neuroblastoma from parental occupational exposures in a case–control study in the USA and Canada. The study was the same as that described by Olshan *et al.* (1999). Cases ($n = 504$) were selected from the hospitals participating in the Children's Cancer Group or the Paediatric Oncology Group during 1992–1994. [The Working Group noted the time for collection of cases for Olshan *et al.* (1999) and De Roos *et al.* (2001) were different, but all other aspects were the same. This may have just been a typo.] Controls ($n = 504$) were selected by random-digit dialling and individually matched to case by date of birth. Telephone interviews were conducted with mothers and fathers o f cases to obtain information on a variety of potential risk factors, including an occupational history and information for occupational exposure to 65 predetermined chemicals or chemical groups 2 years before the index child's birth. These self-reports were also reviewed by an industrial hygienist so that improbable situations could be recorded as unexposed. ORs were adjusted for children's age, maternal race, maternal age, and maternal education. ORs from maternal exposure to paints, inks and pigments were 1.0 (95% CI: 0.5–1.9; 21 cases) for self-reports, and 0.6 (95% CI: 0.2–1.4; seven cases) for the corrected estimate by the industrial hygienist. ORs from maternal exposure to oil-based paints were 1.1 (95% CI: 0.5–2.4; 15 cases) for self-reports, and 0.2 (95% CI: 0.1–1.1; two cases) for the corrected estimate by the industrial hygienist. ORs for maternal exposure to water-based paints were 1.2 (95% CI: 0.5–2.7; 13 cases) for self-reports, and 1.2 (95% CI: 0.3–4.7; 5 exposed cases) for the corrected estimate by the industrial hygienist. ORs from paternal exposures to paints, inks, and pigments were 0.8 (95% CI: 0.5–1.3; 52 cases) for self-reports, and 0.9 (95% CI: 0.5–1.6; 35 cases) for the corrected estimate by the industrial hygienist. ORs from paternal exposure to oil-based paints were 1.0 (95% CI: 0.6–1.7; 40 cases) for self-reports, and 1.4 (95% CI: 0.7–2.8; 27 cases) for the corrected estimate by the industrial hygienist. ORs for paternal exposure to water-based paints were 0.9 (95% CI: 0.5–1.5; 34 cases) for self-reports, and 1.1 (95% CI: 0.6–2.2; 24 cases) for the corrected estimate by the industrial hygienist.

Feychting *et al.* (2001) conducted a cohort study of paternal occupational exposures and risk of childhood cancer. The cohort was composed of all children born to married parents in Sweden in 1976, 1977, 1981, and 1982. The 235 635 children were followed up until their 15th birthday, or through to 1993 by record linkage with the Swedish Cause of Death Registry and the Swedish Cancer Registry. A total of 522 cases of childhood cancer were identified (161 leukaemias, 162 nervous system tumours, and 40 lymphomas). The fathers' occupations were identified from census records in 1975 for the 1976 and 1977 births, and in the 1980 census for the 1981 and 1982 births. A job–exposure matrix using these occupations' titles was constructed for this study by two industrial hygienists. Relative risks were estimated using Cox proportional hazards modelling, adjusting for census year, gender, and maternal age. Control for socioeconomic status was performed for children born in 1981 and 1982. The RR for nervous system cancers was 3.65 (95% CI: 1.71–7.80; seven cases) for fathers occupationally exposed as painters.

Tsai *et al.* (2006) conducted a case–control study of Wilm tumour and residential and occupational exposures to chemicals. The study was located in six American states with toxic waste sites on the National Priorities List. Cases of Wilm tumour among children up to the age of nine years diagnosed during 1992–1995 were obtained from the six states. A total of 303 cases and 575 age- and race-matched population controls that were selected by random-digit dialling were interviewed. A telephone interview obtained information on maternal occupational history 2 years before the child's birth, and an abbreviated questionnaire obtained information on paternal occupational history. ORs were calculated using unconditional logistic regression adjusting for socioeconomic status, parental occupation, and hobbies. ORs for occupational and household exposure to paint and paint strippers were 1.09 (95% CI: 0.64–1.86; 16 cases) during pregnancy, and 1.04 (95% CI: 0.62–1.74; 17 cases) during the 2-year study period.

2.3.3 *Other cancers*

Cases of hepatoblastoma were identified from the Children's Cancer Study Group in the USA (Buckley *et al.*, 1989b). This study has been described previously (Buckley *et al.*, 1989a; Freedman *et al.*, 2001; Shu *et al.*, 1999). A total of 75 cases were identified during 1980–1993. Age-matched population controls ($n = 75$) were selected by random-digit dialling. Interviews obtained information on a variety of factors including detailed parental occupational histories and 51 specific chemicals and substances. Conditional logistic regression was used to estimate ORs. The ORs from exposure to paints or pigments were 3.7 ($P < 0.05$) from mothers, and 1.5 ($P > 0.10$) for fathers. In a multivariate analysis, the OR for maternal and paternal exposure to paint and pigments was 2.8 ($P = 0.11$).

2.3.4 *Synthesis of studies assessing maternal paint exposure and childhood leukaemia* (See Table 2.8)

Eight population-based case-control studies reported on the association between maternal exposure to paints and childhood leukaemia (van Steensel-Moll *et al.*, 1985); Lowengart *et al.*, 1987; Buckley *et al.*, 1989a; Shu *et al.*, 1999, 2004; Schüz *et al.*, 2000; Freedman *et al.*, 2001; Alderton *et al.*, 2006). Most of the studies presented combined results for paints, stains, lacquers. One study presented a case-only analysis that examined if maternal paint exposure was associated with the development of *Ras* mutation in acute lymphocytic leukaemia cases compared to *Ras*-mutation-negative acute lymphocytic leukaemia cases (Shu *et al.*, 2004), and therefore was not directly relevant to the discussion of whether maternal paint exposure to paints increases the risk of childhood leukaemia compared to healthy controls. Two studies reported on acute leukaemias combined (van Steensel-Moll *et al.*, 1985; Lowengart *et al.*, 1987), four studies reported on acute lymphocytic leukaemia (Shu *et al.*, 1999; Schüz *et al.*, 2000; Freedman *et al.*, 2001; Alderton *et al.*, 2006), and two studies reported on acute myeloid leukaemia (Buckley *et al.*, 1989a; Alderton *et al.*, 2006).

Table 2.8. Studies of childhood leukaemia and maternal exposure to paints

Reference, study location, period, study design	Characteristics of the cohort or of cases and controls	Exposure Assessment	Organ Site	Exposure categories	No.of exposed cases	RR (95% CI)	Adjustment for potential confounders	Comments
Van Steensel-Moll *et al.* (1985) Netherlands 1973–82 Case–control study	519 acute leukaemia cases from national cancer registry; <15 years old 507 controls from census lists; matched by region, date of birth, sex	Mailed questionnaire	Acute leukaemia	Paint, petroleum products, other chemicals during pregnancy	25	2.4 (1.2–4.6)	Social class, birth order, age, sex, region	Histological subtype not specified; estimated ~83% ALL cases; the category for paint exposure was combined with petroleum products and other chemicals
Lowengart *et al.* (1987) USA 1980–85 Case–control study	123 acute leukaemia cases ≤ 10 years old enrolled from population-based cancer registry 123 age-, sex-, race-, and Hispanic-ethnicity-matched controls selected from friends or by RDD	Telephone interview using a structured questionnaire	Acute leukaemia	Paint, lacquer exposure during pregnancy ≥ once/week	27 4	1.8 (p=0.03) 1.3 (p=0.30)	Age, sex, race, Hispanic ethnicity	Histological subtype not specified
Buckley *et al.* (1989a) 100 institutions in the USA and Canada 1980–84 Case–control study	204 cases aged <18 years from the CCSG cooperative clinical trial group 262 population controls selected by RDD, matched by date of birth and race	Parental lifetime work history obtained through interviews with each parent	ANLL	Paint & pigment exposure *Duration (days)* 1 to 1000 >1000 *P* for trend *Period of use* Before pregnancy During pregnancy After pregnancy Use of spray paints (prolonged exposure)	 15 15 NG NG NG NG	 1.5 (0.6–3.3) 2.2 (0.9–5.4) 0.05 2.3 (*P*<0.05) 1.5 0.9 3.0 (*P*<0.03)	Date of birth, race	

Table 2.8 (contd)

Reference, study location, period, study design	Characteristics of the cohort or of cases and controls	Exposure Assessment	Organ Site	Exposure categories	No.of exposed cases	RR (95% CI)	Adjustment for potential confounders	Comments
Shu *et al*. (1999) 100 institutions in USA 1989–93 Case–control study	1842 cases from CCG hospitals; <15 years old 1987 population controls selected by RDD, individually matched by age, race, telephone area code and exchange	Detailed lifetime parental occupational history from telephone interview: all jobs held 6 months (father since age 18; mother for two years prior to pregnancy); assessment of specific exposures by an industrial hygenist	ALL	Occupational exposure *Spray paints (time period)* Anytime Preconception During pregnancy Postnatal *Other paints (time period)* Anytime Preconception During pregnancy Postnatal	 53 27 27 38 87 44 37 51	 1.0 (0.7–1.5) 1.3 (0.7–2.3) 1.4 (0.8–2.6) 1.2 (0.7–1.9) 1.3 (0.9–1.7) 1.9 (1.2–3.1) 2.0 (1.2–3.5) 1.3 (0.9–2.0)	Maternal education, race, family income, age, area code	Evaluation of maternal exposures to paints and thinners by duration resulted in a slightly larger OR for the shorter duration category and significant duration–response relationships were observed
Schüz *et al*. (2000) Germany, LSP Study 1992–1996; NIP and WGP 1993–97 Pooled analysis of three case–control studies	1138 cases from the German Childhood Cancer Registry; <15 years old 2962 population controls from population registration files; matched by gender, year of birth and community (NIP study)	Self-reported parental occupational chemical exposures	ALL	Paints or lacquers Any time Preconception During pregnancy Postnatal	 54 45 32 18	 1.8 (1.2–2.6) 1.6 (1.1–2.4) 2.0 (1.2–3.3) 1.0 (0.6–1.8)	Age, gender, year of birth, urbanization, and SES	
Freedman *et al*. (2001) USA (9 midwestern and mid-Atlantic states), 1989–93 Case–control study	640 cases from CCG hospitals; <15 years old 640 population controls selected by RDD; individually matched by age, race, first 8 digits of telephone number	Household exposures of mothers During the interview, mothers provided information on household activities that could result in chemical exposure, including painting	ALL	Mother painted	160	1.1 (0.9–1.5)	Age, income, sex, maternal education, painting during other periods	

Table 2.8 (contd)

Reference, study location, period, study design	Characteristics of the cohort or of cases and controls	Exposure Assessment	Organ Site	Exposure categories	No.of exposed cases	RR (95% CI)	Adjustment for potential confounders	Comments
Shu *et al* (2004) USA and Canada 1989–93 Case–case analysis	837 cases identified from CCG institutions; <15 years old	Telephone interview using structured questionnaires	ALL	Paints or thinners			Maternal race, education, age, family income, age, sex	Case–case comparison to examine whether reported parental occupational exposure to hydrocarbons was related to *Ras* gene mutations
			K-*Ras* mutation positive	Any time	4	1.3 (0.4–3.9)		
				Before pregnancy	2	1.0 (0.2–4.6)		
				During pregnancy	2	1.0 (0.2–4.4)		
				After pregnancy	3	1.4 (0.4–4.9)		
			K-*Ras* mutation negative	Any time	7	1.0 (0.4–2.2)		
				Before pregnancy	6	1.6 (0.6–4.1)		
				During pregnancy	6	1.5 (0.6–3.6)		
				After pregnancy	6	1.1 (0.4–2.7)		
Alderton *et al* (2006) USA and Canada 1997–2002	158 children (≤19 years old) with Down syndrome and acute leukaemia (97 ALL, 61 AML) 173 age-matched control children with Down syndrome but without leukaemia	Interview using a structured, computer-assisted telephone questionnaire	ALL	Exposure to paints, stains, lacquers			Age, sex, mother's educational level	Information available for child's exposure to paints, stains, lacquers
				None	97	1.0 (ref)		
				Any	75	1.10 (0.65–1.86)		
				Low	40	1.26 (0.68–2.34)		
				High	35	0.92 (0.46–1.84)		
				P for trend		0.99		
			AML	None	34	1.0 (ref)		
				Any	27	1.23 (0.64–1.37)		
				Low	14	1.10 (0.49–2.44)		
				High	13	1.41 (0.61–3.23)		
				P for trend		0.44		

ALL, acute lymphocytic leukaemia; ANLL, acute non-lymphocytic leukaemia; CCG, Children's Cancer Group; CCSG, Children's Cancer Study Group; JEM, job exposure matrix; NG, not given; POG, Pediatric Oncology Group; RDD, random-digit dialling; SES, socioeconomic status

Five studies showed significant positive associations with maternal paint exposure either before or during pregnancy (van Steensel-Moll *et al.*, 1985; Lowengart *et al.*, 1987; Buckley *et al.*, 1989a; Shu *et al.*, 1999; Schüz *et al.*, 2000). All of these studies controlled for age and/or sex, race, social class (measured through income, socieoeconomic status, degree of urbanization) or other variables. Additionally, a borderline significant positive association (Freedman *et al.*, 2001) and non-significantly elevated ORs (Alderton *et al.*, 2006) were also observed in two studies. Furthermore, significant exposure–response relationships, according to duration of maternal paint exposure, were observed in two studies (Buckley *et al.*, 1989a; Shu *et al.*, 1999).

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3. Studies of Cancer in Experimental Animals

No data were available to the Working Group.

4. Mechanistic and Other Relevant Data

4.1 Toxicokinetics and metabolism

Painters and paint industry workers are exposed to complex mixtures of organic solvents (aliphatic, aromatic, chlorinated), metals (lead, chromium, cadmium) and many other compounds with potential mutagenic properties (IARC, 1989). It is not possible to provide information on the toxicokinetics and metabolism of all known components of paint or exposures related to painting activities (pyrolysis products of paint stripping, dust from sanding etc.). Selected chemicals profiled were chosen based on 1) their known carcinogenicity, and 2) relatively high frequency of exposure among populations exposed to paint that have been monitored. For a full overview of the main substances and the class of substances to which workers may have been exposed in painting trades, see Section 1.1, Table 1.1. [The Working Group recognized that exposure in paint trades is a complex mixture and that therefore the described toxicokinetics of single agents might be altered in the presence of other chemicals.]

4.1.1 *Aromatic hydrocarbons*

(a) Benzene

Inhalation exposure is probably the major route of human exposure to benzene, although oral and dermal exposure could be important. Benzene is readily absorbed following inhalation (70–80% in humans) or oral exposure (> 90% in rabbits and rodents). Although benzene is readily absorbed through the skin, a significant amount of a dermal application evaporates from the skin when not occluded or immersed (absorbed dose ~0.05%). Absorbed benzene is rapidly distributed throughout the body and tends to accumulate in fatty tissues (ATSDR, 2007a).

The liver serves an important function in benzene metabolism, which results in the production of several reactive metabolites (ATSDR, 2007a). Benzene is oxidized primarily by the cytochrome P450 (CYP) isozyme 2E1 to benzene oxide, which exists in equilibrium with its tautomer oxepin (Kim *et al.*, 2006, 2007). Spontaneous rearrangement of benzene oxide produces phenol that is either excreted or oxidized by CYPs to hydroquinone, which is in turn excreted or oxidized by myeloperoxidase in the bone marrow to 1,4-benzoquinone. Conversely, NAD(P)H quinone oxidoreductase 1

transforms 1,4-benzoquinone to hydroquinone. Hydroquinone and 1,4-benzoquinone are thought to be responsible for the toxic effects of benzene through their ability to inhibit topoisomerase II and microtubule function, induce oxidative stress, and damage DNA. Other major metabolites include catechol, representing the pathway involving hydrolysis of benzene oxide by epoxide hydrolases, and *E*,*E*-muconic acid, representing the pathway involving oxidation of oxepin and ring opening (ATSDR, 2007a). Reaction between benzene oxide and glutathione, possibly mediated by glutathione-*S*-transferases M1 and T1, can produce the minor metabolite *S*-phenylmercapturic acid (ATSDR, 2007a; Kim *et al.*, 2007). Although it is widely accepted that benzene toxicity is dependent on its metabolism, no single benzene metabolite has been found to be the major source of benzene haematopoietic and leukemogenic effects. At low exposure levels, benzene is rapidly metabolized and excreted predominantly as conjugated urinary metabolites. At higher exposure levels, metabolic pathways appear to become saturated and a large portion of an absorbed dose of benzene is excreted as parent compound in exhaled air. Benzene metabolism appears to be qualitatively similar among humans and various laboratory animal species. However, there are quantitative differences in the relative amounts of benzene metabolites (ATSDR, 2007a).

(b) Toluene

Toluene is readily absorbed from the respiratory (about 50%) and gastrointestinal tracts (> 95%) and, to a lesser extent, through the skin (ATSDR, 2000a; Baelum *et al.*, 1993).

The primary initial steps in toluene metabolism in humans and laboratory animals are side-chain hydroxylation (to form benzyl alcohol) catalysed predominantly by CYP2E1, followed by oxidation to benzoic acid. Most of the benzoic acid is then conjugated with glycine to form hippuric acid, but a small portion can be conjugated with UDP-glucuronate to form the acyl-glucuronide (ATSDR, 2000a). Studies with volunteers and human liver microsomes indicate that a very small portion (< 1–5%) of absorbed toluene can be converted by CYP1A2, CYP2B6, or CYP2E1 to *ortho*- or *para*-cresol, which are excreted in the urine as sulfate or glucuronate conjugates (ATSDR, 2000a; Nakajima *et al.*, 1997). In both humans and rats, up to about 75–80% of inhaled toluene that is absorbed can be accounted for as hippuric acid in the urine (Löf *et al.*, 1993; Wang & Nakajima, 1992). Much of the remaining toluene is exhaled unchanged. In humans exposed by inhalation, rates of urinary excretion of *ortho*-cresol were about 1000-fold lower than excretion rates for hippuric acid. The excretion of toluene and its metabolites is rapid, with the major portion occurring within 12 hours of exposure (Baelum *et al.*, 1993; Löf *et al.*, 1993).

(c) Xylenes

Xylenes (mixtures of *ortho*, *meta* and *para* isomers) are well absorbed by the inhalation and oral routes. Approximately 60% of inhaled xylene is retained, and approximately 90% of ingested xylene is absorbed. Absorption of xylene also occurs by

the dermal route, but to a much lesser extent than by the inhalation and oral routes. Following absorption, xylene is rapidly distributed throughout the body through systemic circulation. In the blood, xylene is primarily bound to serum proteins. Xylene accumulates essentially in adipose tissue (ATSDR, 2007b).

All three isomers of xylene are primarily metabolized in the liver by oxidation of a methyl group (mainly by CYP2E1) and conjugation with glycine to yield methylhippuric acid, excreted in urine. In humans exposed to xylene, > 90% of the absorbed xylene is excreted in the urine as the methylhippuric acid, about 5% as other metabolites, and the rest excreted unchanged in the exhaled air. Aromatic hydroxylation of xylene to xylenol occurs to only a limited extent in humans. Less than 2% of an absorbed dose is excreted in the urine as xylenol. Other minor metabolites found in urine include methylbenzyl alcohol and glucuronic acid conjugates of the oxidized xylene. Metabolism in animals is qualitatively similar, but glucuronide conjugates make up a larger proportion of the urinary excretion. In addition, methylbenzaldehyde (the product of the action of alcohol dehydrogenase on methylbenzyl alcohol) has been detected in animals, but its presence has not been confirmed in humans. Elimination from most tissue compartments is rapid, with slower elimination from muscle and adipose tissue (ATSDR, 2007b).

4.1.2 *Chlorinated solvents*

(a) Dichloromethane

Inhalation is the main route of exposure to dichloromethane for humans. Within the first few minutes of exposure, approximately 70–75% of inhaled vapour is absorbed (Environmental Protection Agency, 1994). Distribution data in humans are lacking, but dichloromethane has been found in human breast milk and blood. Dichloromethane is widely distributed in animal tissues after inhalation exposure. The highest concentrations are found in adipose tissue and liver. Dichloromethane has been found in blood from rats' fetuses. Distribution of dichloromethane does not seem to be route-dependent, and it does not bioaccumulate in tissues. After acute exposure, dichloromethane disappears rapidly from fat (ATSDR, 2000b).

There are two main competing metabolic pathways for dichloromethane; one initially catalysed by CYP2E1, and the other by a theta glutathione-*S*-transferase. The CYP pathway produces carbon monoxide and carbon dioxide via formyl chloride and the glutathione-*S*-transferase (GST) pathway produces carbon dioxide via a postulated glutathione conjugate (*S*-chloromethyl glutathione), and formaldehyde. Both pathways can give rise to toxic metabolites. The CYP pathway is preferred at lower exposure concentrations and becomes saturated as exposure levels increase. Oxidative biotransformation of dichloromethane is similar in rats and humans. In rats, the CYP pathway is high-affinity low capacity, whereas the GST pathway has lower affinity, but higher capacity. The GST pathway is more active in mice than in rats and less active in hamsters and humans than in rats. After inhalation exposure, humans eliminate dichloromethane mainly in exhaled air, but also in the urine (ATSDR, 2000b).

(b) Trichloroethylene

Inhalation, oral, and dermal studies in animals and humans indicate that trichloroethylene is rapidly absorbed into the bloodstream, regardless of the route, where it is then widely distributed to its target organs, which include the liver, kidney, and cardiovascular and nervous systems. Metabolism occurs fairly rapidly, and the resulting metabolites may be responsible for much of the toxic effect of trichloroethylene. Metabolites are excreted primarily in the urine, and unabsorbed or unmetabolized trichloroethylene is exhaled in the breath (ATSDR, 1997).

Trichloroethylene is metabolized by two pathways: oxidation by CYP (major pathway), and conjugation with glutathione (Davidson & Beliles, 1991; Lash *et al.*, 2000). Trichloroethylene metabolism through the CYP pathway leads to the formation of major metabolites such as chloral hydrate, trichloroethanol, and trichloroacetic acid. This step primarily takes place in the liver. Four CYP isoforms have been identified as playing a role in trichloroethylene metabolism: CYP2A1/2, CYP2B1/2, CYP2C11/6, CYP2E1 (Guengerich and Shimada, 1991; Koop *et al.*, 1985; Nakajima *et al.*, 1988; Lash *et al.*, 2000). Metabolites produced through this pathway are thought to be associated with liver toxicity and liver carcinogenesis in animals.

The glutathione conjugation pathway leads to the formation of dichlorovinyl glutathione and dichlorovinyl cysteine. Dichlorovinyl cysteine can be further metabolized by β-lyase to reactive species but only at relatively high levels of exposure. These are thought to play a role in trichloroethylene-associated proximal renal tubular toxicity, and renal carcinogenicity in animals (Lash *et al.*, 2000).

4.1.3 *Styrene*

Styrene is absorbed orally, by inhalation, and dermal transfer in both man and experimental animals. In man, 60–70% of inhaled styrene is absorbed. It is rapidly distributed throughout the body, with the highest concentrations found in adipose tissue (IARC, 1994, 2002).

A large percentage of absorbed styrene is excreted as urinary mandelic and phenylglyoxylic acids, following its oxidation to styrene-7,8-oxide. Glutathione conjugates represent a minor fraction of the metabolites of styrene-7,8-oxide. Saturation of metabolic activation of styrene becomes apparent at concentrations above 200–300 ppm (850–1280 mg/m^3) in rats and mice, and above 150–200 ppm (430–850 mg/m^3) in humans. The formation of styrene-7,8-oxide, the dominant first metabolite, appears to be catalysed in humans principally by CYP2E1 and CYP2F but also by CYP2B6. Isolated erythrocytes are also capable of non-enzymatic conversion of styrene to styrene-7,8-oxide. The amounts of styrene-7,8-oxide present in the blood of rats and mice exposed to styrene at concentrations below 100 ppm (430 mg/m^3) were about 5–20-fold greater than those in humans exposed to similar styrene concentrations (IARC, 1994, 2002).

4.1.4 *Metals*

(a) Cadmium

Cadmium enters the body mainly by inhalation, and by ingestion. Fractional intestinal absorption is influenced by dietary factors and increases with dietary cadmium concentration. Pulmonary fractional absorption depends partly on the solubility *in vivo* of the compound. Cadmium induces synthesis of metallothionein, a low molecular-weight protein that binds cadmium primarily in the liver and kidney. Metallothionein production can also be induced by other divalent metals, e.g. zinc. When metallothionein-bound cadmium is released into the blood, it is filtered through the renal glomeruli and then reabsorbed in the proximal tubules. In certain mammalian tissues, such as rat ventral prostate, hamster ovary, and rat, mouse and monkey testis, the concentrations of metallothionein are low and its synthesis is not induced by exposure to cadmium. Most of the body burden of cadmium is retained in the kidney, and the liver. The half-life of cadmium in human kidney is probably 10–20 years. Cadmium concentrations in whole blood are affected by both recent exposure and by body burden. Excretion occurs mainly via the urine. Urinary excretion of cadmium by individuals without renal dysfunction primarily reflects the amount of cadmium retained in the kidney (IARC, 1993).

(b) Chromium

The toxicokinetics of a given chromium compound depends on the valence state of the chromium atom and the nature of its ligands. Absorption of chromium (VI) compounds is higher than that of chromium (III) compounds. This is because the chromate anion CrO_4^{2-} can enter cells via diffusion through nonspecific anion channels (similarly to phosphate and sulfate anions). Absorption of chromium (III) compounds is via passive diffusion and phagocytosis. Absorption of inhaled chromium compounds takes place in the lung via transfer across cell membranes, and in the gastrointestinal tract from particles cleared from the lungs. Absorption after oral exposure in humans varies from essentially none for the highly insoluble chromium(III) compound chromic oxide, to 0.5–2.0% for chromium (III) compounds in the diet, to approximately 2–10% for chromium (VI) as potassium chromate. Dermal absorption depends on the physical and chemical properties of the compound, the vehicle, and the integrity of the skin. Once in the blood, chromium compounds are distributed to all organs of the body. Particles containing chromium can be retained in the lung for years after occupational exposure (ATSDR, 2000c).

Chromium (VI) is unstable in the body and is reduced to chromium (V), chromium (IV), and ultimately to chromium (III) by many substances including ascorbate and glutathione. It is believed that the toxicity of chromium (VI) compounds results from damage to cellular components during this process (e.g. generation of free radicals). There is also evidence in in-vitro experiments that chromium (III) can be reduced to chromium (II), and exert toxic effects (ATSDR, 2000c).

Absorbed chromium is excreted primarily in urine, the half-time for excretion of chromium administered as potassium chromate is estimated to be 35–40 hours in humans. Hair and nails are minor excretion pathways (ATSDR, 2000c).

(c) Inorganic lead

Lead absorption from the gastrointestinal tract in both humans and experimental animals is strongly influenced by age (neonates and the young absorb a larger fraction than adults), fasting/fed status (fasting humans and experimental animals absorb much larger fractions than their fed counterparts), nutrition (fat and caloric intakes; phosphorus, copper, zinc and especially iron and calcium status, all affect lead absorption), solubility (soluble lead compounds are better absorbed) and particle size (in controlled studies in rats, lead absorption from ingested mining wastes was shown to be inversely proportional to particle size). There are no data indicating that the fraction of lead absorbed from an inhalation exposure is dependent on the amount of lead in the lung. Patterns and rates of particle deposition are highly dependent on particle size and ventilation rate, but all lead deposited deep in the lung is eventually absorbed. Limited studies indicate that dermal absorption of inorganic lead is negligible, although slightly increased by high perspiration rates in humans. In both humans and experimental animals, absorbed lead is rapidly distributed from blood plasma simultaneously into erythrocytes, soft tissues, and bone. The half-life of lead in blood and soft tissues is 20–30 days in adult humans, and 3–5 days in adult rats. The majority of lead is stored in bone (in adults > 90%) and is partitioned mainly into trabecular and cortical bone. The higher rate of remodelling in trabecular bone is reflected in a shorter half-life of lead in trabecular bone (2–8 years) compared with that in cortical bone (> 20 years). Bone can be a significant source of endogenous lead, in particular when the bone resorption rate is increased, such as during pregnancy, lactation, and the period just after menopause. After oral ingestion, inorganic lead that has not been absorbed in the gastrointestinal tract is excreted in the faeces. Absorbed lead is primarily excreted in the urine and, via the bile, in the faeces (IARC, 2006).

4.1.5 *Polycyclic aromatic hydrocarbons (PAHs)*

PAH exposure in paint trades might occur due to use of paints containing PAHs or by pyrolysis of paint products at removal. There are more than 100 different PAHs. PAHs generally occur as complex mixtures and not as single compounds. The mixture of PAHs in paints or as a result of pyrolysis of paint residues during paint removal is unknown. Therefore, the toxicokinetics is discussed in broad general terms.

Absorption of benzo[*a*]pyrene following ingestion is low in humans, while oral absorption in animals varies among the PAH compounds depending on their lipophilicity. Oral absorption increases with more lipophilic compounds or in the presence of oils in the gastrointestinal tract. Percutaneous absorption of PAHs appears to be rapid for both humans and animals, but the extent of absorption is variable among these compounds, and may be affected by the vehicle used for administration. Absorption of inhaled PAHs appears to occur through the mucous lining of bronchi, while ingested PAHs are taken up

by the gastrointestinal tract in fat-soluble compounds. Percutaneous absorption is through passive diffusion. PAHs appear to be widely distributed in tissues of animals following oral and inhalation exposure; peak tissue concentrations occur earlier with higher exposure levels. Placental transfer of PAHs appears to be limited, and therefore, fetal levels are not as high as maternal levels (ATSDR, 1995).

Metabolism of PAHs occurs in all tissues and involves several possible pathways. Metabolism products include epoxide intermediates, dihydrodiols, phenols, quinones, and their various combinations. The phenols, quinones, and dihydrodiols can all be conjugated to glucuronides and sulfate esters; the quinones also form glutathione conjugates (ATSDR, 1995; see also Section 4.2.2 (j)).

Quantitative data on the excretion of PAHs in humans are lacking. In general, elimination via faeces is the major route of excretion of PAHs in animals following inhalation exposure. Excretion of benzo[*a*]pyrene appears to be high following low-level exposure in rats but low in dogs and monkeys. PAHs are eliminated to a large extent within 2 days following low- and high-level oral exposure in rats. Following dermal exposure, elimination of PAHs occurs rapidly in the urine and feces of guinea-pigs and rats (ATSDR, 1995).

The mechanism of action of most PAHs involves covalent binding to DNA by PAH metabolites. The bay region diol epoxide intermediates of PAHs are currently considered to be the ultimate carcinogen for alternant PAHs. Once the reactive bay region epoxide is formed, it may covalently bind to DNA and other cellular macromolecules, and presumably initiate mutagenesis and carcinogenesis (ATSDR, 1995; see also 4.2.2 (j)).

4.2 Genetic and related effects

4.2.1 *Direct genotoxicity*

Several studies have evaluated genotoxic effects in painters (Table 4.1). Results of these studies are discussed by genotoxic end-point in chronological order. Paints as a compound have not been tested in experimental systems.

(a) Chromosomal aberrations

Haglund *et al.* (1980) were the first to report on cytogenetic effects among 17 workers exposed to paints (average employment > 10 years). Median exposure levels of xylene, toluene, isobutanol, ethylacetate, *n*-butylacetate, ethanol, *n*-butanol, methylacetate, methylene chloride, white spirit and isopropanol were all below the corresponding exposure limits except for methylene chloride (719 mg/m^3). Five heavily exposed workers in paint manufacturing were compared to an unexposed referent group (factory workers working in: store room, paint grinders, electricians, drivers, carpenters) matched by age, sex, place of residence (rural/urban), and smoking habits. No difference in the frequency of aberrant cells (i.e. presence of a structural and/or numerical chromosomal aberrations) were observed between the exposed workers and their matched reference group (3.4% versus 3.7%, respectively, $0.90 < P < 0.95$).

Table 4.1. Genotoxicity studies of painters

Study Population	Industry	Assay conditions	Result	Reference
Chromosomal Aberrations				
5 workers in paint manufacturing and 5 unexposed controls	Paint industry	Lymphocytes/72 h culture/100 metaphases	– (Individually matched on smoking status)	Haglund *et al*. (1980)
13 painters and 12 unexposed controls	Metallurgy	Lymphocytes/72 h culture/100 metaphases	+ (Frequency matched on smoking status)	Capomazza & Botta (1990)
25 male railroad and underground railroad car painters and 25 unexposed controls	Railroad car construction industry	Lymphocytes/48 h culture/100 metaphases	+	Piña-Calva *et al.* (1991)
13 painters (6 with abnormal blood cell counts) and 4 unexposed controls	Shipyard	Bone marrow precursor cells/10–20 cells	+/–	Cullen *et al.* (1992)
25 male car painters and 20 unexposed controls	Automobile body and painting shops	Lymphocytes/48 h culture/200 metaphases	+	Silva & Santos-Mello (1996)
25 male public building painters and 25 unexposed controls		Lymphocytes/48 h culture/100 metaphases	+	Pinto *et al.* (2000)
104 spray painters employed in 64 workshops and 50 controls	Automobile repainting, steel furniture making and refrigerator painting	Lymphocytes/48 and 72 h culture/100 metaphases	+ (+ S, +/– NS)	Gajalakshmi *et al.* (2002)

Table 4.1. Genotoxicity studies of painters

Study Population	Industry	Assay conditions	Result	Reference
25 car painters and 37 unexposed controls	8 Italian automobile paint shops	Lymphocytes/48 h culture/200 metaphases	+ (+ S, + NS)	Testa *et al.* (2005)
Sister Chromatid Exchanges				
17 workers in paint manufacturing and 17 unexposed controls	Paint industry	72 h culture/20–25 cells	–	Haglund *et al.* (1980)
106 painters of which 21 with minimal or no exposure (controls)	2 union locals	72 h culture/50 cells	+/– (+/– S; – NS)	Kelsey *et al*. (1988, 1989)
13 painters (6 with abnormal blood cell counts) and 4 unexposed controls	Shipyard	Unknown	– (Adjusted for smoking)	Cullen *et al*. (1992)
22 spray painters and 22 unexposed controls	3 automotive workshops	72 h culture/30 cells	+ (Individually matched on smoking status)	Sardas *et al*. (1994)
6 painters (individuals serve as their own controls)	Aircraft maintenance personnel	68–70 h culture/50 cells	+ (Adjusted for smoking)	Lemasters *et al*. (1997, 1999)
25 male public building painters and 25 unexposed controls		72 h culture/30 cells	+	Pinto *et al*. (2000)

Table 4.1. Genotoxicity studies of painters

Study Population	Industry	Assay conditions	Result	Reference
25 car painters and 37 unexposed controls	8 Italian automobile paint shops	72 h culture/100 cells	+ (+ NS, – S)	Testa *et al*. (2005)
Micronuclei				
21 male workers and 19 unexposed controls	2 paint factories	Lymphocytes/72 h culture/1000 binucleated cells Buccal cells/3000 cells	+ (Similar frequency of smoking among exposed and unexposed)	Diaz *et al.* (1990)
33 industrial painters and 200 subjects from the general population	Plastics industry	Lymphocytes/44 h culture/500 binucleated cells	+ (+ NS, + S)	Di Giorgio *et al.* (1994)
6 painters (individuals serve as their own controls)	Aircraft maintenance personnel	Lymphocytes/44 h culture/100 binucleated cells	– (Adjusted for smoking)	Lemasters *et al.* (1997, 1999)
25 public male building painters and 25 unexposed controls		Buccal cells/3000 cells	+	Pinto *et al*. (2000)
10 car painters and 10 unexposed controls	Automobile industry	Buccal cells/2000 cells	+ (Not adjusted for smoking)	Martino-Roth *et al.* (2003)
25 car painters and 37 unexposed controls	8 Italian automobile paint shops	Lymphocytes/72 h culture/1000 binucleated cells	+ + NS (no effect among smokers)	Testa *et al.* (2005)

Table 4.1. Genotoxicity studies of painters

Study Population	Industry	Assay conditions	Result	Reference
DNA strand breaks				
39 spray painters and 39 unexposed controls	14 automotive body repair shops	Non-fractionated alkaline elution method	+ + NS (no effect among smokers)	Fuchs *et al.* (1996a); Oesch *et al.* (1994)
9 bitumen painters and 34 unexposed controls		Non-fractionated alkaline elution method	–	Fuchs *et al.* (1996b)
80 painters and 45 auxiliary workers and two control groups (managerial n=29; assembly workers n=18)	Bus manufacturing factory	COMET	+ + NS	Zhu *et al.* (2001)
10 car painters and 10 unexposed controls	Automobile industry	COMET	+	Martino-Roth *et al.* (2003)
Other genotoxicity assays				
181 painters and 27 unexposed controls	Shipyard	Aromatic-DNA adducts (Bulky DNA adducts) Glycophorin A	+ –	Lee *et al.* (2003)

+, increase; -, no significant increase; NS, non-smokers; S, smokers

In a subsequent study by Capomazza & Botta (1990), frequency of chromosomal aberrations was assessed in 13 painters (30–55 years old), and 12 occupationally unexposed subjects (30–50 years old). Groups were frequency-matched on smoking habits. The results showed a significant increase ($P < 0.001$) of chromosomal aberrations level (chromatid breaks and chromatid gaps) in painters (1.77 ± 1.30), compared to the referent group (0.33 ± 0.45).

In a study among railroad car painters in Mexico, increased levels of chromosomal aberrations were found among 25 exposed individuals when compared to 25 unexposed controls (teachers and students at a college). Total chromosomal aberrations levels were 1.92 ± 6.89 and 12.2 ± 2.9 ($P < 0.01$) for controls and painters, respectively. The mean duration of employment as a painter for the study subjects was 5.2 years (Piña-Calva *et al.*, 1991). [Although solvent exposures were measured, no individual results were reported except that all measurements were below the PELs. The Working Group noted that although the study was not adjusted for smoking, the likelihood of confounding is low as no relation was observed between smoking and chromosomal aberrations].

Cullen *et al.* (1992) reviewed chromosomal aberrations in bone marrow precursor cells obtained from six painters with abnormal blood cell counts, seven painters with normal blood cell counts and four unexposed controls. Between 10 and 20 banded cells per subject were reviewed for chromosomal and chromatid breaks. A single chromatid break was noted in only two painters with normal blood cell counts.

Silva & Santos-Mello (1996) studied 25 male car painters aged 20–56 years in Brasil, who had been working for a period of 1–39 years in this occupation. The control group consisted of 20 unexposed individuals aged 20–47 years. Painters had a higher frequency of individuals with at least one chromosomal aberration in 200 metaphases when compared with controls (96% versus 55%, respectively, $P < 0.05$). This difference was mostly driven by the difference in frequency of chromosomal deletions (60% and 20% for exposed versus unexposed, respectively, $P < 0.05$). However, no association was found between years at work and chromosomal deletion frequency. An association between years at work and aneuploidy was however reported (Kendall coefficient, $\tau = 0.25$, $P < 0.05$). [The Working Group noted that smoking status was not taken into account in the analyses. However, smoking habits among the exposed did not seem to be related to chromosomal aberrations and is therefore unlikely to have confounded the results.]

In a study among 25 male public building painters aged 18–62 years in Mexico, increased chromosomal aberration levels were found when compared to the same number of sex- and age-matched unexposed controls (0.188 ± 0.026 versus 0.037 ± 0.004, respectively, $P < 0.0001$). Individual blood lead levels did not correlate with the observed cytogenetic damage. A strong correlation ($r^2 = 0.73$, $P < 0.001$) was observed between years of employment and chromosomal aberrations (Pinto *et al.*, 2000). [The Working Group noted that the study was not adjusted for smoking habits. However, all controls were non-smokers while seven out of the 25 exposed subjects smoked up to four cigarettes a day. Re-analyses of the data showed that the reported difference was present when comparison was made with non-smokers only ($P < 0.0001$; Wilcoxon).]

In a study of spray painters ($n = 104$) aged 18–61 years, from Chennai, India, Gajalakshmi *et al.* (2002) found that frequency of chromosomal aberrations were significantly higher among painters (3.29 ± 0.29) when compared to 50 age- and sex-matched controls (1.52 ± 0.21, $P < 0.001$). Results were comparable among smokers and non-smokers although statistical significance was only reached with the smokers. Duration of employment was on average 14 years (range, 2–40 years) and was found to be positively associated with chromosomal aberrations ($P = 0.03$).

Chromosomal aberrations were evaluated in 25 car painters working in different automobile paint shops in Italy and 37 unexposed control subjects (healthy blood donors). Air sampling in the workplaces showed that exposures to ethyl acetate, ethyl benzene, xylene, dichloropropane and *n*-butylacetate were below the PELs. Conversely, mean values of benzene and toluene were 9.99 mg/m^3 (range, 1.5–53.2) and 212.4 mg/m^3 (range, 15–938), respectively. Exposed workers had higher frequencies of chromosomal aberrations when compared to controls (2.52 ± 1.58 versus 1.08 ± 0.81, respectively, $P \leq 0.001$). This difference was observed for chromosome and chromatid-type aberrations, and was consistent among smokers and non-smokers (Testa *et al.*, 2005).

Overall, six of the eight published papers on chromosomal aberrations among painters or workers in paint manufacturing showed statistically significant elevated frequencies of chromosomal aberrations. Of these six positive studies, three reported an association with years of employment while the other studies did not report analyses on duration of employment. In the two studies that reported results stratified by smoking status, no marked difference in the association between exposure to paint and chromosomal aberrations was observed. Noteworthy is the negative study by Cullen *et al.* (1992) on bone marrow precursor cells. However, given the small number of exposed subjects ($n = 13$) and the limited number of scored cells (between 10 and 20), no firm conclusions could be drawn from this observation. Exposures in the different studies most likely differed and included among other organic solvents, glycol ethers, and lead (as reported by the authors). However, due to the limited exposure assessment in the studies, no meaningful dose–response analyses could be performed and therefore, none of the studies was able to associate a specific exposure to the observed effects. [The Working Group noted that, overall, the studies were small (generally less than 25 exposed subjects) and that the potential for publication bias (unpublished small negative studies) could not be ruled out.]

(b) Sister chromatid exchanges

Haglund *et al.* (1980) studied 17 workers (average duration of employment > 10 years) in the Swedish paint industry. No difference in the frequency of sister chromatid exchanges (SCEs) was observed between the exposed workers (0.193 SCE/chromosome) and a reference group ($n = 17$) (0.192 SCE/chromosome) matched by age, sex, place of residence (rural/urban), and smoking habits. In addition, no correlation was observed between xylene or toluene exposure and SCE frequency or between total solvent exposure and SCE frequency. SCE frequency was different between

smokers (0.202 SCE/chromosome) and non-smokers regardless of solvent exposure or matching (0.175 SCE/chromosome, $P = 0.02$).

Kelsey *et al.* (1988, 1989) studied 106 painters who were recruited from two union locals of the International Brotherhood of Painters and Allied Tradesman. Of these 106 subjects, eight workers reported no exposure to solvents/paints, and 13 workers (including drywall tapers, wallpaper hangers) reported minimal exposure to solvent/paints. Cumulative exposure based on interviewer questionnaire data was estimated for the working lifetimes of the remaining 85 painters (mean duration of employment 18.9 years). No difference in SCE frequency was observed between the 21 unexposed control subjects (existing out of the unexposed and minimal exposed subgroups), and painters for both the non-smokers (5.73 ± 0.89 and 5.90 ± 0.76, for exposed and controls, respectively) and smokers (6.75 ± 1.17 and 6.84 ± 0.27, for exposed and controls, respectively). In addition, neither lifetime solvent exposure intensity nor cumulative years of painting was associated with an elevation in SCE level. The difference between smokers and non-smokers by exposure status was significantly different ($P < 0.01$) (Kelsey *et al.*, 1988). However, in a subsequent analysis focusing on stratified analyses by smoking and using days worked in the last month before venipuncture as a measure of recent exposure, an association with days worked and increased SCE levels among current smokers was reported ($P < 0.006$) (Kelsey *et al.*, 1989).

Cullen *et al.* (1992) analysed SCEs in lymphocytes from 13 painters (of whom six had been diagnosed with abnormal cell counts and found no difference in SCEs between the painters with low blood cell counts (8.22 ± 1.04), painters with normal counts (8.56 ± 1.56) and four unexposed controls (9.59 ± 2.17). Adjustment for smoking habits did not change the results. Current smoking was, however, strongly associated with SCE levels, smokers having a mean SCE level 1.8 times greater than former or non-smokers ($P = 0.006$).

In a study of 22 spray painters from Turkey aged between 18–56 years, a significant increase in mean SCE levels in spray painters (7.81 ± 1.50) versus 22 unexposed healthy controls matched by age and smoking status (4.92 ± 0.10, $P < 0.001$) was reported. The number of SCEs seemed to increase by duration of exposure although formal significance was only reached among smokers ($P < 0.001$) (Sardas *et al.*, 1994).

In a prospective repeated measures design, SCEs were assessed at baseline, after 15 weeks of exposure, and after 30 weeks of exposure among six aircraft painters. These painters were primarily exposed to solvents and paints. Mean total solvent exposure as measured by industrial hygiene sampling was 2.4 ppm; fuel, 1.4 ppm; and benzene, 0.0 ppm. SCE frequency increased with duration of exposure (5.9 ± 0.7, $P > 0.05$; 6.2 ± 1.0, $P > 0.05$; 6.7 ± 1.0, $P = 0.05$ at baseline, 15 weeks of exposure, and 30 weeks of exposure, respectively) (Lemasters *et al.*, 1997, 1999).

In a study among 25 male public building painters aged between 18–62 years in Mexico, increased SCE levels in lymphocytes were found when compared to the same number of sex- and age-matched unexposed controls (6.60 ± 1.58 versus 5.07 ± 0.90, respectively, $P < 0.05$). Blood lead levels did, however, not correlate with the observed

cytogenetic damage. A correlation ($r^2 = 0.32$, $P = 0.0001$) was observed between years of exposure and SCE (Pinto *et al.*, 2000). [The Working Group noted that the study was not adjusted for smoking habits. However, all controls were non-smokers while seven out of the 25 exposed subjects smoked up to four cigarettes a day. Re-analyses of the data showed that the reported difference was present when comparison was made with non-smokers only ($P < 0.0031$; Wilcoxon).]

SCEs were evaluated in 25 car painters working in different automobile paint shops in Italy and 37 unexposed control subjects (healthy blood donors). Air sampling in the workplaces showed that exposures to ethyl acetate, ethyl benzene, xylene, dichloropropane and *n*-butylacetate were below the PELs. Conversely, mean values of benzene and toluene were 9.99 mg/m^3 (range, 1.5–53.2) and 212.4 (range, 15–938), respectively. The exposed workers had higher frequencies of SCEs than controls (7.55 ± 1.18 versus 6.44 ± 1.32, respectively, $P < 0.05$). This difference was however only observed among non-smokers (7.45 ± 1.14 and 5.25 ± 0.37, for exposed and controls, respectively, $P \leq 0.001$) and not among current smokers (7.61 ± 1.27 versus 7.96 ± 0.84, for exposed and controls, respectively) (Testa *et al.*, 2005).

The results of the cytogenetic studies among painters or workers in the paint industry using sister chromatid exchanges as the biological outcome are less clear than those observed for chromosomal aberrations. Four out of seven published studies reported increased SCEs levels among painters. The negative studies tended to be the older studies. Results among smokers and non-smokers were not always consistent. Exposure–response relationships with duration of exposure were reported in three studies of which the prospective study of Lemasters *et al.* (1997, 1999) showed the clearest association with duration due to the prospective nature of the study. No direct associations with any specific exposures were reported.

(c) Micronuclei

In a study among 21 Cuban paint industry workers aged 21–59 years, elevated levels of micronuclei in lymphocytes and oral mucosal cells were found when compared to 19 controls (5.5 ± 0.5 versus 4.0 ± 0.5, $P < 0.05$, and 0.9 ± 0.2 versus 0.5 ± 0.1, $P < 0.05$ for lymphocytes and oral mucosal cells, respectively). Controls were recruited from the blood bank and were slightly younger than the exposed subjects. Frequency of smoking was similar between exposed subjects and controls. Adjustment for age or smoking did not change the significance of the results. Exposure of the subjects was not measured but the authors stated that benzene should not have been present (Diaz *et al.*, 1990).

Di Giorgio *et al.* (1994) studied 33 male industrial painters in a plastics factory and compared those to an unexposed group of 200 male and female individuals of mixed social class, not occupationally exposed to mutagens or aneugens. Among smokers, micronucleated cell rates observed in painters were 19.1 ± 8.57 while levels in controls were 11.8 ± 3.47, per 1000 binucleated cells ($P < 0.0001$). Among non-smokers, a similar effect was observed with micronucleated cell rates, which were 17.95 ± 8.01 and 8.9 ± 2.53, per 1000 binucleated cells ($P < 0.0001$), for painters and controls, respectively.

In a prospective repeated measures design, micronuclei were assessed at baseline, after 15 weeks of exposure, and after 30 weeks of exposure among six aircraft painters. These painters were primarily exposed to solvents and paints. Mean total solvent exposure as measured by industrial hygiene sampling was 2.4 ppm; fuel, 1.4 ppm; and benzene, 0.0 ppm. Micronuclei frequency increased non-significantly with duration of exposure 15.8 ± 5.6, 16.3 ± 11.4, 20.5 ± 7.0 at baseline, 15 weeks of exposure, and 30 weeks of exposure, respectively (Lemasters *et al.*, 1997, 1999).

In a study among 25 public building painters aged 18–62 years in Mexico, increased micronuclei levels in buccal cells (MN/1000) were found when compared to the same number of sex- and age-matched unexposed controls (0.32 ± 0.01 versus 1.19 ± 0.02, respectively, $P < 0.001$). Blood lead levels did not correlate with the observed cytogenetic damage. A correlation ($r^2 = 0.30$, $P < 0.0001$) was observed between years of exposure and micronuclei frequency (Pinto *et al.*, 2000). [The Working Group noted that the study was not adjusted for smoking habits. However, all controls were non-smokers while seven out of the 25 exposed subjects smoked up to four cigarettes a day. Re-analyses of the data showed that the reported difference was present when comparison was made with non-smokers only, although formal statistical significance was not reached ($P = 0.0580$; Wilcoxon).]

In a study among ten car painters in Brasil, a significant increase in micronuclei frequency in buccal cells was observed when compared to ten individually age- matched unexposed controls (6.9 ± 2.92 versus 2.2 ± 1.75, respectively, $P < 0.0001$). No information about specific exposures was available (Martino-Roth *et al.*, 2003). [The Working Group noted that the study was not adjusted for smoking habits. However, three out of ten controls were smokers while among the painters, five out of ten were smokers.]

Micronuclei were evaluated in 25 car painters working in different automobile paint shops in Italy and 37 unexposed control subjects (healthy blood donors). Air sampling in the workplaces showed that exposures to ethyl acetate, ethyl benzene, xylene, dichloropropane and *n*-butylacetate were below the PELs. Conversely, mean values of benzene and toluene were 9.99 mg/m^3 (range, 1.5–53.2) and 212.4 (range, 15–938), respectively. Exposed workers had higher frequencies of binucleated cells with micronucleus than controls (6.68 ± 3.27 versus 3.00 ± 2.50, respectively, $P \leq 0.001$),. However, this difference was observed only among the non-smokers (for exposed and control subjects, 7.57 ± 2.56 versus 3.00 ± 1.21, respectively, $P \leq 0.001$), and not among smokers (for exposed and control subjects, 5.54 ± 3.83 versus 5.93 ± 2.95, respectively) (Testa *et al.*, 2005).

Five out of six published studies reported increased micronuclei frequencies among painters ($n = 4$), and subjects employed in paint manufacturing ($n = 1$). Although not all studies controlled for smoking, elevated levels of micronuclei frequency was seen among both smokers and non-smokers. Genotoxic effects were found both in cultured lymphocytes and buccal cells. Two studies reported a dose–gradient with years or weeks worked and micronuclei frequency levels.

(d) DNA strand breaks

In a study of 39 (38 male and one female) German spray painters aged 16–62 years, Fuchs *et al.* (1996a) found that spray painters had a significantly higher mean level of single DNA strand breaks using the alkaline elution method in Friday samples (2.05 ± 0.17) compared to their respective Monday samples (1.38 ± 0.07, $P < 0.001$). This effect was observed among smokers and non-smokers, but reached statistical significance only among the non-smokers (Oesch *et al.*, 1994). DNA damage seemed to be reversible as no difference was observed in the level of DNA strand breaks between 39 unexposed controls (1.41 ± 0.62) and the Monday samples of the spray painters (Fuchs *et al.*, 1996a).

In a study of workers exposed to bitumen-based products, nine bitumen painters were assayed for DNA strand breaks using an alkaline elution method. For these nine bitumen painters, mean DNA strand break level was 1.34 ± 0.17 on Mondays and 1.09 ± 0.10 on Fridays. Levels of single DNA strand breaks were also comparable to a control group of 34 office employees and students (1.13 ± 0.05). The authors noted that non-smokers were overrepresented in the control group (Fuchs *et al.*, 1996b).

A study on lymphocyte DNA damage using the COMET assay among 346 male and female employees from a bus-manufacturing factory in Guangzhou, China, included 80 painters and 45 auxiliary workers who took up duties from the painters whenever necessary. Cells of painters (3.25 μm; 95% CI: 2.97–3.55) and auxiliary workers (3.13 μm; 95% CI: 2.82–3.48) had larger tail moments than 29 managerial workers (2.54 μm; 95% CI: 2.22–2.90) or 18 assembling workers (2.32 μm; 95% CI: 2.02–2.67) who were thought not to be exposed to obvious occupational exposures. Stratified analyses of non-smokers showed similar results. Although it is impossible to link the observed effects to any putative chemicals, it is worth noting that exposure levels of benzene ranged from 0.1–138.5 mg/m^3 in painting workshops (Zhu *et al.*, 2001).

In a study among ten car painters in Brasil, a significant increase in comet tail length (COMET assay) in lymphocytes was observed when compared to ten individually matched unexposed controls (33.85 ± 0.51 versus 30.73 ± 0.16, respectively, $P < 0.001$). No information about specific exposures was available (Martino-Roth *et al.*, 2003). [The Working Group noted that the study was not corrected for smoking habits. However, three out of ten controls were smokers while among the exposed, five out of 10 were smokers.]

Three of the four studies that investigated single DNA strand breaks revealed elevated levels of strand breaks among painters. These effects were also present among non-smokers only.

(e) Other genotoxicity assays

In a study among 208 workers (191 male and 17 female) in a Korean shipyard, DNA adducts by ^{32}P-postlabelling and glycophorin A variant frequencies in red blood cells were assessed. The glycophorin A assay is a somatic mutation assay that measures the number of red blood cells that have a change in the M- or N-form of the glycophorin A gene. Employees were grouped into three groups: 111 painters using coal-tar paints,

70 painters using general paints, and 27 on-site controls. Aromatic-DNA adduct levels (adducts/10^8 nucleotides) tended to be higher in coal-tar paint users (0.38 ± 0.23, $P = 0.07$) and general paint users (0.38 ± 0.24, $P = 0.06$) compared to on-site controls (0.26 ± 0.13). When both groups of painters were combined, they showed greater adduct levels than on-site controls ($P < 0.05$). Glycophorin A mutation frequencies measured in 55 individuals with MN heterozygote genotypes were not significantly different among the three job groups (Lee *et al.*, 2003).

Several chromosomal abnormalities could be detected in the bone marrow of most patients with acute myeloid leukaemia. In a study by Crane *et al.* (1996), routine cytogenetic data from 213 patients (129 enrolled in the period 1976–1983, and 84 enrolled in the period 1986–1990) with acute myeloid leukaemia were correlated with environmental exposures to organic chemicals (eg., benzene), paints, pesticides, and other substances such as dyes, glues, or varnishes. A suggestive effect was found between exposure to paints and the –7/7q chromosomal abnormality (odds ratio, 7.50) but this was non-significant and only observed in the set of patients enrolled between 1986–1990.

In summary, most cytogenetic studies among painters measuring a variety of cytogenetic end-points and markers of genotoxicity showed elevated levels of genetic damage. These effects were by and large similar for smokers and non-smokers. In addition, several studies have shown a dose–gradient with years or weeks worked and the cytogenetic end-point. These studies support that painters have increased levels of DNA damage. However, the number and size of the studies is generally small. Furthermore, as no comprehensive exposure assessment has been done in any of these studies, it is difficult to relate the observed genotoxic effects to any specific component(s) of paint

4.2.2 *Genotoxicity information for individual constituents of paints*

It is not possible to provide information on the genotoxicity and mechanism of action of all known components of paint or exposures related to painting activities (for an overview of main substances to which workers may be exposed in painting trades, see Section 1.1). We therefore limit this overview to selected chemicals as described in section 4.1.

(a) Benzene

Chromosomal aberrations in human peripheral lymphocytes have been associated with occupational exposure to benzene and include hypo- and hyperdiploidy, deletions, breaks, and gaps (ATSDR, 2007a). SCE was not found to be a significant effect of benzene exposure in humans. In-vivo animal studies provide convincing evidence of the genotoxicity of benzene. Benzene induced chromosomal aberrations, micronuclei and SCEs in bone marrow cells of mice, chromosomal aberrations in bone marrow cells of rats and Chinese hamsters and sperm-head anomalies in mice treated *in vivo* (IARC, 1987). It induced chromosomal aberrations and mutation in human cells *in vitro*. In-vitro studies strongly imply that benzene's genotoxicity is derived primarily from its metabolites hydroquinone and 1,4-benzoquinone through their ability to inhibit

topoisomerase II and microtubule function, induce oxidative stress, and break DNA (ATSDR, 2007a).

(b) Toluene

Toluene is mainly converted to benzyl alcohol and excreted as hippurate. Human data are inconclusive with regard to the genotoxicity of toluene. Studies of exposed workers are limited by concurrent exposure to other chemicals, small cohort size, and a lack of historical exposure monitoring, and it is likely that they are not sufficiently sensitive to detect small, but significant, manifestations of genetic toxicity in workers exposed to toluene (ATSDR, 2000a). Toluene toxicity is most prominent in the central nervous system after acute and chronic exposure in exposed humans and experimental animals. Reproductive toxicity has been observed in exposed humans and rats. Genotoxicity testing of laboratory animals *in vivo* has been limited, and has produced mostly negative results. In some cytogenetic studies in occupationally exposed populations, increases in chromosomal aberrations (two studies), micronuclei (one study), and of DNA strand breaks (one study) have been described. These effects have also been observed in rats and mice in some studies and in cultured mammalian cells. DNA adducts have not been detected (IARC, 1999).

(c) Xylenes

Genotoxicity studies on mixed xylenes and the individual isomers of xylene have provided consistently negative results in a variety of in-vitro and in-vivo assays and test systems (bacteria, yeast, cultured mammalian cells, mice, rats, and humans). Xylenes may cause DNA fragmentation at cytotoxic concentrations because of nucleases released from lysosomes in moribund cells. There is also limited evidence from bacterial test systems that suggests that xylene metabolites, specifically *meta*-xylenol, *para*-xylenol, 2,4-dimethylphenol, and *ortho*-methylbenzyl alcohol, are also non-mutagenic (ATSDR, 2007b). Renal and hepatic toxicity has been described following human accidental poisonings and experimental exposure of rats and mice. In rats, hepatic CYP content, particularly of CYP2B1, and the activities of certain conjugation enzymes are increased upon inhalation exposure to *meta*-xylene (IARC, 1999).

(d) Dichloromethane

Two dose-dependent alternative pathways involving CYP2E1 and GSTT1–1 are responsible for the metabolism of dichloromethane in human and rodent cells (IARC, 1999; ATSDR, 2000b). Dichloromethane is consistently mutagenic in microorganisms. Weaker and less consistent responses are seen in mammalian systems, predominantly in mice, both *in vitro* and *in vivo*. It induces SCEs, chromosome breakage, and chromosome loss *in vitro* in human cells. In-vitro results in rodent cells have been inconclusive or negative. Dichloromethane-induced DNA single-strand breaks in mammalian cell cultures, but inconclusive or negative effects, have been reported for induction of gene mutations. It has not induced unscheduled DNA synthesis either *in vivo* in rodents or in

human fibroblast cultures. It is genotoxic in fungi but not in *Drosophila* in the sex-linked recessive lethal assay (IARC, 1999).

Mechanistic studies have established a link between GST-mediated metabolism of dichloromethane and its genotoxicity and carcinogenicity in mice. The GST responsible for the metabolism of dichloromethane is expressed to significantly greater extents in mouse tissues than in rat, hamster or human tissues. The available data suggest a plausible mechanism for the development of liver and lung tumours which occur in mice but not in rats exposed to dichloromethane (IARC, 1999).

(e) Trichloroethylene

In rodents, trichloroethylene is rapidly absorbed from the gastrointestinal tract and through the lungs, whereas absorption of the vapour through the skin is negligible. The major pathway is oxidative metabolism leading to the formation of chloroacetic acids. Mice have shown consistently higher rates of oxidative biotransformation than rats. A minor pathway in rodents and humans involves the formation of mercapturic acids (IARC, 1995).

The acute toxicity of trichloroethylene in rodents and humans is low. After high doses of trichloroethylene are administered repeatedly to rodents, damage is seen in the liver and kidney (in mice and rats), and in the lung (in mice only). Repeated exposure of humans in the workplace appears to have no marked toxic effects on the kidney or liver. Trichloroethylene is a more potent peroxisome proliferator in the livers of mice than the livers of rats. The available studies have shown no consistent effect of trichloroethylene on the human reproductive system. Trichloroethylene is metabolized to trichloroacetic acid in the placenta or fetus of many species. There is little evidence of toxic effects in developing rats or mice. Studies of structural chromosomal aberrations, aneuploidy and SCE in peripheral lymphocytes of workers exposed to trichloroethylene were inconclusive but are suggestive of clastogenic effects (IARC, 1995; ATSDR, 1997). Pure trichloroethylene did not induce chromosomal aberrations, dominant lethal mutations, SCE or unscheduled DNA synthesis in rodents, whereas an increased induction of micronuclei and DNA single-strand breaks/alkaline labile sites was observed. In single studies with human cells *in vitro*, trichloroethylene of low purity slightly increased the frequencies of SCE and unscheduled DNA synthesis. Pure trichloroethylene did not induce gene mutation in human cells. In mammalian cells *in vitro*, pure trichloroethylene-induced cell transformation, SCE and gene mutation, but not chromosomal aberrations (IARC, 1995). Although trichloroethylene itself may not be genotoxic, several of its metabolites are reactive and potentially genotoxic compounds. Several isomers of 1,2-dichlorovinyl-cysteine, a product of trichloroethylene metabolism in the kidney, are mutagenic in the in-vitro Ames assay. These products have been identified in the urine of workers exposed to trichloroethylene. Although trichloroethylene itself may not be genotoxic, the evidence that some of its metabolites are genotoxic suggests that genotoxic effects may be a concern for some persons exposed to trichloroethylene (ATSDR, 1997).

(f) Styrene

Exposure to styrene leads to the formation of both protein and DNA adducts in humans, rats, and mice. The levels of the *N*-terminal valine adduct of haemoglobin, *N*-(1-hydroxy-2-phenylethyl)valine, have been found to be four times higher in styrene-exposed workers than in controls, and the levels of the DNA adduct, O^6-(2-hydroxy-1-phenylethyl)-2′-deoxyguanosine-3′-monophosphate, have been found to be about five times higher than in controls. *N*7-deoxyguanosine adducts have also been detected (IARC, 1994).

Inconsistent results have been reported for chromosomal aberrations, micronuclei and SCE in approximately 30 studies of workers exposed to styrene in various industries. These studies were predominantly from the reinforced plastics industry where styrene exposure is high, but there was no indication of a dose–response relationship in any of the studies reporting positive results. Induction of chromosomal aberrations was reported in 12 of 25 studies, sister chromatid exchange in six of 16 studies, and micronuclei in three of 14 studies (IARC, 2002).

SCE and to a lesser degree chromosomal aberrations were induced in rodents *in vivo*, and consistently in human lymphocytes *in vitro*. Styrene was predominantly inactive in assays for gene mutations in bacteria, although some studies reported mutations in the presence of a metabolic activation system (IARC, 2002).

Data from both laboratory (*in vitro* and *in vivo*) and human studies indicate that styrene exposure can result in low levels of DNA adducts and DNA damage in individuals who possess the capacity to activate styrene metabolically to styrene-7,8-oxide. However, as noted above, mice, but not rats, develop lung tumours following exposure to styrene, even though both species form DNA adducts. DNA adducts are also found in organs other than the lung. Circulating styrene-7,8-oxide may also play a role. However, the concentration in rat blood is two orders of magnitude higher than in the mouse. The lung tumours in mice probably develop as a result of in-situ formation of styrene-7,8-oxide which causes cytotoxicity and increased cell proliferation, but the roles of circulating styrene-7,8-oxide and of DNA adducts cannot be discounted. Based on metabolic considerations, it is likely that the proposed mechanism involving metabolism of styrene to styrene-7,8-oxide in mouse Clara cells is not operative in human lungs to a biologically significant extent. However, based on the observations in human workers regarding blood styrene-7,8-oxide, DNA adducts and chromosomal damage, it cannot be excluded that this and other mechanisms are important for other organs (IARC, 2002).

(g) Cadmium

In several studies, the frequencies of chromosomal aberration were increased in peripheral blood lymphocytes of workers exposed to cadmium in the metal industry, where they were usually also exposed to other metals. No effect of cadmium was observed in a limited study of workers from a Swedish alkaline battery factory. In two studies of cadmium pigment plant workers, no increase in the frequency of chromosomal aberrations was observed. No increase in the frequency of SCE was seen in one study of

workers exposed to cadmium. In one study of *itai-itai* disease patients, increased frequency and severity of chromosomal aberrations were observed but these results were not replicated in another study. In one study, no increase in SCE frequency was observed in people living in a cadmium-polluted region of Japan. In a study of subjects living in a cadmium-polluted region of China, there were small but significant increases in chromosomal aberration frequency. A significant dose–effect relationship between urinary levels of cadmium and chromosomal aberration frequency was also observed, and more severe aberration types were observed in individuals with high urinary levels of cadmium. In those studies in which significant responses were observed, the chromosomal aberrations tended to occur in the more heavily exposed groups and were of more complex types (IARC, 1993).

Chromosomal aberrations and aneuploidy were observed in animals exposed to cadmium chloride *in vivo*. Dominant lethal mutations were generally not induced in mice. Cadmium chloride damaged DNA of human cells *in vitro*. In the few studies available, chromosomal aberrations were observed in human cells treated with cadmium sulfide but not in those treated with cadmium chloride. Indications of aneuploidy were observed in human fibroblasts after treatment with cadmium chloride. Studies using cultured animal cells show that exposure to cadmium compounds damages genetic material. DNA strand breaks, mutations, chromosomal damage and cell transformation have been observed *in vitro*. Cadmium compounds inhibit the repair of DNA damaged by other agents, thereby enhancing their genotoxicity. Mutations have generally not been observed in *Drosophila* or bacteria; however, a weak response was observed in some studies in bacteria and there is evidence for cadmium-induced DNA damage in bacteria (IARC, 1993).

Overall, cadmium appears to have the capability of altering genetic material, particularly chromosomes in mammalian cells, but germ cells appear to be protected except at high acute parenteral doses (ATSDR, 1999).

(h) Chromium

Chromium(VI) compounds may cause adverse effects to the skin, the respiratory tract and, to a lesser degree, the kidneys in humans, while chromium(III) is less toxic. Elevated levels of SCE were observed in workers exposed to chromium(VI) compounds in electroplating factories in some but not all studies. Similarly, chromosomal aberrations were found in several studies of exposed workers but not all. The studies on chromium(III) were inadequate to evaluate its cytogenetic effect in humans (IARC, 1990; ATSDR, 2000c).

Chromates, which are chromium(VI) compounds, enter cells more readily than chromium(III) compounds, and are reduced ultimately to chromium(III). The reduction process and the subsequent intracellular activity of reduced chromium species are important for the mechanism of toxicity and carcinogenicity of chromium(VI). Particulate chromium(III) compounds can also enter cells by phagocytosis. Chromium(VI) compounds cross the placental barrier in greater amounts than chromium(III) compounds (IARC, 1990).

Chromium(VI) compounds of various solubilities in water were consistently active in numerous studies covering a wide range of tests for genetic and related effects. In particular, potassium dichromate, sodium dichromate, ammonium dichromate, potassium chromate, sodium chromate, ammonium chromate, chromium trioxide, calcium chromate, strontium chromate, and zinc yellow induced a variety of effects (including DNA damage, gene mutation, SCE, chromosomal aberrations, cell transformation and dominant lethal mutation) in several targets, including animal cells *in vivo*, and animal and human cells *in vitro*. Potassium chromate induced aneuploidy in insects, while chromium trioxide did not; various compounds induced gene mutation in insects. Potassium dichromate produced recombination, gene mutation and aneuploidy in fungi. All of these chromium(VI) compounds induced DNA damage and gene mutation in bacteria. Similar patterns were observed with zinc chromate, barium chromate, lead chromate and the derived pigments chromium orange, chromium yellow and molybdenum orange, which, however, often required preliminary dissolution in alkali or acids. A liquid chromium(VI) compound (chromyl chloride) and its vapours induced gene mutation in bacteria (IARC, 1990).

Although chromium(III) compounds were generally even more reactive than chromium(VI) compounds with purified DNA and isolated nuclei, 12 compounds of various solubilities (chromic chloride, chromic acetate, chromic nitrate, chromic sulfate, chromic potassium sulfate, chromium alum, neochromium, chromic hydroxide, chromic phosphate, chromic oxide, chromite ore, and cupric chromite) gave positive results in only a minority of studies using cellular test systems. This was often under particular treatment conditions or at very high concentrations, which were generally orders of magnitude higher than those needed to obtain the same effects with chromium(VI) compounds. Some of the positive results could be ascribed to contamination with traces of chromium(VI) compounds. In particular, no DNA damage was observed in cells of animals treated *in vivo* with chromic chloride, and no micronuclei were seen in cells of animals given chromic nitrate. The chromium(III) compounds tested did not generally produce DNA damage, gene mutation, SCE or cell transformation in cultured animal and human cells. Chromosomal aberrations were often observed with high concentrations of chromium (III) compounds. Weak effects on gene mutation and mitotic gene conversion were observed in fungi. Negative results were obtained in the large majority of tests for DNA damage and gene mutation in bacteria. Certain complexes of chromium (III) with organic ligands, which favour the penetration of chromium (III) into cells, were reported to induce DNA damage and gene mutation in bacteria and in cultured mammalian cells (IARC, 1990).

A chromium (II) compound (chromous chloride) gave negative results in in-vitro tests with animal cells (DNA damage, chromosomal aberrations and aneuploidy). A water-insoluble chromium (0) compound (chromium carbonyl) did not induce DNA damage in bacteria (IARC, 1990).

(i) Inorganic lead

Evidence of genotoxicity has been shown in humans occupationally exposed to lead, as measured in a variety of assays. In some studies, these effects were correlated with blood lead concentrations. However, all the human genotoxicity studies involved co-exposure to lead and other compounds, making it difficult to attribute genetic and other effects to lead alone. In a limited number of studies on non-occupationally exposed individuals, no genotoxic effects were found that were correlated with blood lead concentrations (IARC, 2006).

Mutations were not induced in bacteria by either lead acetate or lead chloride, but were induced by both lead chromate and lead bromide. In these last two cases, however, the activity appeared to be due to the anions. In cultures of various mammalian cells, lead acetate, lead chromate and lead nitrate induced DNA strand breaks. Furthermore, most studies revealed positive mutagenic responses even though the extent of mutagenicity and the lead concentrations at which the responses were observed varied considerably, depending on cell type and experimental conditions. Tests for SCE and chromosomal aberrations showed variable responses. Micronucleus formation has been shown to occur at low concentrations of lead. In a single study, lead sulfide induced micronuclei, gene mutations, and SCE. Organo-lead compounds do not appear to have been tested *in vitro* (IARC, 2006).

Studies of genetic toxicity in animals have been conducted by the oral, inhalation, subcutaneous, intraperitoneal, and intravenous routes. It should be noted that blood lead concentrations were not available in these studies, except in a single study in cynomolgus monkeys, and that the exposure concentrations were generally far higher than those reported in human occupational studies. DNA strand breakage has been demonstrated in animals exposed to lead, and variable results have been found in tests for induction of SCE. Micronucleus induction in bone marrow cells of animals exposed to lead has been demonstrated in some studies. Most studies of chromosomal aberrations have demonstrated increased frequencies in mice, rats, and in the one study in cynomolgus monkeys. Aneuploidy has been demonstrated in rats and mice exposed to lead. Increases in the proportion of morphologically abnormal sperm have also been found in mice and cynomolgus monkeys, but not in rabbits. Dominant lethal effects were not observed in male mice exposed to lead in a single study (IARC, 2006).

In conclusion, lead is a toxic metal and one expression of this property is genetic toxicity. There is, however, little evidence that it interacts directly with DNA at normally encountered blood lead concentrations. The genetic toxicity of lead appears to be mediated in part by increases in, and modulation of, reactive oxygen species. In addition, lead interacts with proteins, including those involved in DNA repair. This latter mechanism might be responsible for enhancing the genotoxicity of other agents. These properties could result in mutation, changes in gene expression and cell proliferation, all of which would contribute to a carcinogenic response if exposure is sustained (IARC, 2006).

(j) Polycyclic aromatic hydrocarbons

Metabolic activation of lipophilic PAHs occurs primarily in the liver, but also in many other tissues, including the epithelial barriers. Although distribution through the circulatory system is widespread, slow absorption through most epithelia results in higher levels of enzymes that activate PAH substrates at the site of entry. This uneven distribution of dose is a factor that may contribute to the high propensity of PAHs to act as carcinogens at the sites where they enter the body (IARC, 2010).

PAHs are metabolized by phase I enzymes and peroxidases, which produce DNA-reactive metabolites, and phase II enzymes, which form polar conjugates. Phase I enzymes, such as CYPs, catalyse the mono-oxygenation of PAHs to form phenols and epoxides. Specific cytochrome P450 isozymes and epoxide hydrolase can form reactive diol epoxides that comprise one class of ultimate carcinogenic metabolites of many PAHs. Both cytochrome P450s and peroxidases can form radical cations by one-electron oxidation that comprise another class of ultimate carcinogenic metabolites. Further oxidation of PAH phenols leads to the formation of PAH quinones. The major cytochrome P450s that are involved in the formation of diol epoxides are CYP1A1, CYP1A2 and CYP1B1, while CYP2C9 and CPY3A4 play a minor role in the activation of PAHs. Additional enzymes that may play a role in the further activation of some PAH diols include members of the aldo-keto reductase (AKR1) family. NQO1 catalyses the reduction of PAH quinones to hydroquinones which may be re-oxidized and generate reactive oxygen species. The major phase II enzymes include the GSTs, uridine 5′-diphosphate glucuronosyltransferases and sulfotransferases. The major GSTs involved in the conjugation of PAH metabolites are GSTM1, GSTP1 and GSTT1 (IARC, 2010).

The current understanding of the carcinogenesis of PAHs in experimental animals is almost solely based on two complementary mechanisms: those of the diol epoxide and the radical cation. The diol epoxide mechanism features a sequence of metabolic transformations of PAHs, each of which leads to potentially reactive genotoxic forms. In general, PAHs are converted to epoxides and dihydrodiols, which are in turn oxidized to diol epoxides. Both epoxides and diol epoxides are ultimate DNA-reactive metabolites. PAH epoxides can form stable DNA adducts and diol epoxides can form stable and depurinating adducts with DNA through electrophilic carbonium ions, and induce mutations (e.g. in *ras* proto-oncogenes) that are strongly associated with the tumorigenic process. One-electron oxidation creates radical cations at a specific position on some PAHs, resulting in the formation of depurinating DNA adducts which generate apurinic sites that can induce mutations in *ras* proto-oncogenes, and are strongly associated with tumorigenesis (IARC, 2010).

The genotoxic effects of exposure to complex mixtures that contain PAHs have been studied in some populations exposed in industrial settings and in patients who undergo coal-tar therapy. Measured end-points include mutagenicity in urine and the presence of aromatic DNA adducts in the peripheral lymphocytes of exposed workers. In some studies, specific benzo[*a*]pyrene–DNA adducts have been measured. Cytogenetic effects such as micronucleus formation have also been reported. Other mechanisms of

carcinogenesis have been proposed for PAHs, but these are less well developed. They include generation of reactive oxygen species, activation of the aryl hydrocarbon receptor with regulation of phase I and II metabolism, lipid peroxidation, production of arachidonic acid-reactive metabolites, decreased levels of serum thyroxine and vitamin A, and persistent activation of the thyroid hormone receptor, as well as activation of mitogen-mediated protein kinase pathways, suppression of immunity by p53-dependent, and other, pathways (IARC, 2010).

4.2.3 *Indirect effects potentially related to genotoxicity*

(a) Haematological changes

Beving *et al.* (1991) studied haematological parameters, iso-transferrin ratio in plasma in ten men (age range, 21–54 years) with occupational long-term, low-level exposure to vapours from epoxy paints. The mean cellular volume of erythrocytes was significantly higher ($P < 0.05$) for house painters (90.6 fl ± 3.4) than for 10 unexposed healthy controls (86.9 fl ± 3.3). Plasma concentration of iso-transferrin, a major iron transport protein in the blood, and the ratio with total transferrin were significantly higher ($P < 0.05$) in the exposed group (median 51.8 mg/l and 2.12%, respectively) as compared to the controls (median, 33.4 mg/l and 1.55%, respectively).

Cullen *et al.* (1992) studied morphological and biochemical changes in the bone marrow and in circulating red blood cells and lymphocytes in painters exposed to glycol ethers. In a previous study, they reported that although the means of all blood cell counts were comparable between exposed and unexposed subjects, a significant proportion of painters were anaemic (10%) and granulocytopenic (5%); none of the controls were affected. Review of company records documented that most of these abnormalities were acquired during employment; pre-existing disease and other exposure could not explain the findings. In their subsequent follow-up study, the affected exposed painters ($n = 10$) were matched to two control groups: exposed painters without evidence of haematological abnormalities on the previous investigation ($n = 7$) and unexposed controls ($n = 7$). No differences were observed between the groups in terms of bone marrow morphology and cellularity, and stem cell growth kinetics. However, exposed subjects, when compared to unexposed controls, had significantly decreased saturation of glutathione reductase with flavine adenine dinucleotide (68.3% versus 80.3%, $P = 0.05$) suggesting riboflavin deficiency or impaired riboflavin metabolism. Riboflavin deficiency has been implicated as a risk factor for cancer, although this has not been satisfactorily established in humans.

A group of 60 male workers involved in applying lacquer to steel cans were investigated for haematological effects. The lacquer applied contained 3% xylene, 12% butanol, 35% cyclohexanol, 25% 2-ethoxyethanol acetate, and 25% 2-butoxyethanol. Environmental monitoring revealed benzene time-weighted average values between 0–12 ppm with a mean value of 6 ppm. The workplace air also contained toluene and xylene. A significant decrease in peripheral blood T-cell and NK-cell count was observed

among painters when compared to 79 unexposed male workers. In contrast, T-suppressor cell count was increased among exposed workers when compared to controls (Moszczyński *et al.*, 1996).

Kim *et al.* (1999) evaluated haematological effects among 57 shipyard painters exposed to ethylene glycol monoethyl ether acetate (EGEEA), a solvent widely used for paints. Painters were divided in two exposure groups (high/low). Mean EGEEA levels were 3.03 and 1.76 ppm, respectively. In addition, environmental monitoring revealed detectable levels of toluene, ethyl benzene, xylene, butanol, isopropanol, ethanol, ethyl acetate, butyl acetate, methyl isobutyl ketone, and nonane. No benzene or other glycol ethers could be detected in the bulk samples of some paints and thinners or air samples. Mean white blood cell counts in the high exposure group (6033 cells/µl ± 1433) were lower ($P < 0.05$) than in the control group of 41 unexposed workers in non-production areas of the same factory (7031 cells/µl ± 1400). Six (11%) of the 57 painters were leucopenic (leucocyte count < 4500 cells/µl) while none of the controls was affected ($P < 0.05$). Results indicate that EGEEA might be toxic to the bone marrow.

These studies on haematological effects among painters show consistently that peripheral blood cell counts and morphology of the cells are affected by the exposures encountered during the handling or making of paints. The relation between haematotoxicity and cancer are not directly clear except that in a study among subjects exposed to benzene, subjects with benzene poisoning (total white blood cell count < 4000/µl or white blood cell count between 4000 and 4500/µl and platelet count < 80 000/µl, with repeated confirmation of this count in a few months in a peripheral blood examination) had an increased risk for developing acute myeloid leukaemia (relative risk, 70.6; 95% CI: 11.4–439.3; Rothman *et al.*, 1997). However, it needs to be recognized that although this lends plausibility to a possible association between severe haematoxicity and acute myeloid leukaemia, it does not necessarily mean that the association is relevant for less severe, transient haematological effects.

(b) Immunological effects

Hexamethylene diisocyanate (HDI) is an aliphatic diisocyanate that is used almost exclusively in the manufacture of paints and surface coatings. HDI can induce occupational asthma (Vandenplas *et al.*, 1993), and HDI-specific IgE and IgG have been detected in selected patients with diisocyanate asthma or small populations of exposed workers (Grammer *et al.*, 1988; Cartier *et al.*, 1989; Baur *et al.*, 1996; Tee *et al.*, 1998; Redlich *et al.*, 2001). Besides specific Ig responses, increased proliferation of HDI-specific lymphocytes has been observed upon in-vitro cell stimulation with HDI (Redlich *et al.*, 2001). These results indicate that HDI-containing paints can trigger specific systemic immunological responses.

4.3 Susceptible populations

A few studies have addressed the interplay between genetic factors and biological and clinical end-points. Gene–environment interactions related to specific exposures and

metabolites are outside the scope of the current overview but some specific chemicals have been reviewed in previous monographs.

4.3.1 *Gene–environment interactions and clinical end-points*

Golka *et al.* (2001) studied the impact of *N*-acetyltransferase 2 phenotype in painters with bladder cancer and controls. Sixteen painters with bladder cancer and 26 healthy painters (controls) from the same geographic area in Germany were phenotyped for *N*-acetyltransferase 2 based on the molar ratio of two caffeine metabolites in the urine. Cases and controls had comparable smoking habits, similar age at first exposure, and comparable number of persons exposed to colorants before 1960 (at that time, some azo-dyes used by painters were based on carcinogenic aromatic amines, especially benzioline). The slow acetylation status was over-represented in the painters with bladder cancer (88%) compared to their healthy colleagues (65%). The odds ratio for bladder cancer of slow acetylators compared to rapid acetylators was 3.0 (95% CI: 0.64–14.04).

4.3.2 *Gene–environment interactions and biological end-points*

Testa *et al.* (2005) studied multiple cytogenetic effects among 25 car painters and 37 unexposed control subjects (healthy blood donors). The exposed subjects had higher frequencies of chromosomal aberrations, SCE and micronuclei than controls (see section 4.2). Subjects were also genotyped for *GSTM1* polymorphisms (controls, 49% *GSTM1* null; exposed, 48% *GSTM1* null) and *GSTT1* (controls 35% *GSTT1* null; exposed, 24% *GSTT1* null). No significant associations were detected between any of the biomarker responses and either the *GSTM1* or *GSTT1* genotype. However, as the authors indicate, the small size of the study does not allow definite conclusions on the relationship between the genetic polymorphisms and the biomarkers.

In a study by Lee *et al.* (2003) among 181 painters using coal-tar paints ($n = 111$) or general paints ($n = 70$) and 27 on-site controls, no gene–environment interactions between *GSTM1* (all workers, 51% *GSTM1* null), *GSTT1* (all workers, 54% *GSTT1* null) and aromatic-DNA adducts was found among all groups exposed.

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5. Summary of Data Reported

5.1 Exposure data

Thousands of chemical compounds are used in paint products as pigments, extenders, binders, solvents, and additives. The main organic solvents used are toluene, xylene, aliphatic compounds, ketones, alcohols, esters, and glycol ethers. Azo pigments that contain 3,3′-dichlorobenzidine are common, although free aromatic amines are not present in significant quantities. Asbestos was used as a filler in paints and decorative coatings until the early 1990s. Several hazardous chemicals including benzene, some other solvents, phthalates (plasticizers), chromium and lead oxides have been reduced or replaced in paint, although they are still used in some countries. The increasing use of water-based paints and powder coatings has promoted this trend. New formulations contain lower-toxicity solvents, neutralizing agents, such as amines, and biocides.

Workers in the painting industry are potentially exposed to the chemicals found in paint products during their application and removal. Exposure to dichloromethane occurs during paint stripping from wood and metal surfaces. Diisocyanate is present in some binders and is released during painting. Silica is used in the preparation of surfaces. Painters may also be exposed to asbestos or crystalline silica as bystanders during construction activities. During the application of paint, workers are exposed primarily to solvents whereas the mechanical removal of paint leads mainly to exposure to pigments and fillers. In the past, exposure to hazardous substances frequently exceeded current occupational exposure limits, but exposure levels have generally decreased over time.

Inhalation is the predominant route of exposure, followed by dermal absorption to a much lesser extent; higher inhalation exposures are frequently accompanied by higher dermal exposures. Appropriate selection and use of personal protective equipment can substantially reduce uptake, although painters do not generally wear respirators or gloves. Biomonitoring of exposure to paint products reveals elevated levels of paint compounds or their metabolites in blood and urine.

5.2 Human carcinogenicity data

Seventeen cohort and linkage studies of painters have shown consistent and significant, although moderate (36%), excesses of mortality from lung cancer. Three of these studies provided information on tobacco smoking which is strongly associated with this neoplasm. These excesses are consistent with case–control studies which largely controlled for smoking. Twenty-nine case–control studies of lung cancer in painters were evaluated. Although the results were heterogeneous, partially due to small numbers in

some studies, overall, a consistent excess risk of lung cancer was observed over time. Of the 29 studies, three had an odds ratio < 1 with large confidence intervals that included the null value, and the others had odds ratios > 1, 14 of which showed a statistically significant or borderline significant increase. When all independent studies that appropriately adjusted for potential confounders were used in a meta-analysis, a statistically significant excess risk of 35% was obtained. When the analysis and results from the above and from population-based studies were restricted to smoking-adjusted estimates, the statistically significant excess risks were 34% and 41%, respectively.

A borderline significant excess of mortality from mesothelioma was observed in cohort studies and positive results were obtained in two case–control studies of this tumour, which is consistent with the presence of asbestos at some sites where painters work.

The 11 cohort and linkage studies of painters showed consistent, although moderate (21%), excesses of mortality from urinary bladder cancer. Two of these studies provided information on tobacco smoking which is strongly associated with this neoplasm. These excesses are consistent with case–control studies of painters that controlled for smoking in which an excess risk for urinary bladder cancer was seen. Most of the studies that were evaluated had odds ratios > 1. When all independent studies that appropriately adjusted for confounding were used in a meta-analysis, a statistically significant excess risk of 28% was obtained. When the analysis and results from the above and from population-based studies were restricted to smoking-adjusted estimates, the statistically significant excess risks were 26% and 27%, respectively.

Other statistically significant excesses of mortality were observed in the cohort studies for cancers of the pharynx, oesophagus, and liver. Cancers at these sites are associated with tobacco smoking (pharynx and oesophagus) and alcoholic beverage consumption (pharynx, oesophagus, and liver), both of which have been shown to be increased among painters compared with the national populations typically used as referent groups; hence, these might act as positive confounders. However, there are inadequate supportive data from case–control studies of these cancers that control for these potential confounders to conclude that confounding can be excluded as a cause of these excesses. The data were insufficient for evaluation, but the Working Group noted some consistency between case–control and cohort studies for cancers of the pharynx and oesophagus.

More case–control studies evaluated the risk for lymphatic and haematopoietic cancers among painters than that for cancers at other sites. Although some excesses were observed, the data are inadequate to draw a conclusion because of inconsistency among results from these studies, and the lack of any excess mortality from these cancers in the cohort studies. A few case–control studies of cancers of the nose, nasopharynx, larynx, oesophagus, stomach, pancreas, small bowel, kidney, brain, prostate, ovary and breast, mesothelioma, melanoma, and soft–tissue sarcoma were conducted among painters.

Several case–control studies evaluated the risk for childhood cancer and parental occupation as a painter or parental exposure to paints. Seven studies focused on

leukaemia. Five showed significant excesses associated with occupational or non-occupational exposure to paints, primarly among mothers. Despite this relatively small amount of data, the Working Group considered that there was some evidence that maternal occupational or other exposure to paints is associated with childhood leukaemia. The risks tended to be greater when mothers were exposed before or during pregnancy rather than after birth of the child, and two studies showed some evidence of an exposure–response relationship with duration of exposure.

Overall, a weakness of both the cohort and case–control studies is the lack of information on exposure–response trends, and few studies included analyses by duration of work as a painter.

There is also little information on specific work settings. One cohort, one case–control and one proportionate mortality study of artistic painters all showed excess mortality from urinary bladder cancer. Insufficient information is available to judge whether trends for risk for cancer have decreased over time with the changes in components of paints; for example, the levels of solvents, such as benzene, and pigments, such as lead chromates in paints, have decreased over past years. Data from studies carried out since the previous evaluations of painters still involve primarily painters who were exposed in the 1960s and the 1970s before many changes in paint components had taken effect.

Nevertheless, when the cohort and case–control studies were taken together, the Working Group concluded that there is consistent evidence in humans that occupational exposure as a painter causes lung and urinary bladder cancer. It does not appear that the excess mortality from these cancers is caused by the principal potential confounder, which is tobacco smoking.

No particular agent can be identified from epidemiological studies as the cause of excess of lung and urinary bladder cancer. It is improbable that the presence of asbestos would completely explain the excess of lung cancer; if this had been the case, a more pronounced excess of mesothelioma would have been observed. There is little information from epidemiological studies on the risk associated with the use of paint pigments that are known lung carcinogens, such as chromium or cadmium.

5.3 Animal carcinogenicity data

No data were available to the Working Group.

5.4 Other relevant data

Painters and paint industry workers are exposed to solvents (such as benzene, toluene and dichloromethane), paint pigments (such as lead, cadmium and chromium compounds) and many other compounds. Solvents are absorbed by inhalation and through the skin, and are generally rapidly metabolized and excreted as conjugated metabolites. Metal compounds that are used as paint pigments are predominantly

absorbed in the lung. Dermal absorption is generally low and depends on the chemical properties of the compound, the vehicle, and the integrity of the skin. Absorbed metals are distributed to the organs and, in the case of lead, are concentrated in the bone. Elimination of metals varies from several days to several years.

Overall, six of the eight studies on chromosomal aberrations among painters showed consistent and significant elevated frequencies. Of these six positive studies, three reported an association with years of employment while the other studies did not report analyses on duration of employment. Five of six studies reported significant increases in the frequencies of micronucleus formation among painters. Two of these five studies reported a dose gradient with years or weeks worked and levels of micronuclei. Chromosomal aberrations and micronucleus formation were found in both cultured lymphocytes and buccal cells. Four of seven studies on sister chromatid exchange among painters reported significantly increased frequencies. Exposure–response relationships with duration of employment were reported in three of these four studies. Three of the four studies on DNA single-strand breaks reported increased levels among painters.

Haematological changes were observed in several studies of painters. These included decreased levels of total white blood cells, T-cells and natural killer cells. Furthermore, an increased prevalence of leucopenia, anaemia and granulocytopenia was observed among painters. Immunological changes were also observed among painters in several studies. These effects included specific immunoglobulin (G and E) responses to hexamethylene diisocyanate and increased proliferation of lymphocytes after in-vitro stimulation with hexamethylene diisocyanate.

Most cytogenetic studies among painters that measured a variety of cytogenetic end-points and markers of genotoxicity reported elevated levels of genetic damage. Several of these studies showed a dose-gradient with years or weeks worked and the cytogenetic end-point. Stratified analyses by tobacco smoking status generally showed consistent results among smokers and nonsmokers. These data strongly suggest that occupational exposures in painting lead to increased levels of DNA damage. Furthermore, mechanistic data reviewed by the Agency for Toxic Substances and Disease Registry and in previous evaluations by the IARC Monographs on selected specific chemicals that had been or still are prevalent in exposures encountered by painters indicate strong support for the induction of haematopoietic (benzene, trichloroethylene, 1,3-butadiene), liver (trichloroethylene), and lung (asbestos, cadmium, chromium) cancers.

6. Evaluation and Rationale

6.1 Cancer in humans

There is *sufficient evidence* in humans for the carcinogenicity of occupational exposure as a painter. Occupational exposure as a painter causes cancers of the lung, and of the urinary bladder.

There is *limited evidence* in humans, based primarily on studies of maternal exposure, that painting is associated with childhood leukaemia.

6.2 Cancer in experimental animals

There is *inadequate evidence* in experimental animals for the carcinogenicity of occupational exposure as a painter, since no data were available to the Working Group.

6.3 Overall evaluation

Occupational exposure as a painter is *carcinogenic to humans (Group 1)*.

FIREFIGHTING

FIREFIGHTING

1. Exposure Data

1.1 Activities and tasks of firefighters

The terms ‘firefighting’ and ‘firefighters’ are broad and encompass several types of fire scenarios such as municipal, wildland, industrial, aviation, military, and oil wells. Some municipal firefighters may be permanently assigned to tasks other than fighting fires, including fire scene investigation (i.e. the investigation of suspected criminal fires started by arsonists), hazardous material response, building safety inspections, or technical and administrative support. These individuals may or may not have experience fighting fires, and may or may not be working for municipal fire departments. In addition, municipal firefighters are increasingly being called upon for emergency medical response. Finally, the term “firemen” may refer either to firefighters or to individuals who operate and maintain equipment for power generation (e.g. steam boilers), heating, ventilation, humidity control, refrigeration, and air conditioning. Workers in this latter category are also referred to as “stationary engineers” or “stationary firemen” (Decoufle *et al*., 1977), and are not considered in this monograph.

There are two more or less distinct phases in municipal structural firefighting: knockdown and overhaul. During knockdown, firefighters control and extinguish the fire. Approximately 90% of municipal structural fires are either extinguished within 5–10 minutes, or abandoned and fought from the outside. This results in an average duration of heavy physical activity at fires of approximately 10 minutes (Gempel & Burgess, 1977; Gilman & Davis, 1993). Knockdown of large fires may last much longer. During overhaul, any remaining small fires are extinguished. The environment during overhaul is not as hot or as smoky as during knockdown, but it still contains products of combustion from small fires or smouldering material. Exposure can differ widely between the two phases of firefighting. The determination of when overhaul begins varies from one fire department to another, and is often left to the judgement of individual firefighters or group leaders (Jankovic *et al*., 1991; Austin *et al.*, 2001a). Municipal structural fires may

be fought in aggressive attack mode during knockdown, or defensively from the outside. In the past, firefighters may have more often attempted to enter a burning structure to fight the fire. For safety reasons, however, modern fire departments are increasingly adopting a defensive approach, unless there are human victims inside the building.

A municipal fire department is composed of 1st line firefighters (pump, ladder, and rescue crews, and operations chiefs) and 2nd line firefighters (drivers and division chiefs). Combat firefighters assigned to pump trucks, ladder trucks, or rescue trucks perform tasks specific to each of those crews. In some municipalities, there is movement of firefighters between different firehalls, while in others, a firefighter is assigned to the same crew at the same firehall for most of his or her career. It is conceivable that there would be differences in exposures between pump truck and ladder truck crews, although no such difference was observed in one older study (Gold *et al*., 1978).

In addition to fighting accidental fires and criminal fires, firefighters and firefighter recruits may be involved in training fires staged in buildings or simulators. Hill *et al*. (1972) describe a permanent structure used for training purposes where approximately 5500 litres of diesel fuel was burned in the lower portion of the building.

Analogous to knockdown and overhaul, wildland firefighting also comprises two phases, referred to as “attack” and “mop-up.” Attack at a wildland fire generally extends over a long period of time, one fire lasting hours, days or weeks. The frequency of aggressive strategies and tactics by firefighters may increase where there is an attempt to save residential developments. Municipal firefighters may also be called upon to fight wildland fires within or adjacent to municipal limits.

Both municipal firefighters and wildland firefighters engage in heavy work activity at fires. In particular, wildland firefighters who use hand tools and carry a considerable amount of equipment with them engage in heavy work activity levels while fighting forest fires (Budd *et al*., 1997; Ruby *et al*., 2002). Typical tasks include hiking, fire-line construction, chainsaw work, and brush removal. As a result, the amount of chemicals inhaled is greater for a firefighter at heavy work levels without respiratory protection than for a worker engaged in regular levels of work (Reh & Deitchman, 1992; Reh *et al.*, 1994). This needs to be taken into consideration when comparing exposure levels to occupational exposure limits that were developed assuming regular work levels.

Also, studies relating to municipal firefighters usually do not distinguish between the different categories of exposed and unexposed firefighters or between the different task assignments.

1.2 Composition of fire smoke

1.2.1 *Fire chemistry*

Smoke from fires comprises suspended liquid and solid particulate matter, gases and vapours that result from the combustion or pyrolysis of material. There is a very large number of toxic components in smoke (for reviews, see Tuve, 1985; Meyer, 1989; DiNenno *et al*., 2002; Côté, 2003). The basic form of the overall combustion reaction of organic (carbon-containing) compounds is illustrated by the burning of methane:

$$CH_4 + 2O_2 + \text{Energy of activation} \rightarrow CO_2 + 2H_2O + \text{Heat of combustion} + \text{Light}$$

Given the appropriate ratio of fuel (wood, solvent, plastic, rubber), oxygen, and combustion temperature, the products of combustion should be only water and carbon dioxide (CO_2).

Complete combustion is approached only under carefully controlled conditions. Uncontrolled or unintentional combustion tends to be "fuel rich" and therefore incomplete. The combustion of methane (CH_4) illustrates the formation of free radicals in an 11-step chain reaction, the first two of which are:

$$CH_4 \rightarrow CH_3^{\bullet} + H^{\bullet}$$

$$H^{\bullet} + O_2 \rightarrow OH^{\bullet} + O^{\bullet}$$

The free radicals formed during combustion are very reactive and side reactions are propagated to yield hundreds of chemical products, and smoke.

Most polymers found in buildings will burn or thermally degrade to simpler monomers. Thermal degradation products include methane, ethane, ethylene, benzene, toluene, and ethylbenzene in addition to the following monomers: ethylene, vinyl chloride, acrylonitrile, tetrafluoroethylene, styrene, methyl methacrylate, ethylene glycol, terephthalic acid, phenol, formaldehyde, hexamethylenediamine, adipic acid, propene, vinyl chloride, vinyl acetate, vinylidene chloride, chloroprene, 1,3-butadiene, ethyl acrylate, ethylene oxide, methylacrylate, urea, phenol, and isoprene.

The burning of plastics typically produces voluminous amounts of soot, together with higher levels of hydrogen cyanide (HCN), hydrochloric acid (HCl) and acrolein (CH_2=CHCHO) than the burning of materials such as wood, and fossil fuels. More smoke evolves from fires involving aromatic polymers, such as polystyrene, compared to aliphatic polymers, such as polyethylene.

In addition to the chemical agents described above, particulate matter is produced under conditions of incomplete combustion. The particulate matter is an aerosol consisting of condensed phase components of the products of combustion and finely divided carbon particulates that have not undergone combustion but remain suspended in the air. Although the particles themselves are microscopic in size (0.3–1.6 µm), they

rapidly coalesce and thereby become visible. These particles are also adsorbents (similar to activated charcoal) and are an additional vehicle for the transport and inhalation of toxic combustion products. Smouldering yields a substantially higher conversion of fuel to toxic compounds than does flaming, although it occurs more slowly (Ohlemiller, 2002).

1.2.2 *Modern versus pre-modern fires*

All types of fire release toxic and carcinogenic substances, including benzene, 1,3-butadiene, and formaldehyde. The focus has generally been on substances having short-term acute effects: carbon monoxide (CO), carbon dioxide, hydrogen cyanide, nitrogen oxides (NO_x), sulfur dioxide (SO_2) and hydrogen chloride. With the increasing use of polymers in building construction and furnishings, there is concern that the burning of these new materials might release large quantities of other highly toxic substances (Austin *et al*., 2001b).

Combustion and pyrolysis products from newer building materials and furnishings were believed to be more toxic than smoke from fires in buildings built before these materials became commonplace, and more toxic than smoke from wildland fires (Betol *et al*., 1983; Alarie, 1985). However, many of the carcinogenic products of combustion identified are volatile organic compounds and are common to most burning materials. In a more recent study, no new or unusual non-polar volatile organic compounds (VOCs) were observed in current structural fires compared to the combustion of wood (Austin *et al*., 2001b, 2001c). Adding polyvinyl chloride (PVC) to the fire load at simulated apartment fires was observed to significantly increase levels of polychlorinated phenols (IARC Group 2B), while polycyclic aromatic hydrocarbon (PAH) levels remained essentially unchanged (Ruokojärvi *et al*., 2000). The increases in levels of polychlorinated biphenyls (PCBs, 0.021 to 0.031 mg/m^3), polychlorinated benzenes (0.002 to 0.010 mg/m^3) and I-TEQs [or PCDD/F] (3.5 to 5.4 ng/m^3) as products of combustion were not significant [possibly due to the small sample size]. In another study, proportionately higher levels of ethyl benzene (IARC Group 2B) were found at an electronics factory fire when compared to levels at residential and mixed occupancy fires (Austin *et al*., 2001b).

The emission of combustion products (in mg per kg of material burned) for the same material varies greatly depending on combustion conditions such as ventilation (oxygen supply), temperature, and heating rate. Nonetheless, the relative amounts of the various non-polar VOCs found in smoke at municipal structural fires have been found to be remarkably similar from fire to fire, namely with the same 14 of 144 target compounds, dominated by benzene (IARC Group 1), toluene and naphthalene (IARC Group 2B) (Austin *et al*., 2001b, 2001c).

1.2.3 *Carcinogens found in smoke at fires*

Table 1.1 lists the agents in Groups 1, 2A, and 2B that have been detected at fires in one or more studies, together with corresponding IARC evaluations, human and animal evidence of carcinogenicity, and for the agents in Group 1, the cancer sites in humans.

Table 1.1. IARC evaluations and cancer sites in humans of chemicals measured at fires

Chemicals measured at fires	Overall evaluation	Human evidence	Animal evidence	Volume	Cancer sites in humans (For Group 1 agents only)
Acetaldehyde	2B	Inadequate	Sufficient	36, Suppl. 7, 71	
Arsenic	1	Sufficient	Limited	23, Suppl. 7	Skin, lung, liver (angiosarcoma)
Asbestos	1	Sufficient	Sufficient	14, Suppl. 7	Lung, mesothelioma, larynx, gastrointestinal tract
Benz[*a*]anthracene	2B	Inadequate	Sufficient	32, Suppl. 7, 92	
Benzene	1	Sufficient	Limited	29, Suppl. 7	Leukaemia
Benzo[*b*]fluoranthene	2B	No data	Sufficient	32, Suppl. 7, 92	
Benzo[*k*]fluoranthene	2B	No data	Sufficient	32, Suppl. 7, 92	
Benzofuran (coumarone)	2B	No data	Sufficient	63	
Benzo[*a*]pyrene	1	No data	Sufficient	32, Suppl. 7, 92	Lung, bladder, skin
1,3-Butadiene	1	Sufficient	Sufficient	71, 97	Lymphohaematopoietic system
Cadmium	1	Sufficient	Sufficient	58	Lung
Carbon black (total)	2B	Inadequate	Sufficient	65, 93	
Chrysene	2B	Inadequate	Sufficient	3, 32, Suppl. 7, 92	
Dibenz[*a*,*h*]anthracene	2A	Inadequate	Sufficient	32, Suppl. 7, 92	
Dichloromethane (methylene chloride)	2B	Indadequate	Sufficient	71	
Ethylbenzene	2B	Inadequate	Sufficient	77	
Formaldehyde	1	Sufficient	Sufficient	88	Nasopharynx; (nasal sinuses and leukaemia, suggested)
Furan	2B	Inadequate	Sufficient	63	

Table 1.1 (contd)

Chemicals measured at fires	Overall evaluation	Human evidence	Animal evidence	Volume	Cancer sites in humans (For Group 1 agents only)
Indeno-1,2,3-[*cd*]pyrene	2B	Inadequate	Sufficient	32, Suppl. 7, 92	
Isoprene	2B	Not available	Sufficient	60, 71	
Lead				23, Suppl. 7, 87	
Lead compounds, organic	3	Inadequate	Inadequate	23, Suppl. 7, 87	
Lead compounds, inorganic	2A	Limited	Sufficient	23, Suppl. 7, 87	
Naphthalene	2B	Inadequate	Sufficient	82	
2-Nitroamisole	2B	Inadequate	Sufficient	65	
Polychlorophenols	2B	Limited		41, Suppl. 7, 53, 71,	
Pentachlorophenol			Sufficient		
2,4,6-Trichlorophenol			Limited		
Polychlorinated biphenyls (aroclor; 54%) (chlorodiphenyl)	2A	Limited	Sufficient	18, Suppl. 7	
Polychlorinated dibenzodioxins[a]: see TCDD					
Radioactivity (γ activity)	1	Sufficient	Sufficient	78	All sites combined
Radionuclides (α-particle-emitting)	1	Sufficient	Sufficient	78	All sites combined
Radionuclides (β-particle-emitting)	1	Sufficient	Sufficient	78	All sites combined
Silica (crystalline)	1	Sufficient	-	68	Lung
Silica (amorphous)	3	Inadequate	Inadequate	68	

Table 1.1 (contd)

Chemicals measured at fires	Overall evaluation	Human evidence	Animal evidence	Volume	Cancer sites in humans (For Group 1 agents only)
Styrene	2B	Limited	Limited	60, 82	
Sulfuric acid[b]	1	Sufficient	No data	54	
2,3,7,8-tetrachloro dibenzo-*para*-dioxin	1	Limited	Sufficient	69	All sites combined, lung, non-Hodgkin lymphoma, sarcoma
Tetrachloroethylene (perchloroethylene)	2A	Limited	Sufficient	63	Cervix, oesophagus, non-Hodgkin lymphoma
Toluene diisocyanates	2B	Inadequate	Sufficient	39, Suppl. 7, 71	
Trichloroethylene	2A	Limited	Sufficient	63	Liver and biliary tract, non-Hodgkin lymphoma, renal cell
Trichloromethane (chloroform)	2B	Inadequate	Sufficient	73	
Triphenylene	3	Inadequate	Inadequate	32, Suppl. 7, 92	

[a] Polychlorinated dibenzo-*para*-dioxins as a group are classified in Group 3
[b] Evaluation of occupational exposures to strong inorganic acid mists containing sulfuric acid

1.3 Exposure

1.3.1 *Characterization of firefighter exposures*

The characterization of exposures to fire gases and smoke is challenging due to several factors: work schedules of 10- to 24-hour shifts for 188 days in a year; wide variations between firefighters' time spent at fires; intermittent exposures; exposure to a complex mixture of gases, vapours and particulate matter; unknown effect of heat; gases and free radicals may also be adsorbed onto particulate matter; some semivolatile organic compound (SVOC) vapours measured in the air may be distributed between the solid and vapour phase, this equilibrium shifting in either direction depending on the temperature and on the density of the smoke; and, the difficulty in collecting samples at unpredictable locations in a dangerous and rapidly changing environment.

Given the multitude of chemicals in smoke, some substances may produce metabolites that alone or in combination with other substances or metabolites may become hazardous.

1.3.2 *Time spent at fires*

The number of runs and the time spent at fires varies tremendously between firehalls, depending on the geographic location, the social and economic environment, staffing, and the types of call (number of fires, types of fire, medical calls, hazardous materials [HAZMAT]).

Probably as a result of improved building codes compared to past decades, municipal firefighters today spend surprisingly little time at fires. In a study in Montreal, the time spent at fires was calculated based on an extensive database compiled over a period of 12 months (Austin *et al*., 2001a). Firefighters from the least busy firehalls responded to approximately eight structural fires per year or 19 fires of all kinds, spending 15.1 hour/yr per firefighter at fires. Firefighters from the busiest firehalls responded to 3.13 times as many structural fires per year (25 structural fires, or 62 fires of all kinds), and spent 3.3 to 3.6 times as long at fires (54 hours). This study did not distinguish between 1st line and 2nd line firefighters. However, based on discussions with the fire department, it was estimated that 2nd line combat firefighter exposures were less than 50% those of 1st line combat firefighters. Overall, firefighters responding to fires spent between 0.75% and 2.7% of their time at fires over the course of a year. More recently, Kales *et al*. (2007) used a similar method to estimate time spent at fires for a municipal fire department in the USA, and national data supplied by the National Fire Protection Association (NFPA) and the International Association of Fire Fighters (IAFF) to produce estimates for smaller fire departments and large metropolitan fire departments, respectively. Firefighters spent 1%, 2%, and 5% of their time at fires in small, municipal, and metropolitan fire departments, respectively. This would represent 20–100 hours per year. Kales *et al*. (2007) estimated

that firefighters responded to an average of 1.7 (Standard Deviation (SD), 0.1) to 7.0 (SD, 6.3) fire incidents per year.

Burgess *et al*. (2003) estimated the time spent inside structural fires broken down by tasks for two fire departments in Arizona, USA. The results were: entry/ventilation 5.7 ± 11.7 hour/yr (Phoenix), and 3.5 ± 3.7 hour/yr (Tucson); rescue 5.0 ± 8.0 hour/yr (Phoenix), and 2.1 ± 2.7 hour/yr (Tucson); knockdown (extinction) 5.6 ± 8.9 hour/yr (Phoenix), and 4.5 ± 4.4 hour/yr (Tucson); overhaul 15.0 ± 3.7 hour/yr (Phoenix), and 20.8 ± 76.8 hour/yr (Tucson); and, support/standby 16.3 ± 28.6 hour/yr (Phoenix), and 19.1 ± 76.7 hour/yr (Tucson). Total firefighter activity at fires in Phoenix and Tucson was a mean of 47.6 hour/yr and 50.0 hour/yr, respectively.

In a study among firefighters in Washington, DC, (n = 43), at the time of the survey, an average of 9.2 days had elapsed since the last fire. Also, 0.33 fires had been fought in the previous 24 hours, 1.33 in the previous week, 5.91 in the previous month, and 57.1 fires in the previous year (Liou *et al*., 1989).

Little information is available concerning the time that firefighters outside of North America spend at fires. The organization and practices of fire departments might differ, and a greater number of fires may occur at other locations. In one study in Inchon, Korea, firefighters were questioned about their firefighting activity during the previous 5 days; among these, 33% (24 of 73) had had no fire exposure, 49% (36 of 73) had had less than 8 hours' fire exposure, and 18% (13 of 73) had had more than 8 hours' exposure to fire (Hong *et al*., 2000). Four of 13 volunteer firefighters in Sweden reported that they had not fought any fires within the previous 3 months, while the other nine reported having fought one fire each (Bergström *et al*., 1997). All 13 firefighters had been working as active firefighters for at least 3 years.

Wildland firefighters go to fires more frequently and spend more time at fires during a season than do municipal firefighters during an entire year, and all of their exposure occurs during the wildfire season. A total of 47 California wildland firefighters were surveyed to determine the extent of their firefighting activity (Rothman *et al*., 1993). Early in the wildland fire season, firefighters reported that they had spent a mean of 0.11 hours (Standard Error (SE), 0.89) fighting fires during the previous week, 12.06 hours (SE, 2.77) during the previous 2 weeks, and 16.74 hours (SE, 3.15) during the previous 4 weeks. Firefighting activity increased significantly during the late season, when wildland firefighters reported they had spent a mean of 22.36 hours (SE, 5.03) fighting fires during the previous week, 54.81 hours (SE, 9.29) during the previous 2 weeks, and 97.38 hours (SE, 15.26) fighting fires during the previous 4 weeks (Rothman *et al*., 1993). In the USA, Hot Shot crews [highly-skilled wildland firefighters specially trained in wildland fire suppression tactics] have been estimated to spend 64 days at wildfires and 5 days at prescribed burns, on average, per year, (Booze *et al*., 2004). In Quebec, in 2005, the agency responsible for wildland firefighting reported that wildland firefighters had spent a total of 145 689 hours at fires, or 755 hours per firefighter, on average for that year (Austin, 2008).

1.3.3 *Surrogates of exposure*

As a matter of practicality, epidemiologists have generally used years of employment or, in one case, years of active duty fighting fires (Demers *et al*., 1994), as a surrogate for exposure to smoke. This does not take into account the reduction in exposures when respiratory protection was used, differences between exposure groups, the intermittent nature of exposures, differences in tasks, or the fact that not all firefighters actually combat fires. In a Montreal study, only 66% of fire department personnel were 1st line firefighters (Austin *et al*., 2001a). Years of employment has not been found to correlate with exposure to combustion products or related adverse health effects (decline in pulmonary function or airway responsiveness) (Musk *et al*., 1977; Takehito & Maeda, 1981; Sparrow *et al*., 1982; Sherman *et al*., 1989). The number of fires fought has, however, been correlated with the mean annual reduction in pulmonary function (Peters *et al*., 1974). Among firefighters at the same fire, statistically significant differences in exposure to combustion products have been found between front-line firefighters and both squad leaders and ordinary firefighters (Takehito & Maeda, 1981). The same study found no significant difference between ordinary firefighters and the officers who accompanied them.

Two epidemiological studies used estimated cumulative runs as a surrogate for exposure (Austin *et al*., 2001a; Baris *et al*., 2001). In one study (Austin *et al*., 2001a), a good correlation between the number of runs per firehall and time spent at fires was observed ($r = 0.88$). However, different crews could have similar numbers of runs yet spend significantly different lengths of time at fires. The study by Austin *et al*. (2001a) identified distinct firefighter exposure groups based on job title, fire hall assignment, and time spent at fires.

1.3.4 *Exposure to carcinogens found in smoke at fires*

Table 1.2 presents the results of the studies that have measured the substances listed in Table 1.1, and particulate matter (total, respirable, PM_{10}). Unless otherwise indicated, reported levels do not take into consideration the use of respiratory protection. Table 1.3 provides a summary of the results from Table 1.2 for each substance, according to the type of fire or exposure (i.e. wildland, municipal, training fire, or municipal fire scene (arson) investigation).

The carcinogens found in one or more studies include nine known human carcinogens (Group 1), four probable human carcinogens (Group 2A), and 21 possible human carcinogens (Group 2B) (for a review, see Bendix, 1979; Lees, 1995).

Many of the wildland and municipal firefighter studies result from opportunistic sampling with sometimes wide margins of error, and may not be representative of firefighter exposures.

Two studies reported extremely high levels of benzene, up to 165 and 250 ppm (Burgess *et al*., 1979; Brandt-Rauf *et al*., 1988, respectively) [the former study used an accurate and precise sampling and analytical methodology]. Benzene levels in the remaining studies ranged from not detected to 23 ppm.

Table 1.2. Studies of exposures of firefighters to selected chemicals and agents

Reference, location	Type of fire	Sampling period and duration	No. of fires	No. of samples	Units	Mean ± SD (*geometric mean, **median)	Min.	Max.	Comments
Acetaldehyde									
Jankovic *et al*. (1991), USA	Municipal		22 22 22	21 5 4	ppm ppm ppm		ND ND ND	8.1 1.6 0.9	Knockdown Overhaul Inside face mask
Kelly (1991), USA	Wildland	Shift	1	20	ppm		ND	0.1	Mop-up
NIOSH (1992), USA	Wildland	Shift	1	20	ppm		ND	ND	Mop-up
Reh *et al*. (1994), USA	Wildland		1 1	3 2	ppm ppm		0.01 0.03	0.02 0.04	Low smoke levels Medium smoke levels
Kinnes & Hine (1998), USA	Municipal	TWA	5	8	ppm		ND	0.13	Arson investigation
Bolstad-Johnson *et al*. (2000), USA	Municipal	> 20 min	25	96	ppm	0.34 ± 0.41	0.041	1.75	Overhaul lasting min 20 min
Andreae & Merlet (2001), Germany	Wildland	Multiple	Multiple data sources	–	mg/kg[a]	[607 ± 345]			Means of reported mean emissions factors for savanna and grassland, tropical forest, extratropical forest, biofuel burning, charcoal making, and agricultural fires

Table 1.2 (contd)

Reference, location	Type of fire	Sampling period and duration	No. of fires	No. of samples	Units	Mean ± SD (*geometric mean, **median)	Min.	Max.	Comments
Burgess *et al*. (2001), USA	Municipal (testing)	Overhaul > 25 min Overhaul < 25 min	7 9	22 19	ppm ppm	0.158 ± 0.037 0.383 ± 0.494			No respiratory protection SCBA used
Reisen *et al*. (2006), Australia	Wildland		6	25	ppm	< 0.08	ND	0.26	4 prescribed and 2 exceptional burns
Arsenic									
Turkington (1984), USA	Municipal	10–15 min	1	1	mg/m^3	0.14			–
Asbestos (chrysotile)									
Bridgman (2001), U.K.	Municipal			2	f/cm^2	[0.0029]	[0.001]	[0.0043]	Factory fire: chrysotile fibres in the weave of the outer fabric of firefighters' tunics

Table 1.2 (contd)

Reference, location	Type of fire	Sampling period and duration	No. of fires	No. of samples	Units	Mean ± SD (*geometric mean, **median)	Min.	Max.	Comments	
Benzene										
Hill *et al*. (1972), U.K.	Training	Grab sample	NR	1	ppm	1.17			Pool fire	
Burgess *et al*. (1979); Treitman *et al* (1980), USA	Municipal		NR	181/197	ppm		ND	165	Inside burning structures during latter stages of structural fires	
Turkington (1984), USA	Municipal	10–15 min	1	1	ppm	1.00				
Lowry *et al*. (1985a), USA	Municipal	At fire	75	NR	ppm	Detected in most fires			Mixed type of exposure	
Brandt-Rauf *et al*. (1988), USA	Municipal	30 min	6	11	ppm	[59.18 ± 83.86]	ND	250	Low smoke levels	Mostly wood structures
		30 min	2	7	ppm	[26.17 ± 30.59]	ND	83.3	Moderate smoke levels	burning mostly
		30 min	5	6	ppm	[94.87 ± 92.73]	ND	225	High/Intolerable smoke levels	building and contents
		30 min	2	2	ppm		23	34	Automobile	

Table 1.2 (contd)

Reference, location	Type of fire	Sampling period and duration	No. of fires	No. of samples	Units	Mean ± SD (*geometric mean, **median)	Min.	Max.	Comments
Jankovic *et al*. (1991), USA	Municipal		22 22 22	15 2 4	ppm ppm ppm		ND ND ND	22 0.3 21	Knockdown Overhaul Inside mask
Kinnes & Hine (1998), USA	Municipal	TWA	5	4	ppm	trace			Arson investigation; benzene concentration between LOD and LOQ (0.04–0.12 ppm)
Bolstad-Johnson *et al*. (2000), USA	Municipal	> 20 min	25	95	ppm	0.383 ± 0.425	0.07	1.99	Overhaul
Reinhardt *et al*. (2000), USA	Wildland	Shift TWA Fireline TWA			ppm ppm	0.016* 0.028*		0.058 0.088	Prescribed burns (1991–1994)

Table 1.2 (contd)

Reference, location	Type of fire	Sampling period and duration	No. of fires	No. of samples	Units	Mean ± SD (*geometric mean, **median)	Min.	Max.	Comments
Reinhardt & Ottmar (2000), USA	Wildland	Shift TWA Fireline TWA Shift TWA Fireline TWA			ppm ppm ppm ppm	0.004* ± 3.6* 0.006* ± 3.6* 0.02* ± 0.003* 0.04* ± 0.14*		0.25 0.38 0.02 0.04	Project fires (1992–1995) Initial attack (1992–1995)
Andreae & Merlet (2001), Germany	Multiple	–	Multiple data sources	NR	mg/kg[a]	[693 ± 663]			Means of reported mean emissions factors for savanna and grassland, tropical forest, extratropical forest, biofuel burning, charcoal making, and agricultural fires
Austin *et al*. (2001b), Canada	Municipal	15 min	9	9	ppm	3.38 ± 3.45	0.12	10.76	7 mixed occupancy buildings, one electronics industry, one 9-day smouldering fire
Austin *et al*. (2001c), Canada	Municipal (simulated)	Grab sample	15	60	ppm	detected		0.1	In separate burns: wood (spruce), bed mattress, sofa foam, cardboard, plywood, gasoline, varsol, white foam insulation
Burgess *et al*. (2001), USA	Municipal	Overhaul >25 min Overhaul >25 min	7 9	23 20	 ppm	ND 0.557 ± 0.465			No respiratory protection SCBA used
Reisen *et al*. (2006), Australia	Wildland		6	8	mg/m^3	0.12	0.002	0.26	4 prescribed and 2 exceptional burns

Table 1.2 (contd)

Reference, location	Type of fire	Sampling period and duration	No. of fires	No. of samples	Units	Mean ± SD (*geometric mean, **median)	Min.	Max.	Comments
Benzofuran (coumarone)									
Andreae & Merlet (2001), Germany	Wildland emissions	Multiple	Multiple data sources	–	mg/kg[a]	[19 ± 12]			Means of reported mean emissions factors for savanna and grassland, tropical forest, extratropical forest, biofuel burning, charcoal making, and agricultural fires
Austin *et al*. (2001b), Canada	Municipal	15 min	9	9	ppm		0.2	2	7 mixed occupancy buildings, one electronics industry, one 9-day smouldering fire
1,3-Butadiene									
Andreae & Merlet (2001), Germany	Wildland	Multiple	Multiple data sources	NR	mg/kg[a]	[87 ± 79]			Means of reported mean emissions factors for savanna and grassland, tropical forest, extratropical forest, biofuel burning, charcoal making, and agricultural fires
Austin *et al*. (2001b), Canada	Municipal	15 min	9	9	ppm	1.03 ± 1.49	0.03	4.84	7 mixed occupancy buildings, one electronics industry, one 9-day smouldering fire

Table 1.2 (contd)

Reference, location	Type of fire	Sampling period and duration	No. of fires	No. of samples	Units	Mean ± SD (*geometric mean, **median)	Min.	Max.	Comments
Austin *et al*. (2001c), Canada	Municipal (simulated)	Grab sample	15	60	ppm	detected			In separate burns: wood (spruce), bed mattress, sofa foam, cardboard, plywood, gasoline, varsol, white foam insulation
Cadmium									
Bolstad-Johnson *et al*. (2000), USA	Municipal	>20 min	25	46	–	ND			Overhaul
Carbon black (Total)									
Andreae & Merlet (2001), Germany	Wildland	Multiple	Multiple data sources	–	mg/kg[a]	[747 ± 376]			Means of reported mean emissions factors for savanna and grassland, tropical forest, extratropical forest, biofuel burning, charcoal making, and agricultural fires

Table 1.2 (contd)

Reference, location	Type of fire	Sampling period and duration	No. of fires	No. of samples	Units	Mean ± SD (*geometric mean, **median)	Min.	Max.	Comments
Dichloromethane (methylene chloride)									
Lowry *et al*. (1985a), USA	Municipal	At fire	75	–	ppm	detected			Mixed types of exposure
Brandt-Rauf *et al*. (1988), USA	Municipal	30min	1	1	ppm	0.280			Mostly wood structures burning mostly building and contents
Ethylbenzene									
Hill *et al*. (1972), U.K.	Training	Grab sample	NR	1	ppm	0.382			Pool fire
Lowry *et al*. (1985a), USA	Municipal	At fire	75	NR	ppm	detected			Mixed type of exposure
Andreae & Merlet (2001), Germany	Wildland	Multiple	Multiple data sources	NR	mg/kg[a]	[54 ± 58]			Means of reported mean emissions factors for savanna and grassland, tropical forest, extratropical forest, biofuel burning, charcoal making, and agricultural fires
Austin *et al*. (2001b), Canada	Municipal	15 min	9	9	ppm	0.86 ± 1.94	0.01	5.97	7 mixed occupancy buildings, one electronics industry, one 9-day smouldering fire

Table 1.2 (contd)

Reference, location	Type of fire	Sampling period and duration	No. of fires	No. of samples	Units	Mean ± SD (*geometric mean, **median)	Min.	Max.	Comments
Austin *et al*. (2001c), Canada	Municipal (simulated)	Grab sample	15	60	ppm	measured			In separate burns: wood (spruce), bed mattress, sofa foam, cardboard, plywood, gasoline, varsol, white foam insulation
Formaldehyde									
Turkington (1984), USA	Municipal	10–15 min	1	1	ppm	0.71			
Lowry *et al*. (1985a), USA	Municipal	At fire	75	–	ppm	5.0	1	15	Mixed types of exposure
Brandt-Rauf *et al*. (1988), USA	Municipal	30min	6	11	ppm	0.12 ± 0.27	ND	0.8	Mostly wood structures burning with low smoke levels
		30 min	2	7	ppm	0.49 ± 1.24	ND	3.3	Mostly wood structures with moderate smoke levels
		30 min	5	6	ppm	1.74 ± 3.67	ND	8.3	Mostly wood structures with high/intolerable smoke levels
		30 min	2	2		ND			Automobile
Jankovic *et al*. (1991), USA	Municipal	NR	22	16	ppm		ND	8	Knockdown
			22	5	ppm		ND	0.4	Overhaul
			22	5	ppm		ND	0.3	Inside mask

Table 1.2 (contd)

Reference, location	Type of fire	Sampling period and duration	No. of fires	No. of samples	Units	Mean ± SD (*geometric mean, **median)	Min.	Max.	Comments
Kelly (1991), USA	Wildland	Shift	1	20	ppm		ND	0.1	Mop-up
NIOSH (1992), USA	Wildland	Shift	1	20	ppm			0.07	Mop-up
Materna *et al.* (1992), USA	Wildland	Fireline TWA	4 fire seasons	30	ppm	0.16	0.048	0.42	Project fires (1987–1989); mop-up
Reh & Deitchman (1992), USA	Wildland	NR	3 1 1	NR 3 2	ppm ppm ppm		ND 0.01 0.06	0.03 0.02 0.07	Low smoke levels Low smoke levels Medium smoke levels
Kinnes & Hine (1998), USA	Municipal	TWA	5	3	ppm		0.06	0.18	Arson investigation
Bolstad-Johnson *et al.* (2000), USA	Municipal	> 20 min	25	96	ppm	0.25 ± 0.252	0.016	1.18	Overhaul
Reinhardt & Ottmar (2000), USA	Wildland	Fireline TWA	NR		ppm ppm	0.018* ± 2.3* 0.028* ± 3*		0.093 0.092	Project fires (1992–1995) Initial attack (1992–1995)
		Shift TWA			ppm ppm	0.013* ± 2.4* 0.006* ± 3.1*		0.084 0.058	Project fires (1992–1995) Initial attack (1992–1995)

Table 1.2 (contd)

Reference, location	Type of fire	Sampling period and duration	No. of fires	No. of samples	Units	Mean ± SD (*geometric mean, **median)	Min.	Max.	Comments
Reinhardt *et al*. (2000); Slaughter *et al*. (2004), USA	Wildland	Fireline TWA	NR		ppm	0.075*		0.6	Prescribed burns (1991–1994)
		Shift TWA.			ppm	0.047*		0.39	Prescribed burns (1991–1994)
Andreae & Merlet (2001), Germany	Wildland	Multiple	Multiple data sources	NR	mg/kg[a]	[1347 ± 978]			Means of reported mean emissions factors for savanna and grassland, tropical forest, extratropical forest, biofuel burning, charcoal making, and agricultural fires
Burgess *et al*. (2001), USA	Municipal	Overhaul > 25 min	7	22	ppm	0.190 ± 0.182			No respiratory protection
		Overhaul > 25 min	9	19	ppm	0.257 ± 0.249			SCBA used
Reisen *et al*. (2006), Australia	Wildland		6	25	ppm	0.230	0.04	0.79	4 prescribed and 2 exceptional burns
Free radicals (short-lived)									
Jankovic *et al*. (1993), USA	Municipal	At fire	7	7	counts/min		ND	127	Knockdown
		At fire	10	10	counts/min		ND	920	Overhaul

Table 1.2 (contd)

Reference, location	Type of fire	Sampling period and duration	No. of fires	No. of samples	Units	Mean ± SD (*geometric mean, **median)	Min.	Max.	Comments
Free radicals (long-lived)									
Lowry *et al*. (1985b), USA	Municipal (simulated)	1 h; 2 room changes	6	6	ppm			1200	"Low energy fire" producing minimal radiant heat; burning 2 kg of paper, cotton and polyester clothing, plastics (including PVC), and wood
		1 h	6	–	ppm			1000	
Jankovic *et al*. (1993), USA	Municipal	At fire	–	–	detected by ESR	detected	–	–	Knockdown
		At fire	–	–	–	detected	–	–	Overhaul
Leonard *et al*. (2000), USA	Wildland	3.5 h	1	6	–	detected			Experimental fire
Leonard *et al*. (2007), USA	Wildland	3.5 h	1	6	–	detected			Mop-up and back-burn operations
Furan									
Lowry *et al*. (1985a), USA	Municipal	At fire	75	–	ppm	detected			Mixed types of exposure

Table 1.2 (contd)

Reference, location	Type of fire	Sampling period and duration	No. of fires	No. of samples	Units	Mean ± SD (*geometric mean, **median)	Min.	Max.	Comments
Andreae & Merlet (2001), Germany	Wildland	Multiple	Multiple data sources	–	mg/kg[a]	[508 ± 265]			Means of reported mean emissions factors for savanna and grassland, tropical forest, extratropical forest, biofuel burning, charcoal making, and agricultural fires
Austin *et al*. (2001b), Canada	Municipal	15 min	9	9	ppm		0.2	2	7 mixed occupancy buildings, one electronics industry, one 9-day smouldering fire
Isoprene									
Hill *et al*. (1972), UK	Training	Grab sample	–	1	ppm	0.167			Pool fire
Andreae & Merlet (2001), Germany	Wildland	Multiple	Multiple data sources	–	mg/kg[a]	[34 ± 36]			Means of published emissions factors for savanna and grassland, tropical forest, extratropical forest, biofuel burning, charcoal making, and agricultural fires
Lead									
Turkington (1984), USA	Municipal	10–15 min	1	1	mg/m^3	1.4			

Table 1.2 (contd)

Reference, location	Type of fire	Sampling period and duration	No. of fires	No. of samples	Units	Mean ± SD (*geometric mean, **median)	Min.	Max.	Comments
Bolstad-Johnson *et al*. (2000), USA	Municipal	> 20 min	25	46	mg/m^3	0.03	0.03	0.03	Overhaul lasting minimum 20 min
Naphthalene									
Hill *et al*. (1972), U.K.	Training	Grab sample	–	1	ppm	0.418			Pool fire
Kinnes & Hine (1998), USA	Municipal	TWA	5	5	µg/m^3		200	0.038	Arson investigation
Bolstad-Johnson *et al*. (2000), USA	Municipal	> 20 min	25	88	ppm	0.043 ± 0.019	0.014	0.103	Overhaul lasting minimum 20 min
Austin *et al*. (2001b), Canada	Municipal	15 min	9	9	ppm	0.62 ± 0.68	0.01	2.14	7 mixed occupancy buildings, one electronics industry, one 9-day smouldering fire
Austin *et al*. (2001c), Canada	Municipal (simulated)	Grab sample	15	60	ppm			3	In separate burns: wood (spruce), bed mattress, sofa foam, cardboard, plywood, gasoline, varsol, white foam insulation

Table 1.2 (contd)

Reference, location	Type of fire	Sampling period and duration	No. of fires	No. of samples	Units	Mean ± SD (*geometric mean, **median)	Min.	Max.	Comments
Particulate matter, PM_{10}									
Miranda *et al*. (2005), Portugal	Wildland	15 min average	1	–	mg/m^3	–	–	3.0	Near the fire
Particulate matter, respirable									
Kelly (1991), USA	Wildland	Shift	1	26	mg/m^3		0.040	4.3	Mop-up
NIOSH (1992), USA	Wildland	Shift	1	20	mg/m^3	0.49			Mop-up
Materna *et al*. (1992), USA	Wildland	Fireline TWA	5 fire seasons	22	mg/m^3	1.75	0.327	5.14	Project fires (1987–1989); mop-up
					mg/m^3		0.235	2.71	Prescribed burns
McMahon & Bush (1992), USA	Wildland	2.8 h	14		mg/m^3	1.3**	0.2	3.7	Prescribed burn
Reh & Deitchman (1992), USA	Wildland		1	3	mg/m^3		1.3	1.7	Medium smoke levels
Reh *et al.* (1994), USA	Wildland		1	3	mg/m^3		0.6	1.1	Low smoke levels

Table 1.2 (contd)

Reference, location	Type of fire	Sampling period and duration	No. of fires	No. of samples	Units	Mean ± SD (*geometric mean, **median)	Min.	Max.	Comments
Kinnes & Hines (1998), USA	Municipal	TWA	5	5	mg/m^3		ND	1.2	Arson investigation
Bolstad-Johnson *et al.* (2000), USA	Municipal	> 20 min	25	93	mg/m^3	8.01 ± 8.02	0.71	25.7	Overhaul lasting a minimum of 20 minutes
Reinhardt & Ottmar (2000), USA	Wildland	Shift TWA Fireline TWA Shift TWA Fireline TWA	NR	NR	mg/m^3 mg/m^3 mg/m^3 mg/m^3	0.5* ± 2* 0.7* ± 1.9* 0.022* ± 2.5* 1.11* ± 1.6*		2.3 2.9 1.6 2.5	Project fires (1992–1995) Initial attack (1992–1995)
Reinhardt *et al.* (2000); Slaughter *et al.* (2004), USA	Wildland	Shift TWA Fireline TWA			mg/m^3 mg/m^3	0.6* 1*		6.9 10.5	Prescribed burns (1991–1994)
Andreae & Merlet (2001), Germany	Wildland	NR	Multiple data sources	–	mg/kg^a	[7933 ± 3206]			Means of reported mean emissions factors for savanna and grassland, tropical forest, extratropical forest, biofuel burning, charcoal making, and agricultural fires

Table 1.2 (contd)

Reference, location	Type of fire	Sampling period and duration	No. of fires	No. of samples	Units	Mean ± SD (*geometric mean, **median)	Min.	Max.	Comments
Burgess *et al*. (2001), USA	Municipal	Overhaul > 25 min Overhaul > 25 min	7 9	24 19	mg/m^3	ND 6.180 ± 7.800			No respiratory protection SCBA used
Miranda *et al*. (2005), Portugal	Wildland	15 min average	1	NR	mg/m^3			3.0	Near the fire
Particulate matter, total									
Hill *et al*. (1972), U.K.	Training	Grab sample	NR	NR		–			Pool fire; 80% of particle with diameter < 1 μm
Gold *et al*. (1978), USA	Municipal	~10 min	–	90	mg/m^3	21.5* ± 4.7*	4	650	Knockdown and overhaul
Burgess *et al*. (1979); Treitman *et al*. (1980), USA	Municipal		–	66	mg/m^3		ND	20000	Inside burning structures during latter stages of structural fires (knockdown)
Turkington (1984), USA	Municipal	10-15 min	1	1	mg/m^3	36			–

Table 1.2 (contd)

Reference, location	Type of fire	Sampling period and duration	No. of fires	No. of samples	Units	Mean ± SD (*geometric mean, **median)	Min.	Max.	Comments
Atlas *et al*. (1985), USA	Training	During fire smoke	6	11	mg/m^3	47*	–		200 L of diesel oil floating on a pool of water
								300	Heavy smoke levels
			6	11	mg/m^3		0.15	0.5	
Froines *et al*. (1987), USA	Municipal	Shift	0	7	mg/m^3		0.035	0.48	Diesel emissions in firehalls (4 New York, 2 Boston, 4 Los Angeles)
		Shift	0	9	mg/m^3	0.748			
Brandt-Rauf *et al*. (1988), USA	Municipal	30 min	24	5	mg/m^3	83 ± 131	10.1	344	Mostly wood structures burning mostly building and contents
Duclos *et al*. (1990), USA	Wildland	12 days	1	NR	mg/m^3		0.578	4.158	
Jankovic *et al*. (1991), USA	Municipal		22	4	mg/m^3		ND	560	Knockdown
			22	25	mg/m^3		ND	45	Overhaul
Materna *et al*. (1992), USA	Wildland	Fireline TWA	6 fire seasons	22	mg/m^3	9.46	2.7	37.4	Project fires (1987–1989); mop-up
McMahon & Bush (1992), USA	Wildland	0.3–1.6 h	14		mg/m^3	6.3**	2	44.9	Prescribed burns

Table 1.2 (contd)

Reference, location	Type of fire	Sampling period and duration	No. of fires	No. of samples	Units	Mean ± SD (*geometric mean, **median)	Min.	Max.	Comments
Reh & Deitchman (1992), USA	Training		3	NR	mg/m^3		0.1	47.7	
Kinnes & Hine (1998), USA	Municipal	Peak TWA	5 5	5 5	mg/m^3 mg/m^3		3.5 0.2	31.6 5.3	Arson investigation
Bolstad-Johnson *et al*. (2000), USA	Municipal	> 20 min	25	46	mg/m^3	1.82 ± 8.73	0.364	30.79	Overhaul lasting a minimum of 20 min
Reinhardt *et al*. (2000), USA	Wildland	Shift TWA Fireline TWA Shift TWA Fireline TWA			mg/m^3 mg/m^3 mg/m^3 mg/m^3	1.5* ± 1.7* 1.7* ± 1.8* 1.39* ± 1.2* 5.32* ± 1.4*		4.2 4.4 1.81 8.64	Project fires (1992–1995) Initial attack (1992–1995)
Andreae & Merlet (2001), Germany	Wildland	Multiple	Multiple data sources	NR	mg/kg[a]	[10114 ± 4512]			Means of reported mean emissions factors for savanna and grassland, tropical forest, extratropical forest, biofuel burning, charcoal making, and agricultural fires

Table 1.2 (contd)

Reference, location	Type of fire	Sampling period and duration	No. of fires	No. of samples	Units	Mean ± SD (*geometric mean, **median)	Min.	Max.	Comments
Reisen *et al*. (2006), Australia	Wildland		6	21	mg/m^3	0.2– > 9		8–20	4 prescribed and 2 exceptional burns; p gravimetric: 2.6–5 mg/m^3 (*n* = 2)
Leonard *et al*. (2007), USA	Wildland	3.5 h	1	6					Mop-up and back burn operations; 20.2% ultrafine particles (0.042–0.24 µm mean diameter); 43.8% fine particles (0.42–2.4 µm mean diameter)
Pentachlorophenol									
Ruokojärvi *et al*. (2000), Finland	Municipal (simulated)	During fire During fire	5 2	5 2	µg/m^3 µg/m^3	53 ± 45 230 ± 99	14 160	104 300	Apartment without PVCs Apartment with PVCs
Polychlorinated biphenyls (Aroclor; 54%)									
Ruokojärvi *et al*. (2000), Finland	Municipal (simulated)	During fire During fire	5 2	5 2	µg/m^3 µg/m^3	21 ± 16 31 ± 35	2.8 6.1	36 56	Apartment without PVCs Apartment with PVCs
Polychlorinated dibenzodioxins									
PCDD									
Ruokojärvi *et al*. (2000), Finland	Municipal (simulated)	During fire During fire	5 2	5 2	ng/m^3 ng/m^3	43 ± 49 69 ± 5.7	12 75	130 83	Apartment without PVCs Apartment with PVCs

Table 1.2 (contd)

Reference, location	Type of fire	Sampling period and duration	No. of fires	No. of samples	Units	Mean ± SD (*geometric mean, **median)	Min.	Max.	Comments
PCDD/F as I-TEQ									
Ruokojärvi *et al*. (2000), Finland	Municipal (simulated)	During fire During fire	5 2	5 2	ng/m^3 ng/m^3	3.5 ± 2.5 5.4 ± 0.71	1 4.9	7.2 5.9	Apartment without PVCs Apartment with PVCs
PCDF									
Ruokojärvi *et al*. (2000), Finland	Municipal (simulated)	During fire During fire	5 2	5 2	ng/m^3 ng/m^3	96 ± 56 131 ± 24	21 114	160 148	Apartment without PVCs Apartment with PVCs
Polycyclic Aromatic Hydrocarbons									
Feunekes *et al*. (1997), Netherlands	Training	0.5–1.5 h	≥ 1	10	mg/m^3	10.68			Intense firefighting, black smoke
Ruokojärvi *et al*. (2000), Finland	Municipal (simulated)	During the fire During the fire	5 2	5 2	mg/m^3 mg/m^3	121 ± 199 117 ± 33	6.4 94	470 140	Apartment without PVCs Apartment with PVCs
Andreae & Merlet (2001), Germany	Wildland emissions	–	Multiple data sources	–	mg/kg^a	[21 ± 9]			Means of reported mean emissions factors for savanna and grassland, tropical forest, extratropical forest, biofuel burning, charcoal making, and agricultural fires

Table 1.2 (contd)

Reference, location	Type of fire	Sampling period and duration	No. of fires	No. of samples	Units	Mean ± SD (*geometric mean, **median)	Min.	Max.	Comments
Benz[*a*]anthracene									
Jankovic *et al*. (1991), USA	Municipal		3 3	3 3	mg/m^3 mg/m^3	0.015 0.001		0.03 0.003	Knockdown Overhaul
Kinnes & Hine (1998), USA	Municipal	TWA	5	5	mg/m^3		ND	0.00029	Arson investigation
Bolstad-Johnson *et al*. (2000), USA	Municipal	> 20 min	25	88	mg/m^3	0.0249 ± 0.0049	0.019	0.028	Overhaul lasting a minimum of 20 min
Benzofluoranthenes, unspecified									
Atlas *et al*. (1985), USA	Training	During fire	1 1	1 1	mg/m^3 mg/m^3	0.0124 0.00014			200 L of diesel oil floating on a pool of water Heavy smoke levels Very light smoke levels
Benzo[*b*]fluoranthene									
Jankovic *et al*. (1991), USA	Municipal		3 3	3 3	mg/m^3	0.006 ND		0.012	Knockdown Overhaul

Table 1.2 (contd)

Reference, location	Type of fire	Sampling period and duration	No. of fires	No. of samples	Units	Mean ± SD (*geometric mean, **median)	Min.	Max.	Comments
Kinnes & Hines (1998), USA	Municipal	TWA	5	5	mg/m^3		ND	0.00021	Arson investigation
Bolstad-Johnson *et al.* (2000), USA	Municipal	> 20 min	25	88	mg/m^3	0.0223 ± 0.0106	0.01	0.034	Overhaul
Benzo[*k*]fluoranthene									
Jankovic *et al*. (1991), USA	Municipal		3 3	3 3	mg/m^3 mg/m^3	0.003 0.001		0.006 0.004	Knockdown Overhaul
Kinnes & Hine (1998), USA	Municipal	TWA	5	5	mg/m^3		ND	0.00012	Arson investigation
Bolstad-Johnson *et al*. (2000), USA	Municipal	> 20 min	25	88	mg/m^3	0.0238 ± 0.0017	0.023	0.025	Overhaul
Benzo[*a*]pyrene									
Turkington (1984), USA	Municipal	10–15 min	1	1	mg/m^3	0.007			–

Table 1.2 (contd)

Reference, location	Type of fire	Sampling period and duration	No. of fires	No. of samples	Units	Mean ± SD (*geometric mean, **median)	Min.	Max.	Comments
Atlas *et al*. (1985), USA	Training	During fire	1	1	mg/m^3	0.00855	–		200 L of diesel oil floating on a pool of water.
								–	Very heavy smoke levels
		During fire	1	1	mg/m^3	4.5 x 10^{-5}			Very light smoke levels
Jankovic *et al*. (1991), USA	Municipal		3	3	mg/m^3	0.01		0.02	Knockdown
			3	3		ND			Overhaul
Feunekes *et al*. (1997), Netherlands	Training	0.5–1.5 h	≥ 1	10	mg/m^3	0.47			Intense firefighting; black smoke
Kinnes & Hine (1998), USA	Municipal	TWA	5	5	mg/m^3		ND	0.00039	Arson investigation
Bolstad-Johnson *et al*. (2000), USA	Municipal	> 20 min	25	88	mg/m^3	0.0332 ± 0.0136	0.019	0.05	Overhaul

Table 1.2 (contd)

Reference, location	Type of fire	Sampling period and duration	No. of fires	No. of samples	Units	Mean ± SD (*geometric mean, **median)	Min.	Max.	Comments
Chrysene									
Jankovic *et al*. (1991), USA	Municipal		3 3	3 3	mg/m^3 mg/m^3	0.01 0.001		0.02 0.003	Knockdown Overhaul
Bolstad-Johnson *et al*. (2000), USA	Municipal	> 20 min	25	88	mg/m^3	0.0129			Overhaul
Chrysene/triphenylene									
Atlas *et al*. (1985), USA	Training	During fire	1	1	mg/m^3	0.0181			200 L of diesel oil floating on a pool of water Very heavy smoke levels
		During fire	1	1	mg/m^3	0.00014			Very light smoke levels
Dibenzo[*a*,*h*]anthracene									
Jankovic *et al*. (1991), USA	Municipal		3 3	3 3	mg/m^3	0.003 ND		0.005	Knockdown Overhaul
Bolstad-Johnson *et al*. (2000), USA	Municipal	> 20 min	25	88	mg/m^3	0.0455 ± 0.0316	0.023	0.068	Overhaul

Table 1.2 (contd)

Reference, location	Type of fire	Sampling period and duration	No. of fires	No. of samples	Units	Mean ± SD (*geometric mean, **median)	Min.	Max.	Comments
Indeno-1,2,3-[*cd*]pyrene									
Jankovic *et al*. (1991), USA	Municipal		3	3	mg/m^3	0.01		0.02	Knockdown
Kinnes & Hine (1998), USA	Municipal	TWA	5	5	µg/m^3		ND	0.44–1.4	Arson investigation
Bolstad-Johnson *et al*. (2000), USA	Municipal	> 20 min	25	88	mg/m^3	0.0195 ± 0.0084	0.014	0.029	Overhaul
Radioactivity									
Volkerding (2003), USA	Wildland	2 days	1	4	Bq/m^3	–	2 x 10^{-4}	9 x 10^{-4}	α Emitters
			1	4	Bq/m^3	–	8 x 10^{-4}	0.004	β Emitters
			1	4	Bq/filter	–	ND	45.5	Bismuth-212
			1	4	Bq/filter	–	2.4	46.3	Lead-212
			1	4	Bq/filter	–	ND	17	Thallium-208
			1	4	Bq/m^3	–	ND	9.4	Uranium-234
			1	1	Bq/filter	–	–	0.002	Uranium-234

Table 1.2 (contd)

Reference, location	Type of fire	Sampling period and duration	No. of fires	No. of samples	Units	Mean ± SD (*geometric mean, **median)	Min.	Max.	Comments
Silica									
NIOSH (1992), USA	Wildland	Shift	1	10	mg/m^3		0.04	0.35	Mop-up
Styrene									
Hill *et al*. (1972), U.K.	Training	Grab sample	–	1	ppm	0.535			Pool fire
Andreae & Merlet (2001), Germany	Wildland emissions	Multiple	Multiple data sources	–	mg/kg[a]	[102 ± 96]			Means of reported mean emissions factors for savanna and grassland, tropical forest, extratropical forest, biofuel burning, charcoal making, and agricultural fires
Austin *et al*. (2001b), Canada	Municipal	15 min	9	9	ppm	0.5 ± 0.68	0.003	2.01	7 mixed occupancy buildings, one electronics industry, one 9-day smouldering fire
Austin *et al*. (2001c), Canada	Municipal (simulated)	Grab sample	15	60	ppm	detected		0.4	In separate burns: wood (spruce), bed mattress, sofa foam, cardboard, plywood, gasoline, varsol, white foam insulation

Table 1.2 (contd)

Reference, location	Type of fire	Sampling period and duration	No. of fires	No. of samples	Units	Mean ± SD (*geometric mean, **median)	Min.	Max.	Comments
Sulfuric acid									
Turkington (1984), 1984	Municipal	10–15 min	1	1	mg/m^3	28.5			–
Jankovic *et al*. (1991), USA	Municipal		22 22		mg/m^3 mg/m^3		ND ND	8.5 0.9	Knockdown Overhaul
Kinnes & Hine (1998), USA	Municipal	TWA	5	8	mg/m^3		0.08–0.27	0.29	Arson investigation
Burgess *et al*. (2001), USA	Municipal	Overhaul > 25 min Overhaul > 25 min	7 9	23 19	mg/m^3 mg/m^3	4.9 ± 8.5 13.6 ± 14.6			No respiratory protection SCBA used
Tetrachloroethylene (perchloroethylene)									
Brandt-Rauf *et al*. (1988), USA	Municipal	30 min	2	3	ppm	0.092 ± 0.04	0.064	0.138	Mostly wood structures burning (building and contents)
Trichloroethylene									
Brandt-Rauf *et al*. (1988), USA	Municipal	30 min	2	2	ppm	0.15	0.112	0.181	Mostly wood structures burning (building and contents)

Table 1.2 (contd)

Reference, location	Type of fire	Sampling period and duration	No. of fires	No. of samples	Units	Mean ± SD (*geometric mean, **median)	Min.	Max.	Comments
Trichloromethane (chloroform)									
Lowry *et al*. (1985a), USA	Municipal	At fire	75	–	–	detected			Mixed types of exposure
Brandt-Rauf *et al*. (1988), USA	Municipal	30 min	2	2	ppm	1.44	0.96	1.92	Mostly wood structures burning (building and contents)
Austin *et al*. (2001b), Canada	Municipal	15 min	9	9	ppm	detected			7 mixed occupancy buildings, one electronics industry, one 9-day smouldering fire
Austin *et al*. (2001c), Canada	Municipal (simulated)	Grab sample	15	60	ppm		25	465	In separate burns: wood (spruce), bed mattress, sofa foam, cardboard, plywood, gasoline, varsol, white foam insulation
Trichlorophenol									
Brandt-Rauf *et al*. (1988), USA	Municipal	30 min	1	1	ppm	0.1	0.1	0.1	Mostly wood structures burning (building and contents)

[a] emission factors
ESR, electron spin resonnance; LOD, limit of detection; LOQ, limit of quantitation; ND, Not Detected; SCBA, self-contained breathing apparatus

Thus, firefighters may be exposed to benzene levels exceeding the American Conference of Governmental Industrial Hygienists (ACGIH) 15-minute time-weighted average (15-min TWA) short-term exposure limit (STEL) of 2.5 ppm.

Two studies assessed 1,3-butadiene in smoke at structural and experimental fires (Austin *et al*., 2001b,c). Levels as high as 4.84 ppm were found at moments when at least some firefighters might remove their masks.

Formaldehyde levels measured in smoke at fires ranged from not detected to 15 ppm across studies (see Table 1.2).

One study measured pentachlorophenol at fires in simulated apartments with and without polyvinyl chloride (PVC) (Ruokojärvi *et al*., 2000). Levels of pentachlorophenol ranged from 14–160 μg/m^3 in those without PVC, and from 160–300 μg/m^3 in those with PVC.

Measurement of single specific PAHs at fires ranged from not detected to a maximum of 0.068 mg/m^3 for dibenzo[*a*,*h*]anthracene. In two studies, one of apartment fire simulations and one of training fires, measured total PAHs concentrations ranged from 6.4–470 mg/m^3 (Feunekes *et al*., 1997; Ruokojärvi *et al*., 2000).

Firefighter exposures to respirable particulate matter during overhaul rise to approximately 25 mg/m^3; levels of coarser particles range up to 20 000 mg/m^3 or higher (see Table 1.2). [In the case of wildland firefighters, reported results probably underestimated the actual exposures as these would have been collected during periods of low smoke levels.]

Exposures to VOCs are generally in the low ppm range for all categories of firefighters. [The results probably underestimated the exposures because they did not include the fraction adsorbed onto respirable smoke particles.] Austin *et al*. (2001b,c) found that although levels of total VOCs increased with time in fires burning solids, they decreased in time for fires burning liquids even though the levels of particulate matter increased. This suggests that a significant fraction of VOCs is adsorbed by the particulate matter and escapes detection when only the vapour phase is measured.

Overall, exposures of wildland firefighters to “low” levels of smoke appear to be comparable to those experienced by municipal firefighters during overhaul.

1.3.5 *Exposures to other agents*

(a) Asbestos

Asbestos used in constructions will be released during a fire in the form of fibres; asbestos sheets crack, sometimes disintegrating explosively, and more likely so if the sheet is worn or impregnated with resin (Hoskins & Brown, 1994). Chrysotile breaks down at 450–800 °C, and the amphiboles at 400–600 °C (Hoskins & Brown, 1994; Jeyaratnam & West, 1994). Thus, the denaturing of asbestos during fires may reduce exposure to asbestos fibres.

Table 1.3. Summary of reported concentrations of chemicals during firefighting operations (ranges or means)

Chemical	Units	Wildland	Municipal	Training	Arson investigation
Acetaldehyde	ppm	ND–0.26	ND–8.1	–	0.13[b]
Asbestos	f/cm^2		2.7[a]	0–2.3[d]	
Arsenic	mg/m^3	–	0.14[a]	–	–
Benzene	ppm	0.004[a]–0.38	0.07–250	1.17[a]	< 0.12[b]
Benzofuran	ppm	–	0.2–2	–	–
1,3-Butadiene	ppm	–	0.03–4.84	–	–
Cadmium		–	ND	–	–
Polychlorinated dibenzodioxins	ng/m^3	–	12–148	–	–
I-TEQs	ng/m^3	–	1–7.2	–	–
Dichloromethane	ppm	–	0.28[a]	–	–
Ethyl benzene	ppm	–	0.01–5.97	0.38[a]	–
Formaldehyde	ppm	0.01–0.79	ND–15	–	0.06–0.18
Free radicals					
Furan	ppm	–	0.2–2	–	–
Isoprene	ppm	–	–	0.167[a]	–
Lead	mg/m^3	–	0.03[a]	–	–
Naphthalene	ppm	–	0.01–2.14	0.418[a]	30–200mg/m^3
PM_{10}	mg/m^3	3.0[b]	–	–	–
PM respirable	mg/m^3	0.02[c]–10.5	ND–25.7	–	ND–1.2
PM total	mg/m^3	0.2[a]–44.9	ND–650	0.1–300	0.2–31.6
Knockdown only			ND–20 000		
Overhaul only			ND–45		
Pentachlorophenol	µg/m^3	–	14–300	–	–
Polycyclic aromatic hydrocarbons	mg/m^3	–	6.4–470	10.68[a]	–
Polychlorinated biphenyls	µg/m^3	–	2.8–56	–	–
Silica	mg/m^3		0.04–0.35		
Styrene		–	0.003–2.01	0.535[a]	–
Sulfuric acid		–	ND–28.5	–	0.29[b]
Tetrachloroethylene		–	0.064–0.138	–	–
Trichloroethylene		–	0.112–0.181	–	–
Trichloromethane		–	0.96–465	–	–
Trichlorophenol		–	0.1[a]	–	–

[a] mean; [b] maximum; [c] geometric mean; [d] from helmets and fumes of firefighters; ND, not detected

During a leather factory fire in Merseyside, United Kingdom, in 1994, most of the fallout arose from asbestos bitumen roof paper containing roughly 50% chrysotile (Bridgman, 2001). A low number of asbestos fibres were found on firefighter tunics (0.0029 f/cm^3; range 0.0011–0.0043 f/cm^3), and none was found on the firefighters' raincoats or policemen's uniforms. [A fire hose spray may have washed out airborne asbestos.]

Thermal protective clothing, gloves and helmets that contain asbestos usually contain chrysotile asbestos. In the United Kingdom the helmet covers for navy firefighters, which completely enclose their head and shoulders, used to be made of chrysotile asbestos (Lumley, 1971). Breathing zone samples from users of both new and old helmets with unlined asbestos cloth covers were analysed and had fibre concentrations of 2.30 f/cm^3 and 1.38 f/cm^3, respectively (Lumley, 1971).

(b) Polychlorinated biphenyls, polychlorinated dibenzofurans and polychlorinated dibenzodioxins

Synthetic dielectric (non-conducting) fluids are known as askarels. Firefighters may be exposed to PCBs at fires involving PCB-askarel filled transformers and capacitors (Hutzinger *et al*., 1985). When askarels burn, copious quantities of oily black soot are produced with very little fire. Where only PCBs are involved, polychlorinated dibenzofurans (PCDFs) are produced as combustion products. In transformers containing a mixture of PCB-askarel and polychlorobenzenes (PCBz), in addition to PCDFs, polychlorinated dibenzodioxins (PCDDs) combustion products are produced from the PCBz (Buser, 1985). PCDFs and PCDDs might also arise from *de novo* synthesis under certain conditions. PCDFs and PCDDs were reported to have been released from a house fire where a 50 lb [23 kg] container of hypochlorite and two gallons [7.6 L] of hydrochloric acid were stored for swimming pool maintenance along with paint thinners and solvents (Rao & Brown, 1990). Other sources of PCBs at fires may include fluorescent light ballasts, PCB-containing mastic, adhesives, duct liners, and fibreglass insulation wrap used in previous decades (Kominsky, 2000). Total 2,3,7,8-tetrachlorodibenzodioxin (TCDD) equivalent (TEQ) levels were 0.24 ppb in a basement soot sample and 0.39–0.75 ng/m^2 in two wipe samples.

PCB concentrations in wipe samples following a fire in a high rise office building were reported to be 7.1–151 µg/m^2 (range, < 1–87610 µg/m^2) (Kominsky, 2000). Debris from a chemical storage vault fire contained 100–750 ppm PCBs, and 2000 ppm PCBs was found in the lubricating grease from the air-handling units (CDC-MMWR, 1987). No PCBs were stored in the storage vault. The source of the PCBs was the paint that coated the surface of the ceiling tiles (15 300–51 000 ppm PCBs).

The use of PCBs in electrical equipment and its effect on some of the numerous fire-related incidents that have occurred in the USA and in Sweden have been reviewed by NIOSH (1986) and Rappe *et al*. (1985a), respectively. A PCB/PCBz-filled transformer fire occurred at the Binghamton State Office Building, New York, USA, in 1981 (O'Keefe *et al*., 1985). Levels of 2,3,7,8-TCDF and 2,3,7,8-TCDD in a

soot sample collected following the fire were 12 ppm and 0.6 ppm, respectively (Buser, 1985). The analysis of soot collected following a capacitor fire at a power station in Finland revealed 3 ppm of 2,3,7,8-TCDF (Buser, 1985). In an earlier study, the replicate concentrations of 2,3,7,8-TCDF and 2,3,7,8-TCDD in a composite soot were 273 and 124 ppm, and 2.8 and 2.9 ppm, respectively (Smith *et al*., 1982).

Firefighter thermal protective clothing can be contaminated with PCBs following fires involving PCBs. In one report, tests revealed 2.7–72 µg PCB/g of clothing following a fire (Kominsky & Melius, 1983). Following the Staten Island fire in the USA, gloves, outer coat sleeves, and outer pants contained peak PCB concentrations of 4 050 000 pg/100 cm^2, 56100 pg/100 cm^2, and 116 000 pg/100 cm^2, respectively (Kelly *et al*., 2002). Overalls and underwear used following the Surahammar fire in Sweden were washed every day (Rappe *et al*., 1985b). After 14 days of use, overalls were analysed and contained 28 ng/m^2 of 2,3,7,8-TCDF, and approximately 100 ng/m^2 all TCDFs combined. Similar levels were found after 1 month of use.

(c) Diesel and gasoline exhaust

Firefighters may be exposed to diesel/gasoline exhaust when vehicles exit and return to the firehall. In a study of diesel emissions in firehalls, shift mean personal measurements of total particulate matter were 0.035–0.48 mg/m^3 (worst-case scenario 0.748 mg/m^3) (Froines *et al*. 1987). [The sampling equipment was removed during the period of highest concentration of diesel exhaust, thereby underestimating actual exposures]. Background ambient particulate matter from ambient aerosol, smoking, and cooking was approximately 0.040 mg/m^3.

Mechanical systems have been available to fire departments since the early 1990s to divert the engine exhaust to the outside of the building (Peters, 1992).

Firefighters are also exposed to diesel emissions from response vehicles that remain running at the fire scene. Firefighters may be positioned near these vehicles during command operations, operation of pumps, when working in defence mode, and during rest breaks.

Firefighters may be exposed to diesel/gasoline exhaust during the operation of vehicles and gasoline-powered hand tools at both structural and wildland fires. No particular methods are used to reduce these exposures. In addition, wildland firefighters are exposed to vapours and combustion products from drip torches used when setting back fires.

(d) Shiftwork

Depending on the jurisdiction, firefighters may work 10-hour dayshifts and 14-hour night shifts, 24-hour or 48-hour shifts. However, given the low frequency of fires over a year, at least in North America, firefighters are often able to sleep at the firehall during the entire night.

(e) Others

Firefighters may be exposed to agents stored, manufactured, or otherwise present at the scene of fire, particularly in factories. Examples are exposure to 2-nitroanisole (Hengstler *et al*., 1995), and to toluene diisocyanate (Axford *et al*., 1976) (see Table 1.1).

In many cases, firefighters hold down a second job where they may also be exposed to other agents.

1.4 Biomarkers of exposure

New York City firefighters responded to a Staten Island transformer fire in 1998 in the USA. Exposed firefighters exhibited mean fasting blood serum PCB levels of 2.92 ± 1.96 ppb (range 1.9–11.0 ppb; $n = 58$) 2–3 weeks following exposure (Kelly *et al*., 2002). Mean levels of serum 2,3,7,8-TCDF, 2,3,7,8-TCDD, and TEQ were 0.20 pg/g (SD 0.69; range ND–2.78; $n = 60$), 3.77 (SD 4.16; range ND–13.4; $n = 60$), and 39.0 pg/g (SD 21.53; range 8.77–120.63; $n = 60$).

In a study of firefighters in Toronto, Canada, firefighters were exposed to low levels of smoke. Self-contained breathing apparatus was consistently used during knockdown, less consistently during overhaul, and intermittently during external firefighting activities. All urine produced during the 20 hours following the end of exposure was collected. Only two of 43 subjects were smokers. Ranges of urinary *trans,trans*-muconic acid levels in firefighters who were present at fires during knockdown only, during overhaul only, and during both knockdown and overhaul ranged from not detected to 2.82 mmol/mol creatinine ($n = 5$), to 1.12 mmol/mol creatinine ($n = 8$), and to 1.06 mmol/mol creatinine ($n = 24$), respectively (Caux *et al*., 2002). The only two firefighters who wore their masks at all times had no measurable urinary *trans,trans*-muconic. Levels of urinary 1-hydroxypyrene were 0.12 µmol/mol creatinine (range 0.05–0.19; $n = 5$), 0.23 µmol/mol creatinine (range 0.11–0.34; $n = 8$), and 0.38 and µmol/mol creatinine (range 0.08–3.63; $n = 24$), for the three groups respectively. There was no relationship between measured levels of urinary *trans,trans*-muconic acid and 1-hydroxypyrene.

One study was conducted following the September 11th, 2001, attack of the World Trade Center in New York City, USA (Edelman *et al*., 2003). Blood and urine samples were collected from firefighters 20 days following the attack. Table 1.4 presents adjusted geometric means of concentrations of the chemicals detected in blood and/or urine. The maximum levels of blood mercury found in firefighters following the attack were < 1.7 µg/L blood. Elevated total mercury levels > 20 µg/L blood in one control and 3 exposed firefighters represented organic mercury contributions from dietary sources (e.g. fish).

Table 1.4. Blood and urinary levels in firefighters 20 days following the World Trade Center attack in 2001

Agent	Matrix	Unit	Controls (n = 318)	Special command (n = 95)	Other (n = 195)
1,4-Dichlorobenzene	Blood	µg/L	0.165	0.343*	0.231
m-/*p*-Xylene	Blood	µg/L	0.051	0.081*	0.057
Cadmium	Urine	µg/L	0.377	0.351	0.303
Lead	Blood	µg/L	1.93	3.77*	2.43*
	Urine	µg/L	1.01	1.77*	0.96
Uranium	Urine	µg/L	0.00752	0.00610	0.00607
HCDBD	Lipid	pg/g	19.2	30.6*	25.9*
1-Hydroxypyrene	Urine	ng/L	62.5	159*	77.9

*Significantly elevated compared to the controls, $P < 0.01$
HCDBD, heptachlorodibenzodioxin

1.5 Respiratory protection

1.5.1 *Evolution of respiratory protection and protection factors*

In prior decades, firefighters were known as "smoke eaters." However, respiratory protection devices for firefighters have existed for over a century. Early US patented devices included air purifying respirators using charcoal to remove toxic gases and vapours (e.g. Guillemard, 1920), and carbon monoxide (e.g. Loeb, 1893), and self-contained breathing apparatus that supplied air to the user (e.g. Hurd, 1889). Air purifying respirators and self-contained breathing apparatus in use today have improved designs, but the basic principles are the same. Modern positive-pressure type self-contained breathing apparatus with a protection factor of 50 to more than 100 came into more widespread use during the 1960s and 1970s (Hyatt, 1976). These were replaced shortly thereafter with pressure-demand type self-contained breathing apparatus with a protection factor of 10 000 (Hyatt, 1976). Pressure-demand self-contained breathing apparatus are commonly used today by municipal firefighters.

1.5.2 *Efficacy of respiratory protection*

Pressure-demand self-contained breathing apparatus have been determined to be adequate in a firefighter risk assessment given the levels of fire atmosphere contaminants reported in the literature (Burgess & Crutchfield, 1995a,b). In these studies, 50 of

51 firefighters (98%) achieved a protection factor exceeding 10 000; estimates of worst case scenarios yielded a protection factor of 4600.

In 1978, firefighters in Scotland, United Kingdom, reportedly used self-contained breathing apparatus routinely at residential fires (Symington *et al*., 1978). There were no significant differences found in cyanide or thiocyanate levels between these firefighters ($n = 94$) and controls, suggesting that the breathing apparatus used offered adequate protection against hydrogen cyanide.

There is currently no respiratory protection standard for wildland firefighters. One bottle of compressed air used with a self-contained breathing apparatus lasts approximately 15–30 minutes, so self-contained breathing apparatus are not an option for wildland firefighters who work extended shifts at fires for consecutive days or weeks. The only other options are administrative controls to reduce exposure, or the use of air purifying respirators. Air purifying respirators have recently been evaluated for use by firefighters (De Vos *et al*., 2006; Anthony *et al*., 2007). In some jurisdictions, such as Australia, wildland firefighters use negative-pressure air purifying respirators (De Vos *et al*., 2006). In many others, such as in Canada and the USA, wildland firefighters generally do not use any form of respiratory protection (Austin & Goyer, 2007).

1.5.3 *Prevalence of use of self-contained breathing apparatus*

Firefighters tend to use their masks "when they see smoke." In the past, there was some avoidance of the use of respiratory protection (Guidotti, 1992); over the years, firefighters have become much more health and safety conscious.

There are several other reasons why firefighters might be reluctant to use respiratory protection. These include the added physiological demands and heat stress placed upon the user, the difficulty in communicating while wearing a mask, and the desire to conserve air. However, several studies have demonstrated that firefighters are not able to visually assess the level of contamination. A study in Boston, USA, found no clear patterns or trends that would allow firefighters to predict the levels of smoke contaminants to which they were exposed (Burgess *et al*., 1979). In one study, a firefighter who was working without a respirator because he believed that his exposure was insignificant was actually exposed to 27 000 ppm of carbon monoxide (Burgess *et al*., 1977), 680 times the current ACGIH Treshold Limit Value (TLV, 25 ppm). Results of other studies also suggest that structural firefighters cannot estimate levels of smoke contaminants (Brandt-Rauf *et al*., 1988, 1989).

A "Mandatory Mask Rule" was fully implemented in 1977 at the Boston fire department requiring all firefighters to wear respiratory protective equipment before entering a building for firefighting operations. The mask is not to be removed until after knockdown and after the building has been thoroughly ventilated (Paul, 1977).

Since the introduction of modern self-contained breathing apparatus in the fire service, the lack of standard operating procedures (SOPs) mandating the use of respiratory protection equipment or the failure to enforce existing SOPs have resulted

in them not being used appropriately. Even where masks are consistently used during knockdown, they are usually not used or used inconsistently during overhaul.

In a study in West-Haven, CT, USA, half of the firefighters (eight of 16) involved in structural fires did not use breathing apparatus (Loke *et al*., 1976). In Washington DC, USA, the frequency of wearing masks during knockdown was: always (36%); very often (36%); never or seldom (5%). During overhaul, 62% never or seldom wore masks (Liou *et al*., 1989). A NIOSH study of different fire departments in the USA (Pennsylvania Fire Training Academy, Pittsburgh Bureau of Fire, New York City, Phoenix, Boston, and Cincinnati) found that 70% of municipal firefighters wore their self-contained breathing apparatus masks less than 100% of the time, and one third used them less than 50% of the time during knockdown (Jankovic *et al*., 1991). In Sweden, only four of nine volunteer firefighters surveyed reported having used protective equipment while fighting fires within the previous 3 months (Bergström *et al*., 1997). In a 1993–1994 study of Montreal firefighters, the storage and distribution of all compressed breathing air was tracked and records kept of the time and place of all cylinders, including initial and final pressures along with records of firefighter assignments and alarms. The authors concluded that respiratory protection was used for approximately 50% of the time at structural fires, but for only 6% of the time at all types of fires combined (Austin *et al*., 2001a). In Toronto, Canada, firefighters "reported consistent usage of self-contained breathing apparatus during knockdown activities inside structures, less consistent usage throughout internal overhaul activities, and intermittent usage during external fire fighting activities" (Caux *et al*., 2002). In a study in Phoenix and Tucson, AZ, respiratory protection was used during entry/ventilation for 86–95.4% and 74–91.7% of the time, respectively. During overhaul, Phoenix and Tucson firefighters used respiratory protection for 38% and 46.2% of the time, respectively (Burgess *et al*., 2003).

1.6 Regulations and guidelines

Table 1.5 presents occupational exposure limits for selected chemicals to which firefighters are exposed. Occupational exposure limits have been developed for workers generally exposed to single substances and engaged in light levels of work. Firefighters are exposed to a complex mixture of toxic combustion and pyrolysis products while engaged in very high workloads. Also, given the intermittent nature of the exposures, determination of TWAs will result in calculated exposures far below the established TLVs for different substances. In addition, this does not take into account peak exposures and possible synergistic effects of multiple, potential toxicants. Biomonitoring overcomes some of these difficulties and takes into account the use of respiratory protection.

Table 1.5. Regulations and guidelines for the chemicals measured in smoke at fires presented in Table 1.2 (ACGIH, 2007)

Chemicals measured at fires	Units	BEI		TLV/TWA		STEL		Ceiling	Permitted excursion	Maximum excursion
		ACGIH	EU	ACGIH	EU	ACGIH	EU	ACGIH	ACGIH	ACGIH
Arsenic	mg/m^3	Yes		0.01		–		–	0.03	0.05
Asbestos	f/cm^3	–		0.1	0.1	–		–	0.3	0.5
Acetaldehyde	ppm	–		–		–		25	–	25
Benz[*a*]anthracene	mg/m^3			–		–		–		
Benzene	ppm	Yes	Yes	0.5	1	2.5		–	–	–
Benzo[*a*]pyrene	mg/m^3									
1,3-Butadiene	ppm	Yes		2		–		–	6	10
Cadmium	mg/m^3	Yes		0.01		–		–	0.03	0.05
Carbon black (total)	mg/m^3	–	Under discussion	3.5	Under discussion	–	Under discussion	–	10.5	17.5
Dichloromethane (methylene chloride)	ppm	Yes		50	Under discussion	–		–	150	250
Ethylbenzene	ppm	Yes		100	100	125	200	–	–	–
Formaldehyde	ppm	–			Under discussion	–		0.3	–	–
Furan/tetrahydrofuran	ppm	–		–	50	–	100	–	–	–
Isoprene	ppm	–		–		–		–	–	–
Lead	mg/m^3	Yes		0.15	0.15	–		–	0.45	0.75
Naphthalene	ppm	–		10	10	15		–	–	–
Particulate matter (respirable)	mg/m^3	–		3		–		–	9	15
Particulate matter (total)	mg/m^3	–		10		–		–	30	50
Pentachlorophenol	µg/m^3	Yes		0.5						
Polychlorinated biphenyls (Aroclor; 54%) (Chlorodiphenyl)	µg/m^3	–		0.5		–		–	1.5	2.5
Polycyclic Aromatic Hydrocarbons	mg/m^3	Yes		0.2		–		–	0.6	1.0

Table 1.5 (contd)

Chemicals measured at fires	Units	BEI		TLV/TWA		STEL		Ceiling	Permitted excursion	Maximum excursion
		ACGIH	EU	ACGIH	EU	ACGIH	EU	ACGIH	ACGIH	ACGIH
Styrene	ppm	Yes		20		40		–	–	–
Sulfuric acid	mg/m^3	–		0.2	Under discussion	–		–	–	–
Tetrachloroethylene (Perchloroethylene)	ppm	Yes		25	Under discussion	100.0			–	–
Trichloroethylene	ppm	Yes		10	Under discussion	25.0		–	–	–
Trichloromethane (chloroform)	ppm	–		10	2	–		–	30	50
Trichlorophenol	ppm	–		–		–		–	–	–

ACGIH, American Conference of Governmental Industrial Hygienists; BEI, Biological Exposure Index; EU, European Union; STEL, short-term exposure limit; TLV, Threshold Limit Value.

1.7 References

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2. Studies of Cancer in Humans

2.1 Cohort studies (Tables 2.1 and 2.2)

Among municipal firefighters, five studies evaluated the incidence of cancer and 15 assessed mortality – some with multiple reports. None of these was adjusted for smoking, or other potential confounders.

Mastromatteo (1959) conducted a cohort mortality study of all firefighters employed with the city fire department in Toronto, Ontario, Canada during 1921–1953. The cohort consisted of 1039 active and retired firefighters. A total of 325 firefighters (31%) were lost to follow-up. The followed cohort accrued 25 918 person–years of observation; 271 deaths were recorded. Causes of death were determined by the examination of death certificates. Comparison was made to age-specific death rates for the Province of Ontario. Because most of the firefighters were urban dwellers, the author calculated death rates for the City of Toronto. There was no excess mortality from cancer at all sites combined (34 observed, 30 expected), and no site-specific analysis of cancer mortality.

Musk *et al.* (1978) conducted a cohort mortality study in 5655 firefighters with three or more years of service in Boston, USA, during 1915–1975. Firefighters were identified from employment records. The observed cause of death as stated on the death certificates of 2470 deceased firefighters was compared with expected numbers based on rates for the male population of Massachusetts. Cancer risks were only presented by organ system, and no statistically significant increases were seen.

Eliopulos *et al.* (1984) conducted a cohort mortality study of all males employed as full-time firefighters by the Western Australian Fire Brigade during 1939–1978. The cohort consisted of 990 male firefighters and follow-up was 98.3% complete through examination of death certificates. The cohort accrued a total of 16 876 person–years of follow-up; 116 deaths were recorded. Mortality from all causes was less than expected (standardized mortality ratio [SMR], 0.80; 95% confidence interval [CI]: 0.67–0.96). For those firefighters already employed at the study start date, mortality was a little higher (SMR, 0.84) than for those who started later (SMR, 0.74). There was no tendency for rates to rise with increasing duration of employment. SMR for all malignancies was 1.09 (95% CI: 0.74–1.56). Standardized proportional mortality ratios (SPMRs) were calculated for cancers, primarily by organ system, and no statistically significant excesses were seen.

Vena and Fiedler (1987) examined all full-time employees of the City of Buffalo, USA, who worked at least 5 years during 1950–1979. A total of 1867 Caucasian male firefighters employed for at least one year as a firefighter were studied.

Table 2.1 Overview of cohort studies of firefighters

Reference	Location	Outcome, Design	Study Period	Number of Workers	Exposure Surrogates Used
Mastromatteo (1959)	Toronto, Canada	Mortality (SMR)	1921–1953	1039	None
Musk *et al.* (1978)	Boston, USA	Mortality (SMR)	1915–1975	5655	None
Eliopulos *et al.*, (1984)	Australia	Mortality (SMR, SPMR)	1939–1978	990	None
Vena & Fiedler (1987)	Buffalo, USA	Mortality (SMR)	1950–1979	1867	Duration of employment
Heyer *et al.* (1990)	Portland, USA Seattle, USA	Incidence (SIR) Mortality (SMR)	1974–1989 1945–1980	2447 2289	Duration of firefighting Duration of employment
Beaumont *et al.* (1991)	San Francisco, USA	Mortality (SMR)	1940–1970	3066	Duration of employment
Grimes *et al.* (1991)	Honolulu, USA	Proportionate Mortality	1969–1988	205	None
Demers *et al.* (1992a; 1992b; 1994)	Seattle, Tacoma, USA	Mortality (SMR) 1992a Mortality (SMR) 1992b Incidence (SIR) 1994	1944–1979 1944–1979 1974–1989	4546 4528 2447	
Giles *et al.* (1993)	Western Australia	Incidence (SIR)	1980–1989	2865	None
Guidotti (1993)	Calgary, Edmonton, Canada	Mortality (SMR)	1927–1987	3328	Duration of firefighting
Aronson *et al.* (1994)	Toronto, Canada	Mortality (SMR)	1950–1989	5995	Duration of employment
Tornling *et al.* (1994)	Stockholm, Sweden	Mortality (SMR) Incidence (SIR)	1931–1983	1153	Duration of employment Number of runs
Deschamps *et al.* (1995)	Paris, France	Mortality (SMR)	1977–1991	830	None
Baris *et al.* (2001)	Philadelphia, USA	Mortality (SMR)	1925–1986	7789	Duration of employment Number of runs Company type engine, ladder

Table 2.1 Overview of cohort studies of firefighters

Reference	Location	Outcome, Design	Study Period	Number of Workers	Exposure Surrogates Used
Bates *et al.* (2001)	New Zealand	Mortality (SMR) Incidence (SIR)	1977–1995	4221	Duration of employment
Ma *et al.* (2005)	Florida, USA	Mortality (SMR) Incidence (SIR)	1972–1999 1981–1999	36 813	None
Ma *et al.* (2006)	Florida, USA	Mortality (SMR) Incidence (SIR)	1972–1999 1981–1999	222 4528	None

Adapted from LeMasters *et al*. (2006)

Vital status was determined for 99% of the cohort, resulting in 470 observed deaths. Significantly elevated SMRs were found for benign neoplasms (SMR, 417), cancer of the colon (SMR, 183), and cancer of the bladder (SMR, 286). Cause-specific mortality was presented by the number of years employed, calendar year of death, year of hire, and latency. Cancer mortality was significantly higher in the long-term firefighters, and risk of mortality from all malignant neoplasms tended to increase with increasing latency. Statistically significant excesses of colon and bladder cancer were observed among firefighters employed for 40 or more years.

Beaumont *et al.* (1991) calculated mortality rates for 3066 firefighters employed during 1940–1970 at the San Francisco Fire Department, USA. Vital status was ascertained through to 1982, and observed and expected rates were computed using United States death rates. About 3% of the population was lost to follow-up. Mortality was examined by duration of employment as a firefighter. The total number deceased (1186) was less than expected (risk ratio [RR] = 0.90), and there were fewer cancer deaths than expected (RR = 0.95). However, there were significant excess numbers of deaths from oesophageal cancer (12 observed, six expected). A statistically significant excess of biliary and related cancer was observed among firefighters employed for 30 or more years.

Grimes *et al.* (1991) conducted a proportionate mortality study involving all male firefighters with at least one year of service in the fire department of the City of Honolulu, USA. The observed percentage of firefighter deaths from each cause from 1969–1988 was compared statistically to the expected numbers of deaths for all males aged over 20 years in Hawaii's general population. The proportionate risk ratio (PRR) for all malignant neoplasms was 1.19 (95% CI: 0.96–1.49). Significant increases in risk of death were found for brain cancer (PRR, 3.78), prostate cancer (RR, 2.61), and cirrhosis of the liver (PRR, 2.3). [The Working Group noted that it does not appear as though PRRs were standardized by age and calendar period as is standard practice for this type of analysis.]

Heyer *et al.* (1990) examined the mortality among 2289 firefighters from Seattle, Washington, USA employed during 1945–1980. Subsequently, Demers *et al.* (1992a) examined the mortality of 4546 firefighters who were employed by the cities of Seattle and Tacoma (Washington, USA), and Portland (Oregon, USA) for at least one year during 1944–1979. Demers *et al.* (1992b) also examined the cancer incidence in 4528 firefighters from Seattle and Tacoma during 1944–1979. Mortality in these firefighters was compared to United States national mortality rates and to mortality rates of police officers from the same cities. Mortality was examined by the duration of employment as a firefighter (i.e., actually controlling fires) rather than as an inspector or a support person. This mortality was then compared to a reference group of police from the same cities. Complete follow-up was achieved for 98% of the firefighters. During 1945–1989 (the cohort was the same as Demers *et al.* [1992a] but the follow-up lasted until 1989), 1169 deaths occurred in the study population, and 1162 death certificates (99%) were collected. There was no excess risk of overall

mortality from cancer. Excesses of brain tumours (SMR, 2.1; 95% CI: 1.2–3.3) and lymphatic and haematopoietic cancers (SMR, 1.3; 95% CI: 0.9–1.8) were found. Younger firefighters (< 40 years of age) showed an excess risk of cancer (SMR, 1.45; 95% CI: 0.8–2.39), primarily due to brain cancer (SMR, 3.75; 95% CI: 1.2–8.7). The risk of lymphatic and haematopoietic cancers was greatest for men with at least 30 years of exposed employment (SMR, 2.1; 95% CI: 1.1–3.6), especially for leukaemia (SMR, 2.6; 95% CI: 1.0–5.4).

Demers *et al.* (1994) further examined the incidence of cancer in a subcohort of 2447 male firefighters who were employed for at least one year during 1945–1979 in Seattle and Tacoma, who were still alive on January 1st 1974. Incident cancer cases were ascertained through the Cancer Surveillance System of the Fred Hutchinson Cancer Research Center, a population-based tumour registry. The follow-up period was from 1974 to 1989. Cancer incidence in firefighters was compared with local rates and with the incidence among 1878 policemen from the same cities. The overall risk of cancer among firefighters was found to be similar to that of both the police (SIR, 1.0; 95% CI: 0.8–1.3) and the general male population (SIR, 1.1; 95% CI: 0.9–1.2). No excesses were observed for the most common organ sites. An elevated risk of prostate cancer was observed relative to the general population (SIR, 1.4; 95% CI: 1.1–1.7), but was less elevated compared with rates in policemen (incidence density ratio [IDR], 1.1; 95% CI: 0.7–1.8), and was not related to duration of exposure. The risk of colon cancer, although only slightly elevated relative to that of the general population (SIR, 1.1; 95% CI: 0.7–1.6) and the police (IDR, 1.3; 95% CI: 0.6–3.0), appeared to increase with duration of employment.

Giles *et al.* (1993) conducted a cancer incidence study of 2855 male firefighters employed by the fire brigade in Melbourne, Australia, during 1917–1988. All were operational personnel, who would more than likely have been called to combat fires. The follow-up period was from 1980 to 1989, and was estimated to have been 95% complete. To determine cancer incidence during the follow-up period, fire brigade employment records were linked to the Victorian Cancer Registry. SIRs were calculated by the direct method using the population of the State of Victoria as the reference group. The cohort accrued a total of 20 853 person–years, and 50 firefighters developed cancer during the period of observation. The SIR for all cancer sites and all ages combined was 1.13 (95% CI: 0.84–1.48). For firefighters under the age of 65 years, the all-site SIR was 0.84 (95% CI: 0.56–1.20); for those above 65 years of age, the all-site SIR was 2.14 (95% CI: 1.32–2.37). The only site-specific cancer that was elevated in the age group of 65 and older was colorectal cancer, with an SIR of 3.65 (95% CI: 1.13–7.94). The SIR for all other cancers in the age group 65 and above after removing colorectal cancer remained elevated, with a residual SIR of 1.83 (95% CI: 1.03–3.02).

Guidotti (1993) examined the mortality by cause of death for two cohorts totaling 3328 firefighters active during 1927–1987 in Edmonton and Calgary, Alberta, Canada. Associations were examined by cohort (before and after the 1950s) and by

years of service weighted by exposure opportunity. The study attained 96% follow-up of vital status and over 64 983 person–years of observation; 370 deaths were recorded. Excesses were observed for all malignant neoplasms (SMR, 1.3; 95% CI: 1.0–1.6), and for cancers of the lung (SMR, 1.4; 95% CI: 0.9–2.1), bladder (SMR, 3.2; 95% CI: 0.9–8.1), kidney and ureter (SMR, 4.1; 95% CI: 1.7–8.5), colon and rectum (SMR, 1.6; 95% CI: 0.9–2.7), pancreas (SMR, 1.6; 95% CI: 0.5–3.6), and leukaemia, lymphoma and myeloma (SMR, 1.3; 95% CI: 0.6–2.3). The lung cancer excess was confined to Edmonton; there was no consistent association with duration of employment, exposure opportunity, or decade of entry into the cohort (before or after the 1950s) except that the highest risk was observed among Edmonton firefighters with over 35 weighted years of service. Urinary tract cancer excess was observed mostly among firefighters entering service after 1950, and appeared to increase with the length of service and exposure opportunity, and was observed in both cities.

Aronson *et al.* (1994) conducted a retrospective cohort mortality study of all male employees of the six fire departments within metropolitan Toronto, Ontario, Canada (n = 5995). The study population consisted of all male firefighters who had worked for at least 6 full months in metropolitan Toronto at any time during 1950–1989. Mortality was ascertained through computerized record linkage and compared to that of the male Ontario population specific to cause, age, and calendar period during 1950–1989. The cohort accrued 114 008 person–years and the average duration of follow-up was 21 years. Mortality was examined by duration of exposure. The SMR for all malignant neoplasms was 105 (95% CI: 91–120), for brain tumours, 201 (95% CI: 110–337), and for “other” malignant neoplasms, 238 (95% CI: 145–367). Non-significant increases in risk were observed for some other sites, in particular rectum (SMR, 171), larynx (SMR, 140), and testis (SMR, 252).

Tornling *et al.* (1994) conducted a cohort mortality study of all male fire fighters employed for at least 1 year in the City of Stockholm, Sweden during 1931–1983 (n = 1116). The population was identified from annual employment records. Follow-up for mortality was from 1951 until 1986, and for cancer incidence from 1958 to 1986. Except for four persons who had emigrated from Sweden, follow-up was 100% complete. To assess the occupational exposure as a firefighter, an index of participation in number of fires was calculated for each individual based on the number of reports on all fires in Stockholm that had been maintained since the beginning of the twentieth century. The all-site cancer mortality in 1958–1986 was equal to the expected (SMR, 100; 95% CI: 83–119). An excess of stomach cancer incidence (SIR, 192; 95% CI: 114–304; 18 observed versus 9.37 expected) was observed. There was also a tendency for higher incidence and mortality in stomach and brain cancers with increasing number of fires. Four brain cancer cases were observed compared to 0.8 expected (SIR, 496; 95% CI: 135–1270) in the highest exposure category.

Table 2.2. Cohort studies of cancer among firefighters

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Buccal cavity							
Beaumont *et al.* (1991), California, USA	3066 male firefighters employed 1940–70 Buccal cavity and pharynx	Fire department records	Overall	11	1.4 (0.7–2.6)		
Baris *et al.* (2001), Pennsylvania, USA	7789 firefighters employed 1925–86 Buccal cavity and pharynx	Employee service records	Overall	19	1.4 (0.9–2.1)		
			Duration of employment		**SMR**		
			≤9 yrs	4	1.2 (0.4–3.1)		
			10–19 yrs	9	1.8 (0.95–3.5)		
			≥20 yrs	6	1.1 (0.5–2.4)		
			Hiring period				
			Hired before 1935	10	2.1 (1.1–3.9)		
			1935–44	4	0.9 (0.3–2.3)		
			After 1944	5	1.1 (0.5–2.6)		
			Number of runs				
			Low (<3323)	7	1.7 (0.8–3.6)		
			Medium (3323–5099)	0	0		
			High (5099+)	2	0.8 (0.2–3.1)		
Ma *et al.* (2005), Florida, USA	34 796 male and 2017 female professional firefighters	Employment records			**SMR**	Age, calendar year	
			Men	7	0.4 (0.2–0.9)		
			Women	0	–		

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Ma *et al.* (2006), Florida, USA	34 796 male and 2017 female professional firefighters	Employment records	Men Women	39 0	**SIR** 0.7 (0.5–0.9) 0	Age, calendar year	
Oral and pharyngeal cavity / UADT							
Demers *et al.* (1992a), Northwest, USA	4546 male firefighters employed 1944–79 in selected Northwest cities	Employment records	Overall	7	**SMR** 0.8 (0.3–1.7)		
Demers *et al.* (1992b), Northwest, USA	4528 firefighters and police officers employed by the cities of Seattle and Tacoma; oral and pharyngeal	Employment records		19 4	**SIR** 1.2 (0.7–1.9) **SMR** 1.0 (0.3–2.6)		Data for firefighters and police combined
Giles *et al.* (1993), Australia	2865 male firefighters employed 1917–89 Upper aerodigestive	Employment and union records, payrolls	Overall	6	**SIR** 1.5 (0.5–3.2)		

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Guidotti (1993), Alberta, Canada	3328 firefighters employed 1927–87 Oral	Personnel files	Overall	2	**SMR** 1.1 (0.1–4.1)		
Aronson *et al.* (1994), Ontario, Canada	5373 male firefighters employed 1950–89 Pharynx	Employment records	Overall	4	**SMR** 1.4 (0.4–3.6)		
Demers *et al.* (1994), Northwest, USA	2447 male firefighters employed 1974–89	Employment records	Overall <10 yrs 10–19 yrs 20–29 yrs ≥30 yrs	11 2 4 2 3	**SIR** 1.1 (0.6–2.0) 1.4 (0.2–5.1) 2.5 (0.7–6.4) 0.3 (0.0–1.2) 3.9 (0.8–11.0)		
Deschamps *et al.* (1995), France	830 male firefighters employed 1977–91 Pharynx	Employment records		2	**SMR** 0.8 (0.1–2.9)		

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Stomach							
Eliopulos *et al.* (1984), Australia	990 firefighters employed 1939–78	Western Australian Fire Brigade records	Overall	5	**SPMR** 2.0 (0.7–4.7)		
Vena & Fiedler (1987), New York State, USA	1867 male firefighters employed 1950–79	Death certificates	Overall	7	**SMR** 1.2 (0.5–2.5)		
Heyer *et al.* (1990), Washington, USA	2289 male firefighters employed at least 1 yr, 1945–80; follow-up until 1983	Employment records	Overall	6	**SMR** 1.1 (0.4–2.5)		
Beaumont *et al.* (1991), California, USA	3066 male firefighters employed 1940–70	Fire department records	Overall	22	**SMR** 1.3 (0.8–2.0)		
Grimes *et al.* (1991), Hawaii, USA	205 male firefighters	Death certificates	Overall	2	**PRR** 0.8 (0.3–2.1)		Not clear if standardized by age and calendar period

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Demers *et al.* (1992a), Northwest, USA	4546 male firefighters employed 1944–79 in selected Northwest cities	Employment records	Overall	16	**SMR** 1.1 (0.6–1.7)		
Guidotti (1993), Alberta, Canada	3328 firefighters employed 1927–87	Personnel files	Overall	6	**SMR** 0.8 (0.3–1.8)		
Aronson *et al.* (1994), Ontario, Canada	5973 male firefighters employed 1950–89	Employment records	Overall	7	**SMR** 0.5 (0.2–1.1)		
Demers *et al.* (1994), Northwest, USA	2447 male firefighters employed 1974–89	Employment records	Overall <10 yrs 10–19 yrs 20–29 yrs ≥30 yrs	8 2 1 4 1	**SIR** 1.4 (0.6–2.7) 3.0 (0.4–11.0) 1.2 (0.0–6.9) 1.1 (0.3–2.9) 1.4 (0.0–8.1)		
Tornling *et al.* (1994), Stockholm, Sweden	Men working as firefighters for at least 1 yr, 1931–83	Enrollment records	Overall	12	**SMR** 1.2 (0.6–2.1)		

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Baris *et al.* (2001), Pennsylvania, USA	7789 firefighters employed 1925–86	Employee service records	Overall	24	0.9 (0.6–1.4)		
			Duration of employment		**SMR**		
			≤9 yrs	4	0.6 (0.2–1.5)		
			10–19 yrs	14	1.4 (0.8–2.4)		
			≥20 yrs	6	0.7 (0.3–1.4)		
			Hiring period				
			Hired before 1935	17	1.2 (0.7–1.9)		
			1935–44	4	0.6 (0.2–1.6)		
			After 1944	3	0.5 (0.2–1.7)		
			Number of runs				
			Low (<3323)	4	0.7 (0.3–1.8)		
			Medium (3323–5099)	1	0.3 (0.1–2.2)		
			High (5099+)	2	0.7 (0.2–2.6)		
Bates *et al.* (2001), New Zealand	All firefighters employed at least 1 yr, 1977–95	Employment registry	Overall	3	**SIR** 0.8 (0.2–2.2)		Only results for men were presented
Ma *et al.* (2005), Florida, USA	34 796 male and 2017 female professional firefighters	Employment records			**SMR**	Age, calendar year	
			Men	12	0.9 (0.5–1.4)		
			Women	0	–		
Ma *et al.* (2006), Florida, USA	34 796 male and 2017 female professional firefighters	Employment records			**SIR**	Age, calendar year	
			Men	14	0.5 (0.3–0.9)		
			Women	0	–		

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Colon/Colorectal							
Eliopulos *et al.* (1984), Australia	990 firefighters employed 1939–78 Intestinal cancer	Western Australian Fire Brigade records	Overall	4	**SPMR** 1.6 (0.4–4.1)		
Vena & Fiedler (1987), New York State, USA	1867 male firefighters employed 1950–79 Colon	Death certificates	Overall	16	**SMR** 1.8 (1.1–3.0)		
Beaumont *et al.* (1991), California, USA	3066 male firefighters employed 1940–70 Intestine except rectum	Fire department records	Overall	24	**SMR** 1.0 (0.6–1.5)		
Grimes *et al.* (1991), Hawaii, USA	205 male firefighters Colon	Death certificates	Overall	2	**PRR** 0.9 (0.4–2.2)		Not clear if standardized by age and calendar period

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Demers *et al.* (1992a), Northwest USA	4546 male firefighters employed 1944–79 in selected Northwest cities Colon	Employment records	Overall	24	**SMR** 0.9 (0.5–1.3)	Age, calendar year	
Giles *et al.* (1993), Australia	2865 male firefighters employed 1917–89 Colorectal	Employment and union records, payrolls	Overall	9	**SIR** 1.4 (0.6–2.6)		
Guidotti (1993), Alberta, Canada	3328 firefighters employed 1927–87 Colon and rectum	Personnel files	Overall	14	**SMR** 1.6 (0.9–2.7)		
Aronson *et al.* (1994), Ontario, Canada	5373 male firefighters employed 1950–89 Colon	Employment records	Overall	11	**SMR** 0.60 (0.3–1.1)	Age, calendar year	

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Demers *et al.* (1994), Northwest, USA	2447 male firefighters employed 1974–89 Colon	Employment records			**SIR**		
			Overall	23	1.1 (0.7–1.6)		
			<10 yrs	2	0.8 (0.1–2.9)		
			10–19 yrs	2	0.7 (0.1–2.6)		
			20–29 yrs	15	1.1 (0.6–1.9)		
			≥30 yrs	4	1.5 (0.4–3.9)		
Tornling *et al.* (1994), Stockholm, Sweden	Men working as firefighters for at least 1 yr, 1931–83 Colon	Enrollment records			**SMR**		
			Overall	6	0.9 (0.3–1.9)		
Baris *et al.* (2001), Pennsylvania, USA	7789 firefighters employed 1925–86 Colon	Employee service records	Overall	64	1.5 (1.2–1.9)		
			Duration of employment		**SMR**		
			≤9 yrs	18	1.8 (1.1–2.8)		
			10–19 yrs	16	1.1 (0.7–1.8)		
			≥20 yrs	30	1.7 (1.2–2.4)		
			Hiring period				
			Hired before 1935	16	1.0 (0.6–1.6)		
			1935–44	28	2.0 (1.4–2.9)		
			After 1944	20	1.6 (1.0–2.5)		
			Number of runs				
			Low (<3323)	23	1.9 (1.3–2.9)		
			Medium (3323–5099)	16	2.2 (1.4–3.6)		
			High (5099+)	9	1.2 (0.6–2.4)		

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Bates *et al.* (2001), New Zealand	All firefighters employed at least 1 yr, 1977–95 Colon	Employment registry	Overall *Duration of employment* 0–10 yrs 11–20 yrs >20 yrs	7 1 1 5	**SIR** 0.6 (0.2–1.2) 0.4 (0.0–2.3) 0.5 (0.0–2.6) 1.4 (0.4–3.2)		
Ma *et al.* (2005), Florida, USA	34 796 male and 2017 female professional firefighters Colon	Employment records	Men Women	38 1	**SMR** 1.1 (0.8–1.6) 2.3 (0.0–12.7)	Age, calendar year	
Ma *et al.* (2006), Florida, USA	34 796 male and 2017 female professional firefighters Colon	Employment records	Men Women	78 2	**SIR** 1.2 (0.9–1.5) 2.3 (0.3–8.2)	Age, calendar year	
Rectum							
Vena & Fiedler (1987), New York State, USA	1867 male firefighters employed 1950–79	Death certificates	Overall	7	**SMR** 2.1 (0.8–4.3)		

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Beaumont *et al.* (1991), California, USA	3066 male firefighters employed 1940–70	Fire department records	Overall	13	1.5 (0.8–2.5)		
Demers *et al.* (1992a), Northwest, USA	4546 male firefighters employed 1944–79 in selected Northwest cities	Employment records	Overall	8	**SMR** 1.0 (0.4–1.9)	Age, calendar year	
Aronson *et al.* (1994), Ontario, Canada	5973 male firefighters employed 1950–1989 Rectum and rectosigmoid junction	Employment records	Overall	13	**SMR** 1.7 (0.9–2.9)		
Demers *et al.* (1994), Northwest USA	2447 male firefighters employed 1974–89	Employment records	Overall <10 yrs 10–19 yrs 20–29 yrs ≥30 yrs	12 2 3 5 2	**SIR** 1.0 (0.5–1.8) 1.4 (0.2–4.9) 1.9 (0.4–5.4) 0.7 (0.2–1.6) 1.6 (0.2–5.6)		

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Tornling *et al.* (1994), Stockholm, Sweden	Men working as firefighters for at least 1 yr, 1931–83	Enrollment records			**SMR**		
			Overall	8	2.1 (0.9–4.1)		
Baris *et al.* (2001), Pennsylvania, USA	7789 firefighters employed 1925–86	Employee service records	Overall	14	1.0 (0.6–1.7)		
			Duration of employment		**SMR**		
			≤9 yrs	3	0.9 (0.3–2.7)		
			10–19 yrs	6	1.2 (0.5–2.6)		
			≥20 yrs	5	0.9 (0.4–2.2)		
			Hiring period				
			Hired before 1935	7	1.1 (0.5–2.2)		
			1935–44	3	0.7 (0.2–2.3)		
			After 1944	4	1.2 (0.5–3.2)		
			Number of runs				
			Low (<3323)	5	1.4 (0.5–3.3)		
			Medium (3323–5099)	1	0.5 (0.1–3.6)		
			High (5099+)	1	0.5 (0.1–3.9)		
Bates *et al.* (2001), New Zealand	All firefighters employed at least 1 yr, 1977–95	Employment registry			**SIR**		Only results for men were presented
			Overall	9	1.2 (0.5–2.2)		
			Duration of employment				
			0–10 yrs	2	1.2 (0.1–4.4)		
			11–20 yrs	2	1.4 (0.2–5.0)		
			>20 yrs	4	1.6 (0.4–4.1)		

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Ma *et al.* (2005), Florida, USA	34 796 male and 2017 female professional firefighters	Employment records	Men Women	7 0	**SMR** 0.9 (0.4–1.9)	Age, calendar year	
Ma *et al.* (2006), Florida, USA	34 796 male and 2017 female professional firefighters	Employment records	Men Women	23 1	**SIR** 0.9 (0.6–1.3) 5.3 (0.1–29.3)	Age, calendar year	
Skin							
Beaumont *et al.* (1991), California, USA	3066 male firefighters employed 1940–70	Fire department records	Compared to police Overall	6 7	**IDR** 1.1 (0.3–4.8) 1.7 (0.7–3.5)	Age, calendar year	White men only
Demers *et al.* (1992a), Northwest, USA	4546 male firefighters employed 1944–79 in selected Northwest cities	Employment records	Overall	6	**SMR** 1.0 (0.4–2.1)	Age, calendar year	
Guidotti (1993), Alberta, Canada	3328 firefighters employed 1927–87	Personnel files	Overall	0	**SMR** 0 (0–3.3)		

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Tornling *et al.* (1994), Stockholm, Sweden	Men working as firefighters for at least 1 yr, 1931–83; Non-melanoma skin cancer	Enrollment records			**SMR**		
			Overall	5	1.5 (0.5–3.5)		
Baris *et al.* (2001), Pennsylvania, USA	7789 firefighters employed 1925–86	Employee service records	Overall	10	1.2 (0.6–2.2)		
			Duration of employment		**SMR**		
			≤9 years	2	0.8 (0.2–3.0)		
			10–19 years	5	1.7 (0.7–4.1)		
			≥20 years	3	1.1 (0.3–3.3)		
			Hiring period				
			Hired before 1935	3	1.5 (0.5–4.5)		
			1935–44	1	0.4 (0.1–3.0)		
			After 1944	6	1.5 (0.7–3.3)		
			Number of runs				
			Low (<3323)	1	0.4 (0.1–2.5)		
			Medium (3323–5099)	5	3.1 (1.3–7.5)		
			High (5099+)	1	0.5 (0.1–3.8)		
Ma *et al.* (2005), Florida, USA	34 796 male and 2017 female professional firefighters	Employment records			**SMR**	Age, calendar year	
			Men	17	0.9 (0.5–1.4)		
			Women	0	–		

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Ma *et al.* (2006), Florida, USA	34 796 male and 2017 female professional firefighters	Employment records			**SIR**	Age, calendar year	
			Men	99	1.2 (1.0–1.4)		
			Women	5	3.0 (1.0–7.0)		
Melanoma							
Demers *et al.* (1992b), Northwest, USA	4528 male firefighters employed 1944–79	Employment records		15	**SIR** 1.2 (0.7–2.0)		Data for firefighters and police combined
				5	**SMR** 1.6 (0.5–3.8)		
Giles *et al.* (1993), Australia	2865 male firefighters employed 1917–89	Employment and union records, payrolls	Overall	5	**SIR** 1.1 (0.4–2.5)		
Aronson *et al.* (1994), Ontario, Canada	5373 male firefighters employed 1950–1989	Employment records	Overall	2	**SMR** 0.7 (0.1–2.6)		
Demers *et al.* (1994), Northwest, USA	2447 male firefighters employed 1974–89	Employment records			**SIR**		
			Overall	9	1.2 (0.6–2.3)		
			<10 years	0	0 (0.0–2.6)		
			10–19 years	4	2.3 (0.6–5.8)		
			20–29 years	4	1.1 (0.3–2.7)		
			≥30 years	1	2.4 (0.1–13.0)		

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Tornling *et al.* (1994), Stockholm, Sweden	Men working as firefighters for at least 1 yr, 1931–83 Malignant melanoma	Enrollment records	Overall	2	**SMR** 0.8 (0.09–2.9)		
Bates *et al.* (2001), New Zealand	All firefighters employed at least 1 yr, 1977–95	Employment registry	Overall 0–10 years 10–19 years >20 years	23 7 6 6	**SIR** 1.3 (0.8–1.9) 1.7 (0.7–3.5) 1.8 (0.6–3.8) 1.7 (0.6–3.6)		Only results for men were presented
Prostate							
Vena & Fiedler. (1987), New York State, USA	1867 male firefighters employed 1950–79	Death certificates	Overall	5	**SMR** 0.7 (0.2–1.7)	Age, calendar year	
Beaumont *et al.* (1991), California, USA	3066 male firefighters employed 1940–70	Fire department records	Overall	8	**SMR** 0.4 (0.2–0.8)	Age, calendar year	
Grimes *et al.* (1991), Hawaii, USA	205 male firefighters	Death certificates	Overall	4	**PRR** 2.6 (1.4–5.0)	Age, calendar year	Not clear if standardized by age and calendar period

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Demers *et al.* (1992a), Northwest, USA	4546 male firefighters employed 1944–79 in selected Northwest cities	Employment records			**SMR**	Age, calendar year	
			Overall	30	1.3 (0.9–1.9)		
			<10 years	3	2.4 (0.5–7.1)		
			10–19 years	2	1.1 (0.1–4.1)		
			20–29 years	14	1.2 (0.7–2.1)		
			≥30 years	11	1.4 (0.7–2.4)		
					IDR		
			Compared to police	30	1.4 (0.7–2.9)		
Giles *et al.* (1993), Australia	2865 male firefighters employed 1917–89	Employment and union records			**SIR**	Age, calendar year	
			Overall	5	2.1 (0.7–4.9)		
Guidotti (1993), Alberta, Canada	3328 firefighters employed 1927–87	Personnel files			**SMR**	Age, calendar year	
			Overall	8	1.5 (0.6–2.9)		
Aronson *et al.* (1994), Ontario, Canada	5373 male firefighters employed 1950–89	Employment records			**SMR**	Age, calendar year	
			Overall	16	1.3 (0.8–2.2)		
			Duration of employment				
			<15 years	1	1.6 (0.1–9.0)		
			15–29 years	5	2.4 (0.8–5.7)		
			30+ years	9	1.0 (0.4–1.8)		

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Demers *et al.* (1994), Seattle & Tacoma, USA	2447 male firefighters, employed 1974–89	Employment records			**SIR**	Age, calendar year	Subpopulation of Demers *et al.*, (1992)
			Overall	66	1.4 (1.1–1.7)		
			<10 years	7	1.4 (0.6–2.8)		
			10–19 years	6	1.2 (0.4–2.6)		
			20–29 years	47	1.5 (1.1–2.0)		
			≥30 years	6	0.9 (0.3–1.9)		
					RR		
			Compared to police	66	1.1 (0.7–1.8)		
Tornling *et al.* (1994), Stockholm, Sweden	Men working as firefighters for at least 1 yr, 1931–83	Enrollment records			**SMR**	Age, calendar year	
			Overall	14	1.21 (0.7–2.0)		
Baris *et al.* (2001), Pennsylvania, USA	7789 firefighters employed 1925–86	Employee service records			**SMR**	Age, calendar year	
			Overall	31	1.0 (0.7–1.4)		
			Duration of employment				
			≤9 years	15	2.4 (1.4–3.9)		
			10–19 years	5	0.5 (0.2–1.1)		
			≥20 years	11	0.7 (0.4–1.3)		
			Hired before 1935	12	0.8 (0.4–1.3)		
			1935–44	14	1.4 (0.8–2.3)		
			After 1944	5	0.8 (0.3–2.0)		
			Number of runs				
			Low (<3323)	10	1.3 (0.7–2.5)		
			Medium (3323–5099)	3	0.7 (0.2–2.0)		
			High (5099+)	6	1.4 (0.6–3.2)		

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Bates *et al.* (2001), New Zealand	All firefighters employed at least 1 yr, 1977–95	Employment registry	Overall	11	**SIR** 1.1 (0.5–1.9)	Age, calendar year	Only results for men were presented
			Duration of employment				
			0–10 years	3	1.5 (0.3–4.3)		
			11–20 years	1	0.6 (0.1–3.3)		
			>20 years	1	0.3 (0.1–1.6)		
Ma *et al.* (2005), Florida, USA	34 796 male and 2017 female professional firefighters	Employment records	Overall	21	**SMR** 1.1 (0.7–1.7)	Age, calendar year	
Ma *et al.* (2006), Florida, USA	34 796 male and 2017 female professional firefighters	Employment records	Overall	209	**SIR** 1.1 (1.0–1.4)	Age, calendar year	Same population as Ma *et al.*, (2005)
Testis							
Giles *et al.* (1993), Australia	2865 male firefighters employed 1917–89	Employment and union records, payrolls	Overall	2	**SIR** 1.2 (0.1–4.2)	Age, calendar year	

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Aronson *et al.* (1994), Ontario, Canada	5373 firefighters employed 1950–89	Employment records			**SMR**	Age, calendar year	
			Overall	3	2.5 (0.5–7.4)		
			Duration of employment				
			<15 years	3	3.7 (0.8–10.7)		
			15–29 years	0	0.0 (0.0–14.2)		
			30+ years	0	0.0 (0.0–36.9)		
Bates *et al.* (2001), New Zealand	All firefighters employed at least 1 yr, 1977–95 Testicular	Employment registry			**SIR**	Age, calendar year	Only results for men were presented
			Overall	11	1.6 (0.8–2.8)		
			Duration of employment				
			0–10 years	3	1.6 (0.3–4.5)		
			11–20 years	4	3.5 (1.0–9.0)		
			>20 years	2	4.1 (0.5–14.9)		
Ma *et al.* (2006), Florida, USA	34 796 male and 2017 female professional firefighters	Employment records	Men	54	**SIR** 1.6 (1.2–2.1)	Age, calendar year	
Brain / CNS							
Musk *et al.* (1978), Massachusetts, USA	5655 male firefighters employed 1915–75	Death certificates		8	**SMR** 1.0		Confidence interval not provided, not calculated

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Vena & Fiedler (1987), New York State, USA	1867 male firefighters employed 1950–79 Brain	Death certificates	Overall	6	**SMR** 2.4 (0.9–5.1)		
Heyer *et al.* (1990), Washington, USA	2289 male firefighters employed at least 1 yr, 1945–80; follow-up until 1983	Employment records	Overall *Duration of employment* <15 years 15–29 years 30+ years	3 2 1 0	**SMR** 1.0 (0.2–2.8) 1.84 (0.22–6.49) 0.86 (0.10–3.11) 5.03 (1.04–14.70)		
Beaumont *et al.* (1991), California, USA	3066 male firefighters employed 1940–70	Fire department records	Overall	5	0.8 (0.3–1.9)		
Grimes *et al.* (1991), Hawaii, USA	205 male firefighters Brain	Death certificates	Overall	2	**PRR** 3.8 (1.2–11.7)		Not clear if standardized by age and calendar period
Demers *et al.* (1992a), Northwest, USA	4546 male firefighters employed 1944–79 in selected Northwest cities	Employment records	Overall	18	**SMR** 2.1 (1.2–3.3)		

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Guidotti (1993), Alberta, Canada	3328 firefighters employed 1927–87 Brain	Personnel files	Overall	3	**SMR** 1.5 (0.3–4.3)		
Aronson *et al.* (1994), Ontario, Canada	5373 male firefighters employed 1950–89	Employment records	Overall	14	**SMR** 2.0 (1.1–3.4)		
Demers *et al.* (1994), Northwest USA	2447 male firefighters employed 1974–89 Brain	Employment records	Overall <10 years 10–19 years 20–29 years ≥30 years	4 1 0 3 0	**SIR** 1.1 (0.3–2.9) 1.6 (0.0–8.8) 0 (0.0–4.6) 1.6 (0.3–4.6) 0 (0.0–16)		
Tornling *et al.* (1994), Stockholm, Sweden	Men working as firefighters for at least 1 yr, 1931–83 Brain	Enrollment records	Overall	5	**SMR** 2.8 (0.9–6.5)		

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Baris *et al.* (2001), Pennsylvania, USA	7789 firefighters employed 1925–86 Brain	Employee service records	Overall	8	0.6 (0.3–1.2)		
			Duration of employment		**SMR**		
			≤9 years	2	0.5 (0.1–1.9)		
			10–19 years	2	0.4 (0.1–1.8)		
			≥20 years	4	0.9 (0.4–2.5)		
			Hiring period				
			Hired before 1935	1	0.4 (0.1–2.6)		
			1935–1944	3	0.7 (0.2–2.2)		
			After 1944	4	0.7 (0.3–1.8)		
			Number of runs				
			Low (<3323)	3	0.6 (0.2–1.9)		
			Medium (3323–5099)	2	0.8 (0.2–3.1)		
			High (5099+)	2	0.7 (0.2–2.9)		
Bates *et al.* (2001), New Zealand	All firefighters employed at least 1 year, 1977–95 Brain	Employment registry	Overall	5	**SIR** 1.3 (0.4–3.0)		Only results for men were presented
Ma *et al.* (2005), Florida, USA	34 796 male and 2017 female professional firefighters	Employment records	Men	13	**SMR** 0.7 (0.4–1.1)	Age , calendar year	
			Women	0	–		

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Ma *et al.* (2006), Florida, USA	34 796 male and 2017 female professional firefighters	Employment records	Men Women	14 0	**SIR** 0.6 (0.3–1.0)	Age, calendar year	
Non-Hodgkin lymphoma							
Giles *et al.* (1993), Australia	2865 male firefighters employed 1917–89	Employment and union records	Overall	4	**SIR** 1.9 (0.5–4.7)	Age, calendar period	
Aronson *et al.* (1994), Ontario, Canada	5373 male firefighters employed 1950–89 Lymphosarcoma	Employment records	Overall	3	**SMR** 2.0 (0.4–6.0)	Age, calendar year	
Demers *et al.* (1994), Seattle & Tacoma, USA	2447 male firefighters employed 1974–89	Employment records	Overall *Duration fire fighting* <10 years 10–19 years 20–29 years 30+ years	7 1 1 5 0	**SIR** 0.9 (0.4–1.9) 0.9 (0.4–4.9) 0.6 (0.1–4.5) 1.2 (0.4–2.7) 0.0 (0.0–5.8)	Age, calendar year	

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Baris *et al.* (2001), Pennsylvania, USA	7789 firefighters employed 1925–86	Employee service records	Overall	10	1.4 (0.9–2.2)	Age, calendar year	
			Duration of employment		**SMR**		
			≤9 years	6	1.5 (0.7–3.3)		
			10–19 years	5	1.0 (0.4–2.5)		
			≥20 years	9	1.7 (0.9–3.3)		
			Hiring period				
			Hired before 1935	3	0.7 (0.2–2.2)		
			1935–1944	10	2.2 (1.2–4.1)		
			After 1944	7	1.3 (0.6–2.7)		
			Number of runs				
			Low (<3323)	11	2.4 (1.3–4.3)		
			Medium (3323–5099)	4	1.6 (0.6–4.1)		
			High (5099+)	2	0.7 (0.2–2.9)		
Ma *et al.* (2006), Florida, USA	34 796 male and 2017 female professional firefighters	Employment records			**SIR**	Age, calendar year	
			Men	15	1.1 (0.6–1.8)		
			Women	1	33.3 (0.4–185)		

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Multiple myeloma							
Heyer *et al.* (1990), Seattle, USA	2289 male firefighters employed at least 1 yr, 1945–80; follow-up until 1983	Employment records	Overall	3	**SMR** 2.25 (0.47–6.60)	Age, calendar year	
			Duration of employment				
			<15 years	0	0 (0–15.96)		
			15–29 years	1	1.11 (0.03–6.21)		
			30+ years	2	9.89 (1.20–35.71)		
Demers *et al.* (1992a), Seattle, Portland & Tacoma, USA	4546 male firefighters employed at least 1 yr, 1944–79; follow-up until 1989	Employment records			**RR** 1.9 (0.4–8.4)	Age, calendar year	A police cohort used as a reference group. Reference rates for US white men were obtained from the National Institute for Occupational Safety and Health. Overlap with Heyer *et al.* (1990)
Aronson *et al.* (1994), Ontario, Canada	5373 male firefighters employed 1950–89	Employment records	Overall	1	**SMR** 0.4 (0.0–2.2)	Age, calendar year	

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Demers *et al.* (1994), Seattle & Tacoma, USA	2447 male firefighters employed 1974–89	Employment records		2	**SIR** 0.7 (0.1–2.6)	Age, calendar year	Overlap with Demers, 1992
Baris *et al.* (2001), Pennsylvania, USA	7789 male firefighters employed 1925–86	Employee service records			**SMR**	Age, calendar year	
			Overall	10	1.7 (0.9–3.1)		
			Duration of employment				
			≤9 years	1	0.7 (0.1–5.2)		
			10–19 years	3	1.5 (0.5–4.7)		
			≥20 years	6	2.3 (1.0–5.2)		
			Hiring period				
			Hired before 1935	4	2.1 (0.8–5.5)		
			1935–1944	3	1.4 (0.5–4.4)		
			After 1944	3	1.6 (0.5–4.8)		
			Number of runs				
			Low (<3323)	1	0.6 (0.9–4.1)		
			Medium (3323–5099)	3	2.7 (0.9–8.4)		
			High (5099+)	2	1.7 (0.4–6.9)		

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Leukaemia							
Musk *et al.* (1978), Massachusetts, USA	5655 male firefighters employed 1915–75 Lymphatic and haemapoietic	Death certificates	Overall	22	**SMR** 0.6		Confidence interval not provided, not calculated
Heyer *et al.* (1990), Washington, USA	2289 male firefighters employed at least 1 yr, 1945–80; follow-up until 1983 Leukaemia and aleukaemia	Employment records	Overall	7	**SMR** 1.7 (0.7–3.6)		
Beaumont *et al.* (1991), California, USA	3066 male firefighters employed 1940–70 Leukaemia and aleukaemia	Fire department records	Overall	6	0.6 (0.2–1.3)		

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Demers *et al.* (1992a), Northwest USA	4546 male firefighters employed 1944–79 in selected Northwest cities	Employment records		15	**SMR** 1.3 (0.7–2.1)		
Demers *et al.* (1992b), Northwest USA	4528 male firefighters employed 1944–79	Employment records		10 8	**SIR** 1.05 (0.5–1.9) **SMR** 1.3 (0.5–2.5)		Data for firefighters and police combined
Guidotti (1993), Alberta, Canada	3328 firefighters employed 1927–87 Leukaemia, lymphoma, myeloma	Personnel files	Overall	10	**SMR** 1.3 (0.6–2.3)		
Aronson *et al.* (1994), Ontario, Canada	5995 firefighters employed 1950–89 Lymphatic leukaemia	Employment records	Overall	4	**SMR** 1.9 (0.5–4.9)		

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Demers *et al.* (1994), Northwest USA	2447 male firefighters employed 1974–89	Employment records			**SIR**		
			Overall	6	1.0 (0.4–2.1)		
			<10 years	0	0 (0.0–4.4)		
			10–19 years	2	1.9 (0.2–6.8)		
			20–29 years	4	1.1 (0.3–2.8)		
			≥30 years	0	0 (0.0–5.4)		
Baris *et al.* (2001), Pennsylvania, USA	7789 firefighters employed 1925–86	Employee service records	Overall	15	0.8 (0.5–1.4)		
			Duration of employment		**SMR**		
			≤9 years	5	0.9 (0.4–2.3)		
			10–19 years	7	1.1 (0.5–2.4)		
			≥20 years	3	0.5 (0.2–1.4)		
			Hiring period				
			Hired before 1935	2	0.3 (0.1–1.3)		
			1935–1944	6	1.1 (0.5–2.4)		
			After 1944	7	1.1 (0.5–2.3)		
			Number of runs				
			Low (<3323)	5	0.8 (0.4–2.0)		
			Medium (3323–5099)	4	1.4 (0.5–3.6)		
			High (5099+)	4	1.3 (0.5–3.6)		

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Ma *et al*. (2005), Florida, USA	34 796 male and 2017 female professional firefighters	Employment records	Men Women	14 0	**SMR** 0.8 (0.5–1.4) –	Age, calendar year	
Ma *et al*. (2006), Florida, USA	34 796 male and 2017 female professional firefighters	Employment records	Men Women	20 0	**SIR** 0.8 (0.5–1.2) –	Age, calendar year	

IDR, incidence density ratio; PRR, proportional risk ratio; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SPMR, standardized proportional mortality ratio; yr, year

Deschamps *et al.* (1995) investigated all professional male members of the Brigade des Sapeurs-Pompiers de Paris (n = 830) who served for a minimum of 5 years as of January 1st, 1977. They were monitored for a 14-year period, with follow-up terminating on January 1st, 1991. Cause-specific mortality rates in these firefighters were compared with national mortality data provided by the Institut National de la Santé et de la Recherche Médicale. To assess the occupational exposure as a firefighter, data were collected on duration of employment as an active duty firefighter (as opposed to office work). These 830 firefighters accrued a total of 11 414 person–years of follow-up. Follow-up appears to have been 100% complete. There were 32 deaths in the cohort during the 14-year period of follow-up. When compared to the average French male, they were found to have a far lower overall mortality (SMR, 0.52 [95% CI: 0.35–0.75]). None of the cause-specific SMRs was significant. However, a greater number of deaths than expected was observed for genito-urinary cancer (SMR, 3.29) [based on one bladder cancer, and one testicular cancer], and digestive cancer (SMR, 1.14).

Baris *et al.* (2001) conducted a retrospective cohort mortality study among 7789 firefighters in Philadelphia, Pennsylvania, USA, on males employed during 1925–1986. Vital status was ascertained up until 1986. SMRs and 95% CI were calculated with expected numbers of deaths in the United States white male population, as the overwhelming majority of firefighters were white. Occupational exposure histories were abstracted from detailed records maintained by the Philadelphia Fire Department, and a job–exposure matrix was created for each firefighter. To estimate exposure–response relationships, the study used this matrix to compare mortality among groups of firefighters defined by the estimated number of career runs. There were 2220 deaths and a total of 6.2% of the cohort was lost to follow-up. In comparison with white males in the United States, firefighters had a similar mortality from all causes of death combined (SMR, 0.96), and all cancers (SMR, 1.10). Statistically significant excess risks were observed for colon cancer (SMR, 1.51). The risks of mortality from colon cancer (SMR, 1.68), kidney cancer (SMR, 2.20), non-Hodgkin lymphoma (SMR, 1.72), multiple myeloma (SMR, 2.31), and benign neoplasms (SMR, 2.54) were increased in firefighters with at least 20 years of service.

Bates *et al.* (2001) conducted a historical cohort study of mortality and cancer incidence in all remunerated New Zealand firefighters, who served during 1977–1995. Ascertainment of employment was through a registry maintained by the United Fire Brigades Association of New Zealand. The final cohort comprised 4221 male firefighters. To assess the occupational exposure as a firefighter, data were collected on duration of employment. The 4221 male firefighters in this cohort accrued a total of 58 709 person–years of follow-up. Follow-up was successful in tracing 93.5%. There were 117 deaths up until 1995. Cancer incidence was ascertained during 1977–1996. The SIR for all cancers was 0.95. For most sites, no excesses were observed. The only cancer for which this study provided evidence of an increased risk was

testicular cancer. Eleven testicular cancers were observed versus 7.1 expected (SIR, 1.55; 95% CI: 0.8–2.8). For the years 1990–1996, the SIR for testicular cancer was 3.0 (95% CI: 1.3–5.9).

Ma *et al.* (2005) examined age- and gender-adjusted mortality rates of 36 813 professional firefighters employed during 1972–1999 in Florida, USA, and compared those with that of the Florida general population. The study population consisted of 34 796 male and 2017 female professional firefighters. The racial/ethnic composition was caucasian (90.1%), hispanic (7%), and black (6.5%). Employment as a firefighter was ascertained from employment records in the Florida State Fire Marshall Office. Surrogate information on occupational exposures in firefighting was collected by examining the year of certification and duration of employment as a firefighter. No information was collected on smoking histories. A total of 1411 male and 38 female deaths with known causes were identified in this cohort. In male firefighters, a deficit of overall mortality from cancer was observed (SMR, 0.85). Excess risks were observed for male breast cancer (SMR, 7.41; 95% CI: 1.99–18.96), and thyroid cancer (SMR, 4.82; 95% CI: 1.30–12.34), each based on four cases. Mortality from bladder cancer was increased and approached statistical significance (SMR, 1.79; 95% CI: 0.98–3.00). Female firefighters had similar overall cancer mortality patterns to Florida women (SMR, 1.03), but the numbers were small for specific cancer sites.

In a further analysis of the same cohort, Ma *et al.* (2006) determined the relative cancer risk for firefighters in the State of Florida compared with the Florida general population. Employment as a firefighter was ascertained from employment records in the Florida State Fire Marshall Office. Cancer incidence was determined through linkage to the Florida Cancer Data System, a statewide cancer registry estimated to capture 98% of cancers in Florida residents. No pathological verification of cancer diagnoses was undertaken. A total of 970 male and 52 female cases of cancer were identified; 6.7% of the cohort were lost to follow-up. Male firefighters had significantly increased incidence rates of cancers of the bladder (SIR, 1.29; 95% CI: 1.01–1.62), testis (SIR, 1.60; 95% CI: 1.20–2.09), and of the thyroid (SIR, 1.77; 95% CI: 1.08–2.73). Female firefighters had significantly increased incidence rates of overall cancer (SIR, 1.63; 95% CI: 1.22–2.14), cervical (SIR, 5.24; 95% CI: 2.93–8.65) and thyroid cancers (SIR, 3.97; 95% CI: 1.45–8.65), and Hodgkin disease (SIR, 6.25; 95% CI: 1.26–18.26).

2.2 Case–control studies

Case–control studies have been used to examine the risk of firefighting and its association with various types of cancers. In all but one of these studies, ten or fewer firefighters were included in the case and/or control group. Several studies combined broad occupational categories with heterogeneous exposures such as firefighter and fireman, with the latter not necessarily working as a firefighter. These types of studies may result in exposure misclassification. Even within specific occupational groups such as firefighters, all would not have the same intensity or type of exposures. The

magnitude of this form of misclassification is unknown, but it is likely that the resulting misclassification will be non-differential with regard to cases and controls. Another limitation to case–control studies is that cases may be more likely than controls to remember jobs of shorter duration. Those jobs in the more distant past may be more likely recalled by cases than controls resulting in differential bias away from the null. Alternatively, in several of the reported studies, cases were more likely than the controls to provide proxy interviews by their survivors rather than by the cases themselves. Because of the relatively few studies available for individual organ sites, the studies were grouped into four categories including urogenital, brain and central nervous system, larynx and lung, and other.

2.2.1 *Cancers of the urogenital system*

Four cancers of the urogenital organs in relation to employment as a firefighter were considered (Tables 2.3 and 2.6).

Delahunt *et al.* (1995) examined pathologically confirmed incident renal cell carcinomas the New Zealand Cancer Registry during the period 1978–1986. The registry included 95% of those patients diagnosed and treated in both the public and private sector. At time of registration, the current or most recent occupation was recorded. Additional information collected included age, and smoking habits. Renal cell carcinomas with an ICD-9 code of 189.0 (malignant neoplasm of the kidney, excluding the renal pelvis) were evaluated. The control groups were a random sample of registrations drawn from all cases over 20 years of age, having primary tumours from sites other than the urinary tract registered during the same time period. There were a total of 710 male cases and 12 756 controls. There were 52 cases and 737 controls under the occupational classification of "Service" which included firefighters and five other occupational groups. The relative risk for firefighters was 4.7 (95% CI: 2.5–8.9).

Bates (2007) (see Table 2.6) conducted a registry-based case–control study using the California Cancer Registry. Anonymized records of all male cancers for the period 1988–2003 were collected. To identify firefighters, the occupation and industry fields were searched for titles including fire, firefighter, fire fighter, fireman, fire man, and fire chief. If the subjects indicated that they did not carry out firefighting activities, they were not considered. A total of 16 cancer organ sites were examined including kidney, bladder, prostate, and testis. For each analysis, all other cancers were used as controls except for those cancers shown in the initial analysis that had demonstrated a firefighting etiology; these included cancers of the lung, bronchus, bladder, prostate, colorectum, and skin melanomas. Analysis was limited to males aged 21–80 at time of diagnosis. There were 3659 firefighters and 800 448 controls in the analysis after exclusion of 13% of the files (n = 140 000) with no recorded occupation or industry. Logistic regression analyses were performed for each cancer type for which there had been more than 50 cancers recorded in firefighters. This was not done for for cancer of the thyroid (n = 32 cases) or multiple myeloma (n = 37 cases) as these two were based on prior hypotheses.

Table 2.3. Case–control studies of the urogenital system

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds Ratio (95% CI)	Adjustment for potential confounders	Comments
Delahunt *et al*. (1995) New Zealand, 1978–86	Renal cell (189.0)	Total number of renal cell carcinomas for all occupations –710 men (Cancer Registry); coverage of 95% incident cases including pathology coding. Occupational code for 86.2%; 5 categories of service workers including firefighters; in which, 52 cases with an unknown number of firefighters	Random sample drawn from all cancer cases except renal cell carcinoma aged over 20 years, having primary tumours from sites other than the urinary tract. 12 756 (all men, Cancer Registry); matched by age, and registration period. 737 controls for category of service workers	Occupation code used to identify employment	Firefighters unadjusted Firefighters age- and smoking-adjusted	NR NR	3.51 (2.09–5.92) 4.69 (2.47–8.93)	Age, smoking	Firefighters likely represented ~10 cases although exact numbers not reported

Table 2.3 (contd)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds Ratio (95% CI)	Adjustment for potential confounders	Comments
Krstev *et al*. (1998) Atlanta, Detroit and 10 counties in New Jersey, USA 1986–89	Prostate	Population-based incident cases from registry; 981 (479 blacks and 502 Caucasians) aged 40–79 years; cases selected by random sample to ensure broad distribution by age and race, a varying proportion of cases selected by random sampling. Histologically confirmed. Response rate not provided but 6 cases and 17 controls with no employment data	1315 (594 blacks and 721 Caucasians) population-based controls selected aged <65 years by random-digit dialling, and >65 selected by random sampling from computerized records of the Health Care Financing for each geographic area administration; matched by age, sex and race	In-person interviews by trained interviewers	Firefighting and prevention – All firefighting Duration of firefighting <5 years 5–19 years ≥20 years	 10 2 3 5	3.85 (1.34–11.10) 3.34 (1.13–9.91) – 1.66 (0.33–8.36) 3.94 (0.76–25.60) *P* for trend=0.07	Age, sex and race	Small number of cases and controls

Table 2.3 (contd)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds Ratio (95% CI)	Adjustment for potential confounders	Comments
Stang *et al*. (2003) Bremen, Essen, Hamburg, Saarbrücken, and Saarland, Germany, 1995–97	Testicular or extragonadal germ cell tumours	269 cases from an active reporting system of clinical and pathological departments; aged 15–69 years; 78% response rate; histologically confirmed. 4 cases (1.5%) were firefighters	797 controls selected randomly from mandatory registries of residence; 57% response rate; matched by age and region of residence 3 controls (0.4%) were fireghters	In-person and telephone interviews conducted by trained interviewers	Worked as a firefighter Ever ≥10 years of duration Work began ≥5 years before diagnosis	 4 2 3	 4.3 (0.7–30.5) 3.0 (0.2–45.5) 3.1 (0.4–24.4)	History of cryptorchidism	Number of firefighter case and controls too low for precise effect but trend is strong

Table 2.3 (contd)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds Ratio (95% CI)	Adjustment for potential confounders	Comments
Gaertner *et al*. (2004) Newfoundland, Prince Edward Island, Nova Scotia, Manitoba, Alberta, Saskatchewan and British Columbia, Canada, 1994–97	Bladder	Incident cases identified in Cancer Registries: 887 cases from Canadian provincial cancer registries; aged 20–74 years; 58 % male response rate, and 61% female response rate; 8 male firefighters	2847 population-based controls selected by random-digit dialling to recruit controls in Newfoundland and Alberta, and random sampling from the provincial health insurance plan database for other locations; 59% male response rate, and 65% female response rate; matched by age and sex 13 male controls	Mailed questionnaires and telephone follow-ups	Firefighter males only Duration of firefighting in years >1–5 >5–15 >15	8 3 1 4	1.51 (0.59–3.84) 2.00 (0.43–9.49) 0.86 (0.71–8.93) 1.36 (0.36–5.16)	Adjusted for age, province, race, smoking, ex-smoking, consumption of fruit, fried food and coffee	No females were included in the analysis

NR, not reported

Logistic regression analyses adjusted for 5-year age categories, 4-year categories from date of diagnosis, five ethnic categories and five categories of an indicator of socioeconomic status. A total of 101 firefighters with a diagnosis of cancer of the kidney or renal pelvis were assessed, and the OR was 1.07 (95% CI: 0.87–1.31), adjusted for age, calendar period of diagnosis, race, and an indicator of socioeconomic status for the census block of residence.

Krstev *et al.* (1998) investigated incident prostate cancer cases in the USA using population-based cancer registries for Atlanta Georgia and Detroit Michigan, and for ten counties in the state of New Jersey during 1986–1989. Histologically confirmed cases were identified from pathology and outpatient records at hospitals included in these registries. Cases were selected by random sampling among the total number of cases identified in each age–race category. [Three additional cancer sites were investigated but not reported including oesophagus, pancreas, and multiple myeloma, and no published articles were located regarding these cancers.] Control subjects were proportional to the age, sex, and race distribution of the cases. Controls younger than 65 years of age were selected through random-digit dialling. Older controls were systematically selected by random sampling from computerized records of the Health Care Financing Administration stratified by three age groups, and race (african american or caucasian for each geographic area). Cases and controls were interviewed in person. There were 981 cases and 1315 controls analysed using unconditional logistic regression adjusted for age (< 60, 60–69, 70+), study site, and race. A total of ten cases and five controls were classified as firefighting (SOC 512.3). The overall adjusted OR for prostate cancer was 3.85 (95% CI: 1.34–11.10), for caucasians only (nine cases and three controls) 4.75 (1.26–18.00), and for african americans (three cases and two controls), 2.64 (0.43–16.20).

Bates (2007) evaluated 1144 firefighters diagnosed with cancer of the prostate (cohort described above for cancer of the kidney), and found an adjusted OR of 1.22 (95% CI: 1.12–1.33).

Stang *et al.* (2003) examined the risk of testicular cancer or extragonadal germ cell tumours during 1995–1997 in five German regions. Cases were reported through an active reporting system. A pathologist derived histological evaluations for 95% of the cases. Interviews were conducted with 269 of the 353 eligible cases, with a response rate of 78% including the two surrogate interviews. Controls were randomly selected from mandatory registries of residence. Approximately two controls were age- and region-matched for the cases between the ages of 15–34 years. Four controls were matched for those cases aged 35–69 to increase study power related to the fewer number of cases in this older age group. The response rate in the controls was 57%, with 918 interviewed (eight surrogate) of 1982 eligible subjects. Each job held for at least 6 months was recorded including job tasks and hours per week worked. These jobs were coded according to the International Standard Classification of Occupation. Conditional logistic regression models were calculated with matching factors including 5-year age groups, and geographic region. The adjusted ORs for ‘ever’

versus ‘never’ employed as a firefighter were 4.3 (95% CI: 0.7–30.5, four cases and three controls); for working as a firefighter ≥ 10 years, 3.0 (95% CI: 0.2–45.5, two cases and two controls); and for employment ≥ 5 years before the ‘reference’ date [date of diagnosis], 3.1 (95% CI: 0.4–24.4, three cases and three controls).

Bates (2007) also evaluated 70 firefighters diagnosed with cancer of the testis (SEER code 28020, cohort described above for cancer of the kidney), and found an adjusted OR of 1.54 (95% CI: 1.18–2.02).

Gaertner *et al.* (2004) reported on incident cases of bladder cancer with a histological confirmation, identified through the National Enhanced Cancer Surveillance System programme in seven Canadian provinces. The cases were adults aged 20–74, identified during 1994–1997 and interviewed 2–5 months after diagnosis. Random selections of population controls were included in the programme by frequency-matching age and gender to all cancer cases. Random digit dialling was used during the 1996 calendar year to recruit controls living in Newfoundland and Alberta, while all other provinces used a random sample from the provincial health insurance database. Native Indians and subjects in the military were excluded from the study. Mailed questionnaires with telephone follow-up, as necessary, were used to gather data regarding sociodemographics, occupational history, smoking history, dietary habits, and specific agent exposures. The response rates for the male and female bladder cancer cases were 66% and 72%, respectively, and for the controls, 59% and 65%, respectively. The overall analysis included 887 cases and 2847 controls. In the analysis of firefighters, eight male cases and 13 male controls were considered. the Standardized Occupational Classification system was used to code occupations, with up to 12 occupations coded per person. Data analysis also included demographic information provided from the interviews. An unconditional logistic regression analysis was used adjusting for age, province, race, smoking, ex-smoking, and consumption of fruit, fried food, and coffee. For the analysis of ‘ever’ or ‘never’ worked as a firefighter for more than one year, an elevated OR of 1.51 (95% CI: 0.59–3.84) was found. When stratified by duration of employment as a firefighter, the ORs were: 2.0 (95% CI: 0.43–9.49) for > 1–5 years (three cases and four controls); 0.86 (95% CI: 0.708–8.93) for > 5–15 years (one case and three controls); and 1.36 (95% CI: 0.36–5.16) for > 15 years (four cases and six controls).

Bates (2007) assessed 174 firefighters diagnosed with cancer of the bladder (SEER code 29010, cohort described above for cancer of the kidney and Table 2.6), and found an adjusted OR of 0.85 (95% CI: 0.72–1.00).

2.2.2 *Cancer of the brain*

Four studies on brain cancer in relation to firefighting were considered, all from the USA (Tables 2.4 and 2.6).

Brownson *et al.* (1990) evaluated brain cancers using the Missouri Cancer registry. Cancer cases from public and private hospitals have been collected since 1972, and reporting has been mandated since 1984. The group of cases comprised Caucasian

males diagnosed with histologically confirmed brain and other central nervous system cancers (ICD codes 191 and 192). Four controls were randomly selected and frequency-matched from all Caucasian male patients diagnosed with cancers during the same time period. Control group cancers included cancers of the lip, oral cavity and pharynx, digestive organs and peritoneum, respiratory system, skin, bones and connective tissue, genitourinary system, and leukaemia, lymphoma, multiple myeloma, and other sites. Of the initially eligible cases, occupational information was lacking in 34% of the cases, and 38% of the controls. Analysis combined industries with Unites States census code related to justice, public order and safety which included firefighters, and for occupations combining police and fire protection services. Age- and smoking-adjusted ORs were elevated and reported as 2.1 (95% CI: 0.9–4.8, ten cases and 19 controls) for the industry of justice, public order and safety, and 2.2 (95% CI: 1.0–4.7, 12 cases and 22 controls) for police and fire protection workers. This excess risk among police and fire protection workers was confined to the astrocytic cell series (OR, 2.3; 95% CI: 1.0–5.1). The OR for firefighters examined separately was 2.0 (95% CI: 0.4–9.6), with an unknown number of cases and controls.

Carozza *et al.* (2000) conducted a population-based case–control study among adults in the San Francisco Bay area during 1991–1994. Lifetime job histories were available for this study. Using the Northern California Cancer Center population, 603 incident cases of gliomas among adults aged 20 years or older were identified with histological confirmation (ICD 9380–9481). Interviews were completed with 492 cases (82%), and 476 were analysed after additional exclusions. Using random-digit dialling, controls were frequency-matched by 5-year age groups as well as by gender and race/ethnicity. There were 754 potential controls identified with 22 removed because of their residence, insufficient level of English or some relationship to the cases. Of the 732 controls meeting the eligibility criteria, 462 (63%) interviews were completed. The job history data for cases and controls were provided by proxy for 45.6% and 0.9%, respectively. For each job reported, the following information was collected: name and location of the company, description of daily work activities, starting date and duration of job including hours worked per week. Jobs were coded using Standardized Occupational Classification 1980 and Standard Industrial Codes 1987 without knowledge of the case–control status. Duration of all jobs held for at least 6 months was analysed; the most recent 10 years were excluded to allow for a hypothesized 10-year latency period between the exposure and the clinical recognition of the disease. Subjects who were not employed in the occupational category being evaluated served as the ‘unexposed’ referent group. Multiple logistic analyses were used adjusting for age, gender, years of education and race (caucasian, non-caucasian). Astrocytic tumours were evaluated including glioblastoma, multiforme, and astrocytoma. The adjusted OR for ‘ever’ versus ‘never’ employed as a fireman was 2.7 (95% CI: 0.3–26.1), and for being diagnosed with having an astrocytic tumour, 3.6 (95% CI: 0.4–36, three cases, 1 control).

Table 2.4. Case–control studies of the brain

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds Ratios (OR) (95% CI)	Adjustment for potential confounders	Comments
Brownson *et al.* (1990) Missouri, USA 1984–88	Brain and other central nervous system cancers (191 and 192)	312 caucasian males; histologically confirmed brain and central nervous system cancers, identified through the Missouri Cancer Registry, maintained by the Missouri Department of Health	1248 frequency-matched (4:1) sample of controls chosen from all other caucasian male patients diagnosed with cancers in the same time period, including lip/oral cavity/pharynx, digestive organs and peritoneum, respiratory, skin, bones and connective tissue, genitourinary, leukaemia, lymphoma, and multiple myeloma, and other sites. Controls randomly selected within each of six age strata. 38% of controls excluded due to missing occupational information	Hospital medical records	*Brain Cancer by Industry*			Adjusted for age and smoking	Limited to caucasian males due to small numbers of non-caucasians and lack of reported occupational diversity among females. 34 % of cases excluded because of missing occupational data. Analysis combined those in police and fire protection US census codes 413–427
					Justice/public order/safety	10	2.1 (0.9–4.8)		
					Brain Cancer by occupation				
					Police and fire protection services	12	2.2 (1.0–4.7)		
					Astrocytic cell type only	NR	2.3 (1.0–5.1)		
					Firefighters only	NR	2.0 (0.4–9.6)		

Table 2.4 (contd)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds Ratios (OR) (95% CI)	Adjustment for potential confounders	Comments
Carozza *et al.* (2000) San Francisco Bay area including Alameda, Contra Costa, Marin, San Mateo, San Franscisco, and Santa Clara counties, USA 1991–94	Brain (Gliomas, 9380–9481)	603 cases of histologically confirmed incident cases of glioma. Age >20 years	462 controls matched by 5-year age groups, gender, and race/ethnicity, and identified by random-digit dialling	Interviews and Standard occupational and Industrial codes used	Ever employed as firefighter Astrocytic tumours	3 3	2.7 (0.3–26.1) 3.6 (0.4–36.1)	Matched on age, gender, education, and race	Only 3 cases and 1 control were firefighters. Duration of job calculated for every job held at least 6 months during subjects' lifetime also with the most recent 10 years excluded to allow for hypothesized 10-year latency period between exposure and clinical recognition of disease

Table 2.4 (contd)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds Ratios (OR) (95% CI)	Adjustment for potential confounders	Comments
Krishnan *et al*. (2003) Alameda, Contra Costa, Marin, San Mateo, San Francisco and Santa Clara counties, California, USA 1991–94 and 1997–99	Glioma (938.0, 948.1)	879 incident cases identified using Northern California Cancer Center's rapid ascertainment programme; 81% response rate	864 population-based controls selected by random-digit dialling; frequency- matched by age, race, and sex; 66% response rate	Interviews and Standard occupational and industrial codes used	Ever employed	9	2.85 (0.77–10.58)	Age, race and sex	40% of case participants reported by proxy
					Longest-held job as a firefighter	6	5.88 (0.70–49.01)		
					Longest-held job as a firefighter and astrocytic cases only	5	6.31 (0.73–54.40)		Referent group for analysis included those without the given occupational group as their longest-held job, including those who were never employed
					Longest held job as firefighter non-astrocytic cases	1	9.27 (0.55–155.27)		

Krishnan *et al.* (2003) conducted a follow-up study to the one designed by Carozza *et al.* (2000). This follow-up study examined incident glioma cases diagnosed during both 1991–1994 and 1997–1999. All adults newly diagnosed with glioma during these time periods were ascertained using the Northern California Cancer Center's rapid ascertainment programme. Controls were ascertained through random-digit dialling and matched to cases by age, race, and gender. There were 1129 eligible cases with 81% ($n = 896$) completing full interviews. In-person interviews were conducted for 98%, and there were 879 cases with complete information available for analysis. Of the eligible controls, 66% ($n = 864$) completed a full interview. In the analysis of 'ever' employed as a firefighter, the OR was 2.85 (95% CI: 0.77–10.58, nine cases and three controls). Analysis by the longest-held job resulted in an OR of 5.88 (95% CI: 0.70–49.01, six male cases and one male control). In the analysis of astrocytic cases, the OR was 6.31 (95% CI: 0.73–54.4, five cases and one control), and for the non-astrocytic cases, 9.27 (95% CI: 0.55–155.27, one case and one control). [These two studies are very similar with more cases and controls available in the Krishnan report. The Krishnan report, however, did not carry out analyses by 10-year latency period, and therefore both studies may be relevant.]

Bates (2007) also evaluated brain cancers (SEER code 31010) in firefighters as described above under kidney cancer and Table 2.6. There were 71 firefighters with brain cancer. The adjusted OR was 1.35 (95% CI: 1.06–1.72).

2.2.3 *Cancers of the larynx and lung*

One case–control study of cancer of the larynx and two studies of cancer of the lung were considered by the Working Group (Tables 2.5 and 2.6).

Muscat and Wynder (1995) conducted a case–control study of cancer of the larynx in New York City, USA, recorded during 1956–1965. Caucasian men from seven hospitals newly diagnosed with histologically confirmed cancer of the larynx were interviewed. Control subjects were also caucasian men frequency-matched to the cases by hospital of diagnosis, age (within 5 years), and year of interview. Eligibility as a control also required a hospital admission for a condition unrelated to an etiology associated with tobacco exposures including cancer of the prostate, lymphomas, benign prostatic hypertrophy, and various non-malignant conditions. All subjects were interviewed by personnel who were not blinded to the case–control status of subjects, with a 90% response rate. The questionnaire included information on smoking status (never, current or ex-smoker, number of cigarettes, pipe and cigars smoked, and alcohol intake). Data were collected on lifetime occupations and self-reported exposures to chemicals, metals, exhaust, asbestos, and other occupational substances. There were 235 cases and 205 controls. The cases compared to controls were most likely to be: current cigarette smokers, (66.4% and 24.4%, respectively), heavy cigarette smokers (> 31 cigarettes/day), (55.1% and 22.8%, respectively), and drink more than 7 ounces of alcohol per day (29.4% and 11.2%, respectively). Analyses were adjusted for current smoking status.

Table 2.5. Case–control studies of cancers of the larynx and lung

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds Ratios (OR) (95% CI)	Adjustment for potential confounders	Comments
Muscat & Wynder (1995) New York, USA 1956–65	Larynx	235 caucasian men from 7 hospitals with histologically confirmed laryngeal cancer	205 caucasian men, 90% response rate of "eligible patients"; frequency-matched by hospital, age (within 5 years) and year of interview. Controls selected for condition unrelated to tobacco-induced diseases and included prostrate cancer, lymphomas, benign prostatic hypertrophy, non-malignant conditions. Only 2 firefighters (1%)	Interview	Laryngeal Cancer Classified as working in diesel exhaust job Self-reporting exposure to diesel exhaust	2 36 13	 0.96 (0.5–1.8) 1.47 (0.5–4.1)	Smoking	

Table 2.5 (contd)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds Ratios (OR) (95% CI)	Adjustment for potential confounders	Comments
Elci *et al*. (2003) Istanbul and Marmara region, Turkey 1979–84	Lung (ICD: 162.0 and 162.2 combined, and compared to 162.3, 162,4, 162.5 and 162.9)	1354 male cases of lung cancer; 442 cases without histological confirmation	1519 male cancer and non-cancer controls diagnosed with Hodgkin disease, soft tissue sarcoma, testis, bone, male breast and non-cancer benign pathologies	Standardized questionnair eJobs classified by Standard occupational and Industrial codes	*Lung Cancer by*			Age and smoking	22 women were excluded from analyses
					Firefighter	10	6.8 (1.3–37.4)		
					Squamous cell	4	6.2 (0.8–46.2)		
					All bronchus and parenchyma	9	7.0 (1.3–39.1)		

Among the cases, two were employed as firefighters. Of those occupations which self-reported exposure to diesel exhaust, including truck drivers, firefighters, road workers, and mine workers (5.5 cases and 4.4 controls), the adjusted OR was 1.47 (95% CI: 0.5–4.1). For those occupations which self-reported exposure to diesel 'fumes', firefighter was not listed amongst them The authors noted that the self-reported exposure to diesel exhaust or diesel fumes may reflect uncontrolled confounding with cigarette smoking and alcohol consumption as almost all patients who reported diesel exposure were also heavy cigarette smokers, and consumed large amounts of alcohol.

Elci *et al.* (2003) examined the link between occupations and risk of lung cancer by histological types in Turkey. Cases were identified from an oncology treatment centre at one of the largest cancer hospitals, including treatment for workers, in Istanbul. After admission to hospital, all patients completed a standardized questionnaire administered by trained interviewers. There were 1354 male lung cancer cases with complete interview information identified during 1979–1984. An oncologist reviewed hospital records for diagnostic verification and classification of cancer types. When there were four or more cases per cancer type, histopathology and morphological type was examined. Patient controls "with the same sociodemographic background as the cases" were selected having the following diagnoses: cancers of the skin (non-melanoma), testis, bone, male breast, Hodgkin disease, soft-tissue sarcoma, and non-cancer patients. Of the 27 occupations, firefighting ($n = 10$ cases) had an excess risk of lung cancer, with an age- and smoking-adjusted OR of 6.8 (95% CI: 1.3–37.4). In firefighters, for squamous-cell carcinoma ($n = 4$), the age- and smoking-adjusted OR was 6.2 (95% CI: 0.8–46.2), and for peripheral tumours including bronchus and parenchyma ($n = 9$), the age- and smoking-adjusted OR was 7.0 (95% CI: 1.3–39.1).

Bates (2007) investigated cancers of the lung and bronchus in firefighters as described above under kidney cancer and in Table 2.6. There were 495 firefighters with these cancers. The adjusted OR was 0.98 (95% CI: 0.88–1.09).

2.2.4 *Cancers at other sites*

(*a*) *Multiple myeloma, non-Hodgkin lymphoma, and leukaemia*

Demers *et al.* (1993) identified cases of multiple myeloma through SEER tumour registries in four geographic locations including two counties in Washington State, two in Utah including Salt Lake City, five counties of metropolitan Atlanta, Georgia, and three metropolitan Detroit, Michigan, counties. All those potentially eligible included all incident cases diagnosed during 1977–1981. Controls were selected to be similar in age, gender, and region. In Washington State, 1683 population-based controls were selected by using two sampling units of four households. In other areas, a random-digit dialling method was used for selecting controls. Interviews were obtained from 692 (89%) of the cases or their survivors, and from 1683 (83%) of the controls.

Table 2.6. Case–control studies of other or multiple sites

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds Ratios (OR) (95% CI)	Adjustment for potential confounders	Comments
Demers *et al.* (1993) King and Pierce counties, Washington; Davis county, Salt Lake and Weber county, Utah; Atlanta, Georgia; Detroit, Michigan; USA 1977–81	Multiple myeloma	692 cases of multiple myeloma. Total incident cases from tumour registries in the USA, aged <80 years	1683 population-based controls in Washington state selected by two sampling units of four households, and in other areas random-digit dialling; response rate 83%; matched by age, sex, and region	Interview and proxy interviews	All firefighters Employed ≥10 years Self-responding	5 4 4	1.9 (0.5–9.4) 2.9 (0.4–21.6) 2.8 (0.5–14.3)	Sex, race, age, and study area.	Small number of cases and controls. Uncertain as to which jobs represent firefighting and prevention occupations

Table 2.6 (contd)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds Ratios (OR) (95% CI)	Adjustment for potential confounders	Comments
Bates (2007) California, USA 1988–2003	Oesophagus Colorectum Lung Melanoma Prostate Testis Bladder Brain Thyroid Leukaemias Non-Hodgkin lymphoma Multiple myeloma	3659 cases (all men) from the California Cancer Registry, aged 21–80 years; 94% histologically confirmed	All other males in registry that were not firefighters (*n*=800448) from California Cancer Registry except those diagnosed with cancers of the lung, bronchus, prostate, colorectum, and skin melanomas.	California Cancer Registry records	Oesophagus Stomach Colorectum Caecum Pancreas Lung & bronchus Melanoma Prostate Testis Bladder Kidney & renal pelvis cancer Brain Thyroid cancer Leukaemias Non-Hodgkin lymphoma Multiple myeloma	62 51 282 52 63 495 323 1144 70 174 101 71 32 100 159 37	1.48 (1.14–1.91) 0.80 (0.61–1.07) 0.90 (0.79–1.03) 1.09 (0.82–1.44) 0.90 (0.70–1.17) 0.98 (0.88–1.09) 1.50 (1.33–1.70) 1.22 (1.12–1.33) 1.54 (1.18–2.02) 0.85 (0.72–1.00) 1.07 (0.87–1.31) 1.35 (1.06–1.72) 1.17 (0.82–1.67) 1.22 (0.99–1.49) 1.07 (0.90–1.26) 1.03 (0.75–1.43)	SES quintile	Use of other cancer controls may have biased study toward null

SES, socioeconomic status

For the cases, 220 (32%) were interviewed by proxy. Analyses were adjusted for gender, race, 4-year age groups, and study area. The adjusted OR for employment in firefighting and prevention occupations was 1.9 (95% CI: 0.5–9.4, five cases and five controls), and for the self-reporting category, 2.8 (95% CI: 0.5–14.3, four cases). The OR for firefighters employed < 10 years was 0.9 (95% CI: 0.0–22.3, one case and two controls), while for those employed 10 or more years, the OR increased to 2.9 (95% CI: 0.4–21.6, four cases and three controls).

Bates (2007) also investigated multiple myeloma, non-Hodgkin lymphoma, and leukaemia in firefighters (for full study description see Section 2.2.1 and Table 2.6), for which the ORs were reported as 1.03 (95% CI: 0.75–1.43, 37 cases), 1.07 (95% CI: 0.90–1.26, 159 cases), and 1.22 (95% CI: 0.99–1.49, 100 cases), respectively.

(*b*) *Cancers of the gastrointestinal system and pancreas*

Bates (2007) conducted the only study investigating cancers of the gastrointestinal system in firefighters. The ORs for cancers of the stomach were 0.80 (95% CI: 0.61–1.07, 51 cases), of the colorectum 0.90 (95% CI: 0.79–1.03, 282 cases), of the caecum 1.09 (95% CI: 0.82–1.44, 52 cases), and of the pancreas 0.90 (95% CI: 0.70–1.17, 63 cases).

(*c*) *Thyroid cancer*

Bates (2007) assessed 32 firefighters with cancer of the thyroid, and found an OR of 1.17 (95% CI: 0.82–1.67).

(*d*) *Melanoma*

Bates (2007) investigated firefighters (n = 323) diagnosed with melanoma, and found a significant and elevated OR of 1.50 (95% CI: 1.33–1.70).

2.3 Descriptive studies

Several descriptive studies have provided results for firefighters. These have varied in their design including cohort studies based on record linkage, and studies based solely on death certificate or registry data. In some cases, these have been investigations specifically directed at firefighters. They are described in more detail below and in Tables 2.7 and 2.8.

2.3.1 *Cohort and linkage studies of firefighters*

Feuer & Rosenman (1986) conducted a study of deaths among active and retired firefighters from the state of New Jersey, USA, during 1974–1980. Firefighters were identified using pension records, and their duration of employment was also collected. Their mortality was compared to that of the police force, identified in the same manner, and of the general population. Proportionate mortality ratios (PMRs) were calculated based on 263 caucasian male firefighter deaths, and a significant excess of leukaemia was observed using to the police force as reference group.

Table 2.7. Cohort and linkage studies of firefighters

Reference, location, name of study	Study population description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	PMR/SMR/MOR (95% CI)	Adjustement for potential confounders	Comments
Feuer & Rosenman (1986), New Jersey, USA 1974–80	263 active and retired firefighters, identified using retirement system records	Pension records				**PMR**	Age	
			All cancers	Overall, compared to NJ	67	1.0 [n.s.]		
				≤20 years	15	0.9 [n.s.]		
				20–25 years	18	1.0 [n.s.]		
				>25 years	34	1.1 [n.s.]		
				Compared to Police	67	1.1 [n.s.]		
			Digestive	Overall, compared to NJ	20	1.1 [n.s.]		
				≤ 20 years	5	1.2 [n.s.]		
				20–25 years	5	1.0 [n.s.]		
				>25 years	10	1.2 [n.s.]		
				Compared to Police	20	0.9 [n.s.]		
			Respiratory	Overall, compared to NJ	23	0.9 [n.s.]		
				≤ 20 years	4	0.7 [n.s.]		
				20–25 years	7	1.0 [n.s.]		
				>25 years	12	1.0 [n.s.]		
				Compared to Police	23	1.0 [n.s.]		
			Skin	Overall, compared to NJ	4	1.9 [n.s]		
				≤ 20 years	0	0.0 [n.s.]		
				20–25 years	1	1.8 [n.s.]		
				>25 years	3	3.9 [n.s.]		
				Compared to Police	4	1.4 [n.s.]		
			Leukaemia	Compared to NJ	4	1.8 [n.s.]		
				Compared to Police	4	2.8 [P<0.05]		

Table 2.7 (contd)

Reference, location, name of study	Study population description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	PMR/SMR/MOR (95% CI)	Adjustement for potential confounders	Comments
Hansen (1990), Denmark	Mortality among 886 men identified as firefighters in the 1970 census followed through 1980 compared to men in similar occupations	Occupation as reported in the Census		Males		**SMR**	Age, calendar period	
			All	Overall	21	1.2 (0.7–1.8)		
				Age 30–49	NR	4.4 (1.4–10.2)		
				Age 50–59	NR	1.0 (0.3–2.3)		
				Age 60–74	NR	1.9 (0.9–3.7)		
			Lung	Overall	9	1.6 (0.8–3.1)		
				Age 30–49	NR	0.0 (0.0–1.5)		
				Age 50–59	NR	1.4 (0.2–4.9)		
				Age 60–74	NR	3.2 (1.2–6.9)		

Table 2.7 (contd)

Reference, location, name of study	Study population description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	PMR/SMR/MOR (95% CI)	Adjustement for potential confounders	Comments
Ma *et al.* (1998), 24 states, USA	Analysis of 1984–1993 death certificate data, 6607 firefighters identified	Usual occupation on death certificate		Overall, caucasian males		**MOR**	Age, year of death	
			All		1817	1.1 (1.1–1.2)		
			Lip		3	5.9 (1.9–18.3)		
			Colon		149	1.0 (0.9–1.2)		
			Rectum		27	1.1 (0.8–1.6)		
			Pancreas		88	1.2 (1.0–1.5)		
			Lung		633	1.1 (1.0–1.2)		
			Prostate		189	1.2 (1.0–1.3)		
			Bladder		48	1.2 (0.9–1.6)		
			Kidney & pelvis		49	1.3 (1.0–1.7)		
			Brain & CNS		41	1.0 (0.8–1.4)		
			non-Hodgkin lymphoma		76	1.4 (1.1–1.7)		
			Multiple Myeloma		28	1.1 (0.8–1.6)		
			Leukaemia		60	1.1 (0.8–1.4)		
			Soft tissue sarcoma		14	1.6 (1.0–2.7)		
				Overall, black males				
			All		66	1.2 (0.9–1.5)		
			Nasopharynx		1	7.6 (1.3–46.4)		
			Colon		9	2.1 (1.1–4.0)		
			Pancreas		5	2.0 (0.9–4.6)		
			Lung		15	0.8 (0.5–1.3)		
			Prostate		16	1.9 (1.2–3.2)		
			Brain & CNS		5	6.9 (3.0–16.0)		

* specify *P* value if no confidence interval indicated; MOR, mortality odds ratio; NJ, New Jersey; NR, not reported; n.s, not significant; PMR, proportionate mortality ratio; SMR, standardized mortality ratio

Hansen (1990) performed a study of Danish firefighters employed at the time of the 1970 national census. An analysis was then conducted of 57 deaths (21 from cancer) during 1970–1980 occurring among 886 males who had reported employment as firefighter. Men employed in similar occupations were used as the reference group, and an excess of lung cancer among firefighters over the age of 60 was reported, based on small numbers.

Ma *et al.* (1998) conducted a further analysis of a data set collected by Burnett *et al.* (1994) with additional years of follow-up using 1984–1993 death certificate data from 24 states in the USA. A total of 6607 deaths and 1883 cancer deaths among firefighters were identified based on the occupational titles on death certificates. Race-specific cancer mortality odds ratios (MORs) were calculated with all non-cancer deaths as the reference group. Analyses were adjusted for age and year of death. Among caucasian male firefighters, significant excesses were observed for cancers of the lip, pancreas, lung, prostate, kidney, and soft-tissue sarcoma and non-Hodgkin lymphoma. Among black male firefighters, significant excesses were observed for cancers of the nasopharynx, colon, prostate, and brain.

2.3.2 *Descriptive studies with firefighter results.*

There is a large body of descriptive epidemiology carried out for the purpose of occupational cancer and mortality surveillance. The results of these studies are summarized in Table 2.8.

Berg & Howell (1975) examined the risk of colorectal cancer by occupation using death certificate data from the USA and the United Kingdom and observed an excess among firefighters. [The Working Group noted that there was an overlap between the United Kingdom data included in this study and the meta-analysis by Dubrow & Wegman, 1983].

Williams *et al.* (1977) observed excesses of oral cancer, lung cancer, bladder cancer, and non-Hodgkin lymphoma based on the small number of cancers among firefighters that were included in the Third National Cancer Survey, USA. [The Working Group noted that Williams *et al.* (1977) was included in the meta-analysis conducted by Dubrow & Wegman (1983), but was unique in that occupation was ascertained by interview.]

Dubrow & Wegman (1983) summarized the results of ten early USA and United Kingdom studies and reported the results that appeared to be most consistent between the studies. Among those studies that reported results for firefighters, large intestine cancer and multiple myeloma were significantly elevated.

Morton & Marjanovic (1984) examined the incidence of leukaemia by occupation in the Portland–Vancouver metropolitan area in North-western USA, and excesses were observed among firefighters based on very small numbers.

Mortality among a cohort of 293 958 United States military veterans was examined by occupation and industry (Blair *et al.*, 1985). Usual occupation and industry as well as smoking information was determined from questionnaires

completed in 1954 and 1957, and 107 563 deaths were recorded during 1954–1970. Excesses of rectal, bladder, and brain cancers were observed based on very small numbers.

Gallagher *et al.* (1989) conducted a study of mortality by occupation and industry using death certificate data during 1950–1984 from the Canadian province of British Columbia. There were 1202 deaths among firefighters identified based on occupational titles on death certificates. PMRs were calculated with adjustment for 5-year age and calendar period. There were 197 cancer deaths, and a small excess of overall cancer as well as a significant excess of pancreatic cancer was observed.

In the USA, Sama *et al.* (1990) examined cancer incidence among firefighters using the Massachusetts Cancer Registry records for 1982–1986. Employment as a firefighter was based on the usual occupation reported to the Registry. The analysis was restricted to 315 Caucasian male firefighters. Case–control analyses were conducted for nine different cancer types and two 'unexposed' reference populations were used: policemen and statewide males. Standardized morbidity odds ratios (SMORs) were calculated and significant excesses of malignant melanoma and bladder cancer were observed compared to the general population. Excesses of bladder cancer and non-Hodgkin lymphoma were observed when compared to policemen.

An analysis of deaths in England and Wales (1979–1980 and 1982–1990) were examined by occupation (OPCS, 1995). A total of 2968 deaths among male firefighters and 16 deaths among their female counterparts were observed based on the last occupation listed on death certificates. Only statistically significant results were reported, and excesses of oesophageal, stomach, and gall bladder cancer mortality were observed among men.

A follow-up study was conducted in the Finnish working-age population identified in the 1970 census (Pukkala, 1995). A total of 1436 male firefighters were identified during the follow-up period during 1971–1985 through linkage with the Finnish tumour registry. No statistically significant excesses were observed. The largest excess reported was for non-localized prostate cancer.

In Canada, Finkelstein (1995) examined occupations associated with lung cancer using a case–control study based on death certificates in two Ontario cities, and observed an excess among firefighters based on small numbers.

Milham (1997) conducted a study of mortality by occupation and industry using death certificate data (1950–1989) from the state of Washington, USA. A total of 2266 deaths among firefighters were identified based on the occupational titles on death certificates. PMRs were calculated and adjusted by 5-year age group and calendar period. There were 197 cancer deaths and a small excess of overall cancer was observed as well as significant excesses of melanoma and lympho- and reticulosarcoma. [The Working Group noted that there was an overlap between this and the multistate studies conducted by NIOSH, but that this had the longest follow-up period and was the earliest study of its kind in North America.]

Table 2.8. Descriptive studies with results on firefighters

Reference, location, name of study	Study population description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR/SIR/SMR (95% CI)*	Adjustement for potential confounders	Comments
Berg & Howell (1975), USA & UK	US males aged 20–44, who died in 1950, and UK male deaths, 1949–1953 and 1959–1963	Occupation on death certificate	Colorectum	Overall	39	**PMR** 1.72 **SMR** 2.79	Age, calendar period	Overlap with Dubrow & Wegman, (1983)
Williams *et al.* (1977), USA	34 male firefighters with incident cancer included in the Third National Cancer Survey, 1969–1971	Occupation from interview				**OR**	Age, race, education, smoking, alcohol	Overlap with Dubrow & Wegman, (1983)
			Oral cavity	Overall, male	4	2.44 [n.s.]		
			Colon		4	0.80 [n.s.]		
			Lung		8	1.78 [n.s.]		
			Prostate		5	0.90 [n.s.]		
			Bladder		4	2.72 [n.s.]		
			Lymphosarcoma		2	15.30 [n.s.]		
			Other, non-Hodgkin lymphoma		1	3.39 [n.s.]		

Table 2.8 (contd)

Reference, location, name of study	Study population description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR/SIR/SMR (95% CI)*	Adjustement for potential confounders	Comments
Dubrow & Wegman (1983), USA & UK	Meta analysis of 10 surveillance studies	Varied	Large intestine (excl. rectum) Multiple myeloma	Overall, summary result from 5 studies reporting Overall, summary result from 3 studies reporting	 70 11	**Summary RR** 1.3 (P<0.05) 2.0 (P<0.05)	Age, at least	Studies included in the meta-analysis Milham (1976), Petersen & Milham (1980), OPCS (1978), Guralnick (1963), Williams *et al.* (1977), Decoufle *et al.* (1977), Gute (1981), OPCS (1971, 1972,1975), Dubrow & Wegman (1984)
Morton & Marjanovic (1984), Portland–Vancouver, USA	1678 leukaemia cases aged 16–67 from the records of 24 hospitals and death certificates, 1963–1977	Occupation abstracted from hospital records and death certificates	Leukaemia Lymphatic Non-lymphatic	Firefighters Overall leukaemia Lymphatic Non-lymphatic	 4 1 3	**SIR** 3.5 (P<0.01) 2.1 [n.s.] 4.5 (P<0.01)	Age	1970 Census data used for reference

Table 2.8 (contd)

Reference, location, name of study	Study population description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR/SIR/SMR (95% CI)*	Adjustement for potential confounders	Comments
Blair *et al.*, (1985); Walrath *et al.* (1985); USA	Follow–up (1954–1970) of 902 USA Veterans reporting occupation as firefighter	Usual occupation from interview		Overall, Male		**SMR**	Age, calendar period, smoking	
			Intestine		8	1.4 [n.s.]		
			Lung, bronchus		13	1.1 [n.s.]		
Gallagher *et al.* (1989), British Columbia, Canada	Death certificate study 1950–1984. 1202 firefighter deaths	Usual occupation on death certificate				**PMR**	Age, calendar period	
			All		197	1.2 (1.0–1.3)		
			Colon		20	1.4 (0.8–2.1)		
			Rectum		10	1.2 (0.6–2.2)		
			Pancreas		19	1.7 (1.1–2.7)		
			Lung		50	1.0 (0.8–1.4)		
			Prostate		23	1.4 (0.9–2.1)		
			Bladder		9	1.5 (0.7–2.9)		
			Kidney		3	0.7 (0.1–2.1)		
			Brain		6	1.2 (0.4–2.7)		
			Non-Hodgkin lymphoma		7	1.5 (0.6–3.2)		
			Multiple myeloma		2	0.8 (0.1–2.9)		
			Leukaemia		8	1.3 (0.5–2.5)		

Table 2.8 (contd)

Reference, location, name of study	Study population description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR/SIR/SMR (95% CI)*	Adjustement for potential confounders	Comments
Hrubec *et al.* (1992) USA	Follow-up 1954–80 of 902 USA veterans reporting occupation as a firefighter	Usual occupation on death certificate		Occupation as a firefighter		**RR (90% CI)**	Age, calendar period	
			All cancer		110	1.2 (1.1–1.4)		
			Rectum		7	2.2 (1.2–4.2)		
			Prostate		12	1.1 (0.7–1.7)		
			Bladder		8	2.1 (1.2–3.8)		
			Brain		5	2.3 (1.1–4.9)		
			Malignant lymphoma		2	0.4 (NR)		
			Leukaemia		3	0.7 (NR)		

Table 2.8 (contd)

Reference, location, name of study	Study population description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR/SIR/SMR (95% CI)*	Adjustement for potential confounders	Comments
Sama *et al.* (1990) Massachusetts, USA	315 cases of cancer identified from the Massachusettes Tumor Registry between 1982–86 Two reference groups of unexposed cases; state population and police; aged 18 and older at the time of diagnosis	Usual occupation from tumour registry records		Caucasian males		**SMOR**	Age, smoking race	
			Colon	Overall, compared to state population	33	1.2 (0.8–1.8)		
				Overall, compared to Police	33	1.0 (0.6–1.8)		
			Rectum	Overall, compared to state population	22	1.4 (0.8–2.2)		
				Overall, compared to Police	22	1.0 (0.5–1.9)		
			Pancreas	Overall, compared to state population	6	1.0 (0.4–2.3)		
				Overall, compared to Police	6	3.2 (0.7–14.2)		
			Lung	Overall, compared to state population	71	1.2 (0.9–1.7)		
				Overall, compared to Police	71	1.3 (0.8–2.0)		
			Melanoma	Overall, compared to state population	26	2.9 (1.7–5.0)		
				Overall, compared to Police	18	1.4 (0.6–3.2)		
			Bladder	Overall, compared to state population	26	1.6 (1.0–2.5)		
				Overall, compared to Police	26	2.1 (1.1–4.1)		
			Brain & other nervous system	Overall, compared to state population	5	0.9 (0.3–2.2)		
				Overall, compared to Police	5	1.5 (0.4–5.9)		

Table 2.8 (contd)

Reference, location, name of study	Study population description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR/SIR/SMR (95% CI)*	Adjustement for potential confounders	Comments
Sama *et al.* (1990) (contd)			Non-Hodgkin lymphoma	Overall, compared to state population	14	1.6 (0.9–2.8)		
				Overall, compared to Police	14	3.3 (1.2–9.0)		
			Leukaemia	Overall, compared to state population	6	1.1 (0.5–2.6)		
				Overall, compared to Police	6	2.7 (0.6–11.5)		
OPCS (1995), England and Wales UK	Death certificate study 1979–1980, 1982–1990. 2698 deaths among men and 16 deaths among women	Last occupation on death certificate				**PMR**	Age	Only statistically significant results reported
			All cancers	Men	432	1.16		
			Oesophagus		46	1.4 (1.0–1.8)		
			Stomach		91	1.5 (1.2–1.8)		
			Gallbladder		10	2.2 (1.1–4.1)		
			All cancers	Women	2	1.07		
Finkelstein (1995), Ontario, Canada	Population-based case–control study using death certificate data between 1979–1988 Males age 45–75 years	Usual occupation on death certificate		Male firefighters		**RR**	Age, year of death, city of residence	
			Lung		6	1.9 (0.6–6.3)		

Table 2.8 (contd)

Reference, location, name of study	Study population description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR/SIR/SMR (95% CI)*	Adjustement for potential confounders	Comments
Milham (1997), Washington State, USA	Death certificate study 1950–1989. 2266 firefighter deaths	Usual occupation on death certificate				**PMR**	Age, Calendar period	
			All Cancers		476	1.1 (1.0–1.2)		
			Buccal cavity & pharynx		7	0.6 (0.3–1.3)		
			Oesophagus		11	1.1 (0.6–2.0)		
			Stomach		22	0.8 (0.5–1.2)		
			Colon		36	0.9 (0.6–1.2)		
			Rectum		15	1.1 (0.6–1.8)		
			Pancreas		28	1.1 (0.7–1.6)		
			Larynx		3	0.6 (0.1–1.8)		
			Lung		120	1.0 (0.8–1.2)		
			Prostate		56	1.1 (0.8–1.5)		
			Kidney		9	0.9 (0.4–1.6)		
			Bladder & urinary		23	1.4 (0.9–2.1)		
			Melanoma		9	2.1 (1.0–4.1)		
			Brain & nervous system		19	1.6 (0.9–2.4)		
			Lympho- & reticulosarcoma		13	1.8 (1.0–3.0)		
			Hodgkin lymphoma		7	1.8 (0.7–3.7)		
			Other lymphoma		3	0.5 (0.1–1.4)		
			Multiple myeloma		9	1.3 (0.6–2.4)		
			Leukaemia		27	1.4 (0.9–2.1)		

* specify *P*–value if no confidence interval indicated

NR, not reported; n.s, not significant

2.4 Case reports

Individual firefighters have applied for, and sometimes received, workers' compensation for cancer. An apparent cluster of cancer among firefighters was reported in an investigation of a chemical waste dump fire by NIOSH (Hrubec *et al.*, 1992). However, the authors concluded it was not likely to have been related to firefighting. [Given the limitations of these reports and the large number of descriptive, cohort, and case–control studies with data on firefighters, the Working Group did not believe that case reports would contribute to the evaluation.]

2.5 Meta-analyses

Two meta-analyses of studies of firefighters and cancer have been conducted (Howe & Burch, 1990; LeMasters *et al.*, 2006). The most recent meta-analysis included a great majority of the studies considered by the Working Group (LeMasters *et al.*, 2006). Cancer risk was significantly elevated for ten of the 21 cancer types analysed (stomach, colon, rectum, skin, prostate, testis, brain, non-Hodgkin lymphoma, multiple myeloma, and malignant melanoma). With the exception of testicular cancer (summary RR = 2.02), the summary relative risk estimates were moderate, ranging from 1.21 for colon to 1.53 for multiple myeloma. For four of these sites (prostate, testis, non-Hodgkin lymphoma, and multiple myeloma), findings were consistent across study designs and the types of study available. However, since that analysis, two additional large studies of cancer in firefighters had been published (Ma *et al.*, 2006; Bates, 2007). Therefore, another meta-analysis was performed by the Working Group to assess the impact of these recent studies.

Inclusion criteria for studies in this meta-analysis were reported estimates of relative risk with corresponding 95% confidence intervals or information that allowed their computation by the Working Group for 'ever' versus 'never' exposure to firefighting or employment as a firefighter. For those studies that did not report for this category, the relative risks and 95% confidence intervals were estimated by the Working Group from strata-specific relative risk and corresponding number of cases, assuming a normal distribution when possible. Studies that only reported point estimates without confidence intervals were not included. Proportionate mortality studies were also excluded. Statistical heterogeneity among studies was tested with the Q statistic. Summary relative risk estimates were obtained from random-effect models for prostate cancer ($Q = 32.816$, $P = 0.005$), and fixed-effect models for testicular cancer ($Q = 3.928$, $P = 0.560$), and non-Hodgkin lymphoma ($Q = 6.469$, $P = 0.486$). All statistical analyses were performed using STATA (version 9.0; StataCorp, College Station, TX).

Based on the Working Group's meta-analysis, three of the four sites remained statistically significant. Testicular cancer was evaluated based on six studies and

409 cases (Giles *et al.*, 1993; Aronson *et al.*, 1994; Bates *et al.*, 2001; Stang *et al.*, 2003; Ma *et al.*, 2006; and Bates, 2007). The results demonstrated an approximate 50% increased risk (1.47, 95% CI: 1.20–1.80, fixed effects). Prostate cancer was evaluated using 16 available studies and 1764 cases (Aronson *et al.*, 1994; Baris *et al.*, 2001; Bates *et al.*, 2001 ; Bates, 2007; Beaumont *et al.*, 1991; Demers *et al.*, 1994; Firth *et al.*, 1996; Giles *et al.*, 1993; Grimes *et al.*, 1991; Guidotti 1993; Krstev *et al.*, 1998; Ma *et al.*, 1998; Ma *et al.*, 2006; Pukkala, 1995; Tornling *et al.*, 1994; and Vena & Fiedler, 1987). The results showed a 30% elevated risk (1.30; 95% CI: 1.12–1.51, random effects). Non-Hodgkin lymphoma was evaluated based on seven studies and 312 cases, and had a 21% elevated risk estimate (1.21; 95% CI: 1.08–1.36, fixed effects) (Baris *et al.*, 2001; Bates, 2007; Giles *et al.*, 1993; Ma *et al.*, 1998, 2006; Pukkala, 1995; and Sama *et al.*, 1990).

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3. Studies of Cancer in Experimental Animals

No data were available to the Working Group.

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism and excretion

Smoke is a complex mixture of chemicals in aerosol, gas, and vapour forms. The focus of this section of the monograph will be primarily on components of smoke from municipal and wildland fires. There is a paucity of information on the extent of exposure to firefighters from trash fires, vehicle fires, and non-wildfire vegetation fires, during which firefighters typically do not wear respiratory protection. Although not typical of exposures most firefighters encounter, there are published reports on the effects of firefighter exposure to specific incidents, including the World Trade Center fire and collapse, and specific industrial fires or clean-up operations. It should be kept in mind that the magnitude of these exposures are not representative of most fires.

Information on many of the specific chemicals found in smoke is available in previous IARC monographs. The data on absorption, distribution, metabolism, and excretion for select carcinogens contained in fire smoke are listed in Table 4.1. Only inhalation and dermal exposures were considered – the predominant occupational exposure routes in firefighters. One of the difficulties in evaluating the toxicokinetics and metabolism of combustion products in firefighters is the adsorption of chemical components onto particles (Fine *et al*., 2001). This will alter the absorption kinetics of these combustion products and may also cause a proportionally greater effect in the lungs compared to other tissues. Depending on their volatility, these chemicals may also exist at significant concentrations in the gas phase of smoke exposure as well. No chronic toxicity studies could be found on non-human exposure to combustion products from structural materials. Due to limited data, the toxicokinetics of chemical mixtures are not considered in this monograph, although they are likely to be of significant importance given the multiplicity of chemicals in smoke.

4.1.1 *Particles*

Particle deposition depends on the size and shape of the particle. Smoke from combustion of products such as wood tends to produce small particles that can easily reach the alveolar region of the lung, with a mode size distribution of 0.1–0.2 μm diameter (Kleeman *et al*., 1999). Particles not cleared by phagocytosis and transferred to the mucociliary escalator may be translocated to the interstitial tissue and to lung-

associated lymph nodes (International Commission on Radiological Protection, 1994). This local distribution of particles is consistent with the increased rate of lung cancer seen in rats exposed to carbon black (IARC, 1996). Chemicals adsorbed onto particles can be transported deep into the lung where depending on their solubility, they can either remain or slowly desorb into the lung-lining fluid.

Impaired particle clearance due to high loading of carbon black in experiments with rats results in increased accumulation of particles and chronic active inflammation. Increased collagen deposition from proliferating fibroblasts, increased epithelial cell proliferation, and metaplasia have been found at high lung burdens of carbon black. Most assays for mutagenicity are negative for carbon black. However, in rats exposed to carbon black by inhalation, *hprt* mutant frequency was elevated in type II cells following a 12-week exposure. Studies on DNA adducts are mixed with prolonged inhalation exposure not inducing a significant increase in DNA adducts in peripheral lung tissue of rats, but increasing DNA adduct levels in type II cells (IARC, 1996).

A specific exposure in firefighters consisting of mixed particulate and gas or vapour phase components is diesel exhaust, which shares many chemicals in common with wood smoke, including PAHs. Prolonged exposure of experimental animals to diesel engine exhaust leads to particle accumulation in macrophages, changes in the lung cell population, fibrotic effects, squamous metaplasia, and pathological changes in regional lymph nodes, as well as DNA adduct formation, protein adduct formation, and sister chromatid exchange. Particles or their extracts induce mutations and DNA damage in bacteria, and the gaseous phase is also mutagenic to bacteria (IARC, 1996).

In rats, a small fraction of ultrafine particles are translocated from the lungs into other organs (Kreyling *et al*., 2002). In humans, studies of ultrafine 99mTc-labelled carbon particles also support translocation of the particles from the lung into the systemic circulation (Nemmar *et al*., 2002). Translocation of ultrafine carbon particles from the olfactory mucosa to the brain has also been described *in vivo* (Oberdörster *et al*., 2004).

4.1.2 *Aldehydes*

Multiple aldehydes are found in smoke, including but not limited to formaldehyde, acetaldehyde and acrolein. For all of these aldehydes, exposure is predominantly to the respiratory tract due to local metabolism. For formaldehyde, this local exposure is consistent with the human cancer data linking exposure to nasopharyngeal and sinonasal cancer (IARC, 2006). Due to this local metabolism and significant endogenous production of formaldehyde, exposure of humans, monkeys or rats to formaldehyde by inhalation has not been found to alter endogenous concentrations. No information is available on relative absorption by site within the respiratory system in humans. In monkeys, formaldehyde is absorbed in the nasopharynx, trachea and proximal regions of the major bronchi whereas in rats absorption occurs almost entirely in the nasal passages (IARC, 2006). Dermal application of formaldehyde results in a relatively low extent of absorption, so in firefighters the predominant absorption route should be through inhalation.

Table 4.1. Toxicokinetics and metabolism for selected carcinogenic products of structural and wildfire smoke

Chemical	Absorption	Distribution	Metabolism	Excretion	Mechanism	Cancer	Note/Reference
Particles	Inhalation (variable depending on size)	Lungs	Dependent on solubility of adsorbed chemicals	Macrophage phagocytosis followed by migration to mucociliary escalator or transport to interstitium	Inflammation	For carbon black, lung, lymphatic cancer (in presence of PAHs). For diesel exhaust, lung and bladder cancer, possibly non-Hodgkin lymphoma, multiple myeloma, and prostate cancer	IARC (2010c); Oberdörster (1992); Boffetta & Silverman (2001); Lipsett & Campleman (1999); McDuffie *et al*. (2002); Boffetta *et al*. (1988); Lee *et al*. (2003); Hansen (1993); Seidler *et al*. (1998)
Acetaldehyde	Inhalation (45–70%)	Predominantly peripheral blood	Acetic acid	Blood half life 3.1 min (rat)	DNA damage including acetaldehyde–DNA adducts	Nasal cancer	IARC (1999); Egle (1970); Hobara *et al*. (1985); Hardman *et al*. (1996)
Acrolein	Inhalation (81–84%)	Predominantly local	Conjugated rapidly with thiols	Inadequate data in humans, urinary *S*-carboxyethyl-mercapturic acid following oral exposure in rats	DNA damage in cultured mammalian cells	IARC Group 3, urinary bladder papillomas in rats	IARC (1995); Egle (1972); ATSDR (2005)

Table 4.1 (contd)

Chemical	Absorption	Distribution	Metabolism	Excretion	Mechanism	Cancer	Note/Reference
Benzene	Inhalation (20–80%), dermal (<1%)	Preferably to fat, bone marrow and urine	Metabolism predominantly in liver and bone marrow. Reactive metabolites are considered carcinogenic.	Elimination half-life 42 min to 1.2 h	Benzene metabolites hydroquinone and 1,4-benzo-quinone inhibit topoisomerase II and micro-tubule function, induce oxidative stress, and damage DNA	Leukaemia	IARC (1987); Srbova *et al*. (1950); Franz (1984), Schrenk *et al*. (1941); Irons *et al*. (1980); Sherwood (1988)
1,3-Butadiene	Inhalation 43.4–45.6%	Widely distributed throughout the body	Urinary metabolites 1,2-dihydroxylbutyl mercapturic acid and monohydroxy-3-butenyl mercapturic acid	Elimination half life 2–10 h for elimination radiolabel of C^{14} 1,3-butadiene	Induces DNA adducts and damage and activates oncogenes	Lympho-haematopoietic	IARC (2008); Lin *et al*. (2002); Evelo *et al*. (1993); ATSDR (1992a)

Table 4.1 (contd)

Chemical	Absorption	Distribution	Metabolism	Excretion	Mechanism	Cancer	Note/Reference
Formaldehyde	Inhalation (100%) Dermal (3.4% in rats)	Predominantly local before metabolism	Metabolism in all tissues to carbon dioxide, formate, other one-carbon molecules	Plasma half-life 1 min (rat)	DNA–protein crosslinking, chromosomal abberations, and cell proliferation. Gene mutations Sister chromatid exchange	Nasopharyngeal and sinonasal cancer, leukaemia	IARC (2006); Egle 1972); Bartnik *et al*. (1985); Heck *et al*. (1982, 1983)
PAHs	Dermal (20% for pyrene) > inhalation	Following dermal exposure, highest concentrations in liver, kidney, fat, and lung	Metabolism in all tissues. 1-hydroxy-pyrene used as proxy for overall exposure	Elimination half-life (dermal exposure) 30 h for benzo[*a*]pyrene	Metabolites PAH oxides and diol epoxides form stable DNA adducts and induce mutations. Other mechanisms also postulated	Lung, bladder, skin, possibly prostate	IARC (2010a); Van Rooij *et al*. (1993); Withey *et al*. (1993); ATSDR (2007); Sanders *et al*. (1986); Rybicki *et al*. (2006); Seidler *et al*. (1998)

Table 4.1 (contd)

Chemical	Absorption	Distribution	Metabolism	Excretion	Mechanism	Cancer	Note/Reference
PCBs	Inhalation Dermal (variable depending on solvent)	Highest concentration in adipose tissue	Liver metabolism	Elimination half-life (occupational exposure) 1–24 yrs	Covalent modification of proteins and DNA, possible increased cell proliferation following injury caused by reactive oxygen species	Liver and biliary tract	IARC (1987); Fait *et al*. (1989); Fitzgerald *et al*. (1986); Wester *et al*. (1983, 1990); Jensen (1987); Wolff *et al*. (1992)
Styrene	Inhalation 60–70%	Wide distribution with highest concentration in adipose tissue	Liver metabolism	Blood elimination half-life biphasic with rapid phase (0.58 h) and slow phase (13.0 h). Predominant excretion as urinary metabolites, 0.7–4.4% exhaled unchanged	Protein and DNA adducts, other genotoxicity	Lympho-haematopoietic	IARC (2002); ATSDR (1992b)

Table 4.1 (contd)

Chemical	Absorption	Distribution	Metabolism	Excretion	Mechanism	Cancer	Note/Reference
Sulfur dioxide	Inhalation (40–>90% in rabbits)	Large proportion to upper airways	Sulfite and bisulfite in airways	Excreted in urine as sulfate	Conflicting results seen in human studies	Lung cancer	IARC (1992); Strandberg (1964); Balchum *et al*. (1959); Gunnison *et al*. (1987); Yokoyama *et al*. (1971)
Sulfuric acid	Inhalation (50–87%)	Predominantly upper airways	Converted to sulfate before absorption into blood	Excess sulfate excreted in the urine	DNA damage	Laryngeal, nasal sinus, lung	IARC (1992); Amdur *et al*. (1952); Dahl *et al*. (1983); Vander *et al*. (1975)

h, hour; min, minute; PAH, polycyclic aromatic hydrocarbon; PCB, polychlorinated biphenyl; yrs, years

For acetaldehyde, inhalation exposure leads to degeneration of nasal epithelium followed by hyperplasia and proliferation in rats (IARC, 1999). For acrolein, repeated inhalation results in changes in bronchiolar epithelial cells and emphysema in dogs (IARC, 1995). Dermal absorption does not appear to be important for acetaldehyde and acrolein.

Formaldehyde exposure results in DNA–protein cross-links and chromosomal abberations. Cell proliferation, which appears to amplify the genotoxic effects of formaldehyde, is increased at concentrations of around 6 ppm. No clear mechanism has been identified for the induction of myeloid leukemia in humans (IARC, 2006). Acetaldehyde causes gene mutations in bacteria; gene mutations, sister chromatid exchanges, micronuclei and aneuploidy in cultured mammalian cells; DNA damage in cultured mammalian cells and in mice in vivo. Acetaldehyde–DNA adducts have been found in white blood cells from human alcohol abusers (IARC, 1999). Acrolein induces gene mutation, sister chromatid exchange and DNA damage in cultured mammalian cells, but reportedly does not induce DNA damage in rats or dominant lethal mutations in mice treated in vivo (IARC, 1995).

4.1.3 *Benzene*

Benzene is systemically absorbed following inhalation, and due to rapid evaporation, dermal exposure should not be a significant source of systemic dose for firefighters. Benzene is oxidized primarily by CYP2E1 to benzene oxide, which exists in equilibrium with its tautomer oxepin (Kim *et al*., 2006; 2007). Spontaneous rearrangement of benzene oxide produces phenol that is either excreted or oxidized by CYPs to hydroquinone, which is excreted or oxidized by myeloperoxidase in the bone marrow to 1,4-benzoquinone. Conversely, NAD(P)H quinone oxidoreductase 1 transforms 1,4-benzoquinone to hydroquinone. Hydroquinone and 1,4-benzoquinone are thought to influence the toxic effects of benzene through their ability to inhibit topoisomerase II and microtubule function, induce oxidative stress, and damage DNA. Other major metabolites include catechol, representing the pathway involving the hydrolysis of benzene oxide by epoxide hydrolases, and *trans,trans*-muconic acid, representing the pathway involving oxidation of oxepin and ring opening. Reaction between benzene oxide and glutathione, possibly mediated by glutathione-*S*-transferases (GSTM1, GSTT1), can produce the minor metabolite *S*-phenylmercapturic acid (Kim *et al*., 2006; 2007). Although it is widely accepted that benzene toxicity is dependent upon metabolism, no single benzene metabolite has been found to be the major source of benzene haematopoietic and leukemogenic effects (ATSDR 2005). At low exposure levels, benzene is rapidly metabolized and excreted predominantly as conjugated urinary metabolites. The metabolism of benzene in the bone marrow is consistent with the increase in haematopoietic cancers seen in humans (ATSDR, 2005).

Chromosomal aberrations in human peripheral lymphocytes have been associated with occupational exposure to benzene and include hypo- and hyperdiploidy, deletions, breaks, and gaps (ATSDR, 2005). Sister chromatid exchange was not found to be a significant effect of benzene exposure in humans. In-vivo animal studies provide

convincing evidence of the genotoxicity of benzene. Benzene induced chromosomal aberrations, micronuclei and sister chromatid exchanges in bone-marrow cells of mice, chromosomal aberrations in bone-marrow cells of rats and Chinese hamsters and sperm-head anomalies in mice treated *in vivo*. It induced chromosomal aberrations and mutation in human cells *in vitro* (IARC, 1987). In-vitro studies strongly imply that the genotoxicity of benzene is derived primarily from its metabolites hydroquinone and 1,4-benzoquinone through their ability to inhibit topoisomerase II and microtubule function, induce oxidative stress, and damage DNA (ATSDR 2005).

4.1.4 *1,3-Butadiene*

Butadiene is absorbed through inhalation and is systemically distributed. It is metabolized primarily by CYP2E1 and CYP2A6 (Evelo *et al*., 1993). The metabolic rate in lung is greater at lower doses, and in liver, at higher doses. The butadiene metabolite epoxy-1,2-butanediol is reportedly the major electrophile binding with DNA and haemoglobin (Swenberg *et al*., 2001). Adducts formed by reaction of the metabolites 1,2-epoxy-3-butene and 3,4-epoxy-1,2-butanediol with haemoglobin and urinary mercapturic acids derived from 1,2-epoxy-3-butene have been detected in workers exposed to 1,3-butadiene. There is considerable interindividual variability in the ability of human liver microsomes to metabolize 1,3-butadiene and 1,2-epoxy-3-butene *in vitro* (Swenberg *et al*., 2001).

There are conflicting results on whether 1,3-butadiene increases *HPRT* mutations in lymphocytes from humans exposed to 1,3-butadiene compared with unexposed controls (IARC, 1999). One study of workers exposed to 1,3-butadiene demonstrated an increase in *HPRT* variant frequency in lymphocytes with high (mean 1.48 ppm) as compared with low (mean 0.15 ppm) exposures (Ammenheuser *et al*., 2001). However, sister chromatid exchanges, micronuclei, chromosomal aberrations and DNA-strand breaks were not significantly elevated above control levels in peripheral blood lymphocytes of occupationally exposed workers. 1,3-Butadiene induces DNA adducts and damage in both mice and rats *in vivo* and is mutagenic in virtually all in-vitro and in-vivo test systems. Activated K-*ras* oncogenes have been detected in lymphomas and in liver and lung tumours induced in mice by 1,3-butadiene. Mutations in the *p53* tumour suppressor gene have been detected in mouse lymphomas (IARC, 1999).

4.1.5 *Free radicals*

Smoke contains highly reactive oxygen- and carbon-centred radicals, which may initiate cancer through the oxidative activation of a procarcinogen and/or through binding of the radical to DNA. The major effect should therefore be on the epithelial layer of the respiratory tract. Cigarette smoke, which has been better studied than wood smoke, contains a quinone–hydroquinone–semiquinone system that can reduce oxygen to produce superoxide, and hence, hydrogen peroxide and the hydroxyl radical, as well as penetrate viable cells, bind to DNA, and cause nicks (Pryor, 1997; Church & Pryor, 1985).

4.1.6 *Furan*

Furan is rapidly and extensively absorbed after oral administration. Part of the absorbed dose becomes covalently bound to protein, mainly in the liver, although DNA binding has not been demonstrated in this organ. Repeated administration of furan to mice and rats leads to liver necrosis, liver-cell proliferation and bile-duct hyperplasia. In rats, prominent cholangiofibrosis develops. The induction of chromosomal aberrations but not sister chromatid exchange has been observed in rodents treated *in vivo*. Gene mutation, sister chromatid exchange and chromosomal aberrations are induced in rodent cells *in vitro* (IARC, 1995).

4.1.7 *PAHs*

PAHs are a diverse set of chemicals, and their toxicokinetics vary accordingly. PAHs generally occur as complex mixtures and not as single compounds. The percutaneous absorption of PAHs appears to be rapid for both humans and animals, but the extent of absorption is variable among the different compounds. Although distribution through the circulatory system is widespread, slow absorption through most epithelia results in higher levels of enzymes that activate PAH substrates at the site of entry. This uneven distribution of dose may contribute to the propensity of PAHs acting as carcinogens at the sites where they enter the body (IARC, 2010a). Metabolic activation of PAHs occurs primarily in the liver, but also in many other tissues, including the epithelial barriers. Metabolites include epoxide intermediates, dihydrodiols, phenols and quinones, which can be conjugated to glucuronides, sulfate esters and/or glutathione. Specific cytochrome P450 isozymes and epoxide hydrolase can form reactive diol epoxides. The major cytochrome P450s that are involved in the formation of diol epoxides are CYP1A1, CYP1A2, and CYP1B1, while CYP2C9 and CPY3A4 play a minor role in the activation of PAHs. Additional enzymes that may play a role in the further activation of some PAH diols include members of the aldo-keto reductase family. NAD(P)H quinone oxidoreductase 1 catalyses the reduction of PAH quinones to hydroquinones which may be re-oxidized and generate reactive oxygen species. The major phase II enzymes include the glutathione *S*-transferases (GSTs), uridine 5′-diphosphate glucuronosyltransferases, and sulfotransferases. The major GSTs involved in the conjugation of PAH metabolites are GSTM1, GSTP1, and GSTT1. Quantitative data on the excretion of PAHs in humans are lacking. In general, the major elimination route of PAHs in animals following inhalation exposure is through the faeces. PAHs are eliminated to a large extent within 2 days following low- and high-level oral exposure in rats. Following dermal exposure, the elimination of PAHs occurs rapidly in the urine and faeces of rodents (IARC, 2010a).

The current understanding of the carcinogenesis of PAHs in experimental animals is almost solely based on two complementary mechanisms: those of the diol epoxide, and the radical cation. The diol epoxide mechanism features a sequence of metabolic transformations of PAHs, each of which leads to potentially reactive genotoxic forms. In general, PAHs are converted to oxides and dihydrodiols, which are in turn oxidized to

diol epoxides. Both oxides and diol epoxides are ultimate DNA-reactive metabolites. PAH oxides and diol epoxides can form stable DNA adducts and induce mutations (e.g. in *ras* proto-oncogenes) that are strongly associated with the tumorigenic process (IARC, 2010a). Measured end-points in human populations include mutagenicity in urine and the presence of aromatic DNA adducts in the peripheral lymphocytes of exposed workers. Cytogenetic effects such as micronucleus formation have also been reported. Other mechanisms of carcinogenesis have been proposed for PAHs, but these are less well developed and include generation of reactive oxygen species, activation of the aryl hydrocarbon receptor with regulation of phase I and II metabolism, lipid peroxidation, production of arachidonic acid-reactive metabolites, decreased levels of serum thyroxine and vitamin A and persistent activation of the thyroid hormone receptor, as well as activation of mitogen-activated protein kinase pathways, suppression of immunity by p53-dependent and other pathways (IARC, 2010a).

4.1.8 *PCBs*

PCBs are absorbed by inhalation and dermal contact. Wester *et al*. (1990) found that PCBs penetrated skin in a time-dependent manner, but that 93±7% of PCBs were removed from the skin with five successive washes using soap and water, the removal efficiency decreasing with increasing time from initial contact. Washing 24 hours following skin contact removed only 25% of the initial PCBs. The highest concentrations are found in adipose tissue, with metabolism occurring in the liver. PCBs are metabolized by cytochrome P450 followed by conjugation with glutathione or glucuronic acid. The rate of metabolism depends on the extent of chlorination, the location of the chlorine atoms, and the levels of P450 isozymes and other enzymes. Metabolites of PCBs with low chlorine content are predominately eliminated in the urine. PCBs with high chlorine content and substitution patterns resistant to metabolism are either retained or excreted unchanged in the faeces. In one study, following exposure to an electrical transformer fire in New York, USA, serum PCBs were higher in firefighters initially when compared to levels 9 months later (Kelly *et al*., 2002). Orris *et al*. (1986) reported two cases of lesions consistent with chloracne in firefighters, although in both cases the blood PCB level was less than 10 μg/L.

A wide variety of cancers have been reported in association with PCB exposure. Exposure to PCB mixtures predominantly causes liver tumours in rats; although tumours in mouse lung and mouse skin have also been observed (IARC, 1987). Cancer mechanisms that are both dependent on and independent of the aryl hydrocarbon receptor may be involved. PCBs may be involved in tumour initiation and promotion. Metabolism of less chlorinated PCBs in rat microsomes can lead to covalently modified macromolecules including proteins and DNA, although PCB mixtures generally are inactive as mutagens, and are not potent genotoxicants. PCB promotion of liver tumours may involve increased cell proliferation following cell or tissue injury caused by reactive oxygen species, resulting from induction of CYP oxygenases and GSTs, decreased

activity of glutathione peroxidases, and/or disruption of calcium homeostatic processes and signal transduction pathways (ATSDR 2000).

4.1.9 *Styrene*

Styrene is absorbed by inhalation and dermal contact. In humans, 60–70% of inhaled styrene is absorbed. It is rapidly distributed throughout the body in treated rats. A large percentage of absorbed styrene is excreted as urinary mandelic and phenylglyoxylic acids, with glutathione conjugates forming a minor fraction of the metabolites. The dominant first metabolite is styrene-7,8-oxide, the formation of which appears to be catalysed in humans principally by CYP2B6 but also by CYP2E1 and CYP1A2. Isolated erythrocytes are also capable of non-enzymatic conversion of styrene to styrene-7,8-oxide (IARC, 1994).

Exposure to styrene leads to the formation of both protein and DNA adducts in man, rat and mouse. The levels of the *N*-terminal valine adduct of haemoglobin, *N*-(1-hydroxy-2-phenylethyl)valine, have been found to be four times higher in styrene-exposed workers than in controls, and the levels of the DNA adduct, *O*6-(2-hydroxy-1-phenylethyl)-2′-deoxyguanosine-3′-monophosphate, have been found to be about five times higher than in controls. Some 25 studies on chromosomal aberrations, micronuclei and sister chromatid exchange have been performed in workers exposed to styrene in various countries and different industries. These have provided variable results with regard to the association between exposure to styrene and chromosomal damage. Chromosomal aberrations were observed in nine of 22, sister chromatid exchange in three of 12, and micronuclei in three of 11 studies. The frequency of single-strand DNA breakage/alkali-labile sites was increased in workers exposed to styrene at less than 20 ppm (85 mg/m3). Chromosomal aberrations have not been seen in most studies in rodents, while several studies indicate weak induction of sister chromatid exchange in various tissues of rats and mice. Contradictory results have been obtained with regard to the induction of micronuclei in mice. Significant increases have been observed consistently in the frequency of sister chromatid exchange and chromosomal aberrations in human lymphocytes *in vitro*. Most studies did not show mutation in bacteria, although mutation was seen in some studies in the presence of an exogenous metabolic activation system (IARC, 1994).

4.1.10 *Sulfur dioxide and sulfuric acid*

Sulfur dioxide and sulfuric acid are initially converted to sulfite and sulfate respectively, with excretion as sulfate in the urine. Their local effect on the respiratory system is consistent with the increase in respiratory system cancer in humans (sulfuric acid), and animals (sulfur dioxide and sulfuric acid). Conflicting results for the induction of chromosomal aberrations in lymphocytes have been obtained in studies of workers exposed to sulfur dioxide, among other agents. No increase has been reported in the frequency of sister chromatid exchange in lymphocytes of exposed workers. Sulfur dioxide and its aqueous forms do not induce sister chromatid exchange, chromosomal aberrations or micronucleus formation in bone marrow of mice or Chinese hamsters,

although sister chromatid exchange and chromosomal aberrations have been induced in human lymphocytes. Significant increases in the incidences of sister chromatid exchange, micronucleus formation, and chromosomal aberrations in peripheral lymphocytes have been observed in a single study of workers engaged in the manufacture of sulfuric acid. In cultured mammalian cells at pH 6.7 or below, cell transformation, gene mutation, and chromosomal aberrations were induced (IARC, 1992).

4.2 Genetic and related effects

4.2.1 *Humans*

(a) Direct genotoxicity

There are a limited number of studies evaluating genotoxic effects in firefighters (see Table 4.2). In general, these studies did not show evidence of direct genotoxicity, except in the case of atypical exposures.

In the Washington DC area, USA, a study of peripheral blood lymphocytes collected from 43 firefighters selected from two fire stations with frequent firefighting activities demonstrated an increase in sensitivity to mitomycin-C-induced sister chromatid exchange correlated with the number of fires fought in the previous 24 hours, although no difference was seen comparing the firefighters to 40 non-firefighter controls matched by age, gender, and smoking status. Firefighters as a group had a significantly lower level of unstimulated sister chromatid exchange (8.44 per cell) when compared to controls (9.23 per cell, P=0.02), although no significant differences were found when the comparison was limited to those who had not consumed charbroiled food in the last month (Liou *et al*., 1989). No significant association was found between recent firefighting history and the number of sister chromatid exchange. The firefighters did not have a significant increase in benzo[*a*]pyrene diol epoxide–DNA antigenicity when compared to controls (OR: 1.73, 95% CI: 0.60–4.99). However, following stratification by race, the subset of 37 caucasian firefighters had concentrations of detectable benzo[*a*]pyrene diol epoxide–DNA antigenicity that were 3.56-fold (95% CI: 1.04–12.12) higher than caucasian controls (Liou *et al*., 1989).

In a comparison of 53 male Korean firefighters exposed to fire within 5 days of the study compared to 25 that were not, no increase in urinary 8-hydroxy-2′-deoxyguanosine concentration was observed (Hong *et al*., 2000). [The extent of respiratory protection used by the firefighters was not described in the study and the amount of time elapsed between exposure and collection of urine may have limited the ability to discern a difference between groups.]

Ray *et al*., (2005) compared 47 non-smoking firefighters engaged in firefighting for ≥10 years to 40 age-matched non-smoking controls with a comparable alcohol consumption. Micronuclei frequency in firefighters (3.91 ± 0.19 was significantly higher than in controls (1.25 ± 0.12). In addition, the 27 firefighters with ≥ 20 years of service

has more micronuclei than (4.43 ± 0.32) the 20 firefighters with < 20 years of service (3.21±0.24, $P < 0.05$). [The study group was concerned over potential use of smokeless tobacco or other substances by the firefighters which may have confounded the study results, and for which information was not provided in the article.]

Data are available for atypical firefighter exposures, including a study of 16 German firefighters exposed to *O*-nitroanisole and other chemicals during clean-up activities following an industrial accidental release from a methoxylation plant. These firefighters were in training and, with the exception of one individual, were not yet involved in actual firefighting. The firefighters did not use respiratory protection or protective clothing while removing the contaminant with brushes and high power cleaning machines. The firefighters had a small but statistically significant elevation in DNA single-strand breaks measured by alkaline elution 19 days after the exposure (normalized elution rate 1.48 ± 95% CI: 0.21) in comparison to 19 unexposed firefighters (normalized elution rate 1.21 ± 95% CI: 0.21, $P < 0.05$) matched by age, alcohol consumption, town of residence, and, within smokers, numbers of cigarettes smoked. The controls had relatively little firefighting activity, responding to less than two fires per month (Hengstler *et al*., 1995).

In a small study of nine residents of the USA, aged 36–67, volunteering to fight oil fires in Kuwait between April and June, 1991, no increase in DNA adducts in lymphocytes (measured by nuclease PI modification of the ^{32}P-post-labelling assay) was observed after an average of 12 days after return from duty (Darcey *et al*., 1992). Of the subjects, five were current smokers and three were ex-smokers. All subjects were exposed to smoke from the oil fires both while working and at their residence adjacent to the oil fields. The only respiratory protection used was “particle masks” for 1–2 hours per day.

In a study of 47 currently non-smoking (for at least 6 months) California wildland firefighters aged 18–49, Rothman *et al*., (1993) found that white blood cell PAH–DNA adduct concentrations were associated with the frequency of charbroiled food intake and not with occupational exposure. In this analysis, the mean number of hours of firefighting during the previous week was 0.11 for the early season period, and 22.36 for the late season period.

There are several studies associating exposure to wood smoke from cooking and heating with lung cancer (Delgado *et al*., 2005) as described in the IARC Monograph on Indoor Air Pollution (IARC, 2010b). While analysis of these studies is not within the scope of this section, some studies have evaluated biomarkers which help shed light on potential carcinogenic mechanisms of wood smoke. Given that the extent of most firefighters’ exposure to smoke is limited to discreet episodes, and is of a much shorter duration than typical exposures for residential exposure to wood smoke, it is difficult to determine the extent to which the results of the wood smoke studies can be applied to firefighters.

Table 4.2. Genotoxicity studies of firefighters

Effect	Exposure	Country	Note	Reference
Increase in susceptibility to mitomycin C induced sister chromatid exchange correlated with the number of fires fought in the previous 24 hours	43 Firefighters and 40 matched controls	USA (Washington DC)	Municipal firefighters as a group did not have an increased level of SCE as compared with matched controls	Liou *et al.* (1989)
No increase in urinary 8-OHdG	53 Firefighters exposed to fire within 5 days of the study	Korea	Municipal firefighters	Hong *et al.* (2000)
Increased micronuclei in buccal cells	47 Firefighters compared with 40 controls	India	Municipal firefighters	Ray *et al.* (2005)
DNA single strand breaks 19 days after the fire in comparison to control groups	16 Firefighters without respiratory protection exposed to *o*-nitroanisole and other chemicals	Germany	Incident did not involve a fire	Hengstler *et al.* (1995)
No increase in white blood cell DNA adducts	9 Firefighters an average of 12 days after return from duty	Exposures in Kuwait, firefighters from USA	Oil well fires	Darcey *et al.* (1992)
White blood cell PAH–DNA adducts only from diet, not from occupational exposure	47 Firefighters assayed early and late in the 1988 forest fire season	USA (California)	Wildland firefighters, used rabbit antibody 33 capable of recognizing multiple PAH diol epoxides linked with DNA	Rothman *et al.* (1993)

SCE, sister chromatid exchange; 8-OHdG, 8-hydroxy-2′-deoxyguanosine

(b) Indirect effects potentially related to genotoxicity

(i) *Chronic effects in municipal firefighters*

Studies describing the chronic and acute effects from firefighting that could indirectly lead to genotoxicity are reported in Tables 4.3 and 4.4. These effects are mostly inflammatory in nature. For studies of chronic effects of firefighting, more recent studies have failed to demonstrate the previously described accelerated rate of decline in lung function seen in older studies. This difference is likely due to a more assiduous use of respiratory protection, specifically self-contained breathing apparatus.

Markowitz *et al*. (1991) evaluated 212 New York City firefighters (mean age, 57 years) for evidence of asbestos-related pulmonary disease. A total of 42 (20%) had pleural thickening and/or parenchymal abnormalities, including 20 (13%) of the firefighters without a reported previous exposure to asbestos. Only 15 (7%) of the study participants had worked fewer than 20 years as a firefighter. [No data were available for firefighter asbestos-related pulmonary disease in other locales, so it is difficult to determine the generalizability of these findings.] In a sub-analysis of this larger group, Ford *et al*. (1992) evaluated 33 New York City firefighters for serum biomarkers associated with carcinogenic pathways including transforming growth factor β, plate-derived growth factor, and seven oncogene proteins, ras, fos, myc, myb, mos, src, and int in comparison with 16 healthy matched controls from a medical centre. Fourteen of the firefighters and none of the controls were positive for transforming growth factor β ($P < 0.01$). None of the other tumour genes was found in any subject.

In Seattle, a study of 812 firefighters demonstrated a longitudinal decline in the percent-predicted diffusion capacity of carbon monoxide from 1989–1996, suggesting lung tissue loss from inflammation (Burgess *et al*., 1999), although no longitudinal changes in spirometry were noted. Loke *et al*., (1980) evaluated the pulmonary function in 54 firefighters from Connecticut, including 32 smokers and 22 non-smokers. In non-smokers, small airway obstruction was present only in firefighters with at least 25 years of firefighting, again consistent with a lung inflammatory response.

Studies of municipal firefighters published between 1974–1991 reported variable rates of longitudinal decline in spirometry. In Boston, Peters *et al*., (1974) reported an average annual decline in the Forced Expiratory Volume in 1 Second (FEV1) of 68 mL in a group of 1430 firefighters. In another study in the same city, Sparrow *et al*., (1982) reported an increased annual average rate of decline in FEV1 of 12 mL in 168 firefighters when compared to 1474 non-firefighters. Tepper *et al*. (1991) reported a 2.5-fold increased rate of decline in FEV1 in 632 Baltimore firefighters when compared with retired or firefighters that had resigned during the follow-up period. However, Musk *et al*. (1977) evaluated the pulmonary function in 1146 Boston firefighters for whom the average annual decline in FEV1 was in the normal range of 0.03 L/year, and this rate of decline was not associated with number of fires fought. The authors reported a more frequent use of respiratory protection over the period 1970–1974.

Table 4.3. Chronic effects of firefighting exposure with indirect relevance to cancer

Effect	Exposure	Country	Notes	Ref
Asbestos-related pulmonary disease	42 (20%) Firefighters engaged in routine firefighting had pleural thickening and/or parenchymal abnormalities	USA (New York City)	20 (13%) of these firefighters did not report previous exposure to asbestos	Markowitz *et al.* (1991)
Beta-transforming growth factor related proteins	33 Firefighters engaged in routine firefighting	USA (New York City)	Subset of above study	Ford *et al.* (1992)
Longitudinal decline in percent predicted diffusion capacity of carbon monoxide (DL_{CO}) from 1989 to 1996.	812 Firefighters engaged in routine firefighting	USA (Seattle)	Suggests lung tissue loss from inflammation. No change in percent predicted FEV_1 and FVC	Burgess *et al.* (1999)
Small airway obstruction	54 Firefighters engaged in routine firefighting	USA (Connecticut)		Loke *et al.* (1980)
Accelerated decline in FEV_1	Routine firefighting	USA (Boston, Baltimore)	Multiple studies	Peters *et al.* (1974); Sparrow *et al.* (1982); Tepper *et al.* (1991)
No accelerated decline in FEV_1	Routine firefighting	USA and United Kingdom	Multiple studies	Musk *et al.* (1977); Musk *et al.* (1982); Horsfield *et al.* (1988)
Increased lymphocytes, native fibronectin and hyaluronic acid in bronchoalveolar lavage fluid	13 non-smoking municipal firefighters compared with 112 controls	Sweden	Suggests cell activation and inflammation	Bergström *et al.* (1997)

Table 4.3 (contd)

Effect	Exposure	Country	Notes	Ref
Cross-seasonal decline in FEV_1	Wildland firefighters	USA (California, Montana, Oregon, Washington)		Rothman *et al.* (1991); Liu *et al.* (1992); Betchley *et al.* (1997)
Increased percentage of neutrophils and MMP-9 concentrations in sputum	39 New York City Firefighters exposed to World Trade Center dust compared to 12 firefighters and 8 non-firefighters from Tel Aviv	USA (New York City) and Israel (Tel Aviv)	Sputum collected 10 months after the collapse	Fireman *et al.* (2004)
Decline in FEV_1	323 Firefighters exposed to World Trade Center dust compared with a historical referent group (*n*=687) and unexposed firefighters (*n*=34)	USA (New York)	Mean decline of 264 mL compared with 147 mL in the historical referent group and 85 mL in unexposed	Feldman *et al.* (2004)

FEV_1, forced expiratory volume; FVC, forced ventilatory capacity; MMP-9, matrix metallopeptidase 9

A follow-up study of these firefighters (Musk *et al*., 1982) demonstrated an average annual decline in FEV1 of 36 mL in 951 subjects. Horsfield *et al*., (1988) failed to demonstrate an increased rate of decline in spirometry in 96 British firefighters when compared to a control group of 69 non-smoking men from other occupations. [The variable use of self-contained breathing apparatus may help to explain the differences in the rate of decline in lung function.]

Bergström *et al*. (1997) collected bronchoalveolar lavage fluid from 13 non-smoking firefighters and the results were compared to a reference group of 112 non-smoking healthy volunteers (the ethical committee who approved this study was from the Karolinska Hospital, Stockholm, Sweden). Nine of the 13 firefighters had one occasion of firefighting during the previous 3 months and four had no exposure during this time period. Firefighters had an increased percentage of lymphocytes and a decreased percentage of activated macrophages when compared to controls (median 8.2 versus 5.7% and 90.5 versus 92.5%, respectively, $P < 0.05$ for both). Native fibronectin and hyaluronidase were higher in firefighters (median 34.6 versus 22.0 μg/L, and 27.7 versus 10.0 μg/L, respectively, $P < 0.05$).

Table 4.4. Acute effects of firefighting exposure with indirect relevance to cancer

Acute effect	Exposure	Country	Note	Reference
Increased lung permeability, measured by serum concentrations of Clara Cell protein and surfactant-associated protein A	51 Firefighters engaged in structural overhaul	USA (Arizona)	Consistent with lung inflammation caused by smoke	Burgess *et al.* (2001)
Decrease in sputum IL-10 concentration	19 Firefighters engaged in structural overhaul (subset of previous study)	USA (Arizona)	IL-10 may play a role in preventing cancer	Burgess *et al.* (2007)
Transient change in lung permeability	6 Volunteer firefighters exposed to polypropylene combustion in a chemical plant	Not described	Change in serum Clara Cell protein	Bernard & Van Houte (1996)
Reduction in FEV_1	Structural firefighters	USA	Mixture of studies with variable use of SCBA	Musk *et al.* (1979); Sheppard *et al.* (1986); Brandt-Rauf *et al.* (1989); Large *et al.* (1990)
Reduction in FEV_1 and FVC	Cross-shift study of 76 wildland firefighters	USA (Washington and Oregon)		Betchley *et al.* (1997)

FEV_1, forced expiratory volume; FVC, forced ventilatory capacity; IL-10, interleukin-10; SCBA, self-contained breathing apparatus

(ii) *Chronic effects in wildland firefighters*

In wildland firefighters, a cross-seasonal decline in FEV_1 has been reported in several studies. Betchley *et al.* (1997) evaluated spirometry tests in 53 Oregon and Washington wildfire firefighters taken before and after the fire season. On average, participants worked on 9.5 prescribed burns (range 1–25), 5.8 wildfires (range 0–24), and 0.3 urban fires (range 0–5). Testing was performed 1–211 (average 78) days after the last occupational smoke exposure. The mean decline in FEV_1 over this time period was 0.104 litres (P = 0.032) without a significant decline in Force Vital

Capacity (FVC). In 52 California wildland firefighters, a small (−1.2%) but significant cross-season decline in FEV_1 was noted, with firefighters with greater firefighting activity within the previous week having the greatest extent of decline (Rothman *et al*., 1991). In 63 western USA wildland firefighters, cross-season declines in spirometry (FVC 0.09 L, $P < 0.001$, FEV_1 0.15 L), and increased airway responsiveness were observed (Liu *et al*., 1992).

(iii) *Chronic effects of unique exposures*

Fireman *et al*. (2004) analysed sputum samples from 39 New York firefighters highly exposed to the World Trade Center dust and those from firefighters and health care workers (non-firefighters) from Tel Aviv. All 39 New York firefighters were exposed to the World Trade Center dust cloud on the day of collapse. The sputum was collected 10 months after the collapse. The authors stated that it was necessary to recruit control populations from outside New York because of the high percentage of individuals exposed to World Trade Center dust to at least some extent. [However, they did not describe the potential bias from breathing New York City air as compared with Tel Aviv air contaminants other than those produced by the World Trade Center, and no comparisons were provided of ambient air quality in each city.] The percentage of neutrophils in the New York firefighters (mean 50.7 ± 17%) was significantly higher than in the health care worker controls (29.1 ± 8.9%, $P < 0.05$), but not in Tel Aviv firefighters (44.1 ± 22.9%). Sputum matrix metalloproteinase 9 concentrations in the New York firefighters (mean 2.2 ± 2.6 ng/mL) were also significantly higher than in the controls (0.3 ± 0.1 ng/mL, $P < 0.05$), but not in Tel Aviv firefighters (1.2 ± 1.0 ng/mL, $P = 0.057$). Within the New York firefighters, those with ≥ 10 cumulative workdays at the World Trade Center ($n = 16$) had a greater percentage of sputum neutrophils than those with <10 days ($n = 23$) (55.7±15.2% v. 44.2±16.5%, $P = 0.05$). Chemical analysis of the sputum samples from New York firefighters revealed multiple elements including zinc, mercury, gold, tin, and nickel, which were not present in the sputum samples of Tel Aviv firefighters. Feldman *et al*. (2004) noted an increased decline in FEV_1 in New York City firefighters when compared to historical controls and to an unexposed group.

(iv) *Acute effects*

Smoke exposure has also been associated with various acute health outcomes potentially related to cancer (Table 4.4). In a study of 51 Arizona firefighters during overhaul, a phase of firefighting during which fire fighters historically did not and may presently not wear respiratory protection, evidence of increased lung permeability was observed, consistent with lung inflammation caused by smoke. This was assessed by measuring the serum concentrations of Clara Cell protein and surfactant-associated protein A (Burgess *et al*., 2001). Changes in surfactant-associated protein A were correlated with atmospheric exposure to acetaldehyde and formaldehyde, as well as carboxyhaemoglogin levels. In a subset of 19 of these firefighters, smoke exposure also caused a decrease in sputum interleukin-10 (IL-10)

concentrations (Burgess *et al*., 2007), and IL-10 may play a role in cancer prevention (Giordani *et al*., 2003). Bernard and Van Houte, (1996) also found increased serum Clara Cell protein in six volunteer firefighters exposed to polypropylene combustion products in a chemical plant for approximately 20 minutes, as compared to six age-matched controls. When re-tested 10 days after the exposure, the serum Clara Cell protein levels had returned to values similar to that of controls.

Several studies have demonstrated an acute decline in spirometry following smoke exposure in firefighters. Musk *et al*. (1979) evaluated 39 firefighters during routine firefighting duty. Over 137 observations, the average decrease in FEV1 following smoke exposure was 0.05 L. The decline in FEV1 was related to the measured particulate concentration of the smoke, and also to the severity of smoke exposure as estimated by the firefighter. Sheppard *et al*. (1986) evaluated 29 firefighters from a single fire station over an 8-week period, measuring FEV1 and FVC in each firefighter before and after each 24-hour workshift and after every fire. Eighteen of 76 measurements obtained within 2 hours after a fire (24%) showed a greater than 2 standard deviations fall in FEV1 and/or FVC compared to two of 199 measurements obtained after routine shifts without fires (1%; $P < 0.001$). Brandt-Rauf *et al*. (1989) evaluated 37 firefighters with baseline and immediate post-firefighting spirometry tests. In 14 firefighters not wearing a self-contained breathing apparatus, there was an average 0.19 L decline in FEV1 ($P = 0.014$) and a 0.22 L decline in FEV1 ($P = 0.007$), whereas there was no significant decline in spirometry when including all firefighters (those wearing and not wearing a self-contained breathing apparatus). Large *et al*. (1990) evaluated 60 Pittsburgh firefighters before and after exposure to house fires with use of a self-contained breathing apparatus for variable periods of time, finding a 3–11% decline in FEV_1.

Acute decline in spirometry has also been reported in wildland firefighters. Betchley *et al*. (1997) evaluated cross-shift spirometry tests in 76 Oregon and Washington firefighters. The mean decline in FEV1 was 0.190 L ($P < 0.001$), and in FVC, 0.089 L ($P = 0.009$).

4.2.2 *Experimental systems*

Wood smoke has been shown to cause oxidative stress and DNA damage *in vivo* (see Table 4.5). Extensive additional information on the genotoxic effects of wood smoke is summarized in the IARC Monograph on Indoor Air Pollution (IARC, 2010b). Specifically, there are data supporting lipid peroxidation and free radical generation as mechanisms of injury. Demling & LaLonde (1990) exposed sheep to smoke from strips of dyed cotton towelling, 20 breaths at 5 and 10 mL/kg. The 5 mL/kg exposure resulted in an increase in plasma malondialdehyde level without significant lung or systemic physiological changes. Lipid peroxidation has been shown to be associated with cancer (Otamiri & Sjödahl, 1989). At higher exposure levels causing severe respiratory failure, this oxidant activity was felt to be due to smoke-induced systemic inflammation (Demling *et al*., 1994). Leonard *et al*. (2000)

also demonstrated DNA strand breakage by single-cell gel electrophoresis in RAW 264.7 cell cultures incubated with 50 μL smoke collected in saline solution for 24 hours. This damage was felt to be due to the generation of hydroxyl radicals produced from the interaction of H_2O_2 with carbon-centred radicals in wood smoke. In a later study, Leonard *et al*. (2007) also demonstrated an increase in lipid peroxidation following exposure of RAW 264.7 cells to wildfire smoke suspensions, with the ultrafine and fine size particles inducing a significant increase in malonaldehyde levels. Forest fire smoke also induced dose-dependent increases in sister chromatid exchange in cultured human lymphocytes (Viau *et al*., 1982).

Ultrafine particles, similar in size to those produced during combustion, appear to have greater effects and a significant potential to injure the lung compared to an equivalent dose by weight of larger particles (Oberdörster *et al*., 1992). Atlas *et al*. (1985) collected particulate and vapour phase contaminants from diesel oil fires at a firefighter training facility and exposed the *S. typhimurium* strains TA98 and TA100 with and without enzyme (rat liver S-9 mix) activation. They found an approximately 5-fold greater mutagenicity from the contaminant mixture than would be expected from the concentration of benzo[*a*]pyrene alone. Woodsmoke has also been shown to be mutagenic in cellular assays, as reported in the IARC Monograph on Indoor Air Pollution (IARC, 2010b).

Table 4.5. Genetic and related effects of woodsmoke

Effect	Exposure	System	Reference
Lipid peroxidation (plasma malondialdehyde)	Cotton towelling smoke 5–10 mL/kg tidal volume x 20 breaths	Sheep	Demling & LaLonde (1990)
DNA lipid peroxidation and single strand breakage	Pine and fir bark smoke bubbled through saline	Mouse peritoneal macrophage cell line (RAW 264.7)	Leonard *et al.* (2000, 2007)
Sister chromatid exchange	Forest fire smoke (in Kentucky, USA)	Cultured human lymphocytes	Viau *et al*. (1982)
Mutagenicity	Particulate and vapour phase contaminants from oil fire plumes at a firefighter training facility	Ames test bioassay	Atlas *et al.* (1985)

RAW 264.7, mouse peritoneal macrophage cell line

4.3 Susceptible populations

A limited number of studies are available evaluating the effects of genetic polymorphisms on metabolites or clinical end-points likely related to cancer. In a

study of 78 Korean firefighters, including 53 that had been exposed to smoke within 5 days of the study (Hong *et al*., 2000), polymorphisms in the *CYP1A1*, *CYP2E1*, *GSTM1*, and *GSTT1* genes were not associated with an increase in urinary 8-hydroxy-2′-deoxyguanosine concentration [although the sample size was small for a genetic study]. Recent firefighting activity was not a predictor of urinary 8-hydroxy-2′-deoxyguanosine. In studies of decline in lung function in firefighters, a single nucleotide polymorphism at position 1668 in the IL-10 gene, was related to the rate of decline in lung function in 379 firefighters (Burgess *et al*., 2004). In a smaller study of 67 firefighters, TT genotypes at IL-10 (–819) (P = 0.009) and CT or TT genotypes at IL-1RA (2018) (P = 0.050) as well as increased sputum IL-1RA were associated with a slower rate of FEV_1 decline (P = 0.025) (Josyula *et al*., 2007). These genes and protein are all associated with inflammation and the rate of decline in lung function may potentially be associated with cancer end-points. This possible association is supported by research linking IL-10 single nucleotide polymorphisms to lung cancer (Tseng *et al*., 2006) and IL-1RA gene polymorphisms to bulky hydrophobic DNA adducts in the lung (Lind *et al*., 2005). Data on genetic polymorphisms in metabolic genes and DNA repair genes in relation to lung cancer are available in individuals with exposure to smoke (IARC, 2010b) but not firefighters. As described elsewhere in this monograph, shiftwork may increase firefighter susceptibility to certain cancers.

4.4 References

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5. Summary of Data Reported

5.1 Exposure data

Several types of firefighters exist, including municipal, wildland, industrial, aviation, and military firefighters. Municipal firefighters may be assigned to combat firefighting units only or to unexposed activities such as fire prevention or technical support. Firefighters may also be fire-scene investigators who are exposed during fires or shortly following a fire. Many firefighters work in shifts (see the monograph in this Volume).

Both municipal and wildland firefighting involve two phases: in an initial phase (knockdown and attack, respectively), the fire is extinguished; in a second phase (overhaul and mop-up, respectively), small fires and hot-spots are extinguished.

All fires generate an enormous number of toxic combustion products, including known and possible carcinogens, long-lived free radicals, and particulate matter. Smoke particles may serve as vehicles for adsorbed volatile organic compounds. Peak exposures to some carcinogens may be very high, notably for benzene, 1,3-butadiene, and formaldehyde. The concentrations of respirable particulate matter to which firefighters may be exposed during overhaul can reach 50 mg/m^3, or up to 1000 mg/m^3, and above in the case of coarser particles. Exposures of firefighters to volatile organic vapours have generally been in the low parts-per-million range.

Firefighters may be exposed at different levels depending on crew assignment, tasks and/or the time spent at fires. Wildland firefighters appear to spend more time at fires during a fire season than municipal firefighters spend during an entire year. In municipal firefighting, overhaul also involves pulling down ceilings and walls, which may entail exposures to substances other than combustion products. Both municipal and wildland firefighters engage in heavy work levels when combating fires, and the increased respiration rate results in an increase in absorbed dose. In recent decades, very effective respiratory protection equipment has been made available to municipal firefighters. In most jurisdictions, wildland firefighters generally do not use respiratory protection.

5.2 Human carcinogenicity data

The Working Group reviewed 42 studies of cancer in firefighters that included 19 cohorts, 11 case–control studies, and 14 studies that used other designs. The studies that were most relevant to the assessment of the risk for cancer among firefighters were the larger historical cohort studies.

Elevated relative risks for cancer at many different sites were identified by one or more studies, but few were observed consistently. A recent meta-analysis evaluated 32 studies and found that the risk for cancer in firefighters was significantly elevated for ten sites, four of which showed the strongest evidence of an association. Since that analysis, two more large epidemiological studies of cancer in firefighters have been

reported. Therefore, another meta-analysis that included these two studies was performed by the Working Group for the four primary cancer sites. Three types of cancer showed significant summary risk estimates: the incidence of testicular cancer was ~50% in excess based on six studies and approximately 150 cases, that of prostatic cancer was ~30% in excess based on 17 studies and approximately 1800 cases, and that of non-Hodgkin lymphoma was ~20% in excess based on seven studies and more than 300 cases.

Four cohort studies that investigated testicular cancer in firefighters yielded risk estimates that ranged from 1.2 to 2.5 and one case–control study gave odds ratios that ranged from 1.5 to 4.3. One of three studies found a positive trend between duration of exposure and the increased risk for testicular cancer.

Of 20 studies of prostatic cancer, 17 reported elevated risk estimates that ranged from 1.1 to 3.3; however, only two reached statistical significance and only one study showed a trend with duration of employment.

The studies that investigated non-Hodgkin lymphoma in firefighters used different definitions of this tumour. Five cohort and one case–control studies that evaluated non-Hodgkin lymphoma reported risk estimates that ranged from 0.9 to 2.0. Only one study evaluated exposure–response with duration and did not find a positive relationship.

Although firefighters are exposed concurrently to a multitude of chemical compounds that include numerous carcinogens, human epidemiological studies at best used indirect (poor) measurements of exposure to such agents. Also, exposures of firefighters vary considerably depending on their job activities, and only crude measures of exposure, such as duration of employment and number of runs, have been used in these studies. Despite these limitations, increased risks for some cancers were found for firefighters in the meta-analysis.

5.3 Animal carcinogenicity data

No data were available to the Working Group.

5.4 Other relevant data

Smoke is a complex mixture of suspended particulate matter, gas, and vapour. The lack of data on toxicokinetics and toxicity of the adsorption of chemical components onto particles prevents a full understanding of the effects of smoke on firefighters. The toxicokinetics of chemical mixtures are not well understood but are probably of significant importance because of the multiplicity of chemicals in smoke. For individual smoke components, inhalation was considered to be the major source of exposure; however, dermal absorption is also an important route of exposure for polycyclic aromatic hydrocarbons and polychlorinated biphenyls.

There are insufficient studies to evaluate genotoxic effects in firefighters.

There is clear evidence of chronic and acute inflammatory respiratory effects in firefighters, which provides a potential mechanism for carcinogenesis, although the major effect would be expected in the respiratory system.

No genotoxicity studies in animals were found that involved exposure to smoke from the combustion of structural materials. Smoke causes lipid peroxidation, which may be associated with cancer. Wood smoke suspensions has been shown to cause DNA strand breakage and lipid peroxidation in cell cultures.

6. Evaluation and Rationale

6.1 Cancer in humans

There is *limited evidence* in humans for the carcinogenicity of occupational exposure as a firefighter.

6.2 Cancer in experimental animals

There is *inadequate evidence* in experimental animals for the carcinogenicity of occupational exposure as a firefighter, since no data were available to the Working Group.

6.3 Overall evaluation

Occupational exposure as a firefighter is *possibly carcinogenic to humans (Group 2B).*

SHIFTWORK

SHIFTWORK

1. Definition and Occurrence of Exposure

1.1 Definition of shiftwork

The International Labour Office (International Labour Organization, 1990a) defines working in shifts as "a method of organization of working time in which workers succeed one another at the workplace so that the establishment can operate longer than the hours of work of individual workers."

The European Council Directive 93/104 (1993) declares that "concerning certain aspects of the organisation of working time, shiftwork shall mean any method of organising work in shifts whereby workers succeed each other at the same work stations according to a certain pattern. Shiftworker shall mean any worker whose work schedule is part of shiftwork."

Besides these definitions, in the scientific literature, the term "shiftwork" has been widely used and generally includes any arrangement of daily working hours other than the standard daylight hours (7/8 am – 5/6 pm).

In most cases, shiftwork is synonymous of irregular, odd, flexible, variable, unusual, non-standard working hours.

1.2 Types of shiftwork

Several types of shiftwork exist and can be described as follows:

(*a*) permanent – people work regularly on one shift only, i.e. morning or afternoon or night; or rotating – people alternate more or less periodically on different shifts;

(*b*) continuous – all days of the week are covered; or discontinuous – interruption on weekends or on sundays;

(*c*) with or without night work – the working time can be extended to all or part of the night, and the number of nights worked per week/month/year can vary

considerably. Moreover, the definition of "period of night work" varies from country to country, i.e. in some countries it ranges from 8, 9 or 10 pm to 5, 6 or 7 am, and in many others from 11 or 12 pm to 5 or 6 am (See Table 1.1).

Table 1.1. Definitions of night work and night worker in some European countries

COUNTRY	NIGHT TIME/NIGHT WORK	NIGHT WORKER
AUSTRIA	Night work: period between 22:00 and 05:00	The workers who work at least 3 hours between 22:00 and 05:00 on at least 48 nights per year (EU-Nachtarbeits-Anpassungsgesetz 2002)
BELGIUM	Night work: a period, generally of 8 hours, between 20:00 and 06:00	Loi du 17/02/1997 et Loi du 04/12/1998: Act of 17 February 1997
FINLAND	Night work: Work carried out between 23:00 and 06:00	Night shift refers to a work shift with at least 3 hours of duty between 23:00 and 06:00 (Working Hours Act 605/1996)
FRANCE	Night time: a period between 22:00 and 05:00 Night work: whichever work period between midnight and 05:00	Any employee working usually at least 2 times per week for at least 3 hours over the period defined as night work (Loi 461/1998)
GERMANY	Night time: the time between 23:00 and 06:00 (in case of bakers between 22:00 and 05:00). Night work: all work which occupies more than 2 hours of night time	"Night workers" means workers who usually work nights on rotating shifts schedules, or work at night for not less than 48 days in a calendar year (Arbeitszeitgesetz 1994)
GREECE	Night time: a period of 8 hours which includes the period between 22:00 and 06:00	A worker who during night time works at least 3 hours of his/her daily working time or a worker who has to perform night work for at least 726 hours of his/her annual working time (Presidential Decree n. 88/1999)
IRELAND	Night time: period between midnight and 07:00	a) an employee who normally works at least 3 hours of his/ her daily working time during night time; b) an employee whose working hours during night time, in each year, equals or exceeds 50 per cent of the total number of hours worked during the year (Statutory Instruments n. 485/1998)

Table 1.1 (contd)

COUNTRY	NIGHT TIME/NIGHT WORK	NIGHT WORKER
ITALY	Night work: the activity carried out in a period of at least 7 consecutive hours comprising the interval between midnight and 05:00	a) any worker who during the night period carries out, as a normal course, at least 3 hours of his/her daily working time; b) any worker who during the night period, carries out part of his/her daily working time as defined by collective agreements; in default of collective agreements, any worker who works at night at least 80 working days per year (D.Lgs. 66/2003)
NETHERLANDS	Night work: work which covers all or part of the period from midnight to 06:00	
PORTUGAL	Night time: a period between 20:00 and 07:00	a) any worker who works at least 3 hours during the night period; b) any worker who during the night period, carries out part of its daily working time as defined by collective agreements (Decreto Lei 73/1998)
SPAIN	Night time: a period which includes the interval between 22:00 and 06:00	A worker who at night carries out at least 3 hours of his/her daily working time (Real Decreto Lei 1/1995)
SWEDEN	Hours between midnight and 05:00	A worker that works at least 3 hours of his/her daily work during night time, or a worker that most likely will work at least 38% of his/her annual work during the night (Working Hours Act 1982)
UK	Night time: a period lasting not less than 7 hours, and which includes the period between midnight and 05:00	A worker who, as a normal course, works at least 3 hours of his/her daily working time during night time, or who is likely, during night time, to work at least such proportion of his annual working time as may be specified for the purposes of these Regulations in a collective agreement or a workforce agreement (Statutory Instrument No.1833/1998).

Table compiled by the Working Group

The shift systems can also differ widely in relation to other organizational factors:

(*a*) length of shift cycle – a “cycle” includes all shifts and rest days lasting as long as the series of shifts restart from the same point; there can be short (6–9 days), intermediate (20–30 days), or long (up to 6 months or more) cycles.

(*b*) duration of shifts – in general, the length of a shift is 8 hours, but can range from 6 to 12 hours.

(*c*) number of workers/crews who alternate during the working day.

(*d*) start and finish time of the duty periods.

(*e*) speed of shift rotation – this depends on the number of consecutive days worked before changing shift. It can be fast (i.e. every 1, 2 or 3 days), intermediate (i.e. every week), or slow (i.e. every 15, 20 or 30 days). This factor has considerable influence on the number of consecutive night shifts and rest days.

(*f*) direction of shift rotation – it can be clockwise (i.e. morning/afternoon/night) or counter-clockwise (i.e. afternoon/morning/night) with consequent different duration of the intervals between shifts. Clockwise rotation is also referred to as "phase delay" or "forward rotation," and counter-clockwise rotation, "phase advance" or "backward rotation". They have a different impact on the adjustment of the circadian rhythm.

(*g*) number and position of rest days between shifts.

(*h*) regularity/irregularity of the shift schedules.

All of these factors can be combined in different ways depending on the demands specific to the occupation.

In the industrial sectors (i.e. mechanical and chemical), shiftwork is usually arranged in continuous three-shift systems. A similar number of crews/workers work both on day and night shifts, with regular shift schedules either on fast or slow rotating cycles, with fixed start and finishing times.

In the transport sector, schedules are often quite irregular, both in terms of number of consecutive shifts, shift rotation, start and finishing times, duration of the duty periods, location, and amount of rest days.

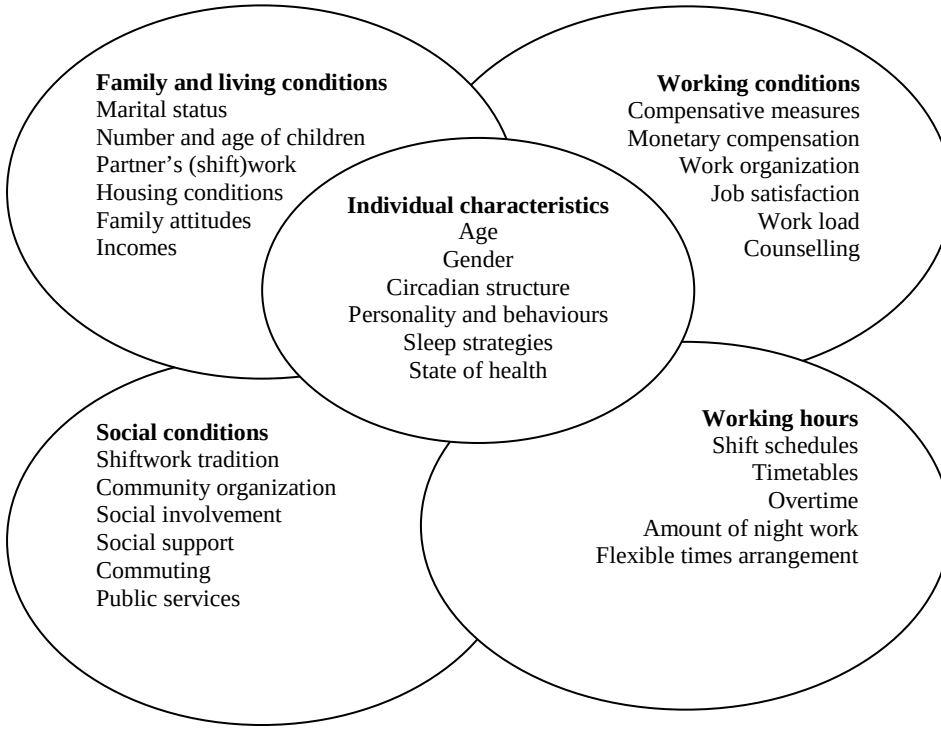
In the health-care sector, quite different shift schedules are operated with different rotation (clockwise or counter-clockwise), variable start and finishing time, and different amount of night shifts.

In the service sector, workers are commonly employed on split shifts, for example, very early morning and late afternoon shifts in road- and office-cleaning, merchandise delivery, or permanent night work (security guards).

In the leisure sector, work is mainly performed during the late afternoon and night hours, with a long duration of shifts.

Different shiftwork systems have potentially different impacts on the health of the workforce, disturbing the circadian rhythm, an essential biological function, in different ways, and also inducing sleep deprivation (see Section 4). In addition to shiftwork schedules, other factors can affect tolerance to shiftwork and night work such as individual characteristics, family situation, social conditions, and working conditions (Fig. 1.1; Costa *et al.*, 1989; Costa, 1996, 2003; Knauth, 1996; Knauth & Hornberger, 2003).

Figure 1.1. Factors that can affect tolerance to shiftwork and night work



(Costa, 2003)

1.3 Occurrence of shiftwork

Increasingly, shiftwork and night work are becoming more common in our so-called "24-hour" (or "24/7") society. Shiftwork and night work enable round-the-clock activities required for meeting technological needs (e.g. power plants, oil refinery, and steel industry), social services/utilities functions (e.g. hospitals, transports, police and security forces, firefighting, hotels, and telecommunications), productive and economic demands (e.g. textile, paper, food, mechanical, and chemical industry), and the needs of the leisure industry.

More than two and a half billion people are officially recognized as workers according to the most recent statistics of the International Labour Organization (International Labour Organization, 2006), two-thirds of which in the Asiatic continent. Reliable data on the numbers of workers employed in shiftwork is not easy to collect due to the lack of robust statistics in many countries, and/or differences in methods of data collection not always being comparable.

However, in Europe, the European Foundation for the Improvement of Living and Working Conditions has been carrying out periodical surveys on working conditions, including working hours, every 5 years since 1990. According to the third survey, carried out in 2000 in 15 European countries and involving 21703 workers, people who do normal or standard daytime work (that is those who do not work more than 40 hours per week, more than 10 hours per day, on shifts, at night, on sundays and/or saturdays, and part-time) represented only 24% of the whole population, 27% of employed workers, 8% of self-employed workers, with men and women sharing the same proportion (24%) (Costa *et al.*, 2004).

According to the results of the fourth survey carried out in 2005 (European Foundation, 2007), the weekly working hours among the 31 European countries examined ranged from an average of 34 hours in the Netherlands to 55 hours in Turkey, and from a minimum of 8 hours (as part-time work) to a maximum of 90 hours (as overtime work). Shiftwork, including night work, involved more than 17% of the total European Union (EU) working population (Table 1.2), with large variations among countries, and between old and new member States (from 6.4% to 30%). There were also quite large differences among EU countries when looking at evening (from 36% to 58%) and night work (from 18% to 24%) (Fig. 1.2). Evening and night work are mostly used in the hotel and restaurant industry, health care, and transport and communication sectors, usually employing an older workforce (Fig. 1.3). More generally, shiftwork in its different definitions is used by one-third of people working in the health-care sector and the hotel and restaurant industry, and in one fourth of cases in the manufacturing, transport, and communication sectors (Table 1.3). According to age and gender (Table 1.4), the average percentage of shiftwork including night work is quite similar in both men and women, with quite a high percentage of workers aged over 55 employed in night work (10.5%).

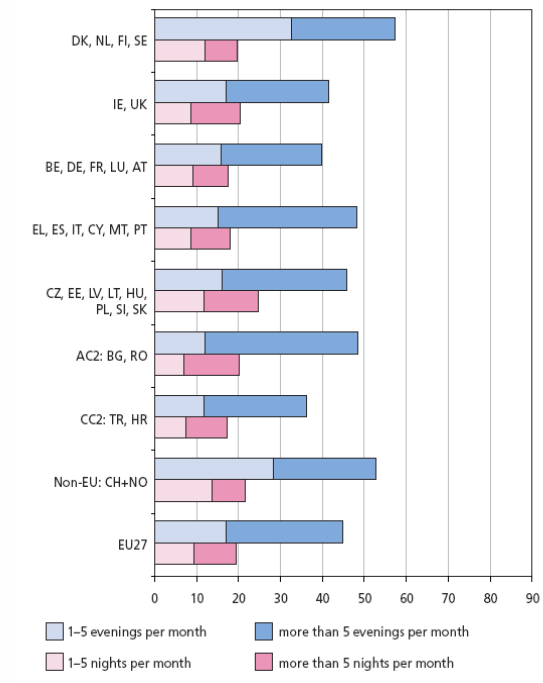
In the USA, according to the Bureau of Labor Statistics (US Bureau of Labor Statistics, 2005), in 2004, almost 15% of full-time salaried workers usually worked on alternate shifts. Men were more likely than women to work such shifts (16.7% and 12.4%, respectively). This was also true for the black population when compared to the caucasian, hispanic or latino, or asian populations, with shiftwork progressively decreasing with increasing age (Table 1.5). The prevalence of shiftwork was greatest among workers in the service industry (32.6%; Table 1.6), particularly the protective service industry (50.4%, includes police, firefighters and guards), food preparation and serving (49.4%), and those employed in production, transportation, and material-moving occupations (29%). The proportion of workers on alternate shifts was highest in the leisure and hospitality (45.8%), mining (31.5%), and transportation and utilities (27.8%) industries.

Table 1.2. Prevalence (%) of shiftwork that includes night work, by country in Europe in 2005 (4th EU Survey on working conditions)

Austria	13.2
Belgium	13.2
Bulgaria	21.0
Croatia*	33.5
Cyprus	11.8
Czech Republic	22.2
Denmark	9.3
Estonia	20.4
Finland	24.3
France	14.9
Germany	15.7
Greece	13.0
Hungary	20.7
Ireland	12.0
Italy	18.1
Latvia	21.9
Lithuania	19.4
Luxembourg	13.9
Malta	22.3
Netherlands	11.8
Norway	23.4
Poland	10.3
Romania	21.0
Slovakia	27.5
Slovenia	30.0
Spain	22.2
Sweden	16.0
Switzerland	12.9
Turkey*	6.4
United Kingdom	15.4
EU27	17.3
EU25	17.1
EU15	16.0
NMS	23.0

EU27: 25 EU Member States, plus the two countries that joined the European Union in 2007 – Bulgaria and Romania
EU25: 15 EU Member States. plus the 10 new Member States that joined in 2004
EU15: 15 EU Member States prior to enlargement in 2004
NMS: 10 New Member States that joined in 2004
* Two candidate countries for membership of the EU: Croatia and Turkey

Figure 1.2. Prevalence of evening and night work by group of country in Europe in 2005 (4th EU Survey on working conditions)



Country codes

EU15	15 EU Member States prior to enlargement in 2004		
NMS	10 new Member States that joined in 2004		
EU25	15 EU Member States, plus the 10 NMS		
EU27	25 EU Member States, plus the AC2		
AC2	Two countries that joined the European Union in 2007: Bulgaria and Romania		
CC2	Two candidate countries for membership of the EU: Croatia and Turkey		
AT	Austria	LU	Luxembourg
BE	Belgium	MT	Malta
BG	Bulgaria	NL	Netherlands
CY	Cyprus	PL	Poland
CZ	Czech Republic	PT	Portugal
DK	Denmark	RO	Romania
EE	Estonia	SK	Slovakia
FI	Finland	SI	Slovenia
FR	France	ES	Spain
DE	Germany	SE	Sweden
EL	Greece	UK	United Kingdom
HU	Hungary	HR	Croatia
IE	Ireland	NO	Norway
IT	Italy	CH	Switzerland
LV	Latvia	TR	Turkey
LT	Lithuania		

Country groups
Continental countries: AT, BE, DE, FR, LU
Ireland and the United Kingdom: IE, UK
Eastern European countries,: CZ, EE, HU, LT, LV, Pl, SI, SK
Southern European countries: CY, EL, ES, IT, MT, PT
Scandinavian countries and the Netherlands: DK, FI, NL, SE
Acceding countries: BG, RO
Candidate countries: HR, TR
EFTA (European Free Trade Association): CH, NO
Typology adapted from Esping-Andersen

Figure 1.3. Prevalence of evening and night work by work sector in Europe in 2005 (4th EU Survey on working conditions)

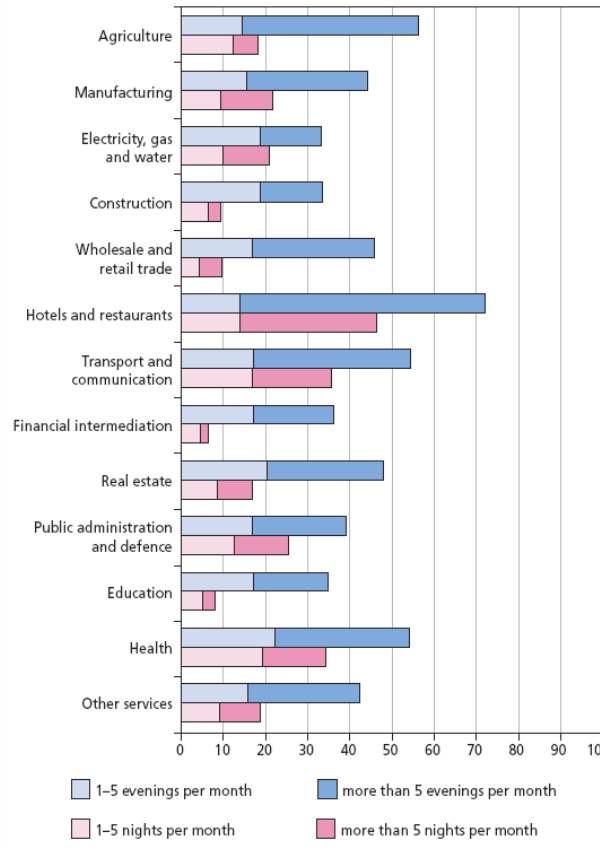


Table 1.3. Prevalence (%) of shiftwork that includes night work, by work activity in Europe in 2005 (4th EU Survey on working conditions)

Agriculture and fisheries	4.5
Armed forces	19.2
Clerks	13.4
Construction	5.3
Craft and related trades	17.6
Education	8
Electricity, gas and water supply	17.4
Elementary occupations	19.2
Financial intermediation	6.2
Health	35.5
Hotels and restaurants	29.9
Legislators, senior officials and managers	8.8
Manufacture and mining	25.8
Plant and machine operators and assemblers	34.5
Professionals	11.6
Public administration and defence	17.7
Real estate	9.5
Service, shop and market sales workers	26.9
Skilled agricultural and fishery workers	2.6
Technicians and associate professionals	14.3
Transport and communications	24.1
Wholesale and retail trade	16.3
Self-employed	5.7
Employee	19.8

Table 1.4. Prevalence (%) of shiftwork, including night work, by gender and age, in Europe in 2005 (4th EU Survey on working conditions)

Gender	Men	17.2
	Women	17.4
Age (years)	≤24	20.7
	25–39	19.1
	40–54	16.7
	≥55	10.5

Table 1.5. Percent distribution of shiftwork in full-time wage and salary workers by sex, race and ethnicity, in the USA in 2004 (US Bureau of Labor Statistics)

Total (>16 years)	14.8
Men	16.7
Women	12.4
White	13.7
Black or african american	20.8
Asian	15.7
Hispanic or latin ethnicity	16

Table 1.5 (contd)

20–24 years	22.3
25–34 years	15.2
35–44 years	14.1
45–54 years	12.8
55–64 years	12.5
≥65 years	10.3

Table 1.6 Percent distribution of shiftwork in full-time wage and salary workers, by occupation and industry, in the USA in 2004 (US Bureau of Labor Statistics)

Occupation	
Management professionals	8.7
Service occupations	36.1
Sales and office occupations	16.4
Natural resources, construction and maintenance	7.6
Production, transportation and material-moving occupations	26.4
Industry	
Private sector	15.4
Agriculture and related industries	9.5
Mining	31.5
Construction	2.8
Manufacturing	17.7
Wholesale and retail trade	22.0
Transportation and utilities	27.8
Information	15
Financial activities	7.0
Professionals and business services	9.4
Education and health services	12.8
Leisure and hospitality	45.8
Other services	13.0
Public sector	11.9
Federal government	14.7
State government	11.5
Local government	11.3

1.3.1 *Exposure assessment*

It is difficult to assess the effective "exposure" and the consequent "risk" of shiftwork with the common methods used (i.e. in toxicology) as the "dose" can widely differ not only in terms of quantitative load, i.e. in relation to the time spent in shiftwork, but mainly in terms of qualitative aspects, i.e. in relation to the interference that different shift

systems may have on biological and psychosocial functions, also taking into account several concurrent individual, social, and working factors.

The various combinations of these aspects can cause a different amount of stress and also different stress-related effects, thus making it difficult to compare groups without adjusting for the amount of "exposure", at least for the type of shift schedule and the years spent in shiftwork.

From a biological perspective, the occurrence and amount of night work is the most important factor to be considered. It is then possible to estimate roughly the effects (more or less severe) the different shift systems may have on health through interference on biological function, and on psychosocial issues.

Several methods have been proposed for assessing working time arrangements to evaluate their potential risk for health and well-being. The criteria most widely used are perturbation of the circadian rhythm, performance at work (ability to work efficiently), health, and social life (Wedderburn, 1994).

The "Rota Risk Profile Analysis," proposed by Jansen and Kroon (1995), describes several risk factors associated with with roster design, related to both physiological and psychosocial aspects, that must be considered. in particular: regularity of shift timetable, periodicity (i.e. the degree to which the "biological clock" is disturbed), shift load (i.e. the average length of shifts) and week load (i.e. the average length of the working week), opportunities for night rest (for sleeping between 11 pm and 7 am) and constancy in night rest (variation in the week), predictability of the shift cycles, opportunities and constancy for household and family tasks, opportunities and constancy for evening recreation (between 7 pm to 11 pm), opportunities and constancy for weekend recreation.

1.3.2 *Factors influencing shiftwork exposure and health*

Many health impairments associated with shiftwork have been reported. These include psychosomatic disorders of the gastrointestinal tract (colitis, gastroduodenitis, and peptic ulcer) and of the cardiovascular system (hypertension, ischaemic heart diseases), as well as metabolic disturbances, that are influenced by other time- and work-related factors and behaviours (Costa, 1996; Knutsson, 2003).

About 20% of all workers have to stop shiftwork altogether after a very brief period because of serious health problems, 10% do not complain about shiftwork during their whole working life, while the remaining 70% withstand shiftwork with different levels of intolerance that can become more or less manifest at different times and with different intensity in terms of discomforts, troubles or diseases (Waterhouse *et al.*, 1992).

1.3.3 *Some lifestyle factors that possibly modify the effects of exposure*

Some personal risk factors can act either as confounders or mediators, and/or modifiers, of the relation between shiftwork and health. Smoking and diet, generally considered as confounders in epidemiological studies, can also be intermediate factors of

the effects of shiftwork (i.e. for cardiovascular and gastrointestinal disorders). Many studies have reported that shiftworkers tend to smoke more (Bøggild and Knutsson, 1999; van Amelsvoort *et al.*, 2006) and/or increase their consumption of caffeinated or alcoholic drinks at night, as well as modify the composition and the caloric distribution of the different meals, i.e. by increasing carbohydrate intake at regular intervals (Reinberg *et al.*, 1979; Romon *et al.*, 1986; Lennernäs *et al.*, 1993). Metabolic disturbances have been found to be prevalent in shiftworkers (Knutsson *et al.*, 1990; Karlsson *et al.*, 2001). Of concern are mainly the risks for cardiovascular disease and obesity (Tenkanen *et al.*, 1998).

1.3.4 *Specificity of exposure to shiftwork for some particular occupations*

(a) Aircraft crew and transmeridian travel over time zones

Aircraft crews operating on long transmeridian flights have to cope with a shift in external time in addition to the shift of the working period. Therefore, the individual biological rhythms have to adjust to abnormal working hours in a changed environmental context. The short-term problems arising from these conflicts are similar to those of normal shiftwork, but are often aggravated by the fatigue due to the extended duty periods, and by a loss of the usual external time cues.

After a long transmeridian flight, the circadian system does not adjust immediately to the new local time, but requires several days in relation to the number of time zones crossed; the greater the number, the longer is the time required, considering that the human circadian system can adjust to no more than 60–90 minutes per day (Wegmann and Klein, 1985).

The adjustment is generally more rapid in westbound (about 1 day per hour of shift) than eastbound flights (about 1.5 day per hour of shift; Ariznavarreta *et al.*, 2002; Gander *et al.*, 1989; Suvanto *et al.*, 1990). In the first case, there is a progressive phase delay of the circadian rhythm in relation to the extended personal day, whereas in the latter there is a phase advance due to the compressed day (*directional asymmetry*). A complete readjustment after transition of six time zones was found to take 13 days and 10 days in eastward and westward flights, respectively (Wegmann and Klein, 1985).

In addition, crews are exposed to many other concurrent risk factors, such as cosmic radiation, electromagnetic fields, lighting, noise, acceleration, vibration, mental stress, fixed postures, and pressurization.

No statistics are currently available on the entire population employed in transmeridian flights, and consequently in related shiftwork, which is generally characterized by very irregular shift schedules. Only in the case of pilots and flight engineers, are there data that can provide a rough idea of the possible number of workers involved, considering that they generally account for about 20% of the total aircraft crew members.

The US Aircraft Owners and Pilots Association (IAOPA 2007) estimated that the civil aviation worldwide during 2004 consisted of approximately 370 000 aircraft and 1.3 million pilots flying some 39 million hours. On balance, roughly 600 000 pilots were employed in commercial air transportation worldwide (including cargo and charter).

The US Bureau of Labor Statistics (2007), reported that civilian aircraft pilots and flight engineers held about 107 000 jobs in the USA in 2006. About 79 000 worked as regular airline pilots, copilots, and flight engineers. The remainder were commercial pilots who worked as flight instructors at local airports or for large businesses that fly company cargo, and executives in their own airplanes or helicopters.

(b) Watchkeeping and driving

Ship's crew members engaged in long distance navigation work on continuous shiftwork, with some differences compare to land-based shiftworkers. For example, they can only take rest time in their place of work after the duty period, and usually have no rest days up until the end of the sea voyage is concluded. Moreover, they also have to cross several time zones (at different speed compared to flight crews), and their leisure time is limited both in terms of space and time. Several different shift systems are used. In merchant fleets, the personnel is generally divided into two or three crews working 12-hour or 8-hour shifts respectively, whereas on warships the crew work more frequently on the "4-hour watch" system, by dividing the 24-hour period into six 4-hour watches, and rotating on a "4-h on/8-h off" schedule, that allows one full night sleep in three. In general, in this shift schedule, the average amount of sleep is nearly the same as that of dayworkers, but the sleep is fragmented into two periods. A further system, the 6-hour on/6-hour off system is becoming more and more common on warships. However, high irregularity and variability of shift duration and rotation are quite frequent due to crew shortage, additional duties and unexpected situations, thus the amount of rest and sleep hours may vary considerably among days and subjects (Eriksen *et al.*, 2006).

The situation is similar for shiftworkers of offshore oil installations, who live in the same environment during both work and leisure time and stay away from home for several weeks, usually working in alternating 12-hour shift schedules (6:00–18:00, 18:00–6:00). In addition, in this occupational setting, the (mal)adjustment of the circadian rhythm may be more or less pronounced and depends on whether the fast or slow rotation is adopted, job characteristics (drilling, maintenance), and working organization (Barnes *et al.*, 1998).

Similar problems can be faced by long-haul truck and train drivers (i.e. coast-to-coast journeys, relay work), in which shiftwork, long working hours and time zone crossing interact in causing circadian disruption of the sleep/wake cycle and biological rhythms, as well as sleep deprivation, and overall fatigue (Jay *et al.*, 2006).

1.4 Biomarkers of circadian regulation and dysregulation

The production and release of nearly all hormones exhibits a circadian timing patterned on approximately a 24-hour cycle (Pandi-Perumal *et al.*, 2007). Agents that disrupt the circadian rhythm may therefore alter hormone levels.

At present, there is no known biomarker of exposure to shiftwork, which is thought to affect circadian regulation. In the past, core body temperature or blood cortisol levels have been used as markers of circadian regulation. However, given the importance of melatonin in the regulation of circadian rhythm, an indicator of melatonin levels is considered a preferable biomarker of circadian regulation and dysregulation, and has been more commonly used in recent studies on the effects of shiftwork in humans. Melatonin levels are comparatively robust in the presence of various external influences (Pandi-Perumal *et al.*, 2007). For example, excessive carbohydrate intake can significantly affect core body temperature and heart rate, whereas melatonin concentration remains relatively unaffected by this factor (Kräuchi *et al.*, 2002). Furthermore, the onset of melatonin production is largely unaffected by biochemical and physiological factors, which further suggests its greater reliability to measure circadian phase position (Lewy, 1999; Lewy *et al.*, 1999).

1.4.1 *Methods of measuring circulating melatonin*

(a) Melatonin in serum and plasma

Plasma melatonin, which has a very short biological half-life and is rapidly metabolized by the liver, reflects the amount of melatonin circulating at the point in time of the sample collection. Thus, measurement of melatonin in plasma at regular intervals (e.g. hourly) will map out a circadian rhythm, enabling identification of the onset of melatonin secretion, the duration of melatonin secretion, peak levels of circulating melatonin, and the time at which peak secretion occurred, and the total amount of melatonin secreted. Although such detailed information may be very useful in identifying the characteristics of the circadian rhythm in an individual, such measurement is possible only in a controlled setting (e.g. sleep laboratory), and is impractical in other applications such as an epidemiological study or other widespread population use.

(b) Melatonin in saliva

Melatonin can also be measured in saliva, using several different laboratory techniques. Salivary testing is a useful method for measuring melatonin in epidemiological studies, given that it is relatively non-invasive and generally acceptable to study participants. With proper training, study subjects can collect their own samples at home, to be later delivered to the laboratory for assay. Several researchers have found a high correlation between serum and salivary melatonin concentrations, and have concluded that salivary melatonin concentrations are reliable indices of serum melatonin

concentrations (Arendt *et al.*, 1985; Laakso *et al.*, 1990; Klante *et al.*, 1997; Davis *et al.*, 2001; Gooneratne *et al.*, 2003). However, Laakso *et al.* (1990) compared salivary and serum melatonin levels and found that saliva and serum measurements were not highly correlated in individuals with low serum melatonin levels, and that the proportion of melatonin found in saliva decreased with increasing serum melatonin levels. They concluded that melatonin concentrations measured in saliva do not always consistently reflect the absolute concentrations in blood. Gooneratne *et al.* (2003) reported similar results in that serum and saliva melatonin levels were less correlated in individuals with low serum melatonin levels. The primary drawback to measuring melatonin in saliva is that, similar to plasma and serum measurements, salivary melatonin reflects the amount of melatonin circulating in the body at a given time-point. To capture details of the rhythm of melatonin secretion, such as the time of onset, peak levels, and cumulative secretion, one has to collect the subject's saliva samples at regular intervals throughout the night.

(c) Melatonin in urine

Arendt *et al.* (1985) suggested that measurement of the primary metabolite of melatonin excreted in urine would allow the non-invasive study of pineal function, useful in a broad range of applications. If appropriately executed, measurement of melatonin in the urine reflects the cumulative amount of circulating melatonin corresponding to the time period between the prior urine void and the collection of the subsequent urine sample. Using this approach to quantify melatonin levels in urine is typically accomplished through the measurement of 6-hydroxymelatonin sulfate (aMT6s), the primary metabolite in urine, although some studies directly measure urinary melatonin. The principal methods for determination of urinary aMT6s include assay by either radioimmunoassay (RIA) or enzyme-linked immunosorbant assay (ELISA); commercial kits are available for both methods. Concentrations of aMT6s are often adjusted by urinary creatinine concentrations to account for differing urine output volume from one individual to the next, and for separate urine collections within individuals (Klante *et al.*, 1997).

The stability of such measurements further promotes the usefulness of this technique, since long-term levels of hormones are often of interest in diseases with long latency periods. Davis *et al.* (2001) evaluated nocturnal aMT6s levels in a group of women 20–74 years of age over 3 consecutive days, then repeated the measurement protocol 3–6 months later. Urinary aMT6s concentrations have been shown to be highly and significantly correlated on consecutive days, as well as between measurements sessions over long time period until 5-year time period in several studies (Levallois *et al.*, 2001; Travis *et al.*, 2003). Levallois *et al.* (2001) measured urinary aMT6s concentrations over 2 consecutive days and a found similarly high correlation.

(d) Comparison between blood and urinary melatonin levels

As melatonin is secreted primarily at night, studies have focused on nocturnal samples when evaluating the correlation between melatonin levels in blood and urine, and found a high degree of correlation between nocturnal measurements of urinary melatonin or urinary aMT6s, and plasma or serum melatonin. Graham *et al.* (1998) found a significant relationship between total nocturnal plasma melatonin and both urinary aMT6s corrected for creatinine and urinary melatonin. Combining the two urinary measures of aMT6s and melatonin accounted for 72% of the variance in total plasma melatonin. Furthermore, peak nocturnal levels of plasma melatonin were significantly related to morning levels of urinary melatonin and aMT6s. Cook *et al.* (2000) assessed the differences in melatonin levels between blood and urine samples collected in a laboratory-based setting with nocturnal urine samples collected in a field study, and found very high correlations ($P < 0.001$) between first morning void melatonin and creatinine-corrected aMT6s and both total nocturnal plasma melatonin output and peak nocturnal plasma melatonin.

Similarly high correlations have been found in studies that compared melatonin in plasma and serum with urinary melatonin and/or urinary aMT6s over a 24-hour period (Markey *et al.*, 1985; Baskett *et al.*, 1998). Bojkowski *et al.* (1987) found that total 24-hour urinary excretion of aMT6s was significantly correlated with the area under the curve of the respective profiles for plasma melatonin ($r = 0.75$), and plasma aMT6s ($r = 0.70$).

In conclusion, both urinary melatonin and urinary aMT6s are good indicators of melatonin secretion in blood with a significantly smaller variation for the former molecule (Pääkkönen *et al.*, 2006). Such measurements in urine samples would provide a suitable tool in epidemiological settings to study the modulation of the circadian rhythm in shiftworkers.

1.5 Regulations on shiftwork

Some international directives have been issued in the last decades addressing the need for a careful organization of shift and night work and the protection of shiftworkers' health: in particular, the International Labour Office (ILO) "Code of practice on working time" (1995) and Convention no. 171 (C171) on "Night work" (1990), and the European Directive no. 93/104/EC "concerning certain aspects of the organization of working time" (1993), which in European countries has been implemented through national legislation.

1.5.1 *ILO Night Work Convention and Recommendation*

(a) General population

The ILO C171 Night Work Convention (International Labour Organization, 1990a) refers only to *night work*, that is "all work which is performed during a period of not less than seven consecutive hours, including the interval from midnight to 5am," and *night worker*, who is "an employed person whose work requires performance of a substantial number of hours of night work which exceeds a specified limit, fixed by the competent authority. This convention applies to all employed persons except those employed in agriculture, stock raising, fishing, maritime transport and inland navigation."

In addition, the ILO R178 Night Work Recommendation (International Labour Organization, 1990b), supplementing the Night Work Convention C171, points out the following:

"Normal hours of work for night workers should not exceed eight in any 24-hour period in which they perform night work, except in the case of work which includes substantial periods of mere attendance or stand-by, in cases in which alternative working schedules give workers at least equivalent protection over different periods or in cases of exceptional circumstances recognized by collective agreements or failing that by the competent authority.

The normal hours of work of night workers should generally be less on average than and, in any case, not exceed on average those of workers performing the same work to the same requirements by day in the branch of activity or the undertaking concerned.

In occupations involving special hazards or heavy physical or mental strain, no overtime should be performed by night workers before or after a daily period of work which includes night work, except in cases of force majeure or of actual or imminent accident.

Where shift work involves night work: (a) in no case should two consecutive full-time shifts be performed, except in cases of force majeure or of actual or imminent accident; (b) a rest period of at least 11 hours between two shifts should be guaranteed as far as is possible."

(b) Women during pregnancy and around childbirth

At any point during pregnancy, once this is known, women night workers who so request should be assigned to day work, as far as is practical.

Measures shall be taken to ensure that an alternative to night work is available to women workers who would otherwise be called upon to perform such work: (a) before and after childbirth, for a period of at least 16 weeks of which at least 8 weeks shall be before the expected date of childbirth; (b) for additional periods in respect of which a medical certificate is produced stating that it is necessary for the health of the mother or child: (i) during pregnancy; (ii) during a specified time beyond the period after childbirth fixed pursuant to subparagraph (a) above, the length of which shall be determined by the

competent authority after consulting the most representative organizations of employers and workers. These measures may include transfer to day work where this is possible, the provision of social security benefits or an extension of maternity leave. During those periods, a woman worker shall not be dismissed or given notice of dismissal, except for justifiable reasons not connected with pregnancy or childbirth, and shall not lose the benefits regarding status, income, seniority and access to promotion which may attach to her regular night work position (ILO C171, 1990).

(c) Young people

With regard to young people, following the first Night Work of Young Persons (Industry) Convention (1919), the ILO Night Work of Young Persons (Industry) Convention (Revised) (1948), stated that: "young persons under eighteen years of age shall not be employed or work during the night in any public or private industrial undertaking (i.e. mines, quarries, manufactures, construction, transports, electrical-gas works, etc.). "Night" means a period of at least twelve consecutive hours. In the case of young persons under sixteen years of age, this period shall include the interval between ten o'clock in the evening and six o'clock in the morning. Moreover, in the case of young persons who have reached the age of sixteen years but are under the age of eighteen years, this period shall include an interval prescribed by the competent authority of at least seven consecutive hours falling between ten o'clock in the evening and seven o'clock in the morning. For purposes of apprenticeship or vocational training in specified industries or occupations which are required to be carried on continuously, the Convention stated that the competent authority may, after consultation with the employers' and workers' organizations concerned, authorise the employment in night work of young persons who have reached the age of sixteen years but are under the age of eighteen years."

(d) Seafarers

For specific groups of workers, the ILO Convention No. 180 "Concerning Seafarers' Hours of Work and the Manning of Ships" (1996) states limits on hours of work or rest, in particular: "a) maximum hours of work shall not exceed 14 hours in any 24-hour period, and 72 hours in any seven-day period; b) minimum hours of rest shall not be less than ten hours in any 24-hour period, and 77 hours in any seven-day period; c) hours of rest may be divided into no more than two periods, one of which shall be at least six hours in length, and the interval between consecutive periods of rest shall not exceed 14 hours. Moreover, no seafarer under 18 years of age shall work at night (which means a period of at least nine consecutive hours, including the interval from midnight to five a.m.)."

(e) Long-distance drivers

According to the US Bureau of Labor Statistics (2007) long-distance drivers may drive for 11 hours and work for up to 14 hours – including driving and non-driving duties – after having 10 hours off-duty. Moreover, they may not drive after having worked for

60 hours in the past 7 days or 70 hours in the past 8 days unless they have taken at least 34 consecutive hours off-duty.

(f) Airline pilots

According to the National Aeronautics and Space Administration guidelines (Dinges *et al.* 1996), for standard operations including day and night flying, the duty period for air pilots should not exceed 10 hours within a 24-hour period; in case of extended flight duty periods, the limit should be fixed at 12 hours, and accompanied by additional restrictions and compensatory off-duty periods. It is also recommended that in any 7-day period, there be no extended flight duty period that encroaches on any portion of the window of circadian low (i.e. period between 2–6 am for an individual's normal day–wake/night–sleep schedule).

Because of Federal Aviation Administration regulations, airline pilots flying large aircraft, cannot fly more than 100 hours a month or more than 1000 hours a year. Most airline pilots fly an average of 75 hours a month and work an additional 75 hours a month performing non-flying duties. To guard against pilot fatigue, which could result in unsafe flying conditions, the Federal Aviation Administration requires airlines to allow pilots at least 8 hours of uninterrupted rest in the 24 hours before finishing their flight duty.

Many countries in the world have national laws regulating night work according to ILO recommendations, whereas in many others this topic is regulated by means of collective or local agreements between parties (International Labour Organization, 1995).

1.5.2 *European Directive on Working Time*

(a) General population

In Europe, the EU Council Directive No 93/104/EC (European Council Directive, 1993) "concerning certain aspects of the organization of working time" (re-confirmed by EU Directive 2003/88/EC):

– defined "night time" as "any period of not less than seven hours, as defined by national law, and which must include in any case the period between midnight and 5 am"; and "night worker" as (a) any worker who, during night time, works at least three hours of his/her daily working time as a normal course, and (b) any worker who is likely during night time to work a certain proportion of his/her annual working time, as defined at the choice of the Member State concerned either by national legislation or by collective agreements. On the other hand, shift work means "any method of organising work in shifts whereby workers succeed each other at the same work stations according to a certain pattern, including a rotating pattern, and which may be continuous or discontinuous, entailing the need for workers to work at different times over a given period of days or weeks; consequently, "shift worker shall mean any worker whose work schedule is part of shift work."

– forced Member States to take the measures necessary to ensure that: normal hours of work for night workers do not exceed an average of 8 hours in any 24-hour period for normal work activities, but not more than 8 hours in any 24-hour period in case of work involving special hazards or heavy physical or mental strain; every worker is entitled to a minimum daily rest period of 11 consecutive hours per 24-hour period; where the working day is longer than 6 hours, every worker is entitled to a rest break; per each seven-day period, every worker is entitled to a minimum uninterrupted rest period of 24 hours plus the 11 hours daily rest; and it should preferably include Sunday; the average working time for each seven-day period, including overtime, does not exceed 48 hours; every worker is entitled to paid annual leave of at least four weeks in accordance with the conditions for entitlement to, and granting of, such leave laid down by national legislation and/or practice; the minimum period of paid annual leave may not be replaced by an allowance in lieu, except where the employment relationship is terminated.

Implementing such directive at national level, some European countries added the quantitative criterium of 80 night shifts worked per years as minimum level for establishing the compulsory periodical medical surveillance for night workers: this limit appears as a mere technical compromise among social parties (i.e. one third of the total working days), being not supported by any evidence based on the scientific literature.

There are also some differences among countries in the definition of both "night work" and "night worker" (see Table 1.7).

Table 1.7. Legislation on night work in 15 EU[a] countries

Country	Max. length of night work in hours	Legislation
AUSTRIA	**–**	Nachtschwerarbeitsgesetz nr. 354/1981 (rev. 1993)– "Night work": period of at least 6 hours between 22:00 and 06:00 for at least six nights a month. Additional breaks: 10 min paid break during the night shift. Additional vacations: 60 nightshifts per year, 2 work days, after 5 years on shift, 4 work days, after 15 years on shift, 6 work days. Health service, possibility of early retirement.
BELGIUM	**8**	Loi du 17/02/1997 et Loi du 04/12/1998: "Night time": a period, generally of 8 hours, between 20:00 and 06:00. "Night work": in principle, prohibited, but various derogations are possible.
DENMARK	**–**	The notions of night time and night worker have been defined generally in collective agreements**.**

Table 1.7 (contd)

Country	Max. length of night work in hours	Legislation
FINLAND	**–**	Working Hours Act 605/1996: “Night work”: work of at least 3 hours between 23.00 and 06.00. An employer must notify the labour protection authorities of regular night work, when the said authorities so request.
FRANCE	**–**	Loi 461/1998: “Night time”: period between 22:00 and 05:00 or whichever night work period between midnight and 05:00. “Night workers”: any employee working usually at least 2 times per week at least 3 hours on the period defined as night work.
GERMANY	**8/10**	Arbeitszeitgesetz 1994: “Night time”: a period which includes the time between 23.00 and 06.00, in the case of bakers between 22.00 and 05.00. “Night work”: every kind of work which includes more than 2 hours of night time. The working time of a night worker and shiftworker shall not exceed 8 hours, or 10 hours if within a month or a 4-weeks period where the average working hours are 8 hours per day. The night workers are entitled to a health assessment before they take up the assignment and after that, every 3 years. After the age of 50, the time is reduced to 1 year. “Night worker”: a worker who works at least 2 hours during night time. “Night workers” are those workers who usually work nights in rotating shifts system or works at night on not less than 48 days during a year. The working time of a night worker and shiftworker shall be laid out according to evidence based knowledge about human centred design of working hours from ergonomics.
GREECE	**8**	Presidential Decree no. 88/1999: “Night time”: period of 8 hours which includes the period between 22:00 and 06:00. “Night worker”: a worker who during night time works at least 3 hours of his daily working time or a worker who has to perform night work for at least 726 hours of his annual working time.
IRELAND	**9**	Statutory Instruments no. 485/1998: “Night time”: period between midnight and 07.00. “Night worker”: a) an employee who normally works at least 3 hours of his or her daily working time during night time; b) an employee whose working hours during night time, in each year, equals or exceeds 50 per cent of the total number of hours worked during the year.

Table 1.7 (contd)

Country	Max. length of night work in hours	Legislation
ITALY	**–**	D.Lgs. 66/2003: "Night work": the activity carried out in a period of at least 7 consecutive hours comprising the interval between midnight and 05.00 in the morning. "Night worker": a) any worker who during the night period carries out, in a not exceptional way, at least 3 hours of his daily working time; b) any worker who carries out, during the night, at least a part of his normal working hours. Night work does not have to be done obligatorily by: a) the working mother of a child under 3 years of age or, alternatively, by the cohabiting father; b) the worker who is the only entrusted parent of a cohabiting child of less than 12 years of age; c) the worker who takes care of a disabled subject. Women are forbidden to work from 24.00 to 06.00, from the assessment of state of pregnancy until the first year of age of the child. Thereafter their assignment to night work is on voluntary basis until the third year of age of the child.
LUXEMBOURG	**–**	There is no general legislation on night work or night worker.
NETHERLANDS	**–**	Wet van 23/11/1995: "Night work": work which covers all or part of the period from midnight to 06:00.
PORTUGAL	**8**	Decreto Lei 259/98: "Night time": a period between 20:00 and 07:00 L.73/98: "Night work": shall not exceed 8 hours. The night workers with risks shall not work more than 8 hours in a period of 24 hours. The employer ensures the worker the opportunity of a free health assessment before he takes up the assignment and during the period of work.
SPAIN	**8**	Real Decreto Lei 1/1995: "Night time": the period which includes the interval between 22.00 and 06.00. "Night work": shall not exceed the 8 hours in a work period of 15 days. The employer, who usually utilizes night work, has to inform the authority. "Night worker": the worker who at night carries out at least 3 hours of its daily working time".

Table 1.7 (contd)

Country	Max. length of night work in hours	Legislation
SWEDEN	**–**	Working Hours Act 1982: All employees shall be afforded free time for nightly rest. Such free time shall include the hours between midnight and 05:00. Exception could be made depending on the nature of the work. "Night worker": a worker that works at least 3 hours of his daily work during night time, or a worker that most likely will work at least 38% of his annual work during the night.
UK	**8**	Statutory Instruments.1833/1998: "Night time": a period the duration of which is not less than 7 hours, and which includes the period between midnight and 05:00. A nightworker's normal hours of work, in any reference period which is applicable in his case, shall not exceed an average of 8 hours for each 24 hours. "Night worker": a worker who, as a normal course, works at least 3 hours of his daily working time during night time, or who is likely, during night time, to work at least such proportion of his annual working time as may be specified for the purposes of these regulations in a collective agreement or a workforce agreement. An employer shall not assign an adult worker to work which is to be undertaken during periods such that the worker will become a night worker unless the employer has ensured that the worker will have the opportunity of a free health assessment before he takes up the assignment; or the worker had a health assessment before being assigned to work to be undertaken during such periods on an earlier occasion, and the employer has no reason to believe that that assessment is no longer valid.

[a] Council Directive 93/104/EC of 23 November 1993 concerning certain aspects of the organization of working time.
Compiled by the Working Group

(b) Women during pregnancy and around childbirth

For women, the EU Council Directive 92/85/EEC (European Council Directive, 1992), "on the introduction of measures to encourage improvements in the safety and health at work of pregnant workers and workers who have recently given birth or are breastfeeding," forced Member States to take the necessary measures to ensure that such workers are not obliged to perform night work during their pregnancy and for a period following childbirth which shall be determined by the national authority competent for safety and health. These measures must entail the possibility, in accordance with national

legislation and/or national practice, of transfer to daytime work, or leave from work or extension of maternity leave where such a transfer is not technically and/or objectively feasible.

In most legislations of European countries, women are prohibited to work at night from the assessment of state of pregnancy until the first year of age of the child. Thereafter, in many cases, assignment to night work is on voluntary basis until the third year of the child.

(c) Young people

For young people, the European Council Directive 94/33/EC (1994) on the protection of young people at work states that: "Member States shall adopt the measures necessary to prohibit work by children (less than 15 years of age) between 8 pm and 6 am (in case of cultural or similar activities allowed to children), and by adolescents (15–18 years of age) either between 10 pm and 6 am or between 11 pm and 7 am. For adolescents, there may be some exceptions in specific areas provided that they are supervised by an adult, but work between midnight and 4 am continues to be prohibited.

1.5.3 *Scientific guidelines*

The main indications for the design of better shift systems according to ergonomic criteria are (Knauth, 1996; Knauth and Hornberger, 2003; Wedderburn, 1994):

a) Quickly rotating shift systems are better than slowly rotating ones.

b) Clockwise rotation (morning/afternoon/night) is preferable to counter-clockwise (afternoon/morning/night).

c) Early starts for the morning shift should be avoided.

d) Prolonged work shifts (9–12 hour) should only be considered when the workload is suitable, there are adequate breaks, and the shift system is designed to minimize accumulation of fatigue and exposure to toxic substances.

e) Shift systems should be regular and able to guarantee as many free weekends as possible.

f) Permanent night work can be acceptable only for particular working situations which require a complete adjustment to night work to guarantee the highest levels of safety. Be aware that such complete adjustment requires people to maintain the inverted sleep/wake cycle also on rest days and to avoid exposure to bright light after night shifts (i.e. wearing dark sun glasses while commuting home).

g) Adequate time off between shifts should be allowed to compensate for fatigue and sleep as quickly as possible (i.e. two shifts in the same day must be avoided), and rest days should come preferably after the night duty period to allow prompt recovery from sleep deficit and an easier return to the normal sleep/wake cycle.

h) Some flexibility in working times is desirable to give the workers the possibility of combining better work duties with family and social life.

1.6 References

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2. Studies of Cancer in Humans

2.1 Introduction

Airline personnel flying over time zones are exposed to frequent disruptions of circadian rhythm, which has similarities with exposure to shiftwork. There are studies reporting cancer risk in about ten cohorts of airline cabin crew and a similar number of studies in cockpit personnel. The cabin crew cohorts support the strong evidence of significantly increased risk of breast cancer incidence found in most independent studies. Higher diagnostic activity (screening during annual health controls) may explain part of the excess when comparing with national population rates, and it should not confound internal comparisons within differently exposed subcohorts of cabin crew. Unfortunately, the studies published so far do not demonstrate precise dose–response evaluations according to the frequency of disruptions of circadian rhythm, for which the best proxy has been duration of work as flight attendant. In most studies, the excess is observed at around 10 years after first employment, and increases weakly with increasing duration. Differences in reproductive factors explain only a small fraction of the excess, while risk attributable to radiation may explain a quarter of the excess. It is unclear whether the substantial neutron component of cosmic radiation (25–50% of the effective dose but less than 5% of the absorbed dose) increases the proportion of risk attributable to radiation – this exposure can only be studied in flight crew personnel – but it is likely that there is a major part of the excess risk in breast that must be attributable to factors others than the factors listed above. Disruptions of circadian rhythm and related hormonal effects have been repeatedly mentioned as possible causal factors, and there are no data to exclude this possibility.

Prostate cancer incidence rates from the airline pilot cohorts are above the national reference levels. This excess has decreased over decades and is likely to be related to the prostate-specific antigen tests, common among pilots much earlier they became so in the general population. In the most recent follow-up reports, the SIRs among pilots have been only slightly increased. Only one study that combined cohorts of all pilots from five Nordic countries, with detailed individual level flight histories, was able to study the independent role of the long-haul flights over time zones in an internal analysis. A significant trend in risk for prostate cancer with increasing number of long-haul flights was observed, though there were only eight cases in the highest exposure category. Hence, the evidence related to the role of circadian rhythm disruptions in causing prostate cancer is weak.

2.2 Shiftwork

2.2.1 *Breast cancer*

Eight studies reported relative risk estimates for histologically confirmed breast cancer for female night shiftworkers, with vastly differing definitions of shiftwork in each study. The characteristics of these studies are presented in Tables 2.1–2.3. Two were prospective cohort studies (Schernhammer *et al.*, 2001; Schernhammer & Hankinson, 2005), one was a nationwide census-based cohort study (Schwartzbaum *et al.*, 2007), three were nested case–control studies (Tynes *et al.*, 1996; Hansen, 2001a; Lie *et al.*, 2006), and two were retrospective case–control studies (Davis *et al.*, 2001; O'Leary *et al.*, 2006). All eligible studies included caucasian women; only one study (O'Leary *et al.*, 2006) included a small proportion of Latino and African-American women (less than 10%). The majority of women studied were postmenopausal.

(a) Prospective cohort studies (Table 2.1)

The two prospective cohort studies of night shiftwork and breast cancer risk used data from the Nurses' Health Study cohorts (NHS and NHS II) (Schernhammer *et al.*, 2001; Schernhammer *et al.*, 2006). The NHS began in 1976, when 121 701 registered nurses 30–55 years of age and living in 11 large US states were enrolled and completed a questionnaire comprising items about their health status, medical history, and known or suspected risk factors for cancer. Since baseline, questionnaires have been mailed biannually with the exception of lifetime history of night work in years, which was only assessed once (in 1988). Follow-up data are available for more than 90% of the ongoing cohort. In 1988, the study participants were asked how many years in total they had worked rotating night shifts with at least three nights per month, in addition to days or evenings in that month. The second cohort, NHS II, was designed in a very similar fashion. It started in 1989, when 116 671 registered female nurses (no overlap with NHS) 25–42 years of age, and from 14 US states were enrolled. Since 1989, they have completed biennial questionnaires that include items about their health status risk factors for chronic disease. Response rates to questionnaires are at 90%. In NHS II, the 1989 baseline questionnaire included detailed questions on total months during which study participants had worked on rotating night shifts for at least three nights per month in addition to days or evenings in that month. This information was updated in 1991, 1993, 1997, and 2001. Questions were asked regarding both rotating night shifts and permanent night shifts for 6 months or more in this cohort.

In the NHS, Schernhammer *et al.* (2001) followed a total of 78 562 women who answered the 1988 question on night work and were cancer-free at baseline over 10 years (1988–1998): of these women, 2441 incident breast cancer cases were documented during that time. The relative risks (RRs) for breast cancer associated with rotating night work compared to women who reported never having worked rotating night shifts, after

Table 2.1. Cohort studies of night shiftwork and breast cancer

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	OR or RR (extreme group versus referent)	Adjustment for potential confounders	Comments
Schernhammer *et al.* (2001) USA Nurses' Health Study (NHS)	Prospective cohort study of 121 701 registered nurses from 11 large states, established in 1976; follow-up from 1988–1998	Self-reported life time years on rotating night shifts, one-timed assessment in 1988; rotating night shifts were defined as "at least 3 nights per month, in addition to evenings and afternoons in that month"	Breast cancer	*Years of rotating night work* Never 1–15 15–29 ≥30 *P* for trend	 925 1324 134 58	 1.0 (ref) 1.08 (0.99–1.18) 1.08 (0.90–1.30) 1.36 (1.0–1.78) 0.02	Age, age at menarche, parity, age at first birth, weight change, BMI, family history of breast cancer, benign breast disease, oral contraceptive use, age at menopause, alcohol consumption, use of postmenopausal hormones, menopausal status, height	

Table 2.1 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	OR or RR (extreme group versus referent)	Adjustment for potential confounders	Comments
Schernhammer *et al.* (2006) USA Nurses' Health Study II (NHS II)	Prospective cohort study of 116 087 registered nurses from 14 states, established in 1989; follow-up from 1989–2001	Self-reported life time years on rotating night shifts, one-timed assessment in 1989; biannual update; rotating night shifts were defined as "at least 3 nights per month, in addition to evenings and afternoons in that month"	Breast cancer	*Years of rotating night work*			Age, age at menarche, parity, age at first birth, BMI, family history of breast cancer, benign breast disease, alcohol consumption, oral contraceptive use, smoking status, menopausal status, age at menopause, physical activity, postmenopausal hormone use	
				Never	441	1.0		
				1–9	816	0.98 (0.87–1.10)		
				10–19	80	0.91 (0.72–1.16)		
				20+	15	1.79 (1.06–3.01)		
				P for trend		0.65		

Table 2.1 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	OR or RR (extreme group versus referent)	Adjustment for potential confounders	Comments
Schwartzbaum *et al.* (2007) Sweden Register-based – all female residents of Sweden in the work force at census in 1960 and 1970	Register-based retrospective cohort study; 1 148 661 female workers; follow-up 1971–1989; 70 breast cancer cases among 3057 women with night work (40%)	Usual occupation & work hours (three-shift schedules and others) to define occupations with a large proportion of workers with night work; from in-person interview from annual survey of living conditions (1977–1981) among 55 323 randomly invited Swedes (84% participated)	Breast cancer	Shiftwork in 1970 Shiftwork in both 1960 & 1970	70 28	0.94 (0.74–1.18) 0.97 (0.67–1.40)	Age, socioeconomic status, occupational position (employed manager, other employee, self-employed with employees, self-employed without employees), county of residence (marital status and urbanization not important)	Shiftwork defined as occupations with at least 40% of the workers either reporting that they worked rotating shifts with 3 possible shifts or had work hours during the night ≥1 day before interview

controlling for known breast-cancer risk factors, were as follows: for 1–14 years, 1.08 (95% CI: 0.99–1.18); for 15–29 years, 1.08 (95% CI: 0.90–1.30); and for 30 or more years, 1.36 (95% CI: 1.04–1.78). The risk increased with increasing numbers of years in shiftwork (P for trend = 0.02). [The main strengths of this study are the prospective assessment of night work information and a wide range of potential confounding factors in a well defined occupation cohort of nurses, as well as the high follow-up rate (> 90%). Limitations of this study are its one-time assessment of night work and the inclusion of permanent night workers as well as those who worked < 3 nights per month among the unexposed reference group, which may have skewed the results towards the null].

Similarly, in 115 022 predominantly premenopausal women in the NHS II, Schernhammer *et al.* (2006) found an elevated breast cancer risk of 1.79 (95% CI: 1.06–3.01; $P = 0.65$) among women who worked 20 or more years of rotating night shiftwork compared with women who reported never having worked rotating night shifts, with 1352 incident breast cancer cases accruing over 12 years of follow-up (1989–2001). [The main strengths of this study are the prospective and updated assessment of rotating night work history and a wide range of potential confounding factors in a well defined occupational cohort of nurses, as well as the high follow-up rate (90%). Limitations are the inclusion of those who worked < 3 nights per month among the unexposed reference group, and the relatively small number of women ($n = 15$ women) in the category with longer durations of night work].

Schwartzbaum *et al.* (2007) found no increase in risk in female breast cancer from their definition of night work, based on 28 observed breast cancers versus 28.91 expected, diagnosed during 1971–1989. The design is a retrospective registry-based ecological cohort study comprising all 1 148 661 Swedish women that were active in the workforce according to both 1960 and 1970 census reports. Workers were followed up for breast cancer morbidity by linkage to the Swedish Cancer Registry. Information on occupation was derived from the censuses, which included each worker's industry and socioeconomic status. The annual surveys of living conditions (conducted during 1977–1981) among 46 438 randomly selected Swedish subjects who participated in a personal interview were used for assessing night work. Questions were asked regarding the usual occupation, work hours, and when they had started and ended working each day during the week preceding the interview. Shiftworkers were then defined as those who reported that their workplace had a rotating schedule with three or more possible shifts per day or had work hours during the night (any hour between 01:00 and 04:00) at least one day during the week preceding the interview. They classified as shiftworkers people working in job titles and industry combinations (from the censuses) with at least 40% shiftwork (as defined above). The reference group in their analyses comprised people in occupation–industry combinations in which less than 30% stated that they were shiftworkers. In analyses using 1970 census information for the definition of exposure, no increase in risk was reported among women with an occupation that was classified as shiftwork. Sub-analyses in this paper (which comprised all men and women working in Sweden) also considered 70% of shiftworkers as definition for occupation classification but due to

small sample size, this was not done for the women. [The weaknesses of this study include the implausibly small proportion of women working night shifts (only 0.3% worked in occupations with at least 40% shiftworkers working at least 20 hours per week), inadequate control for confounding, and that the three most common occupations that fell into their shiftwork classification were rather unusual (crane and hoist operators, delivery women in paper and paper-products manufacturing, printing and publishing industries, and midwives)].

(b) Nested case-control studies (Table 2.2)

Tynes *et al.* (1996) conducted a case–control study nested within a population-based cohort study of 2619 female Norwegian radio and telegraph operators working at sea and certified to work between 1920–1980, and followed up during 1961–1991. In total, 50 breast cancer cases were identified by linkage to the National Norwegian Cancer Registry, and each case was matched to four to seven disease-free controls from the cohort. For cases and controls, job histories on ships were collected and shiftwork as well as travel through time zones were classified for each ship mentioned in the job histories to define shiftwork. Shiftwork constituted frequent presence in the radio room both at night and during the day. After controlling for duration of employment, the SIR for breast cancer in this cohort was 1.5 (95% CI: 1.1–2.0). In the nested case–control study, there appeared to be an increased risk of breast cancer in women ≥ 50 years of age with increasing cumulative exposure to shiftwork, compared to no shiftwork (low exposure 0–3.1 years, adjusted for duration of employment, RR, 3.2, 95% CI: 0.6–17.3; high exposure 3.1–20.7 years, adjusted for duration of employment, RR, 4.3, 95% CI: 0.7–26.0; *P* for trend = 0.13). [The strength of this study is the use of internal controls, whereas the main limitation is its lack of control for confounding by breast cancer risk factors].

Hansen (2001a) conducted a population-based case–control study nested within the cohort of all female employees in Denmark established from the nationwide pension fund data, including information on all employments held since 1964. In total, 7035 women with incident breast cancer were identified by individual linkage to the files of the nationwide Danish Cancer Registry. Control subjects free of breast cancer were randomly drawn from the pension fund files and matched on year of birth and sex. The individual employment histories for cases and controls were reconstructed using files of the nationwide pension fund. Night work definition was based on information obtained from a nationwide interview-based survey on living and working environment conditions in 1976 among 2603 women. Trades in which at least 60% of female responders worked at night were considered to have a predominant night time schedule, whereas responders working in most trades with less than 40% reported night time schedules were regarded as day workers. The RR of breast cancer was 1.5 (95% CI: 1.2–1.7; 434 cases) among women who worked at least half a year at least 5 years before diagnosis in such trades, after controlling for age, social class, age at birth of first child, age at birth of last child, and number of children. For the subgroup of women with more than 6 years predominantly working at night, the RR was 1.7 (95% CI: 1.3–1.7; 117 cases). In further

Table 2.2. Nested case–control studies of night shiftwork and breast cancer

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	OR or RR (extreme group versus referent)	Adjustment for potential confounders	Comments
Tynes *et.al*. (1996) Norway Telecom cohort	Cohort of 2619 female radio and telegraph operators at sea, certified between 1920–1980; follow-up from 1961–1991. The nested case–control component comprised 50 cancer registry-identified cases and 4–7 matched (year of birth) controls	Collected detailed job histories from Norwegian seamen registry; "Work at night with exposure to artificial light." From cases and controls, detailed information on job histories on ship as well as shiftwork and travel through time zones was collected, classified by "ship"	Breast cancer	*Shiftwork in women age <50*			Age, duration of employment, parity, and age at first birth	
				None	12	1.0 (ref)		
				<3.1 yrs.	5	0.3 (0.1–1.2)		
				>3.1 yrs	12	0.9 (0.3–2.9)		
				P for trend		0.97		
				Aged 50+				
				None	3	1.0 (ref)		
				<3.1 yrs.	6	3.2 (0.6–17.3)		
				>3.1 yrs	12	4.3 (0.7–26.0)		
				P for trend		0.13		

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	OR or RR (extreme group versus referent)	Adjustment for potential confounders	Comments
Hansen (2001a,b) Denmark Linkage of Nationwide registries	Nested case–controls study; 7565 cancer-registry-derived women with breast cancer, 1:1 matched controls (year of birth and sex), follow-up 1964–1999	Individual employment histories were obtained from files of national pension fund	Considered as night workers if employed ≥0.5 year in ≥1 trade in which ≥60% of the female responders had night time schedules (e.g., hospitals, furniture manufacture, cleaning services, etc.)	All night work combined in trades with >60% night work Employed >6 years Nurses	434 117	1.5 (1.3–1.7) 1.7 (1.3–1.7) 1.3 (1.1–1.4)	Age, social class, age at birth of first child, age at birth of last child, number of children	Trades: hospitals, furniture manufacture, cleaning, beverage manufacture, land transport, catering, air transport

Table 2.2 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	OR or RR (extreme group versus referent)	Adjustment for potential confounders	Comments
Lie *et al.* (2006) Norway Cohort of Norwegian nurses	Case–control study [537 cancer-registry-identified cases and 1:4 matched (year of birth) controls] nested within the 44 835 nurses-comprising cohort of Norwegian nurses; cases occurred between 1960–1982	Total work history reconstructed from occupational information for nurses from Norwegian Board of Health's registry, censuses 1960, 1970, & 1980	Breast cancer	*Years night work*			Total employment time as a nurse & parity; matched by birth year	
				0	50	1.0 (ref)		
				1–14	362	0.95 (0.67–1.33)		
				15–29	101	1.29 (0.82–2.02)		
				30+	24	2.21 (1.10–4.45)		
				P for trend		0.01		

sub-analyses, the RR for nurses was also evaluated, a group in which 41% were considered having predominant night work (Hansen, 2001b), and a significantly increased risk of breast cancer was found (RR, 1.3; 95% CI: 1.1–1.4). [The strength of this study is its high number of incident cases and the apparent lack of selection and information bias due to use of routine data; its limitations include the crude exposure assessment with potential for non-differential misclassification as well as incomplete adjustment for confounding, in particular alcohol drinking.]

Lie *et al.* (2006) conducted a nested case–control study within a cohort of 44 835 Norwegian nurses based on information from the registry of the Norwegian Board on Health,established in 1949. In total, 537 breast cancer cases diagnosed during 1960–1982 were identified by linkage with the files of the nationwide cancer registry. Four age-matched controls were selected at random from the cohort, using incidence density sampling. Reconstruction of total work history was based on the nurses' registry (self-report of work history; until 1960 yearly updates, thereafter sporadically) and census information (1960, 1970, and 1980), accumulating from first year of employment until termination of the last employment. Based on experience, it was assumed that nurses employed at infirmaries worked nights (with the exception of managerial jobs, teaching, physiotherapy, and outpatients departments), whereas it was assumed that work sites other than infirmaries involved day work only. The authors found an association between duration of night work and breast cancer risk (*P* for trend = 0.01). The RR associated with > 30 years of night work was 2.21 (95% CI: 1.10–4.45), after adjustment for total employment time as a nurse and parity. [The main strength of this study is its high number of cases and the internal comparison, whereas limitations of this study are a lack of complete control for confounding as well as the potential for exposure misclassification, which is likely to be non-differential.]

(c) Case–control studies (Table 2.3)

Davis *et al.* (2001) conducted a case–control study of 813 women with breast cancer aged 20–75 years and 793 controls free from breast cancer. Cases were identified by the Cancer Surveillance System of Seattle, Washington, USA and controls were identified by random-digit dialling, frequency-matched on age (75% participation rate for controls). In-person interviews were performed from 1992–1995 to collect information about sleeping habits and light-at-night exposure during the 10 years before diagnosis as well as lifetime occupational history. The authors defined night work as at least one "graveyard" shift per week in the 10 years before diagnosis. "Graveyard" shiftwork was described as "beginning work after 19:00 and leaving work before 09:00". The RR of breast cancer was 1.6 (95% CI: 1.0–2.5) among women who had ever worked "graveyard" shifts. The RR of breast cancer was 1.06 for each hour increase per week of "graveyard" shift work (*P* = 0.03), after controlling for parity, family history of breast cancer, oral contraceptive use, as well as recent discontinued use of hormone replacement therapy. [The strengths of this study include its attempt to accurately define shiftwork assessment. One of the main

Table 2.3. Case–control studies of night shiftwork and breast cancer

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	OR or RR (extreme group versus referent)	Adjustment for potential confounders	Comments
Davis *et al.* (2001) Washington, USA	Cancer register based case–control study; case ascertainment (*n*=813) between 1992–1995, 793 matched (5-year age groups) controls identified by random-digit dialling	Information on sleeping habits, light exposure, lifetime occupational history obtained from in-person interview, considered as night workers if ≥1 graveyard shift/wk (8 hrs) in 10 years before diagnosis.	Breast cancer	*Years worked ≥3 nights/wk*			Parity, family history of breast caner (mother or sister), oral contraceptive use (ever), and recent (<5 years) discontinued use of hormone replacement therapy	Graveyard shift work defined as "beginning work after 7:00 pm and leaving work before 9:00 am."
				None	682	1.0 (ref)		
				<1	19	1.2 (0.6–2.3)		
				1–3	20	1.4 (0.7–2.8)		
				3–4.6	9	0.6 (0.3–1.5)		
				4.7+	33	2.3 (1.2–4.2)		
				P for trend		0.01		
O'Leary *et al.* (2006) Long Island, New York, USA Electromagnetic Fields and Breast Cancer on Long Island Study (EBCLIS)	Case–control study with 576 registry-identified cases and 585 1:1 matched (age in 5-year age groups) population-based controls; cases occurred between 1996–1997	Occupational history since age 16 & residential light-at-night exposures (sleep hours; frequency of turning on lights during night; length of time light was on) from in-person interview	Breast cancer	Any evening or overnight shiftwork	174	1.04 (0.79–1.38)	Age (matched by 5-year age groups); parity; education; family history of breast cancer; history of benign breast disease	
				Any evening shiftwork only	148	1.21 (0.90–1.64)		
				Any overnight shiftwork only	26	0.55 (0.32–0.94)		

limitations is the retrospective assessment of shiftwork with a modest potential for recall bias].

O'Leary *et al.*, (2006) conducted a case–control study in Long Island, New York, USA – the Electromagnetic Fields and Breast Cancer on Long Island Study (EBCLIS). They did not observe an association between night work and breast cancer risk (any evening or overnight shiftwork versus none, OR, 1.04; 95% CI: 0.79–1.38; only overnight shiftwork, OR, 0.55; 95% CI: 0.32–0.94). This study was built into another population-based case–control study among residents of Nassau and Suffolk counties. Cases were recorded during 1996–1997. Controls were frequency-matched by age and came from two different sources: 1) controls less than 65 years old were identified by random-digit dialling; 2) controls of age 65 and above were selected from the Health Care Financing Administration rosters. To evaluate the effects of electromagnetic frequency, women from within this case–control study were selected according to their degree of residential stability (EBCLIS component). EBCLIS comprised 576 breast cancer cases and 585 matched (1:1) population-based controls. In-person interviews were held to gather information on occupational history since the age 16 years as well as residential light-at-night exposures (sleep hours; frequency of turning on lights during night; length of time light was on). Shiftwork was defined as 'ever' working in at least one job during the past 15 years that included evening shifts (could start in the afternoon and end as late as 02:00), overnight shifts (could start as early as 19:00 and continue until the following morning), and various combinations thereof. The reference group comprised women who reported never having had a job involving shiftwork. Results were adjusted for age (matched by 5-year age groups), parity, education, family history of breast cancer, and history of benign breast disease. [An extreme and unlikely high proportion of controls (36.9%) and cases (35.7%) reported any 'evening or overnight shiftwork'; other limitations were the retrospective assessment of exposures and that the control selection was conducted from two different sources, introducing additional potential for bias].

(d) Meta-analysis

Megdal *et al.* (2005) conducted a meta-analysis that summarized six of the eight studies on night work (excluding the two most recent studies that gave negative results) and breast cancer, and found an increased risk for breast cancer (RR, 1.51; 95% CI: 1.36–1.68).

(e) Studies of biomarkers for night work (urinary melatonin) and breast cancer risk (Table 2.4)

Melatonin, the main biomarker for circadian dysregulation, can be measured in the urine by 6-sulphatoxymelatonin (aMT6s), the major metabolite of melatonin.

Skene *et al.* (1990) compared mean urinary aMT6s levels (measured by RIA) collected from 24-hour urine samples from British women attending a breast cancer screening clinic before biopsy and 160 normal female residents of Guernsey, the United Kingdom.

Table 2.4. Studies of biomarkers for light exposure (urinary melatonin) and breast cancer risk

Reference, study	Country or cohort and time period under observation	Source of information for exposure (i.e., light-at-night exposure)	Definition of biomarker for light exposure	Exposure category	No. of exposed cases	OR or RR (extreme group versus referent)	Adjustment for potential cofounders	Comment
Travis *et al*., (2004)	Nested case-control study; 5093 female residents of Guernsey (UK) recruited into a cohort of hormones and breast cancer (Guernsey III). Questionnaire at baseline (between 1977–1985);127 incident breast cancer cases that occurred before November 1, 2001 (mean follow-up ~12.6 yrs); 353 controls subjects; (1:2 matched for age, recruitment date, menopausal status, day of menstrual cycle/years postmenopausal); premenopausal: 77 cases, 214 controls postmenopausal: 50 cases, 139 controls	24-hour urine sample collected within ~16 days of recruitment	aMT6s by RIA; adjusted for urinary creatinine; tertiles of melatonin concentrations	aMT6s ng/mg creatinine High ≥18.32 ≥12.98	 46 26 20	*Overall* 0.99 (0.58–1.70) *Premenopausal* 0.99 (0.45–2.17) *Postmenopausal* 1.09 (0.46–2.60)	Matching factors (age ; date of recruitment, menopausal status, day of menstrual cycle that urine was collected or number of years post-menopausal); age, BMI, medication use thought to influence melatonin production, family history of breast cancer, parity and age at first birth, age at menarche, oral contraceptive use, season of urine collection, stage of menstrual cycle	

Table 2.4 (contd)

Reference, study	Country or cohort and time period under observation	Source of information for exposure (i.e., light-at-night exposure)	Definition of biomarker for light exposure	Exposure category	No. of exposed cases	OR or RR (extreme group versus referent)	Adjustment for potential cofounders	Comment
Schern-hammer & Hankinson (2005)	Nested case–control study; USA, Nurses Health Study II, prospective cohort study; 147 incident invasive breast cancer cases that occurred between 1996–1999 and 2001 and ≥91 matched (1:2) controls	First morning urine collection	aMT6s by ELISA; adjusted for urinary creatinine; quartiles of melatonin concentration	Urinary aMT6s ng/mg creatinine	23	*Overall* 0.59 (0.4–1.00) *P* for trend 0.13	Matching factors (year of birth, menopausal status at urine collection, month, year, time of day & luteal day of menstrual cycle at urine collection, fasting status at urine collection, ethnicity); age at menarche, parity, age at first birth, BMI, family history of breast cancer, benign breast disease, alcohol consumption, antidepressant use	Sub-analyses excluding night workers provided similar results; ~24% of the sample were postmenopausal

Mean levels for aMT6s excretion were 7.8±1.1 μg/24 hours in 14 benign cases, and 4.1±0.9 μg /24 hours in ten malignant cases.

Only two studies have been published to date evaluating an association between melatonin, the main biomarker for the circadian rhythm, and risk of breast cancer.

Travis *et al.* (2004) conducted a case–control study nested within 5093 female residents of Guernsey, the United Kingdom, which were recruited into a cohort for the study of hormones in relation to breast cancer (Guernsey III). Overall, 127 incident breast cancer cases occurred before November 2001 (mean follow-up ~12.6 years). A total of 353 control subjects were matched 1:2 to these cases. There were 77 premenopausal cases (214 controls), and 50 postmenopausal cases (139 controls). A questionnaire was distributed at baseline between 1977–1985. Urine samples (24-hour) were collected within ~16 days of recruitment, and aMT6s concentrations were measured by RIA, and adjusted for urinary creatinine. Tertiles of melatonin concentrations were created, and the overall RR was 0.99 (95% CI: 0.58–1.70, comparing highest versus lowest tertile). [The weakness of this study was primarily due to the type of urine sample used (24-hour urine).]

Schernhammer & Hankinson (2005) also conducted a nested case–control study of similar size and with primarily premenopausal women in the USA, and nested within the NHS II, a prospective cohort study of registered nurses only. A total of 147 incident invasive breast cancer cases that occurred in this cohort were enrolled into the nested case–control study during 1996–1999 and in 2001, and 291 controls were matched (1:2) to these cases; approximately 24% of participants were postmenopausal. During 1996–1999, a first morning urine sample was collected from roughly a third of the NHS II cohort. Concentrations of aMT6s were measured by ELISA, and adjusted for urinary creatinine. Quartiles of aMT6s level were created. Overall, there was a reduction in breast cancer risk among those in the highest quartile of melatonin (RR, 0.59; 95% CI: 0.4–1.00). Sub-analyses excluding night workers provided similar results.

2.2.2 *Prostate cancer*

(a) Cohort studies (Table 2.5)

A total of 14 052 men from 21 areas in Japan, 40–65 years old at baseline in 1988–1990, were extracted as a subcohort of the Japan collaborative cohort study for evaluation of cancer risk (Kubo *et al.*, 2006). A self-administered questionnaire was used to gather information at baseline on exposures related to lifestyle and work. At baseline, study participants were asked which form of work had they primarily been engaged in: daytime, fixed night or rotating shiftwork. In total, 31 cases of prostate cancer were documented from cancer registries during follow-up, based on 111 974 person–years (mean 8.0 years) from baseline until the end of 1997. Multivariate adjusted relative risks based on Cox proportional hazards models of fixed night shifts and rotating shifts were 2.3 (95% CI: 0.6–9.2; three cases), and 3.0 (95% CI: 1.2–7.7; seven cases), respectively, compared with

Table 2.5. Cohort studies

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Kubo *et al.* (2006), Japan, Japan Collaborative Cohort	Prospective cohort of 14 052 males, aged 40–65 years old enrolled from 45 areas in Japan between 1988–1990. Information on prostate cancer was obtained from cancer registries	Self-administered questionnaires at baseline included information on type of work schedule	Prostate	Day time work Fixed night Rotating shift	21 3 7	1.0 (ref) 2.3 (0.6–9.2) 3.0 (1.2–2.7)	Age, study area, family history of prostate cancer, BMI, smoking, alcohol drinking, job type, physical activity at work, workplace, perceived stress, educational level and marriage status	
Schernhammer *et al.* (2003) USA, American Nurses Health Study	Prospective cohort of 78 586 American nurses with a baseline question on rotating night work in 1988. Follow-up for colorectal cancer was through 1998	Self-reported from postal questionnaires: Rotating night shift was defined as “at least 3 nights per months, in addition to evenings and afternoons in that month”	Colorectal	No rotating night shifts 1–14 years ≥15 years	229 303 70	1.00 (ref) 1.00 (0.84-1.19) 1.35 (1.03-1.77) *P* for trend 0.04	Tobacco smoking, BMI, physical activity, aspirin use, colorectal cancer in relatives, endoscopy use, consumption of red meat, alcohol consumption, total calorie intake, postmenopausal hormones, menopausal status, height	No major differences in risk were seen for right or left colon, or colon and rectum separated
			Colon	No rotating night shifts 1–14 years ≥15 years	137 169 41	1.00 (ref) 0.93 (0.74–1.17) 1.32 (0.93–1.87) *P* for trend 0.26		
			Rectum	No rotating night shifts 1–14 years ≥15 years	41 48 14	1.00 (ref) 0.86 (0.56–1.30) 1.51 (0.82–2.81) *P* for trend 0.15		

Table 2.5 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Viswanathan *et al*. (2007), USA, American Nurses Health Study	Prospective cohort of 53 487 American nurses with a baseline question on rotating night work in 1988. Follow-up for endometrial cancer to 2004	Self-reported from postal questionnaires: Rotating night shift was defined as "≥3 nights/month, in addition to evenings & afternoons in that month"	Endometrial	No rotating night shifts 1–9 yrs 10–19 yrs ≥20 yrs	210 224 43 38	1.00 (ref) 0.89 (0.74–1.08) 1.06 (0.76–1.49) 1.47 (1.03–2.10) *P* for trend 0.04	Age, age at menarche, age at menopause, parity, BMI, duration of oral contraceptive, postmenopausal hormones, hypertension, diabetes, and pack–years of tobacco smoking	When stratifying for obesity, women with BMI>30 and having at least 20 years with rotating shifts had a more than 2-fold significant increased risk (*P* for trend 0.003)

Table 2.5 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Taylor & Pocock, (1972), England and Wales	Retrospective cohort study of 8603 manual workers all born before 1920 from 10 companies in England & Wales continuously employed for ≥10 years followed-up for death during 1956–1968.	Detailed job information since 1946, including work hours and types of shifts was obtained from payrolls kept at the companies	All cancers	Day	201	[1.02 (0.88–1.17)]	Age, calendar time	
				Shift	219	[1.16 (1.02–1.32)]		
				Ex-shift*	29	[1.12 (0.75–1.61)]		
				[Shift/Day]	[219/201]	[1.14 (0.94–1.38]		
			Lung	Day	95	[1.09 (0.80–1.33)]		
				Shift	94	[1.11 (0.90–1.36)]		
				Ex-shift	13	[1.15 (0.60–1.97)]		
			Stomach	Day	33	[1.24 (0.85–1.74)]		
				Shift	36	[1.43 (1.00–1.98)]		
				Ex-shift	4	[1.14 (0.31–2.93)]		
			Bladder	Day	4	[0.56 (0.15–1.44)]		
				Shift	7	[1.06 (0.42–2.19)]		
				Ex-shift	2	[4.00 (0.48–14.4)]		
			Leukaemia	Day	6	[1.54 (0.57–3.35)]		
				Shift	2	[0.54 (0.07–1.95)]		
				Ex-shift	2	[4.00 (0.48–14.4)]		

Table 2.5 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Schwartzbaum, (2007), Sweden	Ecological cohort study including male and female members of the working Swedish population participating in censuses in both 1960 and 1970, including information on usual job and industry, and followed-up for cancer in the cancer registry during 1971–1989	Job–exposure matrix based on surveys from 1977 to 1981; exposed defined as working in industries (≥20 hours/week) where at least 40% had work schedules with three or more possible shifts per day or work hours during the night at least one day per week	All cancers (29 for men and 18 for women)	Men Women	3799 103	1.01 (0.98–1.05) 1.00 (0.82–1.21)	Age, socioeconomic status, occupational position, county of residence	Significantly increased relative risks observed for kidney, skin, and other and unspecified cancers (men), whereas none of the female cancers were significantly different from unity. [Misclassification of shiftwork status is an invalidating problem]

BMI, body mass index
Ex-shift, men who did not qualify as shiftworkers but had done > 6 months on shiftwork & subsequently transferred to day work. They came under observation when they had completed 10 yrs' employment & the first 6 months of day work following their period of shiftwork. They remained under observation until the end of 1968 or until they had done a further 6 months of shiftwork.

predominantly day workers. [The major limitation of the study is the lack of statistical power, short follow-up for prostate cancer and a limited measure for shiftwork.]

(b) Case-control studies (Table 2.6)

A case–control study based on a cancer registry among residents of north-eastern Ontario, Canada, included 760 cases of prostate cancer, 45–85 years of age, and diagnosed during 1995–1998 (Conlon *et al.*, 2007). Cases were frequency-matched by age to 1632 male controls. A comprehensive mailed questionnaire was designed to gather information on exposures to lifestyle factors, and on each job held for one or more years, including information on usual work time (daytime shift, evening/night shift, rotating shift or other). The adjusted OR for 'ever' having worked rotating shifts on a full-time basis was 1.19 (95% CI: 1.00–1.42, 369 cases). Analyses of the duration in years of full-time rotating shifts (P for trend = 0.05) and age working the first full-time rotating shift (P for trend = 0.03) showed significant trends, but years since first full-time shifts did not show a significant trend (P for trend = 0.16). [The Working Group noted that the proportion of cases and controls classified with rotating shiftwork seemed unrealistically high and there was a lack of statistical power.]

2.2.3 *Colorectal cancer* (Table 2.5)

A prospective cohort study based on the American Nurses Health study including 78 586 nurses at baseline in 1988 was used for evaluating the association between colorectal cancer risk and rotating night work (Schernhammer *et al.*, 2003). Nurses completed a comprehensive questionnaire, including a question on how many years in total they had worked rotating night shifts at least three nights per month in addition to working days or evenings in that month. Based on 758 903 person–years during 1988–1998, a total of 602 cases of colorectal cancers were recorded. Cox proportional hazard models were used to estimate relative risks adjusted for potential confounders (tobacco smoking, body mass index, physical activity, aspirin use, colorectal cancer in relatives, endoscopy use, consumption of red meat, alcohol consumption, total caloric intake, postmenopausal hormones, menopausal status, and height). Compared with nurses who had never worked night shifts for at least three days per month, nurses who worked such shifts for 1–14 years and for at least 15 years had multivariate-adjusted RRs of 1.00 (95% CI: 0.84–1.19) and 1.35 (95% CI: 1.03–1.77), respectively. RRs adjusted for age only were similar and were reported as 1.00 (95% CI: 0.84–1.18) and 1.44 (95% CI: 1.10–1.89), respectively. Results for distinct sites such as right and left colon, combined colon, and rectum only marginally changed the results for the combined colorectal results. [Misclassification due to the relative crude definition of night shiftwork was likely to have resulted in bias towards the null.]

Table 2.6. Shiftwork - other sites than breast cancer. Case–control studies

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	No. of exposed cases	Exposure categories	Relative risk (95% CI)*	Adjustment for potential confounders
Conlon *et al*. (2007), Ontario, Canada, 1995–98	Prostate	760 cancer-registry-identified cases, aged 45–84 years and diagnosed during 1995–1998	1632 controls frequency-matched on age and from the same residence	Postal questionnaire (25 pages)	369	Rotating shiftwork	1.19 (1.00–1.42)	Age, family history of prostate cancer
						Years of shiftwork		
					115	≤7	1.44 (1.10–1.87)	
					87	7.1–22.0	1.14 (0.86–1.52)	
					81	22.1–34.0	0.93 (0.70–1.23)	
					86	>34.0	1.30 (0.97–1.74)	
						P for trend	0.05	

2.2.4 *Endometrial cancer* (Table 2.5)

Another prospective study based on the American Nurses Health study cohort included 53 487 women with an intact uterus who answered a question on rotating night work in 1988 (Viswanathan *et al.*, 2007). They were followed-up for endometrial cancer up to mid-2004, resulting in 515 cases (720 698 person–years). The RR was 1.47 (95% CI: 1.03–2.10) for nurses with 20 or more years of rotating shiftwork. When stratifying by body mass index, the RR was 2.09 (95% CI: 1.24–3.52) in the subgroup of nurses with a body mass index >30 kg/m^2 and at least 20 years of rotating shiftwork. In contrast, there was no difference in calorie consumption across night work categories. A significant trend (P = 0.003) of increasing relative risk was seen with increasing duration of rotating shiftwork in the group classified as obese. No significantly increased risk was observed in the group with a body mass index <30. The RRs were adjusted for potential confounders (age, age at menarche, age at menopause, parity, body mass index, duration of oral contraceptive use and postmenopausal hormones, hypertension, diabetes, and pack–years of tobacco smoking). [Misclassification due to the relative crude definition of night shiftwork was likely to have resulted in bias towards the null.]

2.2.5 *Other cancers* (Table 2.5)

A cohort of 8603 male full-time manual workers from England and Wales were followed-up during 1956–1968 for cause-specific mortality, including all neoplasms, cancer of lung, stomach, bladder, and leukaemia (Taylor & Pocock 1972). Study subjects were from ten different companies in which they were employed on 1 January 1956. They were born before 1920 and had all been continuously employed at the same company for at least ten years during 1946–1968. Detailed information on all jobs held since 1946 was obtained from company payrolls, including information on working hours, and types of shifts. Based on this information, each worker was allocated into one of three groups: day worker (n = 3860), shiftworker (n = 4188), and ex-shiftworker (n = 555). The criteria for being classified as either a day worker or a shiftworker were that the worker had completed at least 10 years of either work since 1946, with a maximum of 6 months interruption during that period. The term shiftwork covered six types of working hours other than regular day work. The start of follow-up was initiated as soon as each worker met the 10 years of duration of employment criterion. At the end of follow-up, on 31 December 1968, it was possible to trace all but 22 men (0.25%). Information on date and cause of death for the 1578 men who died during the follow-up period was obtained from death certificates. Expected numbers of cause-specific deaths were calculated from the mortality experience of men in England and Wales in 5 year age-groups and calendar time groups. Observed versus expected numbers for all-cause mortality were not significantly different in any of three groups of day workers, shift- and ex-shiftworkers (736/756.4; 722/711; 120/100.9). For the all-neoplasms group, the shiftworkers experienced a significantly higher than expected all-cancer mortality than the general

population [SMR, 1.16; 95% CI: 1.02–1.32; 219 observed cases]. For the small group of ex-shiftworkers, 29 deaths were observed versus 25.9 expected [SMR, 1.12; 95% CI: 0.75–1.61], and in the group of day workers, 201 deaths versus 197.1 were observed during follow-up [SMR, 1.02; 95% CI: 0.88–1.17]. For death from cancers of the lung, stomach, bladder, and leukaemia, observed versus expected numbers were, respectively, 94/84.4, 36/25.2, 7/6.6, and 2/3.7 among shiftworkers. Similar patterns were seen in day workers and in ex-shiftworkers. [This study was based on a survivor population with 10 years or more experience of shiftwork which may have underestimated a true increased risk if less than 10 years of shiftwork increased the mortality.]

A census-based ecological cohort study from Sweden included all members of the Swedish population (≥ 20 hours/week) in both 1960 and 1970 (Schwartzbaum *et al.*, 2007). The censuses included individual information about social status and industry but not about work schedules. Therefore, a job–exposure matrix was established for assessment of shiftwork. It relied on a sample of the Swedish population (n = 46 438) collected during 1977–1981, which included information on usual occupation and work schedules. Shiftwork was defined as a schedule with three or more possible shifts per day or work hours during the night for at least one day during the week preceding the interview. About 3% of the men and less than 0.3% of the women participating in the censuses were classified as having done shiftwork, defined by working in industries in 1960 and 1970 where at least 40% of the participants from the survey had reported such a work schedule. Follow-up for cancer in the Swedish Cancer registry was from 1971–1989, and SIRs were calculated on the basis of person–years of follow-up and national rates of specific cancers taken from the Swedish Cancer registry. The SIRs for cancer among men were all close to unity during the 19 years of follow-up, except for kidney (1.14; 95% CI: 1.00–1.31), skin (1.20; 95% CI: 1.02–1.41), and other and unspecified cancers (1.27; 95% CI: 1.07–1.50). For the subgroup of men participating in the 1970 census only, the SIR for thyroid cancer was elevated (1.35; 95% CI: 1.02–1.79). Results changed minimally when the shiftwork status was based only on the 1970 census or other attempts to change the exposure definition. [The major limitation of this study was an unavoidable potential for misclassification of exposure resulting in null results, and to some extent, uncontrolled confounding. Cohort members were followed-up to 1989, although follow-up through 2006 had been possible].

2.3 Aircraft crew

Cancer risk of airline personnel has been studied since the 1990s in about ten countries. The main reason to study these cohorts has been exposure to cosmic radiation, and sometimes passive smoking or electromagnetic fields. Shiftwork as causal factor has not been explicitly mentioned, but in the latest studies, there has be discussion on the potential role of frequent disruptions of circadian rhythm. An alteration in melatonin metabolism decreasing the oncostatic function of this hormone has been hypothesized to be a potential biological mechanism. [It has been questioned whether flight attendants should be considered as shiftworkers.]

For most cabin crew, annual exposure to radiation ranges from 1–6 mSv, compared with approximately 2.4 mSv annually from background radiation. Cosmic radiation includes a substantial neutron component (25–50% of effective dose but less than 5% of absorbed dose). Because flight personnel are the only source of human data on the health effects of exposure to neutron radiation, it is hard to estimate how a large excess risk would be expected due to cosmic radiation. This further makes it difficult to judge how much of the observed excess could be for other risk factors such as shiftwork.

The number of flights over several time zones is used as a proxy of frequency of circadian rhythm disruptions. This number correlates with the dose of cosmic radiation, and therefore estimates of cancer risk in cumulative dose categories can also be interpreted to roughly reflect frequency of circadian rhythm disruptions. On the other hand, separation of the independent roles of these two factors is possible only in large studies with precise information on flight histories. Only one study, combining information on all pilots from the five Nordic cancers has been able to make this distinction to a certain extent. In general, the detailed flight histories of airline pilots are known quite well; while for cabin crew, normally only the beginning and end of employment is known. In the airline companies where the principle has been that all cabin crew members fly all routes, an approximation of the radiation dose and numbers of long flights over time zones for each person can be made based on his/her own annual numbers of flight hours, and the flight profile of the company.

All studies published on aircraft crew have been included in this evaluation, irrespective of whether they mention shiftwork or not. Only observations related to breast cancer and prostate cancer have been included in this review, because they are the only ones which have been considered to be associated with shiftwork. The observations related to breast cancer come from cabin crew personnel and those related to prostate cancer mainly from cockpit personnel, because almost all airline pilots are male, and the majority of the cabin crew, female.

In addition to the breast and prostate cancer findings presented below in detail, there is a consistent pattern of increased incidence of skin melanoma and basal cell carcinoma of the skin that are likely to be related to the more frequent sunbathing and sunburns among flight personnel in previous decades. Male cabin crew have also been shown to have a significantly increased risk of Kaposi sarcoma in most studies that included this cancer category. The risk of leukaemia, one of the main target sites in studies on effects of radiation, has been shown to be non-elevated in most studies.

2.3.1 *Breast cancer* (Table 2.7)

(a) Cohort studies

Pukkala *et al.* (1995) collected a cohort of 1577 all-female flight attendants who had ever worked for Finnish airline companies (first employment starting in the 1930s). This cohort was followed-up for cancer incidence during 1967–1992. The SIR for breast cancer was 1.87 (95% CI: 1.15–2.23, 20 cases), and the SIR was highest 15–19 years after

Table 2.7. Cohort studies of flight personnel and breast cancer

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustement for potential confounders	Comments
Pukkala *et al*. (1995), Finland	1577 female cabin attendants who worked for Finnish airline companies; from files of Finnair Flight Company; follow-up for cancer incidence from date of recruitment as cabin crew worker (or January 1967 if later) to emigration, death, or December 1992	Calendar period, length of employment	Breast	Any Employment ≥2 years	20 NG	**SIR** 1.87 (1.15–2.23) 2.0 (1.2–3.2)	Age	Control for parity on group level (cohort vs. reference population): parity cannot explain the difference
Lynge (1996), Denmark	915 female airline cabin attendants in Denmark, follow-up for cancer incidence from 1970–1996	Cross-sectional census occupation 1970	Breast	Any	14	**SIR** 1.61 (0.90–2.70)	Age	
Wartenberg & Stapleton (1998), USA	287 retired flight attendants from one US airline; follow-up for cancer incidence		Breast	Any	7	**SIR** 2.0 (1.0–4.3)	Age	

Table 2.7 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustement for potential confounders	Comments
Haldorsen *et al*. (2001), Norway	3105 female and 588 male airline cabin attendants with licences issued 1950–1994; follow-up for cancer incidence from 1953 to 1996 (≤38 years)	Total length of employment; length of employment before 26 years of age	Breast	Any Employment ≥15 years	38 5	**SIR** 1.1 (0.8–1.5) 1.0 (0.3–3.0)	Age, number children, age at first birth	
Rafnsson *et al*. (2001), Iceland	1532 cabin attendants, from Icelandic Cabin Crew Association and two airline companies; follow-up for cancer incidence 1955–1997	Year of employment, hired before or in/after 1971	Breast	Any	26	**SIR** 1.50 (1.00–2.10)	Age	Control for parity on group level (cohort vs. reference population): parity cannot explain the difference
Blettner *et al*. (2002), Germany	16 014 female cabin attendants who had been employed by two German airlines in 1953 or later; mortality follow-up through 1997		Breast	Any	19	**SMR** 1.28 (0.72–2.20)	Age	

Table 2.7 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustement for potential confounders	Comments
Reynolds *et al*. (2002), California, USA	44 021 members of the Association of Flight Attendants in California; follow-up for cancer incidence 1988–1995	Route – international/domestic, length of service, age at entry	Breast			**SIR**	Age	
				Any	60	1.42 (1.09–1.83)		
				International	31	1.79 (1.21–2.54)		
				Employment ≥15 years	49	1.57 (1.16–2.08)		
				Starting age <25 years	41	1.72 (1.23–2.34)		
Linnersjö *et al*. (2003), Sweden	2324 women from Swedish Scandinavian Airline System employed 1957–1994; follow-up 1961–1996	High altitude, long distance flight hours	Breast			**SIR**	Age	Control for parity on group level (cohort vs. reference population): parity cannot explain the difference
				Any	33	1.30 (0.85–1.74)		
						Odds ratio		
				>5000 block hours in high altitude, long distance flights	5	3.27 (0.54–19.7)		
Zeeb *et al*. (2003), European countries	Cabin crew working 1961–1997 in Denmark, Finland, Germany, Greece, Iceland, Italy, Norway and Sweden, a total of 33 063 females and 11 079 male; follow-up for mortality up to 1997		Breast			**SMR**	Age	Overlap with the national incidence studies; breast cancer in women
				Ever	174	1.11 (0.82–1.48)		
				>0–<10	33	1.12 (0.75- 1.63)		
				10–<20 years	19	1.27 (0.74–2.07		
				≥20 years	7	0.80 (0.32–1.77)		

NG, not given

first employment (SIR, 3.4, 95% CI: 1.5–6.8), and slightly increased with increasing duration of employment. [The flight attendants were more likely than the general population to have multiple reproductive risk factors for breast cancer but these differences were insufficient to explain the magnitude of excesses observed.]

This observation was followed by other observations published in letters in the same journal. Lynge (1996) reported SIRs obtained from a routine tabulation of occupation-specific cancer risks in Denmark. In a 17-year follow-up, the SIR of breast cancer among the 915 women who had reported their occupation in 1970 as a flight attendant was 1.61 (95% CI: 0.90–2.70) when compared to average Danish women. Wartenberg and Stapleton (1998) also reported an increased breast cancer incidence in a small cohort of retired flight attendants from a US airline (SIR, 2.0; 95% CI: 1.0–4.3). This risk seems not to depend on the number of flights, and they suggest that exposure to dicophane (DDT), an organochlorine pesticide used to rid airplanes of insects during 1950–1970, may be a risk factor for breast cancer.

In 2001, two other Nordic studies were published with a setting similar to the earlier Finnish study. Haldorsen *et al.* (2001) studied a Norwegian cohort of 3144 female flight attendants and observed 38 cases of breast cancer. The SIR was 1.1 (95% CI: 0.8–1.5), and did not increase with increasing length of employment. The authors also had access to the dates of births of the children of the flight attendants for every woman born since 1934. The risk remained largely unchanged after controlling for age at first birth and parity.

Rafnsson *et al.* (2001) published a cohort study of 1532 cabin attendants from the Icelandic Cabin Crew Association and two airline companies and followed-up for cancer incidence during 1955–1997. The risk of breast cancer was significantly increased (SIR, 1.6, 95% CI: 1.0–2.1, lagged 15 years; SIR, 1.5, 95% CI: 1.0–2.1). Those hired in 1971 or later had the heaviest exposure to cosmic radiation at a young age, and had a signicantly increased risk of breast cancer (SIR, 4.1; 95% CI: 1.7–8.5). The information on reproductive factors among the cabin attendants and the Icelandic female population, obtained from the register of the Genetical Committee of the University of Iceland, provided an opportunity to evaluate the possible confounding due to reproductive factors on the risk of breast cancer in the present study in a similar way as has been recommended when evaluating confounding due to cigarette smoking in occupational studies. Predictive values were calculated on the basis of reproductive factors among the cabin attendants and the population. The risk of breast cancer was 1.0 for parous versus nulliparous, 1.0 for the number of children, and 1.1 for the age at birth of first child.

Rafnsson *et al.* (2003) also published a case–control study nested in the cohort of Icelandic cabin crew personnel. An increased risk of breast cancer was related to length of employment before 1971, the period before jet aircrafts were taken into operation. The authors concluded that the exposure related to the increased risk of breast cancer was solely confined to the period before 1971, because a long lag time may be required for inducing breast cancer, see Table 2.8. [Their result was compatible with the view that corresponds to a long induction period between ionizing radiation exposure and development of breast cancer.]

Table 2.8. Nested case–control studies of airline crew and cancer

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Rafnsson *et al*. (2003), Iceland	Breast	35 histologically confirmed cases, including 4 in situ cancers	140 age-matched flight attendants		≥5 versus <5 years work during:			Age at first delivery, parity	
					pre-jet era (<1971)	29	5.24 (1.58–17.4)		
					jet era (≥1971)	43	0.82 (0.34–1.97)		
Kojo *et al*. (2005), Finland	Breast	27 breast cancer cases diagnosed in 1975–2000 among cabin attendants (response proportion of 60%)	517 non-case cabin attendants (response proportion of 52%)	Self-administered questionnaire	Cumulative dose (per 10 mSv).	NG	0.93 (0.68–1.27)	Cumulative radiation dose, number of fertile years, parity, family history of breast cancer, alcohol consumption	To assess possible selection bias OR was also calculated for all the subjects in the cabin attendant cohort (44 breast cancer cases and 921 non-cases)
					Disruption of menstrual cycle sometimes or often	NG	0.56 (0.12–2.61)		
					Disruption of sleep rhythm sometimes or often	NG	1.52 (0.49–4.74)		

NG, not given

Blettner *et al.* (2002) studied cancer mortality among 16 014 female and 4537 male cabin attendants who had been employed by two German airlines in 1953 or later. The SMR for breast cancer was 1.28 (95% CI: 0.72–2.20; 19 observed deaths). The SMR did not increase with duration of employment.

In the largest of the studies, Reynolds *et al.* (2002) linked a group of 44 021 female members of the Association of Flight Attendants in California with the California Cancer Registry. They had to use a computer programme to conduct automated probabilistic record linkage, and to make several assumptions for estimations in the person–year accumulation which may have caused some inaccuracy in the results. During the follow-up, 60 cases of invasive and 12 cases of in-situ breast cancer were recorded during 1988–1995. The SIR for invasive breast cancer across all ethnicities was 1.42 (95% CI: 1.09–1.83) while the incidence of in-situ tumours did not differ significantly from what may have been expected compared to rates from the non-Hispanic Caucasian population or from the population of all races. Invasive breast cancer appeared to be significantly elevated (SIR, 1.79; 95% CI: 1.21–2.54) in flight attendants who were assigned to international routes compared with the general Californian reference population rates.

Linnersjö *et al.* (2003) observed 33 cases of breast cancer during 1961–1996 among the 2324 women employed at the Swedish Scandinavian Airline System. The SIR of breast cancer was 1.30 (95% CI: 0.85–1.74) when compared to the general population, and did not increase with increasing duration of employment. A case–control analysis nested within the cohort gave ORs for cancer incidence. For cabin crew with at least 5000 block hours in high altitude or long-distance flight hours compared with cabin attendants without this experience, the OR was 3.27 (95% CI: 0.54 –19.7).

Zeeb *et al.* (2003) reported the combined results from cabin crew cohorts from eight European countries employed during 1921–1997 in Denmark, Finland, Germany, Greece, Iceland, Italy, Norway, and Sweden. During follow-up of 485 831 person–years for women (until 1997), 174 breast cancer deaths were reported (SMR, 1.11; 95% CI: 0.82–1.48).

Kojo *et al.* (2005) reported on a nested case–control study of breast cancer among Finnish cabin crew attendants. The adjusted ORs were 0.93 (95% CI: 0.68–1.27) for cumulative dose per 10mSV, 0.56 (95% CI: 0.12–2.61) for disruption of menstrual cycle (sometimes or often), and 1.52 (95% CI: 0.49–4.74) for disruption of sleep rhythm (sometimes or often), see Table 2.8.

2.3.2 *Prostate cancer* (Table 2.9)

Band *et al.* (1990, 1996) reported cancer incidence and mortality in similar studies among pilots of two Canadian airline companies. Both of them demonstrated an increased incidence from prostate cancer (SIR, 1.54; SMR, 1.87), but only one study demonstrated slightly elevated mortality from prostate cancer (SMR, 1.52; 90% CI: 0.71–2.85; seven deaths) with no dependence on duration of the employment (Band *et al.*, 1996). The authors concluded that detection bias could be a likely explanation, as throughout their

Table 2.9. Cohort studies of flight personnel and prostate cancer

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustement for potential confounders	Comments
Band *et al*. (1990), Canada	913 male pilots employed for 1 year or more by Canadian Pacific Airlines since 1950; cause of death and cancer incidence information up to October 31, 1988 ascertained through the divisions of vital statistics and the cancer registries of the Canadian provinces		Any	6	**SIR** 1.54 [0.56–3.35]	Age	
Band *et al*. (1996), Canada	2680 male pilots of Air Canada working 1year or more since 1950; cancer incidence and mortality up to 1992.		Any	34	**SIR** 1.87 [1.30–262]	Age	

Table 2.9 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustement for potential confounders	Comments
Irvine & Davies (1992)	446 deaths among serving and retired British Airways (BA) pilots 1966–1989; deaths were ascertained from pension and registry listings, death registries, newspaper obituary listings	BA Personnel and pension records			**PMR**	Age	
			Pilots	10	2.12 (1.02–3.89)		
					PCMR		
				10	1.54 (0.74–2.83)		
Irvine & Davies (1999), England & Wales UK	6209 male pilots and 1153 male flight engineers employed since 1939 and for at least 1 year 1950–1992; followed for mortality	Years as flight deck crew, long/shorthaul			**SMR**	Age	
			Pilots	15	1.11 (0.62–1.84)		
			Flight Engineers	3	0.92 (0.19–2.69)		
					RR		
			Longhaul vs shorthaul	4	2.47 (0.83–7.65)		
Gundestrup & Storm (1999), Denmark	3790 male and 87 female pilots from 1921 and up, followed for cancer incidence 1943–1995	Flight hours			**SIR**		
			Jet	3	0.8 (0.2–2.2)		
			Non-jet	3	0.8 (0.2–2.2)		

Table 2.9 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustement for potential confounders	Comments
Haldorsen *et al*. (2000), Norway	3815 authorized male pilots 1946–1994; follow-up for cancer incidence up to 1996	Block hours, estimated dose			**SIR**		Smoking among current pilots compared with reference population (slightly lower proportion among pilots)
			Any	25	1.0 (0.7–1.5)		
			≥10 000 block hours	14	1.1 (0.6–1.9)		
			≥20 mSv	6	1.8 (0.7–4.0)		
Rafnsson *et al*. (2000), Iceland	458 male pilots 1937–1985; follow-up for cancer incidence 1955–1997	Block hours, estimated dose, crossing time zones (yes/no)			**SIR**		
			Any	5	1.28 (0.41–2.98)		
			International flights	4	1.41 (0.38–3.61)		

Table 2.9 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustement for potential confounders	Comments
Hammar *et al*. (2002), Sweden	1490 aircraft pilots and 2808 military pilots and navigators in the Swedish Air Force employed during 1957–1994; follow-up for cancer incidence 1961–l996	Numbers of block hours, high-altitude flights and long-distance flights			**SIR**		
			Civil	18	1.24 (0.74–1.97)		
			Military	49	1.17 (0.84–1.49)		
Pukkala *et al*. (2002), Denmark, Finland, Iceland, Norway, Sweden	10 032 male airline pilots employed 1921–1996; follow-up for cancer incidence through 1997	Employment duration, cumulative block hours (by aircraft type), estimated dose			**SIR**		The relative risk of prostate cancer increased with increasing number of flight hours in long distance aircraft (*P* for trend, 0.01)
			Any	64	1.21 (0.93–1.54)		
					RR		
			>10 000 hours long-haul (as compared with <5000 hours), ages 60+	8	3.88 (1.26–11.9)		

Table 2.9 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustement for potential confounders	Comments
Zeeb *et al*. (2002), Germany	6061 male pilots 1960–1997; mortality follow-up through 1997	Employment durations, cumulative block hours, estimated dose	Any	8	**SMR** 1.26 (0.5–2.59)	Age	
Zeeb *et al*. (2003), European countries	Cabin crew working 1961–1997 in Denmark, Finland, Germany, Greece, Iceland, Italy, Norway and Sweden, a total of 33 063 females and 11 079 male; follow-up for mortality up to 1997			5	1.09 (0.35–2.68)		

Table 2.9 (contd)

Reference, location, name of study	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)*	Adjustement for potential confounders	Comments
Blettner *et al*. (2003), European countries	Cockpit crew working 1921–1997 in Denmark, Finland, Germany, Great Britain, Greece, Iceland, Italy, Norway and Sweden, a total of 27 797 persons; follow-up for mortality		Any	54	**SMR** 0.94 (0.71–1.26)		Overlap with the national incidence studies

career, pilots underwent yearly physical examinations, including a digital rectal examination.

Irvine and Davies (1992, 1999) studied cancer mortality in British Airways pilots using the proportional mortality ratio (PMR) method (1992), and later (1999) based on SMRs. In the PMR study, there were ten deaths due to prostate cancer. The PMR was 2.12 (95% CI: 1.02–3.89) if the reference was all-cause mortality (excluding aircraft accident), and 1.54 (95% CI: 0.74–2.83) if the reference was all-cancer mortality. [It was however evident from other studies that both overall mortality and all-cancer mortality among airline pilots is markedly below the population mortality rates. In the British Airways pilots (Irvine & Davies, 1999), the SMR was 0.61 for all causes and 0.64 for all cancers, and therefore the PMRs in Irvine & Davies (1992) did not indicate excess prostate cancer mortality among pilots compared to the average population]. In the SMR study (Irvine & Davies, 1999), there were 15 prostate cancer deaths among British Airways pilots (SMR, 1.11; 95% CI: 0.62–1.84), and three deaths among flight engineers often travelling in cockpit (SMR, 0.92; 95% CI: 0.19–2.69). In the internal analysis, the age-adjusted RR between persons flying long-haul versus mainly short-haul (European) flights was 2.47 (95% CI: 0.83–7.65). Flight engineers were assumed to operate in long-haul operations.

Gundestrup & Storm (1999) studied cancer incidence among 3790 male and 87 female commercial Danish cockpit crew members, with records starting from 1921. They were followed for cancer mortality during 1943–1995. Three prostate cancer deaths were observed among both jet pilots and non-jet pilots versus 3.5–4.0 expected.

Haldorsen *et al.* (2000) published SIRs from a Norwegian cohort of 3815 authorised male pilots employed during 1946–1994. During the follow-up from 1953–1996, 25 cases of prostate cancer were observed (SIR, 1.0; 95% CI: 0.7–1.5); six were in the category of exposed to ≥ 20 mSv (SIR, 1.8; 95% CI: 0.7–4.0).

Rafnsson *et al.* (2000) studied a cohort of 458 Icelandic male pilots employed during 1937–1985, followed-up for cancer incidence from 1955–1997. There were only four cases of prostate cancer among pilots who had flown international flights (SIR, 1.41; 95% CI: 0.38–3.61), and therefore no dose–response analyses were performed for this cancer site.

The study by Hammar *et al.* (2002) reported cancer incidence both among civil and military pilots in Sweden. The incidence was about 20% above the national level in both categories, and did not vary with increasing number of block hours, high-altitude flights or long-distance flights.

Zeeb *et al.* (2002) analysed mortality data of 6061 German male pilots who had worked during 1953–1997. A total of eight deaths from prostate cancer were observed (SMR, 1.26; 95% CI: 0.53–2.59).

Zeeb *et al.* (2003) reported the combined results from cabin crew cohorts from eight European countries employed during 1921–1997 in Denmark, Finland, Germany, Greece, Iceland, Italy, Norway, and Sweden. During follow-up of 170 634 person–years for men (until 1997), five prostate cancer deaths were reported (SMR, 1.09; 95% CI: 0.35–2.68).

Blettner *et al.* (2003) combined mortality data from cockpit crew cohorts from nine European countries working during 1921–1997 in Denmark, Finland, Germany, Great Britain, Greece, Iceland, Italy, Norway and Sweden. During the approximately 28 000 person–years of follow-up, 54 prostate cancer deaths were reported (SMR, 0.94; 95% CI: 0.71–1.26).

Pukkala *et al.* (2002) conducted an analysis among cohorts of airline pilots from Denmark, Finland, Iceland, Norway, and Sweden. When compared to the national studies described above, the length of follow-up was extended. Unpublished Finnish data were added to this analysis. There were 10 032 male airline pilots employed during 1921–1996 who were followed-up for cancer incidence up until 1997. A total of 64 cases of prostate cancer were reported (SIR, 1.21; 95% CI: 0.93–1.54). The RR of prostate cancer increased with increasing number of flight hours on long-haul flights (*P* for trend = 0.01): the RR was 3.88 (95% CI: 1.26–11.9) for a duration of 10 000 hours long-haul compared with a duration < 5000 hours.

2.3.3 *Meta-analyses*

Ballard *et al.* (2000) published a meta-analysis of cancer incidence and mortality among flight personnel. The combined relative risk (meta-RR) based on a fixed effect model for breast cancer was 1.89 (95% CI: 1.40–2.56) overall, or 1.35 (95% CI: 1.00–1.85) if corrected for socio-economic status (based on two studies). The respective meta-RRs for prostate cancer incidence were 1.82 (95% CI: 1.31–2.52) overall and 1.65 (95% CI: 1.19–2.29) if corrected for socio-economic status, also based on two studies.

Seven observational studies among female air cabin crew (Pukkala *et al.*, 1995; Rafnsson *et al.*, 2001; Reynolds *et al.*, 2002; Wartenberg & Stapleton, 1998; Haldorsen *et al.*, 2001; Lynge, 1996) were considered in the review by Megdal *et al.* (2005) (studies are listed in Table 2.7). With only one exception (Haldorsen *et al.* 2001), these studies uniformly indicated an increased risk of breast cancer (meta-SIR, 1.44; 95% CI: 1.26–1.65; fixed effects model). All seven studies are incidence studies with the general population as the referent group. [The original rationale for these studies had been that the occupational exposure to cosmic radiation caused an anticipated excess cancer risk. In most studies, the excess starts about 10 years after first employment and increases weakly with increasing duration. Differences in reproductive factors can explain only a small fraction of the excess, and the risk attributable to (non-neutron) radiation, a similar fraction of the excess. Hence, it is likely that there is a major part of the excess risk in breast that must be attributable to factors others than reproductive factors and radiation]. It was reasoned subsequently that the observed increase in breast cancer risk could have been due as well to a melatonin deficiency resulting from work-associated light exposure at night (Mawson, 1998).

Buja *et al.* (2006) published a similar meta-analysis on cancer risk among female flight attendants, based on the same seven studies. They obtained a meta-SIR of 1.40 for

breast carcinoma (95% posterior interval, 1.19–1.65). The only other significant excess was in the incidence of melanoma (meta-SIR, 2.15; 95% CI: 1.56–2.88).

No publication bias was detected by any of the tests used in any of these two meta-analyses.

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3. Studies of Cancer in Experimental Animals

3.1 Modification of carcinogenesis by alteration of light/dark environment and central circadian pacemaker function

Introduction

The regular alternation of light and darkness over 24 hours synchronizes the endogenous circadian timing system of mammals through multiple pathways that involve (*a*) the elicitation of multiple gene transcription responses to glutamate and pituitary adenylcyclase activating peptide, the neuromediators that convey light messages to the suprachiasmatic nuclei (SCN) in the hypothalamus (Harmar *et al.*, 2002); the SCN are the main circadian pacemakers that coordinate the rhythmic organization of biological functions over 24 hours (Hastings *et al.*, 2003); and (*b*) the elicitation of multiple hormonal responses, including melatonin and corticosterone, in response to light. These neuroendocrine or endocrine effects seem to require SCN mediation and their extent depends upon the endogenous circadian time of exposure (Ishida *et al.*, 2005; Schibler & Brown, 2005); glucocorticoids, including corticosterone, can reset both the molecular clock and downstream clock-controlled genes in peripheral tissues, such as liver (Balsalobre *et al.*, 2000). In experimental systems, light exposure plays a key role in the resetting of the circadian timing system, that can involve, but does not require, melatonin signalling (Skene *et al.*, 1999).

The relevance of environmental light-dark schedules for cancer development or growth has been studied (see Table 3.1) with regard to the respective effects of (*a*) circadian time of carcinogen exposure in rodents kept in 24-hour light-dark regimens; (*b*) constant exposure to light or constant darkness; (*c*) experimental jet lag or other alterations of photoperiodic regimens; and (*d*) experimental mutations of clock genes. The intrication between carcinogen effects and circadian disruption was obvious in most reports. Conversely, circadian disruption, through experimental jet lag exposure, as well as clock genes mutations or SCN ablation, also leads to malignant processes taking place.

The influence of circadian time on carcinogen or promoter exposure and malignant growth was studied in intact mice or rats kept in a regular alternation of 12 hours of light and 12 hours of darkness (LD12:12) before exposure to carcinogens. Modifications to the regular alteration of light and darkness over 24 hours can disrupt both the circadian timing system at one or several levels of its hierarchical organization and the clock-controlled rhythms in mammals. The multifaceted changes that can occur range from clear whole organism response such as significant modifications in rest–activity rhythms and inability to rhythmically control core body temperature, to more subtle changes such as altered

Table 3.1. Summary of significant positive studies for each type of model and protocol: effect of light exposure during biological darkness and the circadian disruption on cancer incidence and growth

Experimental focus	Study type				
	No other exposure	Chemical initiation/ promotion models	Chemical transplacental carcinogenesis models	Tumour cell or graft transplantation studies	Total
Alterations in light exposures[a]	2/3[b]	5/6	1/1	10/10	18/20
SCN lesions[c]	–	–	–	1/1	1/1
Chronic experimental jetlag	–	–	–	2/2[d]	2/2
Pinealectomy-induced melatonin suppression	–	2/8	–	11/13	13/21
Direct effect of physiological concentration of melatonin on tumorigenesis	–	–	–	5/5	5/5
Clock gene mutations	1/1	1/2[e]	–	–	2/3
Circadian timing of carcinogen administration	–	4/4	–	–	4/4
Total	3/4	12/20	1/1	29/31	45/56

[a] Continuous bright light at night, dim light at night, intermittent or pulsed light at night
[b] The one negative study in this category was designed to be negative through the use of an inbred mouse with a genetic predisposition to retinal degeneration and was part of a study with one of the positive findings that had inadequate reporting.
[c] Electrolytic ablation of the superchiasmic nuclei
[d] Both of these studies were performed in the same laboratory with an experimental model that has not yet been used by other groups for cancer studies.
[e] These two studies used a radiation exposure in knockout animals as the cancer-initiating agent rather than a chemical.

activation of rhythmic signal–transduction pathways in multiple cell types in the body (Hastings *et al.* 2003: Levi & Schibler 2007). The rhythms that exist in the body in such diverse systems such as melatonin release, immune surveillance or cellular proliferation/apoptosis/DNA repair can be altered in different ways by different environmental exposures in different species (Deprés-Brummer *et al.*, 1995; 1997; Fu & Lee, 2003; Filipski *et al.*, 2005). The wide range in effects observed resulting from disruptions of the regular light-dark environment can make interpretation of the reported carcinogenic findings difficult. The rhythm alterations that most often result from chronic changes in the light-dark environment can either persist permanently or be restored through system feedback and adjustment over time. Finally, advancing light onset, as occurs with jet lag, has its own novel impacts on the circadian clock system and the clock-controlled rhythms at all three levels of the circadian timing system: hypothalamic pacemaker, circadian physiology, and molecular clocks (Reddy *et al.*, 2002; Nagano *et al.*, 2003; Filipski *et al.*, 2005). In essence, the circadian disruption that can occur through alterations in the light-dark environment is systematic and can lead to complex phenotypical changes that can only truly be understood in the context of the state of the entire circadian timing system and the downstream pathways it controls.

3.1.1 *Chronic alteration of light-dark environment*

Groups of 50 2-month old CBA mice, 50% females, were kept under a standard 300 lux light-dark regimen (LD12:12) or a constant 2500 lux light regimen until their natural death. All gross tumours and all tissues and organs with suspected tumour development were examined microscopically. [The Working Group noted that the microscopic examination of all relevant tissues in animals was not done but only done for cases where tumour development was suspected. This may have led to missing microscopic tumours.] No body weight difference between the groups was seen even though there was a significant 30% reduction in food consumption in the constant light group at 6 ($P < 0.01$), 8 ($P < 0.001$), 12 ($P < 0.02$) and 16 ($P < 0.02$) months. No cataracts were seen in either group. There were no significant changes in length of the estrous cycle, although mice in the constant light group were more likely to have irregular cycles at 3 ($P < 0.05$), 6 ($P < 0.001$) and 12 ($P < 0.002$) months. The total number of animals with malignant tumours was significantly increased in the constant light group (35% versus 10% of tumour-bearing mice; $P < 0.001$) as was the incidence of lung adenocarcinomas (7/50 (14%) versus 1/50 (2%); $P < 0.05$) and malignant lymphomas and leukaemia combined (6/50 (12%) versus 0/50; $P < 0.02$). There was also a marginal increase in hepatocellular carcinomas (4/50 (8%) versus 0/50; $P = 0.058$) (Anisimov *et al.*, 2004).

3.1.2 *Role of circadian time on two-stage models of carcinogenesis*

(a) Two-stage skin cancer carcinogenesis mouse model

(i) *Methylnitrosourea*

Six groups of 77 to 105 hairless mice (hr/hr Oslo strain), 60–90 days of age, were kept in LD12:12 (06:30 to 18:30) and painted with methylnitrosourea (MNU, 0.2 mg) once at 08:00, 12:00, 20:00, and 24:00 or once a week for 3 weeks at 08:00 and 20:00. There were equal numbers of male and female mice in each group. The mice were examined for appearance of skin papillomas once a week for 18 months. No difference was found between animals painted once at 05:30 or at 17:30 hours after light onset. The number of animals having tumours from the remaining four groups were 5/95 (5%) in the group painted once at 01:30, 6/77 (8%) in the group painted three times at 01:30, 10/104 (10%) in the group painted once at 13:30 and 13/96 (14%) in the group painted three times at 13:30. The difference between tumour incidence for the two single painting groups (01:30 and 13:30) were not significantly different ($P = 0.105$), the difference in the groups painted three times was marginal ($P = 0.054$). When the 01:30 groups were combined and compared to the combined 13:30 groups, the difference was significant ($P = 0.0137$). The authors noted that the highest incidence of papillomas was achieved when exposure to MNU occurred at a time corresponding to the lowest DNA synthesis rate when relatively large numbers of late G1 cells accumulated [no data presented] (Clausen *et al.*, 1984).

A total of 670 hairless mice (hr/hr Oslo strain, 50% females) kept in LD12:12 with light from 07:30 to 19:30 were exposed to a single topical application of two doses of MNU dissolved in 100 μL reagent-grade acetone. Mice (n = 351) were exposed in groups to a single application of 1 mg MNU at either 00:00, 04:00, 08:00, 12:00, 16:00 or 20:00. Also, several mice (n = 287) were exposed in three groups to a single application of 2 mg MNU at 08:00, 12:00 or 20:00. An additional group of 32 mice were also treated with 10 mg MNU to study the dose–response relationship. The development of all types of skin tumours was observed and the results presented as tumour rates (percentage of tumour-bearing animals in relation to the number of animals alive, appearance of the first tumour related to time), and tumour yields (the cumulative occurrence of all skin tumours standardized for comparison of groups of 32 mice related to time). Most animals were examined once a week for 54 weeks, but those to which 10 mg MNU was applied were observed for only 34 weeks. A circadian variation in tumour production after a single application of 1 mg MNU was demonstrated with a high tumour incidence after application in the period from 16:00 to 00.00, and a lower incidence between 04:00 and 12:00. When 2 mg MNU was applied, there was definitely a low tumour incidence after application at 04:00 compared to the two other times. There was a good and almost straight-lined dose–response relationship after the application of 1, 2, and 10 mg MNU. [Publication unavailable to the Working Group] (Iversen & Iversen, 1995).

(ii) *7,12-dimethylbenz[α]anthracene/12-O-tetradecanoylphorbol-13-acetate*

Groups of 25 female CD1 mice, 8–10 weeks of age, were kept in LD12:12, with light onset at 06:00 and were administered a single dose of 9,10-dimethyl-1,2-benzanthracene (DMBA, 2.5 μg/mouse). Starting 2 weeks later, the back of the mice were painted twice a week for 12 weeks with tumour promoter 12-*O*-tetradecanoylphorbol-13-acetate (1.9 μg). The application of 12-*O*-tetradecanoylphorbol-13-acetate was tested at: 05:00, 11:00, 17:00 (during the light span), and 23:00 (5 hours after the onset of darkness). The experiment was terminated at Week 15 following the first 12-*O*-tetradecanoylphorbol-13-acetate administration. In the group painted at 23:00 as compared to that exposed at 17:00, there were nearly twice as many mice with tumours within Weeks 8–11, and the weekly average number of tumours per mouse was nearly twice as high within Weeks 9–15 (Wille, 2003). [The Working Group noted that the tumour type was never clearly given but was assumed to be skin papilloma or carcinoma.]

(b) Intestinal carcinogenesis models in rats

(i) *1,2-dimethylhydrazine*

Male non-inbred rats from a local strain kept in LD12:12 were injected subcutaneously with five weekly doses of 21 mg/kg body weight 1,2-dimethylhydrazine 1 hour after light onset (10:00; $n = 23$) or 13 hours after light onset (22:00; $n = 24$). Injections at 13 hours after light onset were followed by a significant decrease in the incidence (from 91 to 75%; $P < 0.05$) and mean size of tumours (from 27.2 to 15.5 mm^2; $P < 0.05$) 6 months after the first injection; there were also relatively fewer large tumours (Dubina *et al.* 2002).

(ii) *Azoxymethane*

The effect of the time of administration of azoxymethane during the day to alter the yield of foci (recognized as precancerous lesions) in the colon was evaluated in six groups of 14 male Fischer 344 rats, 7 weeks of age. Azoxymethane was subcutaneously administered in a 15 mg/kg body weight saline solution on Days 7 and 14 of the experiment. Foci of aberrant crypts were evaluated with microscopy 28 days after the first azoxymethane dose in whole mounts of colons stained with methylene blue. In each of the three groups of rats, azoxymethane induced twice as many foci when administered between 8.40 and 11.00 than in the three other groups that were administered azoxymethane between 14.45 and 17.55 (205.7 ± 16.0 versus 110.2 ± 12.9; ANOVA, $P < 0.01$). [No indication as to the light-dark schedule in the animal rooms was given by the authors] (Pereira *et al.*, 1994).

Groups of 30 female mice from two inbred substrains of C3H mice, 100 days of age, were exposed to constant light [intensity not given] or LD12:12 (control) over 400 days. In substrain C3H-A, lifetime exposure to chronic light extended estrus by approximately 24 hours, and resulted in a significant increase in the incidence of and mortality from

mammary tumours [data only given in the form of a graph with no statistical details; 50% versus 0% and 70% versus 20% mammary tumour incidence at 151–200 and 201–250 days of age, respectively]. In substrain C3H-HeJ [this substrain has an inherited autosomal recessive retinal degeneration and has been well characterized in circadian behavioural paradigms], lifetime exposure to chronic light resulted in permanent estrus [onset time not given], a delayed onset of mammary tumour development, a reduced number of tumours, and an increased longevity [data only given in the form of a graph with no statistical details] (Jöchle, 1963; Joechle 1964).

3.1.3 *Constant light, light during darkness and constant darkness on experimental cancer*

(a) DMBA on mammary cancers in female rats

A group of 28 female non-inbred virgin rats was injected intravenously with 1.5 mg DMBA in saline emulsion six times once every 10 days. Four weeks after the last injection of the carcinogen, animals were divided into two equal groups. Females of the first group were exposed to constant electric light [300-W electric bulb], while the animals of the second group were kept under conditions of natural light. Animals of the constant light group had an increased multiplicity of mammary gland tumours (3.1 versus 1.7). Altogether, tumours developed in 12/14 rats (86%) in the first group and in 10/14 rats (71%) in the second group. In a second experiment, exposure to constant light that started 7 weeks before DMBA treatment resulted in mammary gland tumours in 5/17 rats (29%) while 6/15 females (40%) animals kept under natural light developed tumours (Khaetski, 1965).

Female Sprague-Dawley rats were exposed to LD12:12 or constant illumination starting on the 42nd day of life. At 50 days, the animals received 30 mg DMBA intragastrically. Eight months later, mammary tumours were found in 15/26 rats (58%) in LD12:12, with 16/36 (44%) tumours being adenocarcinomas. Conversely, 20/21 rats (95%) on constant light displayed mammary tumours, however, 53/57 (93%) tumours were fibroadenomas and only 4/57 (7%) were adenocarcinomas. Constant light reduced ($P < 0.001$) the weights of both the ovaries and pineal glands (Hamilton, 1969). [No information was given on the time of DMBA administration, sampling times or circadian effects of constant light.]

Pregnant female Holtzman rats, 10–12 days of age, were exposed to LD10:14 or to constant light, with light intensity of 150 lux, and their pups were subsequently exposed to the same regimen. The female offsprings were fed with 100 mg/kg DMBA intragastrically on Days 55 to 60. This procedure led to 20% mortality. Animals were palpated once weekly. Over the 180 days that followed DMBA delivery, 60% of the 25 rats in LD10:14 and 94% of the 47 rats in constant light developed tumours ($P < 0.02$). Of these tumours, 60% were adenocarcinomas in the LD10:14 group as compared to 95% in the constant light group ($P < 0.001$). The latency period of tumour appearance was also

significantly shorter in the constant light group ($P < 0.001$). Constant light exposure was associated with a 3-fold increase in plasma prolactin and a 5-fold increase in DNA synthetic activity in the mammary gland. Minor changes in plasma estradiol were found between the LD10:14 and constant light groups (Shah *et al.*, 1984; Kothari *et al.*, 1982, 1984; Mhatre *et al.*, 1984). [No information was given on the time of DMBA administration, sampling times or circadian effects of constant light, three factors that can help in the interpretation of these clearcut differences in carcinogenesis.]

A total of 100 female Sprague-Dawley rats were divided by weight into two groups of 50 animals. Starting at Day 26, one group was exposed to constant light, and the second group was exposed to LD8:16. Both groups received an 8 mg intragastric dose of DMBA at 52 days of age. At 13 weeks post-DMBA administration, there were significantly fewer mammary tumours in the constant light group compared with the LD8:16 group: the respective number of tumour-bearing rats were 8/50 (16%) vs 19/50 rats (38%) ($P < 0.05$), with an average mean number of tumours per rat of 1.1 and 2.6, respectively. The protective effect of constant light on tumorigenesis was ascribed to a substantial acceleration of mammary-gland development, past the temporal window of DMBA susceptibility in virgin animals. This was supported by the observation that 29/50 rats (58%) on constant light had lactating mammary nodules at necropsy compared to 0/50 in LD8:16 (Anderson *et al.*, 2000).

The effects of four light–dark schedules on the growth of established mammary carcinomas was investigated using 64 female Sprague Dawley rats, exposed to a single intragastric dose of 20 mg/kg DMBA at 55 days of age. When the number of rats with palpated mammary tumours of size 1-cm in diameter was sufficient, the rats were randomized into four groups of 16 animals each. These groups were subjected to LD12:12, constant light (300 lux), LD12:12 (300 lux) with a 30-minute exposure to light near mid-dark, or exposed to low light intensity (0.21 lux) rather than real darkness during the 12-hour dark span. Tumour growth was fastest in the rats exposed to dim light during the dark phase, and slowest in those remaining in LD12:12 ($P < 0.01$). Tumours also grew faster ($P < 0.05$) in the rats exposed to light at night for 30 minutes and in those exposed to constant light, when compared to the LD12:12 group. The onset of accelerated tumour growth occurred at Week 4 for the dim-light-at-night group, at Week 6 for the light-pulsed-at-night group, and at Week 10 for the constant light group. On Weeks 11 and 12, the mean tumour surface of the three experimental groups with altered light–dark schedules were similar and differed significantly from the control LD12:12 group ($P < 0.05$). A significant decrease in night time urinary excretion of aMT6s was observed in all experimental groups. The usual light/dark difference in aMT6s excretion was eliminated in the dim-light-at-night and constant light groups but not in the light-pulsed-at-night group. A significant 5-fold increase in serum estradiol was observed in the dim-light-at-night group only (Cos *et al.*, 2006).

(b) NMU

The effects of altered endogenous night time melatonin concentrations on mammary tumour production were investigated in an NMU-induced breast cancer model in female Fischer 344 (F344)/N rats, as were the effects of suppressed serum melatonin concentrations on the incidence and progression of NMU-induced breast cancer. In-vivo studies were used to assess serum melatonin concentrations and the incidence of NMU-induced tumours after 1 day, 2, and 10 weeks of nightly administration of short-duration intermittent light exposure at night. Five 1-minute exposures to incandescent light every 2 hours after the start of the dark phase of the light–dark cycle decreased the magnitude of the nocturnal rise of serum melatonin concentrations in rats by approximately 65%. After 2 weeks of nightly intermittent light exposures, the peak night time serum melatonin concentrations decreased by approximately 35% on average. The amelioration continued and, at 10 weeks, peak night time serum melatonin concentrations had decreased further, by approximately 25%. Because peak endogenous night time serum melatonin values could be moderately suppressed for at least 10 weeks, a 26-week NMU mammary tumour experiment was conducted. Serum melatonin concentrations and incidence, multiplicity, and weight of NMU-induced mammary tumours were assessed. No effect on the development of mammary tumours in an NMU-induced tumour model in rats occurred when endogenous night time serum melatonin concentrations were moderately suppressed by short-duration intermittent light exposures at night. At necropsy, there were no alterations in mammary tumour incidence (28/40 NMU controls (70%), 28/40 NMU + light (70%)), multiplicity (2.18 tumours/tumour-bearing NMU control, 1.89 NMU + light), or average tumour weight (1.20 g NMU control, 1.19 g NMU + light). Tumour burden had no effect on the serum melatonin cycle. At 26 weeks, however, animals exposed to intermittent light at night exhibited an approximately 3-fold higher serum melatonin concentrations when compared to controls (Travlos *et al.*, 2001).

(c) Diethylnitrosamine on liver carcinogenesis in male rats

A total of 65 male Wistar rats were administered diethylnitrosamine (10 mg/kg/day p.o. in drinking-water) for 6 weeks and were randomized into three groups. Rats received either diethylnitrosamine only ($n = 20$), phenobarbital ($n = 22$, 30 mg/rat/day p.o. in drinking-water) for 4 weeks as a promoting agent or were exposed to constant light ($n = 23$). All three groups received diethylnitrosamine in LD12:12 for the initial 21 days and in constant light from Days 22 to 43. This procedure was chosen to suppress the main circadian physiology outputs expected to occur in the continuous light group by Day 77, simultaneously with the maximum phenobarbital promoting effect expected to occur in the phenobarbital group. In the constant light group, there was a 4-fold drop in 24-hour mean urinary aMT6s excretion when compared to the other groups (P from ANOVA < 0.001). The aMT6s rhythms were suppressed in constant light, but remained similar in the other groups. Laparotomy was then performed and macroscopic nodules were counted and measured in each of the four liver lobes, using a 1-mm scale, without knowing the

allocated group of the animal. The proportion of rats with macroscopic nodules was 72% (LD12:12 group), 89% (phenobarbital group), and 95% (constant light group) (P from $\chi^2 = 0.10$). Both the frequency of the lesions and the size of the largest lesion differed significantly among the three groups ($P < 0.05$). Nodules were more numerous and larger in the constant light group and in the phenobarbital group when compared to the LD12:12 group (P from $\chi^2 < 0.05$). Similarly, there were more rats with large tumours (≥ 3 mm) in the constant light group and in the phenobarbital group when compared to the LD12:12 group ($P < 0.05$). All the rats died with hepatocellular carcinomas, with a median survival of 5 months – this was similar in all three groups. (Van den Heiligenberg *et al.*, 1999). [Light-induced circadian clock suppression exerted a promoting effect similar to that caused by phenobarbital in this model. Reduced body weight through manipulation of feeding schedules has usually been associated with decreased tumour growth. Animals on constant light had increased incidence and volume of tumours and gained the least weight.]

(d) Transplanted Glasgow osteosarcoma in mice

Three groups of 10 male B6D2F1 mice were randomly assigned to remain in LD12:12 or exposed to constant darkness or to constant light throughout the whole study duration (5 weeks). Environmental conditions were confirmed to maintain circadian coordination in mice, with a period of 23.8 hours for the constant darkness group, and 26.5 hours for the constant light group. After 3 weeks, all the mice were inoculated subcutaneously with 3x3-mm fragments of mouse Glasgow osteosarcoma in each flank. Tumour size was measured three times weekly for 2 weeks. Exposure to constant darkness or to constant light had no significant effect on tumour growth (ANOVA: $P = 0.8$) nor survival (log-rank: $P = 0.66$) when compared to mice kept in LD12:12 (Filipski *et al.*, 2004). [The Working Group noted that in B6D2F1 mice, constant light and constant darkness did not suppress circadian outputs or melatonin secretion, explaining why the study was negative.]

(e) Tissue-isolated Morris rat hepatoma 7288CTC

Young adult male Buffalo rats (BUF/BUF/Ncr), 5 weeks of age, were allowed to acclimatize to a photoperiod of LD12:12 for 1 week, and were provided with standard laboratory chow and water *ad libitum*. Rats were randomly assigned to three different light exposure groups ($n = 12$ rats/group): LD12:12 (1st group), LD12:12 with a dark phase contaminated with dim light coming from an indirect light leak of 0.2 lux (2nd Group) through the door of the final animal group of constant bright light of 810 lux (3rd Group). Half of the animals were exposed to these lighting conditions for 4 weeks after which blood samples were collected at 4-hour intervals over a 24-hour period. The remaining animals were exposed to these lighting conditions for 2 weeks before their subcutaneous implantation of a single 3 mm cube of MT_1/MT_2 melatonin-receptor positive Morris rat hepatoma 7288CTC in a tissue-isolated manner ($n = 6$ rats/group).

Tumour growth (estimated tumour weights calculated from serial measurements of tumour size) was monitored throughout the course of exposure to these different lighting conditions for up to 3 additional weeks following tumour implantation. At the end of each tumour growth period in each light exposure group, tumour linoleic acid uptake and 13-hydroxyoctadecadienoic acid (13-HODE) release were measured via arteriovenous difference measurements; tumours were removed for analysis of linoleic acid content. Compared with the 1st group in which the nocturnal circadian increase in plasma melatonin and linoleic acid levels were intact, the mean tumour growth rate was increased over 2-fold ($P < 0.05$) and tumour latency decreased by 6 days [no statistical analysis peformed] in the 3rd group in which the nocturnal rise in the levels of both plasma melatonin and linoleic acid were extinguished. Plasma melatonin levels were consistently low while plasma linoleic acid levels remained the same throughout the 24-hour day in the 3rd group. Tumour linoleic acid uptake was increased 2-fold while 13-HODE release was augmented over 4-fold when compared to 1st group ($P < 0.05$). In the 2nd group, the mean tumour growth rate was increased nearly 2-fold ($P < 0.05$) and tumour latency decreased by 2 days [no statistics performed] when compared with the 1st group; the plasma profile of low plasma melatonin levels was similar to the 3rd group while the nocturnal circadian rise in plasma linoleic acid levels was preserved, as per the 1st group. Tumour linoleic acid uptake was increased 2-fold while 13-HODE release was augmented 3-fold when compared to the 1st group ($P < 0.05$). Under all three lighting conditions the total consumption of food throughout the day was virtually identical (Dauchy *et al.*, 1997).

In a follow-up confirmatory study of essentially identical design as that described above, virtually the same results were obtained on the growth, linoleic acid uptake and 13-HODE release in tissue-isolated rat hepatoma 7288CTC. The only substantial difference between the two studies was that the source of dim light exposure during the dark phase was from direct illumination (0.2 lux) provided by a mounted fluorescent lighting fixture placed directly in front of the animal cages rather than from an indirect, contaminating light leak in the previous study (Dauchy *et al.*, 1997).

In a light intensity dose–response study, adult male Buffalo rats were acclimatized to an LD12:12 photoperiod and then randomly assigned to one of six different light intensity exposures during the dark phase of an LD12:12 photoperiod in specially constructed light exposure chambers: total darkness, 0.02, 0.05, 0.06, 0.08 and 345 $\mu W/cm^2$; $n = 6$ rats per exposure. Indirect white, polychromatic fluorescent light reflected off of the walls of the chamber were used rather than direct light from the fluorescent tubes. Rats were exposed to these different lighting conditions for 2 weeks before the implantation of tissue-isolated Morris rat hepatoma (MT_1/MT_2 melatonin-receptor positive) 7288CTC. Following tumour implantation, rats were maintained on their respective light exposure regimen until the end of their respective tumour growth periods. Following 2 weeks of exposure, nocturnal serum levels of melatonin were suppressed in a dose–response manner until full suppression was reached at the highest light intensity. There was a marked dose-related increase in tumour growth rates, [^{3}H]thymidine incorporation into DNA, and DNA

content relative to the control animals exposed to the dark phase over a period of up to 3 weeks following tumour implantation ($P < 0.05$). Similary, tumour linoleic acid uptake, 13-HODE release, cyclic adenosine monophosphate (cAMP) levels ($P < 0.05$), extracellular signal-regulated kinase kinase (MEK) and extracellular signal-related kinase (ERK1/2) activation [no statistical analysis] were markedly increased as the light intensity during the dark phase increased. No significant dose–response effects of light were observed on the serum levels of corticosterone (Blask *et al.*, 2005).

(f) Tissue-isolated MCF-7 human breast cancer xenografts in female nude rats

Adult female inbred nude rats maintained on an LD12:12 photoperiod were implanted with estrogen/progesterone-receptor positive (ER+/PgR+) and MT_1/MT_2 melatonin-receptor positive MCF-7 human breast cancer xenografts in a tissue-isolated manner. Tumour growth was monitored for 40 days (estimated tumour weight of 2.5 g) at which time a subgroup of tumour-bearing rats ($n = 3$) was tranferred to constant bright fluorescent white light (300 lux) while the remaining rats ($n = 4$) were maintained on an LD12:12 photoperiod for the duration of the tumour growth period. Serum melatonin levels were measured in parallel groups of rats during the mid-day and mid-dark phases of an LD12:12 photoperiod, and during the subjective dark phase during constant bright light exposure ($n = 6$/group) after 5 weeks of being maintained under these conditions. In the group of tumour-bearing rats switched from LD12:12 to constant light, which induced a complete suppression of nocturnal circulating melatonin levels, the tumour growth rate increased ($P < 0.05$) 7-fold when compared to the control group maintained on LD12:12, and exhibited a robust nocturnal melatonin rise in the blood ($P < 0.05$). Tumour linoleic acid uptake increased 2-fold whereas 13-HODE production increased over 5-fold in the group exposed to constant bright light relative to the LD12:12 controls ($P < 0.05$) (Blask *et al.*, 2003).

Identical in design to the above study, a light intensity dose–response study was performed in adult female nude rats, implanted with tissue-isolated ER–/PgR– and MT_1 melatonin receptor positive MCF-7 human breast cancer xenografts (Blask *et al.*, 2003). Two weeks of exposure of rats to increasing intensities of white light before tumour implantation resulted in nocturnal serum levels of melatonin that were suppressed in a dose–response manner until full suppression was reached at the highest light intensity. Continued exposure of these tumour-bearing rats to the same conditions of increasing light intensities over a period of up to 5 weeks following tumour implantation resulted in a marked dose-related increase in tumour growth rates, [^{3}H]thymidine incorporation into DNA, and DNA content relative to the control animals exposed to the dark phase ($P < 0.05$). Similarly, tumour linoleic acid uptake, 13-HODE release and cAMP levels were significantly increased ($P < 0.05$) whereas extracellular MEK and extracellular ERK1/2 activation were markedly increased [no statistical analysis]. No significant dose–response effects of light were observed on the serum levels of either estradiol or corticosterone (Blask *et al.*, 2005).

3.1.4 *Effect of experimental chronic jet lag on cancer in the mouse*

Two groups of 16 male B6D2F1 mice each were assigned randomly to remain in standard lighting (LD12:12) or to be exposed to experimental chronic jet lag (through serial 8-hour advances of LD12:12 cycles every 2 days). This schedule was considered as being the most disruptive on the nest-activity circadian rhythm among schedules tested in previous experiments. The locomotor activity and body temperature of the mice were monitored with a radiotransmitter. Ten days after the start of light–dark cycle advances, animals in both groups were inoculated subcutaneously with a 3 × 3-mm fragment of transplantable mouse Glasgow osteosarcoma. Three mice in each group served as non-tumour-bearing controls. Survival was checked daily and tumour size measured with a caliper three times a week. Tumour weight was computed as (length × width^2)/2. Fifteen days after tumour inoculation, mice were sacrificed following exposure to constant darkness for up to 48 hours at four different circadian times, i.e. 0, 6, 12 or 18 hours after light onset. Tumour and liver samples were taken to measure the circadian expression of the clock genes mPer2 and mReverbα with an RNase protection assay (Filipski *et al.*, 2004). This experiment was replicated using 12 control mice in LD12:12 and 14 animals subjected to experimental chronic jet lag. Tumour size was measured daily or every alternate day. Tumours progressed significantly faster in animals undergoing "jet lag" when compared to those kept in LD12:12 in both experiments (ANOVA: $P < 0.001$ and $P = 0.002$, respectively). Both experiments indicated that chronic jet lag accelerated tumour growth predominantly between the 8th and the 11th day following tumour inoculation. In the first experiment, mean tumour weight (± SEM) on Day 11, i.e. before the death of the first animal, was 1330 ± 151 mg in experimental jet lag mice, and 647 ± 56 mg in controls (*t*-test: $P = 0.001$). In the replicated experiment, it was 1376 ± 131 mg, and 847 ± 107 mg in experimental jet lag and control mice, respectively (*t*-test: $P = 0.005$). The survival curves further differed with statistical significance as a function of lighting schedule with poorest survival seen in the experimental jet lag group, in each experiment considered separately (log-rank: $P = 0.013$ and $P = 0.0025$), or pooled ($P < 0.0001$) (Filipski *et al.* 2004).

The same protocol was applied to 13 male B6D2F1 mice on LD12:12 and to 14 mice undergoing experimental chronic jet lag for the previous 10 days. On Day 12, mean tumour weight was 1317 mg in the LD12:12 group and 1997 mg in the experimental chronic jet lag group ($P = 0.04$). Experimental chronic jet lag suppressed the circadian rhythms in mRNA transcription of the clock genes *Rev-erbα* and *Bmal1*, while dampening and phase-shifting that in *Per2* in the liver of male B6D2F1 mice. This resulted in a significant derepression of c-Myc that became profoundly rhythmic, while P53 was repressed. Both effects favour genomic instability and cellular proliferation [two effects that could favour liver carcinogenesis]. In the tumours of mice kept in LD12:12, the mRNA expression patterns of the clock genes was suppressed for *Rev-erbα* and markedly damped for *Per2* and *Bmal1*, when compared with liver. Experimental chronic jet lag suppressed these mRNA rhythms in tumours (Filipski *et al.*, 2005).

3.1.5 *Endogenous circadian disruption on experimental cancer*

(a) SCN ablation in mice

The SCN of male B6D2F1 mice were destroyed by bilateral electrolytic lesions, and body activity and body temperature were recorded with a radiotransmitter implanted into the peritoneal cavity. Mice were inoculated subcutaneously with 3 × 3-mm fragments of mouse Glasgow osteosarcoma tumours ($n = 16$ with SCN lesions, $n = 12$ sham-operated) or pancreatic adenocarcinoma tumours ($n = 13$ with SCN lesions, $n = 13$ sham-operated) to determine the effects of altered circadian rhythms on tumour progression. Complete SCN destruction was ascertained postmortem. Both types of tumours grew two to three times faster in mice with SCN lesions when compared to sham-operated mice ($P < 0.001$). The survival of mice with SCN lesions was significantly shorter compared with that of sham-operated mice (log-rank $P = 0.0062$). The 24-hour rest–activity cycle was ablated and the daily rhythms of serum corticosterone level and lymphocyte count were markedly altered in 75 additional mice with complete SCN destruction when compared to 64 sham-operated mice ($P < 0.001$). Thus, disruption of circadian rhythms in mice was associated with an accelerated growth of malignant tumours of two types, suggesting that the host circadian clock may play an important role in the endogenous control of tumour progression (Filipski *et al.*, 2002).

(b) Clock gene mutations in mice

Fu *et al.* (2002) observed that knock-out mice without expression of mPer2 (mPer2$^{m/m}$ mice) displayed salivary gland hyperplasia in both males and females and teratomas, predominantly of the epidermis in males at 6 months, with no other apparent pathological defect. By the age of 12 months, all mPer2$^{m/m}$ mice showed salivary gland hyperplasia, and all male mPer2$^{m/m}$ mice developed teratomas around the genital areas. In addition, 30% of the 34 mPer2$^{m/m}$ mice in the study died before the age of 16 months and 15% of the mPer2$^{m/m}$ mice died of lymphoma, an event that was not observed before the age of 20 months in the 40 wild-type mice studied ($P < 0.001$).

To examine further the role of *mPer2* in suppressing neoplastic growth, wild-type and mPer2$^{m/m}$ mice at 8 weeks of age were challenged with a single dose of whole-body radiation of 4 Gy 10 hours after light onset, and were monitored for illness and survival. The mPer2$^{m/m}$ mice were more sensitive to gamma radiation, as indicated by premature hair graying and hair loss, and an increased rate of tumour formation. Hair graying was observed in 50% of mutant mice at 12 weeks after irradiation, a difference that held up also at 22 weeks after irradiation. The irradiated mPer2$^{m/m}$ mice also showed an earlier onset of hyperplastic growth. At 7 months after irradiation, teratomas were observed in all irradiated male mPer2$^{m/m}$ mice, but not in any irradiated wild-type mice. At 16 months after irradiation, 71% of the mPer2$^{m/m}$ mice had developed malignant lymphomas, with a first case discovered at 5 months. Malignant lymphomas were found in multiple organs – liver, lung, spleen, heart, intestine, salivary glands, etc. Conversely, only 5% of the *wt*

mice displayed malignant lymphomas 16 months after irradiation. [The core circadian genes are induced by gamma radiation in wild-type mice but not in *mPer2* mutant mice. Temporal expression of genes involved in cell cycle regulation such as cyclin D1, cyclin A, *Mdm-2*, and *Gadd45*α, is deregulated in *mPer2* mutant mice. In particular, the transcription of *c-myc* is controlled directly by circadian regulators and is deregulated in the *mPer2* mutant. In this study, *c-myc* transcription in liver was derepressed and became rhythmic in mPer2$^{m/m}$ mice as compared to *wt* animals.] In the mPer2$^{m/m}$ mice, P53 was repressed when compared to *wt*. These studies suggested that the *mPer2* gene functions in tumour suppression through regulating DNA-damage-responsive pathways (Fu *et al.*, 2002).

Gauger and Sancar (2005) studied Cry1$^{-/-}$/Cry2$^{-/-}$ mice and fibroblasts derived from these mice for radiation-induced cancer and killing, as well as DNA-damage checkpoints and killing, respectively. They administered a single dose of 4 Gy to 24 *wt* C57/Bl6 and to 27 double mutant mice kept in LD12:12, 10 hours after light onset. No difference in survival was found between the two groups over the 90 weeks following radiation exposure and no overt lymphoma or other tumour was found in these mutant mice. Similarly, the Cry1$^{-/-}$/Cry2$^{-/-}$ mutant fibroblasts were indistinguishable from the wild-type controls with respect to their sensitivity to ionizing radiation and UV radiation and ionizing-radiation-induced DNA damage checkpoint response. According to the authors, their data suggest that disruption of the circadian clock in itself did not compromise mammalian DNA repair and DNA damage checkpoints and did not predispose mice to spontaneous and ionizing-radiation-induced cancers (Gauger & Sancar, 2005).

[A single timepoint of radiation exposure was tested here. No demonstration was offered in this study that Cry1$^{-/-}$/Cry2$^{-/-}$ mice had an ablated circadian clock. The in-vivo part of this study was performed in mice kept in LD12:12, an environmental condition that dampens, yet does not disrupt, 24-hour physiology in Cry1/Cry2 double mutants, while constant darkness exposure does (Nagashima *et al.*, 2005). The Working Group noted that recent data show that Crys do not seem to be required for normal circadian clock function in mouse fibroblasts (Fan *et al.*, 2007).]

3.1.6 *Transplacental carcinogenesis*

Three groups of 24 pregnant Wistar rats were exposed to different light–dark regimens consisting of either LD12:12 (control), constant darkness, or constant light from Day 1 of pregnancy. On the 18th to 19th day of pregnancy, the dams were injected with a single intravenous dose of 80 mg/kg *N*-nitrosoethylurea, a chemical known to cause tumours of the peripheral nervous system and kidney when administered under these conditions. Dams from the continuous darkness group were subjected to approximately 10 minutes of light during injection. All pups were kept with their dams during the lactating period (1 month) where they remained in the dams' initial light–dark regimen. Following lactation, pups were removed from the dams, housed in groups of 5–7 animals separated by sex and kept under the 12:12 light–dark cycle until their natural death. [The

rats were kept in this regimen since their conception until one month of age.] Full necropsies were performed on all animals with all suspected tumours and all tissues suspected for tumour growth examined microscopically. [The Working Group noted that the microscopic examination of all relevant tissues in animals was not systematically done and only for cases where tumour development was suspected. This may have led to mining microscopic tumours.] The incidence of any tumour, tumours of the peripheral nervous system, and tumours of the kidney in the perinatal constant light group were 2.6, 2.5 and 8.5 times higher than the LD12:12 controls, respectively. As for tumour-bearing animals, the incidences were: males (29/34 (85%) vs 16/61 (26%); $P < 0.01$) and females (38/54 (70%) versus 21/66 (32%); $P < 0.01$). Similar results were seen for the peripheral nervous tissue (males 21/34 (62%) versus 12/61 (20%); $P < 0.01$ and females 29/54 (54%) versus 17/66 (26%); $P < 0.01$) and for the kidney tumours (males 7/34 (21%) versus 1/61 (1.6%); $P < 0.01$ and females 5/54 (9%) versus 1/66 (1.5%); $P > 0.05$). All kidney tumours were classified as mesenchymal tumours with approximately equal localization to the left and right lobes. The nervous system tumours were equally distributed between benign (fascicular neurinoma, reticular neurinoma) and malignant (neuroblastoma, other malignant) [Even though this information was available, the Working Group was unable to separate malignant from benign tumours due to tumour multiplicity within animals in the same group]. The group exposed to perinatal constant darkness demonstrated a significant drop in the number of tumour-bearing animals for males (5/40 (12%); $P < 0.01$) and females (5/44 (11%); $P < 0.01$) and for both sexes combined ($P < 0.01$). For peripheral nervous system tumours (males 4/40 (10%); $P > 0.05$ and females 3/44 (7%); $P < 0.05$) the significant drop in tumour incidence applied only to females or both sexes combined. Kidney tumours (males 1/40 (2.5%); $P > 0.05$ and females 4/44 (9%); $P > 0.05$) showed no change from control in the perinatal constant darkness group. Finally, the mean survival of tumour-bearing rats [detected at necropsy] was significantly reduced in the constant light group ($P < 0.01$ for nervous system tumours, $P < 0.05$ for kidney tumours) for both tumour types and significantly extended ($P < 0.05$ for both tumour types) in the perinatal constant darkness group for both tumour types when combining both sexes (Beniashvili *et al.*, 2001).

3.2 Effects of pinealectomy and nocturnal physiological melatonin levels on the development and/or growth of chemically induced or transplantable experimental tumours in animals

Introduction

Pinealectomy consists in the surgical removal of the pineal gland from the brain. It is the only means of eliminating the nocturnal melatonin signal emanating from the pineal gland without also affecting the central circadian pacemaker in the SCN of the hypothalamus. Pinealectomy has been employed as one means of determining whether

the specific suppression of the physiological nocturnal melatonin signal leads to the enhancement of cancer development and/or growth in experimental animal models of tumorigenesis (see Table 3.1). At the same time, this procedure indirectly addresses whether the physiological nocturnal melatonin signal from the pineal gland is inhibitory to the process of tumorigenesis in experimental animal models. However, it is important to note that unidentified, non-melatonin compounds (i.e. small peptides) that possess anticancer activity both *in vivo* and *in vitro* have been isolated from the pineal gland (Bartsch *et al.*, 1992). Therefore, the mere removal of the pineal gland in the absence of physiological melatonin replacement would not unequivocally prove that only melatonin is responsible for the antineoplastic effects of the pineal or that the promotion of tumorigenesis by pinealectomy is exclusively due to the elimination of the nocturnal physiological melatonin signal. However, in view of the fact that these putative oncostatic substances have never been structurally identified, measured in the blood or other extracellular fluids or determined to be mediators of pineal/circadian physiology, their role in the pineal regulation of tumorigenesis will not be considered. In all of the studies that follow, the melatonin levels were not measured. Other sources of melatonin have been identified in rodents, including the Harderian gland and the intestine. Their relative contribution to the physiological rhythm in circulating melatonin levels are still poorly understood. [However, the Working Group felt confident that, in these studies, pinealectomy resulted in marked reduction in melatonin levels.]

3.2.1 *Undifferentiated neoplasms (Yoshida and Ehrlich tumour)*

Neonatal pinealectomy 24 hours after birth was evaluated on the growth and metastatic spread of Yoshida solid tumour cells transplanted intramuscularly into Sprague-Dawley rats [sex unspecified] 10–12 weeks following pinealectomy. Survival time was decreased in pinealectomized rats ($n = 10$) over intact control rats ($P < 0.001$) ($n = 4$). There was no difference in tumour weight between the pinealectomized and control groups. The prevalence of tumour metastases to the pancreas was markedly increased whereas metastatic foci were much less in liver [no statistical analysis] (Lapin, 1974).

The growth and mitotic index of another undifferentiated tumour, Ehrlich tumour, intraperitoneally or subcutaneously injected into six groups of Swiss inbred mice (25 g) that were either pinealectomized or sham-operated or not operated (controls) were evaluated. [The number of animals per group was not precisely provided but was assumed to be 17–18. Because of the high mortality, the Working Group had concerns regarding the adequacy of the sample size.] Pinealectomized animals were found to have more intraperitoneal ascite tumours ($P < 0.05$) with a greater mitotic index ($P < 0.01$). Solid subcutaneous tumour weight did not change, although there was an increase in the solid tumour mitotic index ($P < 0.001$) (Billitteri & Bindoni, 1969).

3.2.2 *Sarcoma*

As early as the 1940s it was demonstrated that pinealectomy could stimulate the growth of transplantable sarcomas in rats (Nakatani *et al.*, 1940; Katuguiri, 1943).

Thirty years later, the effects of pinealectomy were demonstrated 7 weeks following the subcutaneous injection of previously pinealectomized Holtzman rats [sex unspecified] with fibrosarcoma cells derived from rats treated with methylcholanthrene. Mean tumour volume in these animals was over 2-fold greater in pinealectomized rats than that in the intact control rats, and nearly 2-fold greater than in sham-operated rats. The prevalence of lymph node metastases was 2.5-fold ($P < 0.05$) [$P = 0.013$; pinealectomized versus sham-operated] greater in the pinealectomized group than in the combined control groups while the number of animals with lung metastases was virtually the same among all treatment groups (Barone *et al.*, 1972). The comparison of mean tumour volume in pinealectomized rats with that in the combined controls showed a significant increase ($P < 0.01$). [The Working Group questioned whether to use combined intact and sham group was reasonable.]

In contrast, exposure of Wistar rats [sex unspecified] to the polyoma virus failed to induce neosarcoma in neonatally pinealectomized or intact control animals (Wrba *et al.*, 1975). [The lack of details and of an effect in the controls make an interpretation of this study problematic.]

3.2.3 *Hepatocarcinoma*

Pinealectomy has been reported to inhibit the development of chemically induced hepatocarcinomas in rats (Lacassagne *et al.*, 1969).

More recently, the effects of pinealectomy versus sham-pinealectomy were examined to evaluate the growth of transplantable tissue-isolated Morris rat hepatoma (7288CTC) in male Buffalo rats over a 2-week period. The tumour growth rate in animals that were pinealectomized ($n = 8$) one week before tumour implantation was 2-fold ($P < 0.05$) greater than the tumour growth rate in sham-pinealectomized controls ($n = 8$) over a 3-week period, and latency to tumour onset was reduced by 50% ($P < 0.05$). The tumour uptake of linoleic acid and production of its metabolite 13-HODE, the mitogenic signal upon which hepatoma 7288CTC is dependent, were markedly increased in pinealectomized rats versus their sham-pinealectomized counterparts ($P < 0.05$) (Blask *et al.*, 1999).

3.2.4 *Ovarian and small bowel adenocarcinoma*

Previously pinealectomized ($n = 12$), sham-pinealectomized ($n = 10$) or intact ($n = 10$) hamsters [sex and strain not specified] were inoculated subcutaneously with ovarian tumour cells [type not specified]. The interval of time between the surgical procedures and tumour cell inoculation was not specified. Tumour growth evaluated over

a 30-day period following tumour inoculation revealed that tumour volume was about 5-fold greater in pinealectomized animals versus sham-pinealectomized; tumour volumes in sham-operated and intact hamsters were virtually equivalent [no *P* values shown]. No significant differences were observed in the growth of small bowel adenocarcinomas in the same pinealectomized versus sham-operated animals 2 weeks following tumour cell inoculation (Das Gupta, 1968). [The Working Group cannot clearly interpret the results of this study due to lack of details.]

3.2.5 *Walker 256 carcinosarcoma*

The effects of pinealectomy have been determined on the growth and spread of transplantable Walker 256 carcinosarcomas (carcinomatous variant) in male Sprague-Dawley rats. Young adult rats (40–50 g; 13 rats per group) were either pinealectomized, sham-pinealectomized or left intact 2 weeks before being injected into the thigh muscle with a homogenate of Walker carcinoma. Tumour size was measured every 2 days until the occurrence of spontaneous death from the tumour. The survival time of pinealectomized rats was significantly decreased by 14.6% compared to sham-pinealectomized rats ($P < 0.02$). Tumour size was significantly increased in pinealectomized animals by 43% versus sham-pinealectomized animals ($P < 0.01$). There were a greater number of rats with lung or lymph node metastases in the pinealectomized group than in either the sham-pinealectomized or intact groups, although the statistical significance of these differences were not determined (Rodin, 1963) [A Fisher's exact test performed by the Working Group revealed that the prevalence of nodal, but not lung, metastases in pinealectomized rats was significantly higher than in the sham-operated group ($P < 0.04$).]

In another confirmatory study in young inbred male Holtzman rats (40 – 60 g) (Barone & Das Gupta, 1970), it was demonstrated that the mean tumour volume in pinealectomized rats ($n = 27$) 24 days following subcutaneous injection of a cell suspension of Walker 256 carcinoma was 42% greater than in sham-operated animals ($n = 24$) ($P < 0.01$); pinealectomy and sham-pinealectomy were carried out 5 weeks before tumour cell injection. There was also a greater number of pinealectomized animals ($n = 39$) with metastatic lesions localized to the lungs as well as axillary and mediastinal lymph nodes than sham-pinealectomized rats ($n = 35$); however, no statistical analysis was performed [A Fisher's exact test revealed that these differences were statistically different for axillary nodes ($P < 0.02$), mediastinal nodes ($P < 0.001$), and lung ($P < 0.001$).]

3.2.6 *Melanoma*

The effects of pinealectomy were evaluated on the growth and metastatic spread of transplantable hamster melanoma cells – Melanotic Melanoma No. 1 (MM1) – in adult male and female Syrian hamsters. Animals were inoculated with a melanoma cell

suspension 5 weeks following pinealectomy or sham-operation; an additional control group was left intact. Tumour volume was measured every week for 5 weeks following tumour cell inoculation. At the end of the first 2 weeks following tumour cell inoculation, tumour volume was 10-fold higher in the pinealectomized group ($n = 10$) versus the sham-pinealectomized animals ($n = 10$) ($P < 0.001$). The overall tumour growth rate over the subsequent 3 weeks in the pinealectomized group was 3-fold higher than in the sham-pinealectomized group ($P < 0.001$); no significant differences were observed between the sham-operated and intact controls. There was also a higher frequency of metastasic foci in the lungs, liver, kidneys, spleen and axillary lymph nodes in the pinealectomized group when compared to sham-operated animals ($P < 0.001$) through 21 days; no significant differences were observed between the sham-operated and intact controls (Das Gupta & Terz, 1967).

In a follow-up study, melanoma growth was examined in young adult male Syrian hamsters, 4–6 weeks of age, that were either pinealectomized or sham-pinealectomized. One week following pinealectomy or sham surgery, the animals were injected subcutaneously with a tumour suspension of MM1 hamster melanoma cells derived from solid tumour tissue, and tumour weights were evaluated 3 and 6 weeks following tumour injection. After 3 weeks, mean tumour weight in the pinealectomized animals ($n = 12$) was 2.3-fold higher ($P < 0.05$) than in sham-operated animals ($n = 11$), and after 6 weeks it was 1.6-fold higher (pinealectomized, $n = 13$; sham-operated, $n = 12$; $P < 0.05$); tumour weight was not significantly different between sham-operated and intact animals either after 3 or 6 weeks ($n = 10$–11) (El-Domeiri & Das Gupta, 1973).

In a later study by this group, the effects of pinealectomy versus sham-pinealectomy were evaluated on the growth of MM1 hamster melanoma growth in young adult male Syrian hamsters, 5–6 weeks of age, under the conditions of a long photoperiod (LD14:10) or short photoperiod (LD6:18). Animals were maintained on either long or short days for 2 weeks before pinealectomy or sham surgery and continued on these photoperiods thereafter. One week following surgery, animals were injected subcutaneously with a suspension of cells derived from MM1 hamster melanoma. Under long days, the tumour growth rate in the pinealectomized hamsters ($n = 16$) was higher than in sham-operated animals ($n = 11$) over 38 days as determined by serial measurement of tumour volumes (no statistical comparison); tumour latency was identical in both groups. The final mean tumour weight in pinealectomized hamsters was 37% higher than in sham-operated controls ($P < 0.01$). In contrast, under short days, the tumour growth rate was lower in pinealectomized hamsters ($n = 8$) than in sham-operated controls ($n = 9$) over 51 days (no statistical comparison); tumour latency was significantly longer in pinealectomized versus sham-operated animals ($P < 0.05$). The final mean tumour weight in pinealectomized animals was nearly 50% lower than in sham controls ($P < 0.01$) (Stanberry *et al.*, 1983).

In a study by another group in a carcinogen-induced model of melanoma, the effects of pinealectomy versus sham-pinealectomy were examined on the development of melanomas induced by the intragastric administration of DMBA in male and female Syrian hamsters 2 days after pinealectomy or sham surgery. Thirteen months following

DMBA administration, the number of melanomas (> 1 mm and < 5 mm) in pinealectomized male animals ($n = 26$) was 74% higher than in sham-operated animals ($n = 45$) ($P < 0.001$), and 44% higher in pinealectomized females ($n = 11$) than in sham-operated females ($n = 20$) ($P < 0.001$). No significant differences were observed in tumour number in pinealectomized versus sham-operated males or females for tumours > 5 mm although tumour number tended to be smaller in the pinealectomized groups than in the sham-operated groups. The effects of pinealectomy on mean tumour size or incidence was not determined in this study (Aubert *et al.*, 1970). [No direct comparisons were done to compare direct measures of tumour size between groups.]

3.2.7 *Prostate carcinoma*

Only one study has examined the effects of pinealectomy on the growth of a fast-growing, androgen-independent transplantable rat Dunning R3327 prostate cancer in adult male Copenhagen-Fischer F_1 rats. Tumours were transplanted subcutaneously into pinealectomized ($n = 11$) or sham-operated rats ($n = 10$) [timing of surgery and tumour implantation in relationship to surgery were not specified]; no differences in growth rates were observed over a 75-day period following tumour transplantation (Toma *et al.*, 1987).

3.2.8 *Uterine carcinoma (Guerin malignant epithelioma)*

DMBA

Guerin malignant spontaneous epitheliomas of the Wistar rat uterus were transplanted into adult male Wistar rats that were either pinealectomized ($n = 7$) or left intact ($n = 17$). Three days after the pinealectomy, all rats were transplanted subcutaneously with Guerin epitheliomas. Mean life span in tumour-bearing pinealectomized animals was significantly reduced by 14 days when compared to intact controls ($P < 0.001$); the mean mitotic activity of tumours in pinealectomized rats was moderately (15%) but significantly higher than in intact controls ($P < 0.05$) 35–45 days after tumour transplantation (Lewiński *et al.*, 1993).

3.2.9 *Mammary carcinoma*

The effects of neonatal pinealectomy (24 hours after birth) on the development of mammary tumours induced by the intragastric administration of DMBA in adult female Wistar rats were evaluated against intact animals. Both groups of animals received a total of three intragastric DMBA treatments separated by 10-day intervals 3–3.5 months after pinealectomy, and were treated with saline following the first DMBA treatment. The incidence and final prevalence of DMBA-induced mammary tumours was the same in both pinealectomized ($n = 12$) and intact animals ($n = 12$) over the 400-day period following the first DMBA administration (Lapin, 1978).

In a subsequent study, the effects of pinealectomy versus sham-pinealectomy in animals on an LD12:12 light dark cycle were examined on DMBA-induced mammary tumorigenesis in young adult female Sprague-Dawley rats (58 days of age). Pinealectomy and sham surgery were performed 2 days before the administration of DMBA. Latency to onset and incidence of mammary tumours in pinealectomized rats ($n = 17$) versus sham-operated animals ($n = 20$) were not statistically different during the 140 days of tumorigenesis (Aubert *et al.*, 1980).

Pinealectomized young adult (50 days of age) female Sprague-Dawley rats administered a single low dose of DMBA (7 mg) 30 days following surgery showed a 4-fold higher incidence of mammary tumours in the pinealectomized group relative to the sham-operated controls 240 days following DMBA treatment ($P < 0.002$). When pinealectomized and sham-pinealectomized rats were administered a higher dose of DMBA (10 mg), tumour development in pinealectomized rats ($n = 30$) was 2-fold higher than in the sham-pinealectomized group ($n = 30$, $P < 0.03$) (Tamarkin *et al.*, 1981).

In a series of publications from one study that addressed the effects of neonatal (2 days of age) pinealectomy or sham surgery on DMBA-induced (Day 55) mammary tumorigenesis in adult female Holtzman rats maintained on a short photoperiod (LD10:14 light–dark cycle) from birth, no significant differences were found in the final prevalence of mammary tumours, mammary tumour number, mean latency to tumour onset, [^{3}H]thymidine incorporation into DNA in mammary tissue or the number of terminal end or alveolar buds in pinealectomized rats ($n = 23$) versus sham-operated rats ($n = 15$). The total duration of tumour-monitoring was 180 days after DMBA administration. No tumour incidence curves were presented in either of these studies so that the rates of tumour development could be statistically compared (Kothari *et al.*, 1984; Shah *et al.*, 1984).

In a subsequent study, it was similarly demonstrated that the incidence, final (55 days of age) prevalence, and number of DMBA-induced mammary tumours in adult female Holtzman rats that undergone pinealectomy neonatally (2 days of age) were not significantly different at the end of the tumorigenic period (30 weeks post-DMBA) between neonatally pinealectomized ($n = 20$) and intact animals ($n = 20$) maintained on a short photoperiod (LD10:14). However, 80% tumour prevalence in pinealectomized animals was achieved 12 weeks following DMBA treatment when compared to intact control animals that had a 10% prevalence at 12 weeks and a maximal tumour prevalence that was not apparent until 24 weeks following DMBA administration (70% tumour prevalence). [It was clear that under short photoperiod conditions, mammary tumours in pinealectomized animals developed at a rate that was substantially faster than in intact animals; however, these investigators did not statistically analyse the tumour incidence curves presented in their report.] (Subramanian and Kothari, 1991).

In another carcinogen-induced mammary tumour model, pinealectomized (3 days before the first MNU injection) adult female Sprague-Dawley rats ($n = 11$) maintained on an LD12:12 light–dark cycle and treated with the carcinogen NMU, on Day 50 and Day 57, exhibited a trend for an overall increase in the incidence and number of mammary

tumours over intact animals ($n = 14$) for the period encompassing 19 weeks following NMU injection; however, this increase was not statistically significant. Similarly, no significant difference was observed in tumour latency in pinealectomized rats versus intact controls (Blask *et al.*, 1991).

In a subsequent study using adult female Fischer 344/N rats maintained on an LD12:12 photoperiod, animals were pinealectomized ($n = 40$) at 4 weeks of age or left intact ($n = 40$) and given NMU intraperitoneally (50 days of age). Tumour development was documented over a 26-week period following NMU administration. There were no significant differences in tumour incidence, final prevalence, number, size or latency between the pinealectomized and intact groups even though the circadian melatonin rhythm was fully expressed in the intact animals and completely extinguished in the pinealectomized rats during the first half of the study. However, by the end of the study, a nocturnal melatonin signal was present in pinealectomized rats (Travlos *et al.*, 2001). [This latter result was difficult to explain; one possibility was that an extrapineal source of circulating melatonin (i.e. the gut) may have compensated for the loss of the pineal gland.]

3.3 Effects of physiological melatonin administration on experimental tumour growth activity in animals

Introduction

Most of the studies have demonstrated an oncostatic action of melatonin on tumour development and growth in experimental animal models of cancer. However, these studies have been performed using pharmacological doses of melatonin. The nocturnal, physiological blood concentrations of melatonin *in vivo* are inhibitory to tumorigenesis and have been inferred from studies employing pinealectomy as a technique for specifically eliminating the nocturnal melatonin signal and observing a stimulation of tumour development and growth (see section 3.2 above). Only a handful of recent studies (see Table 3.1) have directly investigated the role of physiological, nocturnal concentrations of melatonin on experimental cancer growth *in vivo*.

3.3.1 *Rat hepatoma*

In one study, 3-mm^3 of tissue-isolated Morris rat hepatomas (7288CTC) were sutured to the tip of a vascular stalk formed from the superficial epigastric artery and vein of groups of 5–9 male Buffalo rats. When these tumours reached approximately 5 g, the carotid artery and tumour vein were either cannulated or perfused *in situ*. Perfusion experiments used rat whole blood harvested during the early light phase just a few hours following light onset when endogenous melatonin levels were low. Perfusion studies using a high physiological concentration of melatonin (1 nM) for 2.5 hours reversibly

($P < 0.05$) blocked the uptake of linoleic acid, production of 13-HODE, and significantly decreased ($P < 0.05$) the incorporation of [^{3}H]thymidine into DNA. [These findings were strengthened by studies using several melatonin receptor antagonists that completely reversed the effects of the melatonin.] In the cannulated animals measured every 4 hours for 24 hours, tumour linoleic acid uptake and metabolism to 13-HODE were temporally correlated ($P < 0.05$) with the circadian rhythm and a significant difference was demonstrated between peak dark and peak light phase values ($P < 0.05$). Finally, pinealectomized rats hosting tumour tissue and given either daily subcutaneous injections of melatonin or provided oral melatonin (200 µg) demonstrated a significant delay in the latency to tumour palpability when compared to appropriate sham controls ($P < 0.05$) (Blask *et al.*, 1999).

In a subsequent dose–response study using the same experimental protocol, increasing concentrations of exogenous melatonin were administered to perfused in-situ tissue-isolated Morris rat hepatomas hosted in Buffalo rats, 4–5 weeks of age, using whole blood harvested from pinealectomized Sprague-Dawley donor rats. Final whole blood concentrations of melatonin reproduced those levels characteristic of the ascending limb of the nocturnal, endogenous melatonin surge. A significant ($P < 0.05$) dose-dependent suppression of tumour linoleic acid uptake and 13-HODE production occurred following melatonin perfusion. Similarly, a dose-dependent suppression of tumour-DNA content ($P < 0.05$) and [^{3}H]thymidine incorporation into DNA ($P < 0.05$) was seen in response to melatonin along this concentration range as well. The inhibitory effects of melatonin on tumour linoleic acid metabolism and cellular replication activity saturated at the highest physiological concentration of 1 nM. Additionally, tumour uptake and retention of melatonin itself, as a function of supply, ranged from 20 to 45% across all concentrations tested. In the same study, melatonin was added to a semi-purified 5% corn oil diet so that pineal gland intact animals ingested, primarily during the dark phase, either 50 ng, 500 ng or 5 µg/day of additional dietary melatonin to produce physiological, nocturnal concentrations of melatonin that added to the endogenous nocturnal surge. When animals began receiving melatonin in their diet 2 weeks before tumour implantation and continuously thereafter, tumour growth as well as linoleic acid uptake and metabolism to 13-HODE were significantly inhibited ($P < 0.05$) in a dose-dependent manner (Blask *et al.*, 2004).

3.3.2 *Human cancer xenograft*

Adult male Buffalo rats were implanted with 7288CTC hepatoma cells as described above (positive control), and adult female nude rats were implanted with tissue-isolated steroid receptor negative (SR–, no estrogen or progesterone receptor expression) or steroid-receptor positive (SR+) human breast cancer xenografts. The SR+ xenografts when perfused with Sprague-Dawley rat donor whole blood to which was added 1 nmol/L of synthetic melatonin showed significant reduction in [^{3}H]thymidine incorporation ($P < 0.05$) and in camp levels ($P < 0.05$). This reduction was completely

eliminated by coperfusion with 13-HODE. Although not shown, similar findings were reported for the SR– xenographs. The authors further investigated these models using differing levels of light at night to control melatonin levels. Using six animals per group and six different light intensities resulted in significant changes ($P < 0.05$) in Phos, ERK1/2, linoleic acid uptake, 13-HODE, c-AMP, [^{3}H]thymidine incorporation and tumour onset in both the 7288CTC model and the SR– model. Similarly, tissue-isolated SR–, MT_1 melatonin-receptor positive MCF-7 human breast cancer xenografts were perfused *in situ* for 1 hour with human whole blood from premenopausal females collected in daytime, night time and after exposure to bright light at night. There was a significant reduction of [^{3}H]thymidine incorporation (63% to 73%) between samples perfused at night time and daytime ($P < 0.05$) which was eliminated in experiments using blood from volunteers exposed to bright light at night. Other markers as noted above (linoleic acid uptake, 13-HODE, cAMP) behaved as expected. Finally, to determine if this was entirely driven by melatonin, 500 pmol/L of melatonin was added to blood from donors exposed to bright light at night for 90 minutes. The results were identical to what was seen for the night time blood sample experiments and these results could easily be blocked by using MT_1/MT_2 antagonists. Using a new perfusion system that minimized delivery time, it was subsequently demonstrated that perfusion of tissue-isolated estrogen-receptor negative MCF-7 human breast cancer xenografts *in situ* with melatonin-containing (1 nM final concentration) daytime-collected rat donor blood completely suppressed ($P < 0.05$) linoleic acid uptake and 13-HODE formation within 5 minutes of melatonin reaching the tumour, indicating that the melatonin suppression of tumour linoleic acid metabolism is extremely rapid (Dauchy *et al.*, 2006).

Using the same basic protocol used above, tissue-isolated FaDu human squamous-cell cancer xenografts (grade II human hypopharyngeal squamous cell carcinoma) were implanted into male athymic nude rats. Cancer xenografts were perfused *in situ* for 2 hours with daytime-collected male adult Buffalo rat donor whole blood to which melatonin was added at a final concentration of 1 nM. This perfusion resulted in a total blockade of linoleic acid uptake ($P < 0.05$) and 13-HODE formation ($P < 0.05$) as well as a significant ($P < 0.05$) 76% suppression of cAMP levels and a 50% inhibition ($P < 0.05$) of [^{3}H]thymidine incorporation into DNA and DNA content when compared to vehicle-containing daytime-collected control whole blood (Dauchy *et al.*, 2007).

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4. Mechanistic and Other Relevant Data

4.1 The pineal gland and melatonin

Introduction

There is considerable interest in the role of the pineal gland in the development and growth of malignant tumours and in the ability of melatonin, its main secretory product, to act as an oncostatic agent.

Melatonin is a messenger of time in the mammalian organism which transmits the information of environmental light and darkness obtained from the eye through the hypothalamus to all tissues of the body. It interacts with the mechanisms that form the mammalian time structure, and has to be understood in its relation to the organism's biological clock.

Melatonin has anti-proliferative effects on human cancer cells cultured *in vitro*. These oncostatic effects have been observed at physiological concentrations, and include reduction of cell-cycle progression by increasing the expression of the tumour-suppressor gene *TP53*, and inhibition of DNA synthesis. In addition, melatonin reduces the invasive and metastatic properties of human cancer cells *in vitro*, and increases intercellular communication between these cells. There is evidence from animal models that melatonin inhibits or reduces the induction of DNA damage by free radicals. Pinealectomized rats showed a higher level of DNA damage in response to treatment with a carcinogen than did rats with intact pineal glands. Melatonin also upregulates anti-oxidant enzyme systems.

4.1.1 *The pineal gland and its innervations*

The mammalian pineal is a secretory organ with specialized glandular cells, the pinealocytes, interstitial glial cells, and perivascular macrophages. The principal innervation is sympathetic and arises from the superior cervical ganglion. In addition, parasympathetic, commissural and peptidergic innervation are present. The sympathetic fibres contain norepinephrine and neuropeptide Y as neurotransmitters. The parasympathetic fibres contain vasoactive intestinal peptide and peptide histidine isoleucine. Neurons from the trigeminal ganglion reach the pineal gland containing substance P, calcitonin-gene-related peptide, and pituitary adenyl-cyclase-related activating peptide. Through the pineal stalk, nerve fibres originating in the brain and containing a variety of neurotransmitters innervate the pineal. In addition to its principal noradrenergic innervation, numerous receptors have been found in the pinealocyte cell

membrane, which are able to bind numerous neurotransmitters and influence the pinealocyte (for a review, see Møller & Baeres, 2002).

The secretory products of the pineal consist of melatonin which plays a major role in plant, animal, and human physiology, and several peptides the action of which is less well characterized.

4.1.2 *Melatonin and its production*

Melatonin (*N*-acetyl-5-methoxytryptamine) was first isolated by Lerner *et al.* (1958) from bovine pineal glands. Tryptophan is taken up from the blood stream and transformed to melatonin in four successive intracellular steps which are catalysed by tryptophan hydroxylase (EC1.14.16.4), aromatic amino acid decarboxylase (EC 4.1.1.28), arylalkylamine-*N*-acetyltransferase (EC 2.3.1.87), and hydroxyindole-*O*-methyltransferase (EC 2.1.1.4) (Axelrod & Weissbach, 1960; Lovenberg *et al.*, 1967). Arylalkylamine-*N*-acetyltransferase is thought to be the rate-limiting enzyme in the process of melatonin synthesis (Klein, 2007).

Melatonin is present in bacteria, in eukaryotic unicells, in numerous plants, vegetables, fruits, seeds, rice, wheat, and medicinal herbs, and diverse species of invertebrates (Hardeland & Poeggeler, 2003).

4.1.3 *Extrapineal production of melatonin*

The main source of circulating melatonin in mammals is the pineal gland. However, many extrapineal mammalian tissues and organs have the enzymatic mechanism to produce melatonin (Carrillo-Vico *et al.*, 2004, 2005).

The apparently large quantity of melatonin produced in tissues other than the pineal gland does not appear to contribute substantially to the circadian-rhythm-related plasma melatonin concentration as suppression of pineal function induced by surgical pinealectomy or constant light exposure markedly diminishes the circulating melatonin concentration (e.g. in Syrian hamsters) (Vaughan & Reiter 1986) and eliminates the nocturnal plasma melatonin concentration surge.

4.1.4 *Pineal production of melatonin*

In contrast, melatonin production in the pineal region is, in all mammalian species, periodic with high values during the dark phase irrespective of the activity or rest span of the species studied. In darkness, a marked 7–150 fold increase of arylalkylamine-*N*-acetyltransferase activity has been measured in the pineal region. The rhythm of production is endogenously generated by the activity of the suprachiasmatic nucleus (SCN) in the hypothalamus by a closed loop negative feedback of clock-gene expression. The rhythm is synchronized primarily by the environmental light–dark cycle. With irregular schedules of light exposure, it may be altered in its timing and in the duration of melatonin production. The pineal melatonin rhythm is driven by the circadian clock in the

hypothalamus through a multisynaptic pathway which consists of ganglion cells in the retina containing non-vision-dependent photoreceptors (Lucas *et al.*, 1999; Freedman *et al.*, 1999). Retinal ganglion cells containing the pigment melanopsin are thought to be the photoreceptors for the photic entrainment of circadian rhythms (Berson *et al.*, 2002). The photic information is transmitted to the central pacemaker in the SCN via the retino-hypothalamic tract.

The neural pathway from the SCN to the pineal region passes through pre-autonomic neurons of the paraventricular nucleus of the hypothalamus through the upper part of the spinal cord where synaptic connections are made with sympathetic preganglionic neurons relating to the superior sympathetic ganglia of the sympathetic chain (Møller & Baeres 2002). From there, postganglionic noradrenergic sympathetic neurons extend to the pineal gland. Norepinephrine is the neurotransmitter stimulating melatonin release in the pineal gland. It is released during the daily dark span in response to stimulating signals from the SCN.

Once formed, melatonin is not stored within the pineal gland but diffuses out into the capillary blood and cerebrospinal fluid (Tricoire *et al.*, 2003). The half-life of melatonin is bi-exponential with a first distribution half-life of 2 minutes and a second of 20 minutes or longer (Claustrat *et al.*, 2005). Melatonin released into the cerebrospinal fluid via the pineal recess reaches in the third ventricle concentrations up to 20–30 times higher than in the blood but decreases in concentration with increasing distance from the pineal region, suggesting cerebral tissue uptake (Tricoire *et al.*, 2003).

4.1.5 *Metabolism of melatonin*

Circulating melatonin is metabolized mainly in the liver which clears over 90% of the circulating melatonin. Melatonin is first hydroxylated and then conjugated as sulfate and excreted as 6-sulfatoxymelatonin (aMT6s) and in a small amount as glucuronide (Arendt, 1995; Claustrat *et al.*, 2005). Urinary and salivary aMT6s excretion closely parallels the plasma aMT6s profile. Melatonin passes into saliva in a low concentration which in its relative amount and timing corresponds also to the plasma profile. Urinary aMT6s and salivary melatonin lend themselves to the non-invasive study of melatonin secretion and its timing (Nowak *et al.*, 1987; Arendt, 1995).

Melatonin can also be metabolized non-enzymatically in cells and extracellularly by free radicals and other oxidants. Owing to its lipophilic character, it diffuses through cell membranes easily and can exert not only receptor-dependent but also receptor-independent actions (Claustrat *et al.*, 2005).

Once released into the blood, melatonin is primarily bound to albumin (70%) (Cardinali *et al.*, 1972), α-1-acid glycoprotein (Morin *et al.*, 1997), and haemoglobin (Gilad & Zisapel, 1995). Changes in circulating melatonin levels may be due in part to changes in the concentrations of one or more of these binding proteins. This could influence the availability of melatonin to various target tissues and its bioactivity in these tissues (Di *et al.*, 1998).

4.1.6 *The circadian rhythm of melatonin in plasma in humans*

The plasma melatonin rhythm in humans develops between the 2nd and 3rd month of life with peak melatonin concentrations found in prepubertal children (Waldhauser *et al.*, 1988). In the elderly, the nocturnal melatonin concentrations decrease at the end of the 5th decade and beyond to levels between 20–80% of levels found in young adults (Touitou *et al.*, 1984; Ferrari *et al.*, 1995; Magri *et al.*, 1997). This drop was not found in all studies probably due to different lifestyle, state of health, sampling techniques, etc (Kennaway *et al.*, 1999; Zeitzer *et al.*, 1999). The circadian melatonin profile varies considerably between clinically healthy human subjects, with some having no detectable melatonin concentrations during daytime or night time (Arendt, 1985). On the other hand, in healthy individuals, the timing, amplitude, and even the shape of the melatonin profile can be highly reproducible and characteristic for a given person (Arendt, 1988; Klerman *et al.*, 2002). Individual living habits like 'morningness' and 'eveningness' are expressed in differences in the phase of the circadian melatonin profile (Duffy *et al.*, 1999; Gibertini *et al.*, 1999). No consistent gender difference has been found in regard to melatonin concentrations, the melatonin profile, or its suppression by light (Arendt, 1985).

4.1.7 *Light and regulation of pineal melatonin production in humans and animals*

The light–dark cycle is the main entraining agent ("zeitgeber," synchronizer) of the regulating system of pineal melatonin secretion. Light suppresses melatonin secretion in humans (Lewy *et al.*, 1980) in an intensity-related manner (Bojkowski *et al.*, 1987a; McIntyre *et al.*, 1989). The endogenous rhythm governing melatonin synthesis and release is entrained to the daily dark span in different mammalian systems irrespective of the diurnal or nocturnal activity of the species. In diurnally active human subjects, high values of melatonin concentrations are released during the night. Light, in addition to acting as entraining agent of the circadian clock, will act as a masking agent when the subject is exposed to light during the habitual dark span. The photoreceptor system involved in clock regulation is distinct from the pathways associated with image formation. The sensitivity of the circadian system to light entrainment does not depend upon rod and cone photoreceptor integrity, and/or the loss of visual function (Foster *et al.*, 1991). Eye loss in mammals, including humans, confirms that photoentrainment originates within the eye (Haus *et al.*, 1967; Lockley *et al.*, 1997; Foster, 1998). The daily alteration between light and dark entrains the endogenous circadian clock in the hypothalamus to the astronomical day length (24 hours). The innate period of the hypothalamic clock tends to be slightly longer than 24 hours. Absence of this input due to loss of the eye leads to a tendency of the organism to "free-run" from the 24-hour environment following the non-24-hour endogenous period of the hypothalamic clock (Haus *et al.*, 1967; Lockley *et al.*, 1997; Skene *et al.*, 1999).

The photoreception acting as synchronizer upon the SCN is based upon a population of about 1% of retinal ganglion cells, which are photosensitive and respond to light directly (Sekaran *et al.*, 2003). These photoreceptors contain a photopigment based on an

opsin/vitamin A complex with peak sensitivity in the blue part of the spectrum, near 480 nm. In rodents as well as in humans this agent is more than likely OPN4 or melanopsin (Brainard *et al.*, 2001, Thapan *et al.*, 2001; Ruby *et al.*, 2002; Hattar *et al.*, 2003;).

The exploration of the human photoreceptors and the related circadian time organization requires the appropriate use and measurement of light stimuli (Foster *et al.*, 2007). The establishment of action spectra has been helpful in associating photopigments with the responses of photobiological systems. An action spectrum for spectral sensitivity of suppression of nocturnal melatonin concentration was identified by Thapan *et al.* (2001) using monochromatic light exposure for 30 minutes in clinically healthy subjects. The light pulse was administered at circadian time 16–18 hours at numerous wavelengths (λmax range, 424–548 nm), and a wide range of irradiance (0.7–65.0 μW/cm2). At each wavelength, suppression of plasma melatonin increased with increasing irradiance. The action spectrum revealed a peak in sensitivity at a λmax of 459 nm, which fitted best with the rhodopsin wavelength profile. A comparable action spectrum for wavelength was obtained in humans of both genders in night time melatonin suppression tests (over a wavelength range from 420–600 nm) with 446–477 nm as the most potent region for regulating melatonin secretion (Brainard *et al.*, 2001). The suppression of nocturnal melatonin concentrations by 1-hour light exposure of 200 or 500 lux was equal in both men and women, and proportional to the light intensity. Also, the levels and amplitude of the circadian rhythm in melatonin were not significantly different (Nathan *et al.*, 2000). In quantifying the biological response to light, the suppression of melatonin in a constant routine protocol showed a close relation to subjective alertness, slow eye movement, and theta-α activity (detected by electroencephalography, Cajochen *et al.*, 2000). These studies showed that light intensities as found in usual room-light illumination (90–180 lux) already have alerting and melatonin-suppressing effects (Bojkowski *et al.*, 1987a; Cajochen *et al.*, 2000; Zeitzer *et al.*, 2000). In clinically healthy subjects, maximal alertness in response to light exposure was found at very short wavelengths (420, 440 and 470 nm) of the visible spectrum (Revell *et al.*, 2006).

Human photosensitivity measured by melatonin suppression depends in part also on prior light exposure of the subjects. It increases after prior exposure of the subjects to dim light, indicating an adaptation of the photoreception or photoresponse to the recent photic history (Owen & Arendt, 1992; Hébert *et al.*, 2002; Smith *et al.*, 2004).

The blocking of the biologically most active short-wavelength light by the use of goggles that excluded all wavelengths of less than 530 nm prevented the suppression of the nocturnal salivary melatonin concentrations by 800 lux light intensity (Kayumov *et al.*, 2005). All subjects (11 men and eight women, 24.7 ± 4.6 years of age) preserved their melatonin levels in filtered light similar to their dim-light secretion profile, while unfiltered bright light drastically suppressed melatonin production. Normalization of the nocturnal melatonin production by elimination of short-wavelength light apparently did not impair the measures of performance, subjective sleepiness, or alertness. Relatively good colour recognition was maintained and visual light transmittance with the filters used was approximately 73% (Kayumov *et al.*, 2005).

Bright light exposure was able to phase shift and reset the circadian phase (Broadway *et al.*, 1987; Czeisler *et al.*, 1986). Also, much lesser light intensity like normal room light, (approximately 180 lux) produced a phase shift (Boivin *et al.*, 1996), and even very dim light (20 lux) was able to synchronize the circadian system in a subject following a regular sleep, wakefulness and meal schedule (Klerman *et al.*, 1997). In these studies with very low light intensity, the time of the daily dark span with sleep of the subjects may have reinforced the synchronizing effect of light. In a study carried without these time cues (scheduled sleep, darkness, activities), 14 days exposure of subjects to a schedule of light dark (LD) 12h:12h with 200 lux:< 8 lux were unable to maintain the initial circadian phase position (Middleton *et al.*, 2002).

Circadian phase shift after exposure to monochromatic short-wavelength light (with two peaks at 436 and 456 nm) in a 4-hour pulse mode (8 lux, 28 $\mu W/cm^2$) after habitual wake time led to a phase shift of the human melatonin profile comparable to an exposure to white light (12000 lux, 4300 $\mu W/cm^2$), in spite of the white light pulse containing 185-fold more photons than the short-wavelength light (Warman *et al.*, 2003).

Similarly, the circadian phase resetting of the free running plasma melatonin rhythm in clinically healthy subjects after a 6.5-hour exposure to monochromatic light at 460 nm induced a 2-fold greater circadian phase delay than the same time of exposure to 555 nm monochromatic light of equal photon density (Lockley *et al.*, 2003).

The sensitivity of the circadian pacemaker varies according to the resetting effect of retinal light exposure depending upon the circadian phase at which the light exposure occurs (Honma *et al.*, 1987; Dawson *et al.*, 1993; Van Cauter *et al.*, 1993). Using pre- and post-stimulus constant routines in dim light (approximately 2–7 1ux) with maintained wakefulness in a semi-recumbent posture, Khalsa *et al.* (2003) described a phase–response curve to a bright light exposure stimulus consisting of 6.7 hours first of a 6-minute fixed gaze exposure to 10000 lux followed by 5000–9000 lux for the remainder of the time span. Plasma melatonin was used to describe the phase of the onset, offset and midpoint of the melatonin profile. The resultant phase–response curve of the midpoint of the melatonin rhythm (with a peak-to-trough amplitude of 5 hours) showed phase delays when the light stimulus was centred before the critical phase of the core body temperature minimum, and phase advances when the stimulus was centred after the critical phase. No phase shift occurred when the stimulus was centred at the critical phase (the body core temperature minimum).

4.1.8 *Photoperiod and seasonal variations*

In addition to information on onset and offset of the daily photoperiod, melatonin provides information on day length. The duration of the melatonin secretion in animals and humans varies with the length of the dark span. The longer the dark span in the laboratory or the night in nature, the longer the time of melatonin synthesis and secretion, irrespective of whether the dark span is the time of activity in nocturnal rodents or of rest in diurnally active species, including humans (Arendt, 1995). Most mammals use the

changes in the length of the daily light and dark period to detect a change in seasons, and to regulate seasonal behaviour and/or synchronize circannual rhythms (Tamarkin *et al.*, 1985; Goldman, 2001). Seasonal variation in reproduction is directly controlled by the relative length of the light–dark span (Lincoln, 2002).

Under laboratory conditions imitating the winter season (short photoperiods), a longer sleep phase (recorded by electroencephalography) and a longer duration of nocturnal melatonin secretion was observed in human subjects (Wehr 1991, 2001). However, in the modern urban electrified environment, these changes are masked and not always detectable. In general, investigators found no seasonal change in duration of melatonin secretion at low- or mid-latitudes (Illnerová *et al.*, 1985; Bojkowski & Arendt 1988; Matthews *et al.*, 1991). In contrast, seasonal change with longer duration of melatonin secretion in winter was found at subpolar and polar high latitudes with marked changes in photoperiod and luminosity (Beck-Friis *et al.*, 1984; Martikainen *et al.*, 1985; Kauppila *et al.*, 1987; Makkison and Arendt 1991; Levine *et al.*, 1994), with higher daytime melatonin concentrations reported (Rönnberg *et al.*, 1990). Also, when people spent more time outdoors in the summer, even in temperate climate (mid-latitude), seasonal changes in secretion of melatonin and of cortisol were found (Vondrasová *et al.*, 1997). Kauppila *et al.*, (1987) suggested that these elevated melatonin concentrations may be associated with diminished reproductive function. A photoperiodic influence on human fertility was observed, resulting in increased fertility in spring, but appeared to be modified by different lifestyles (Wehr, 2001).

4.1.9 *Melatonin in relation to the circadian system*

It is well established that ocular light exposure in humans can affect hormonal secretion, either acutely as a direct response to the presence or absence of retinal light exposure, or indirectly as a result of the influence of light on circadian mechanisms. Indeed, light is the most powerful circadian synchronizer in humans (Czeisler & Wright, 1999), and can exert a profound effect on the phase and amplitude of the human circadian pacemaker (Czeisler & Klerman, 1999). Of particular interest in the context of melatonin as a biomarker is the effect of light on the pineal function in humans: nocturnal illumination of sufficient intensity completely suppresses melatonin production (Lewy *et al.*, 1980; Bojkowski *et al.*, 1987a); there is considerable individual variability in sensitivity to light at night (McIntyre *et al.*, 1990; Hébert *et al.*, 2002; Herljevic *et al.*, 2005); there appears to be a dose–response to light at night in that the brighter the light, the greater the reduction in nocturnal circulating melatonin (Bojkowski *et al.*, 1987a; McIntyre *et al.*, 1989; Zeitzer *et al.*, 2000); bright light shifts the phase of melatonin rhythm, with morning hours being associated with phase advance and evening hours with phase delays (Duffy & Wright, 2005); and light quality during the day affects night time melatonin production (Wehr *et al.*, 1995; Wehr, 1996; Lewy *et al.*, 1987; McIntyre *et al.*, 1990; Boivin *et al.*, 1996), as well as the human circadian pacemaker (Czeisler *et al.*, 1986).

Because melatonin is the best marker of internal clock timing and is quantifiable in the urine via well proven and reliable techniques applicable to non-laboratory studies, it has become a powerful tool as a biomarker of circadian dysregulation.

(a) Laboratory-based studies of melatonin and exposure to light at night

Using sleep laboratory-based protocols, several studies have used melatonin measurements to determine phase advance and delays resulting from controlled exposure to light at night. Deacon & Arendt (1996), Eastman and Martin (1999), Burgess *et al.* (2002), and Revell & Eastman (2005) have used the 'nudging' technique to simulate circadian rhythm disturbance in a laboratory environment. Progressively changing the timing of bright light exposure day by day (nudging) leads to a synchronized shift of the circadian system to a desired new phase. This method has been used to prepare astronauts for space flights (Eastman *et al.*, 1995). Using bright light exposure for 9 hours on five consecutive days, the same authors reported that urinary aMT6s acrophase took at least 5 days post-treatment to return to normal baseline pattern (Deacon & Arendt, 1996). Van Cauter *et al.* (1994) exposed volunteers to 3 hours of bright light (5000 lux) during constant routine conditions following a 7-day entrainment period, measured plasma melatonin at 20-minute intervals, and reported rapid phase shifts within 24 hours of bright light exposure. Results after exposure for 6.5 hours to light of dim to moderate intensity early in the biological night (Zeitzer *et al.*, 2000) showed that even small changes in ordinary light exposure during the late evening hours can significantly affect both plasma melatonin concentrations and the entrained phase of the human circadian pacemaker (Zeitzer *et al.*, 2000). Roach *et al.* (2001) conducted a simulated night shiftwork study in which participants 'worked' during seven consecutive 8-hour shifts, and reported a mean phase delay of 5.5 hours by Night 7, using salivary melatonin measurements to detect the phase shift. A later study by the same team reported similar results using urinary aMT6s levels to assess phase delay (Roach *et al.*, 2005).

(b) Field studies assessing the effects of shiftwork on melatonin secretion

Several studies have used measurements of melatonin in the blood or urine to evaluate and describe the effects of shiftwork on the circadian rhythm. Touitou *et al.* (1990) found that fast-rotating shiftwork modifies peak values and rhythm amplitudes of serum melatonin.

A series of studies on offshore oilrigs using aMT6s as a marker of internal timing and of melatonin suppression have shown complete circadian adaptation in some, but not all offshore schedules. When night-shift adaptation occurs, subjects experience desynchrony and melatonin suppression (approx. 20%) on the subsequent day shift. Thus, in addition to concerns for the health of unadapted night-shift workers, one should consider the implications of adaptation for subsequent health effects (Midwinter & Arendt, 1991; Ross *et al.*, 1995; Gibbs *et al.*, 2002, 2007).

Using data from the Nurses Health Study II, Schernhammer *et al.* (2004) reported a significant inverse association between increasing number of nights worked within the 2 weeks preceding morning-void urine collection and urinary melatonin levels. Along similar lines, Hansen *et al.* (2006) reported lower 24-hour urinary concentrations of aMT6s in nurses working the night shift compared to nurses working the day shift; urinary concentrations of aMT6s were also lower during a day off for night-shift workers, relative to day-off levels in day-shift workers. Several authors have reported inter-individual variability in the response of the melatonin rhythm to night shift (e.g. Sack *et al.*, 1992, 1997; Dumont *et al.*, 2001;; Gibbs *et al.*, 2007). In a study conducted by Quera-Salva *et al.* (1996, 1997) rapid change in sleep time and melatonin acrophase was reported in some night-shift workers, but not others, suggesting that some people have a physiological ability to readily adapt to rotating shift schedules, and reported for the first time a corresponding rapid shift in melatonin secretion. Dumont *et al.* (2001) measured urinary aMT6s every 2 hours during a 24 hour period after three consecutive nights of work in another group of nurses. Using cosinor analysis to estimate phase position, they reported individual variability in adaptation to night shiftwork, with five participants showing a phase delay, three a phase advance, and the remaining 22 demonstrating no phase shift (i.e. the timing of their melatonin secretion was typical of a day-shift worker). In a study involving offshore oil workers employed in a 1-week alternating shift schedule (1 week of nights, 1 week of days), Gibbs *et al.* (2002, 2007) reported adaptation to the night-shift schedule via a delay of aMT6s at the end of the week of night shifts. In another study of offshore oil workers employed in a 2-week alternating shift schedule (2 weeks of days 06:00h-18:00h, 2 weeks of nights 18:00-06:00h), Barnes *et al.* (1998a) reported similar results, with the delay of aMT6s occurring during the first week of the night shift. They also conducted another study in which urine samples were collected every 2 to 3 hours throughout the wake period (subjective days) and one collection over the sleep period (over-sleep sample) from a group of offshore oil workers employed in a 1-week alternating shift schedule (1 week of days (12:00-00:00h), 1 week of nights (00:00-12:00h)), and reported differing adaptation to the night shift depending on season of the year, using measurement of urinary aMT6s to detect phase shift (Barnes *et al.*, 1998b). Prior to this, Midwinter and Arendt (1991) reported differing shifts in the acrophase of melatonin secretion depending on the season of the year, using urine samples collected over 48 hours during a week of night-shift work in a group of workers stationed in the Antarctic; they further reported a slower readaptation to the rhythm following night-shift work during the winter compared to the summer.

A study conducted by Burch *et al.* (2005) compared melatonin levels among workers on permanent day, swing, and night shifts. Urinary aMT6s was measured in post-work and post-sleep samples, and disrupted circadian melatonin production was evaluated using the sleep:work aMT6s ratio. They reported that night workers had altered melatonin levels, disrupted sleep, and elevated symptom prevalence. Subjects grouped by their sleep:work aMT6s ratio rather than shift had even greater symptom prevalence. Risks for two or more symptoms were 3.5 to 8 times greater among workers with sleep:work ratios

≤ 1 compared to those with ratios > 1 (Burch *et al.*, 2005). The sleep:work ratio may be an objective means to assess circadian disruption.

(c) Melatonin as an indicator of diurnal type

Several studies have used melatonin measurements to compare whether diurnal type (morning versus evening) is associated with cumulative nocturnal melatonin secretion and/or onset of melatonin secretion. Madokoro *et al.* (1997) reported pronounced inter-individual differences in plasma melatonin concentration measured before and 1 year after beginning shiftwork. They constructed a ratio of melatonin concentration measured at 6 am to total melatonin concentration measured during the night, and reported that a higher Morningness-Eveningness score (indicating morning type according to Horne & Ostberg, 1976) was correlated with this ratio. Gibertini *et al.* (1999) measured nocturnal melatonin levels in blood on an hourly basis, and assessed the circadian type of each participant; they found that the circadian type was strongly related to the melatonin acrophase but not to the amplitude or the time of year of assessment, and that morning types experienced a more rapid decline in melatonin levels after the peak relative to evening types. Similarly, Liu *et al.* (2000) reported that morning type was associated with an earlier melatonin acrophase. More recently, Griefahn *et al.* (2002) found that the onset of melatonin synthesis was 3 hours earlier in morning than in evening types, using hourly salivary melatonin measurements; they also reported melatonin measurements to be a better indicator of diurnal type than rectal temperature measurements. Diurnal preference may be related to the ability to cope with shiftwork. Importantly, Duffy *et al.* (1999) and Wright *et al.* (2005) have established the close relationship between individual 'free-running' periodicity, entrained phase (entraining in a normal environment) and diurnal preference (Horne-Ostberg score).

(d) Melatonin as chronobiotic agent

Exogenous melatonin given at the right biological time can synchronize (Lockley *et al.*, 2000; Sack *et al.*, 2000; Arendt, 2000) and phase-shift the circadian time organization (Arendt *et al.*, 1984; Arendt, 1985). Depending upon the stage of the circadian rhythms of a subject at a given clock hour, melatonin is able to shift circadian timing to both later and earlier times (Lewy *et al.*, 1992). Appropriate timing of treatment to delay or advance can be predicted from a phase–response curve in subjects whose body clock phase is known (Lewy *et al.*, 1998).

Low doses (0.3–10 mg) of melatonin given during the 'biological day', when endogenous melatonin levels are low, can induce sleepiness or sleep, and lower body temperature (Cagnacci *et al.*, 1992; Deacon & Arendt, 1995, Arendt, 1995; Brzezinski *et al.*, 2005). A single melatonin treatment (5 mg fast release) given at light time in controlled studies can advance the timing of the internal clock by up to about 1.5 hours (Deacon & Arendt, 1995).

Timed melatonin administration (0.5–5.0 mg) given at 24-hour intervals, usually at desired bedtime can fully entrain the free-running (non-24 hour) circadian rhythm of most blind subjects (Lockley *et al.*, 2000; Sack *et al.*, 2000; Arendt, 2005). By acting as a circadian coupling agent countering desynchrony among central and peripheral clocks, and optimizing phase with respect to external time cues, cellular and system processes may be optimized and defence systems augmented (Arendt, 2005), with a broad range of potential therapeutic applications to be explored, including in medical oncology (Lissoni *et al.*, 1994a,b, 2003; Bartsch & Bartsch, 2006).

4.1.10 *Melatonin receptors*

Melatonin displays pleiotropic physiological functions. Owing to its small lipophilic structure, it can freely enter cells and can exert an effect independent of the specific receptors found widely in human tissues (Morgan *et al.*, 1994; Morgan & Williams, 1996; Dubocovich & Markowska 2005). For example, in over 130 locations within the brain alone (Masson-Pévet *et al.*, 1994; Pévet *et al.*, 2006; Wu *et al.*, 2006) melatonin receptors are co-localized with vasopressin-, oxytocin- and corticotropin-releasing neurons. In mammalian, two subtypes of high affinity membrane receptors for melatonin have been cloned, the MT1 and MT2 subtypes (Reppert *et al.*, 1994, 1995). They belong to the super-family of G-protein-coupled receptors. The two types show a different action spectrum with large variability among species in their distribution. The receptors are responsible for the chronobiological effects of melatonin at the level of the SCN. In most mammalian systems, MT1 receptors modulate neuronal firing, arterial vasoconstriction, affect the cell proliferation in cancer and other cells, and regulate reproductive and metabolic functions. Activation of MT2 melatonin receptors phase-shift circadian rhythms of neuronal firing in the suprachiasmatic nucleus, inhibit dopamine release in the retina, induce vasodilation and inhibit leukocyte movement in arterial beds, and enhance immune responses (Dubocovich and Markowska 2005).

Endogenous pineal melatonin is believed to feed back onto the master clock in the SCN and regulate neuronal activity and circadian rhythmicity through activation of the specific MT1 and MT2 receptors (Gillette and Mitchell 2002). The response to receptor activation varies with the circadian stage of the cell systems involved. Neurons in the SCN are most sensitive to inhibition of neuronal firing by melatonin in diurnally, as well as nocturnally, active species at dusk suggesting changes in clock excitability, possibly as expression of an endogenous circadian rhythm (Stehle *et al.*, 1989). Melatonin phase-shifts circadian rhythms with two windows of sensitivity corresponding to the day–night (dusk) and night–day (dawn) transitions (Dubocovich *et al.*, 1998; McArthur *et al.*, 1997). The MT1 and MT2 receptors are targets for drug development with receptor agonists and antagonists, which are of interest for eliciting or blocking the wide variety of actions related to melatonin (Zlotos, 2005).

4.2 Proposed mechanisms for carcinogenicity of shiftwork and circadian disruption

Epidemiological studies on genetic polymorphisms in clock-related genes and phenotypes such as morning/evening preference and depressive symptoms, have shown a significant association between a single-nucleotide polymorphism in the *PER3* gene and diurnal preference. In a wider sense, the circadian clock may function as a tumour suppressor at the systemic, cellular, and molecular levels. Clock-controlled genes and related factors involved in cell-cycle control include c-*Myc*, *Mdm2*, *Tp53* and *Gadd45a*, as well as caspases, cyclins, and various transcription factors. In transgenic mice, a deletion in *Per2* results in a shorter circadian period, a higher susceptibility to radiation-induced tumours, and reduced apoptosis in thymocytes. Disruption of the circadian rhythm in mice is associated with an accelerated growth of malignant tumours.

4.2.1 *Melatonin and cancer*

(a) Oncostatic effects of melatonin

Thirty years ago, it was hypothesized that diminished pineal function may promote the development of human breast cancer (Cohen *et al.*, 1978). The primary argument was that increased pineal calcification, presumably leading to lowered melatonin production, was most strongly associated with increased breast cancer risk. Although this was the first reference to environmental lighting, which necessarily includes both sunlight and artificial light, as a potential source of one of several endocrine abnormalities that may underlie the development of breast cancer, light at night was not specifically postulated as an etiological factor. It was proposed incorrectly that altered visual stimulation, by blindness or darkness, would impair pineal melatonin production, thereby leading to unopposed estrogen secretion and increased breast cancer risk. It is now known that overall melatonin production is not compromised in blind individuals (Lockley *et al.*, 1997) and that breast cancer risk is actually diminished in blind women (Hahn, 1991; Verkasalo *et al.*, 1999). It was postulated by Stevens (1987) that light exposure at night may represent a unique risk factor for breast cancer in westernized societies via its ability to suppress nocturnal melatonin production by the pineal gland. This postulate, referred to as the ‘melatonin hypothesis’, was based on in-vivo studies demonstrating that melatonin inhibits, while pinealectomy or constant bright light stimulates, the development and growth of experimental breast cancer in rodents, and by in-vitro studies showing that the proliferation of estrogen receptor positive (ER+) human breast cancer cells was directly suppressed by nocturnal physiological levels of melatonin (Stevens, 2006).

Many studies using pharmacological concentrations of melatonin have demonstrated a direct antiproliferative and/or apoptotic effect on cancer cells (usually human cancer cell lines) *in vitro*. A substantial number of investigations have also shown that nocturnal physiological concentrations of melatonin exert direct oncostatic effects on cancer cell

proliferation as well. However, several studies have also demonstrated cytotoxic effects of pharmacological levels of melatonin on cancer cells *in vitro*. A large number of studies in experimental animal models of tumorigenesis have shown that properly timed (i.e. relative to the light–dark cycle) administration of pharmacological doses of melatonin can inhibit the development and/or growth of a wide variety of murine tumours (i.e. chemically induced, transplantable, spontaneous) and human cancer xenografts. The mechanisms by which these tumour inhibitory effects are exerted are not totally clear but in some cases may involve the inhibition of tumour linoleic acid uptake and metabolism as well as direct oncostatic, immune enhancing, and/or free-radical/antioxidant actions (Blask, 1993, 2001; Blask *et al.*, 2002, 2005a).

In most of these in-vitro studies, ER+ MCF-7 human breast cancer cells were cultured for several days in the presence or absence of melatonin, usually at a high physiological concentration of 1 nM. Depending on the study, the robustness of melatonin's oncostatic effects could be quite variable ranging from 80% to less than 20% inhibition of cell proliferation. In several investigations involving either human MCF-7 human breast cancer, neuroblastoma, uveal melanoma or murine colon carcinoma cells, the dose–response to melatonin exhibited a bell-shaped pattern with the most robust antiproliferative effects occurring in nocturnal physiological range (Blask *et al.*, 2002). In a small number of studies, no oncostatic effects of melatonin were reported in the physiological range on MCF-7 cells or on several other human cancer cell lines (human cervical carcinoma [Hela], osteosarcoma [MG-63] and lymphoblastoid [TK6]) while cytotoxic effects were observed at pharmacological levels (Panzer *et al.*, 1998; Baldwin & Barrett, 1998; Baldwin *et al.*, 1998). These discrepancies were most likely due to the use of different culture conditions as well as subclones of cells with lower sensitivity to melatonin (Bartsch & Bartsch, 1981; Bartsch *et al.*, 2000).

The oncostatic action of melatonin at physiological concentrations, particularly on ER+ MCF-7 human breast cancer cells *in vitro*, encompasses a variety of molecular and cellular mechanisms, some of which involve the inhibition of the mitogenic action of hormones and growth factors, most notably estradiol (E2), epidermal growth factor, and prolactin. Major effects of physiological concentrations of melatonin on the cellular biology and cell-cycle control of ER+ MCF-7 cells include a slowing of the progression of cells from the G0-G1 phase of the cell cycle to the S phase (DNA synthetic phase) with a resultant lengthening of the transit time through the cell cycle. Evidence indicates that this is accomplished by a melatonin-induced increase in the expression of the tumour suppressor gene *TP53* which in turn activates p21WAF1 protein expression leading to eventual cell-cycle arrest via inhibition of the ability of cyclin-dependent kinases to phosphorylate the retinoblastoma protein (Rb). Additionally, melatonin inhibits DNA synthesis in that reduced proportion of MCF-7 cells that progress to the S phase of the cell cycle (Sánchez-Barceló *et al.*, 2003). While evidence indicates that pharmacological concentrations of melatonin can induce apoptosis in cancer cells, there is no convincing experimental evidence that programmed cell death is activated at physiological levels of this indoleamine (Cos *et al.*, 2002).

In addition to its oncostatic effects, melatonin is able to reduce the invasive and metastatic properties of MCF-7 cells *in vitro*. This appears to be mediated, in part, by a melatonin-induced upregulation in the expression of cell surface proteins E-cadherin and β1-integrin (Cos *et al.*, 1998). Melatonin at physiological levels can increase gap-junction-mediated intercellular communication between MCF-7 cells in culture (Cos & Fernández, 2000) and cause alterations in the cytoskelelal arrangements of ER+ T-47D human breast cancer cells in culture (Matsui & Machado-Santelli, 1997).

Melatonin exerts a major role as an antiestrogen in ER+ human breast cancer cell proliferation by suppressing the activity of the estrogen growth response pathway (Hill *et al.*, 1992). In MCF-7 cells in particular, the molecular mechanisms of this antiestrogen action centre around the fact that melatonin downregulates the transcription of ERα, prevents estrogen-dependent transcriptional activation by destabilizing the E2-ER complex from binding to the estrogen-responsive element of DNA via antagonism of calmodulin interactions with ERα, and by blocking E2-induced upregulation of cyclin D1 expression (Molis *et al.*, 1994; Rato *et al.*, 1999; del Río *et al.*, 2004; Cini *et al.*, 2005). Melatonin does not bind to ERα nor does it interfere with the binding of E2 to the ligand-binding domain of ERα. These molecular events mediating melatonin's oncostatic actions through suppression of the activity of the estrogen-response pathway appear to involve the MT1 melatonin receptor suppression of cAMP production as well as calmodulin antagonism (Ram *et al.*, 2002; Kiefer *et al.*, 2002; Rato *et al.*, 1999).

(b) Melatonin, aromatase and telomerase

In-vitro and in-vivo studies have examined the influence of melatonin, either at nocturnal physiological circulating concentrations or pharmacological doses, on the local biosynthesis of estrogens from androgens via modulation of aromatase activity by ER+ MCF-7 human breast cancer cells (Cos *et al.*, 2005) or dimethylbenzanthracene (DMBA)-induced rat mammary cancers (Cos *et al.*, 2006), and the impact on cell proliferation and tumour growth. Melatonin downregulated aromatase expression at the transcriptional level in MCF-7 cells and reduced aromatase activity in both MCF-7 cells and DMBA-induced rat mammary tumours resulting in a diminished rate of tumour cell proliferation and growth. This anti-aromatase action of melatonin is mediated via the MT1 melatonin receptor (González *et al.*, 2007).

Melatonin at physiological nocturnal circulating levels and pharmacological concentrations inhibits both the expression and activity of telomerase in MCF-7 human breast cancer cells in culture, and in xenografts in female nude mice. Telomerase, an enzyme responsible for the elongation of telomeres at the ends of chromosomes, is activated in most human cancers. Melatonin appears to regulate telomerase mRNA expression via both membrane and nuclear melatonin-receptor-mediated mechanisms (Leon-Blanco *et al.*, 2003, 2004).

(c) Effects of melatonin on sex hormones

In animals, the effects of physiological levels of melatonin, either endogenously produced or exogenously administered, on reproductive hormones (pituitary gonadotrophins, prolactin, gonadal steroids) are well known, particularly in animal species that breed seasonally (Goldman, 1999, 2001). In these animals, melatonin can exert either inhibitory, stimulatory or modulatory effects on these hormones depending upon the species and situation.

In humans, the situation is more problematic. While low pharmacological doses of melatonin administered to human subjects over the course of several days to a few weeks had no effect on either pituitary or gonadal hormones (Arendt, 1985; Wright *et al.*, 1986; Luboshitzky *et al.*, 2000; Arendt, 1995), extremely high doses of melatonin produced a slight reduction in blood levels of pituitary gonadotrophic hormones (Voordouw *et al.*, 1992). As part of a contraceptive study, the administration of large oral doses of melatonin (300 mg) on a daily basis for 30 days to young adult women with normal menstrual cycles, caused significantly decreased mean circulating levels of luteinizing hormone (LH), estradiol and progesterone compared with non-treated controls, possibly through mechanisms dependent on (i.e. enhanced) or independent of steroid negative feedback (Voordouw *et al.*, 1992). On the other hand, much lower doses of oral melatonin (3 mg) enhanced LH and follicle-stimulating hormone (FSH) levels in response to a gonadotropin-releasing hormone (GnRH) challenge during the follicular but not luteal phase of the menstrual cycle (Cagnacci *et al.*, 1995a). Pharmacological levels of melatonin (2–5 mg) have been demonstrated to stimulate prolactin secretion into the blood following oral administration in adult men and women (Terzolo *et al.*, 1993; Kostoglou-Athanassiou *et al.*, 1998) whereas in another study, it had no effect at this dose range (Terzolo *et al.*, 1990).

(d) Melatonin, free radical scavenging and antioxidation

The role of free radicals in oncogenesis encompasses the initiation, promotion and progression stages of tumour development and growth. For example, the exposure of normal somatic cells to chemical carcinogens can generate free radicals that can cause DNA damage that, in turn, may lead to the initiation of cancer. DNA mutations caused by free radicals may become fixed as a consequence of a wave of clonal expansion due to the relative growth advantage that new mutations confer on cells. Additional genomic instability induced by faulty cell division or defective DNA-repair mechanisms may further increase the rate of tumorigenic mutations. Moreover, free radicals and other reactive oxygen species may provide additional stimulation of signal transduction mechanisms that may lead to enhancement of cell proliferative and survival mechanisms (Marte, 2004). While there is no question that melatonin at pharmacological concentrations has potent direct free radical scavenging effects, the role of physiological levels in free radical scavenging remains controversial (Reiter *et al.*, 2001). At

pharmacological levels, melatonin pretreatment substantially reduces the formation of DNA damage in liver tissue in rats caused by the chemical carcinogen safrole, implying that these levels of melatonin have the potential to prevent the initiation of hepatic carcinogenesisby reducing free radical-induced DNA damage. In pinealectomized rats, a further increase in DNA-adduct formation over pineal-intact controls was observed, indicating that the endogenous physiological melatonin signal confers a degree of partial protection against free-radical-induced nuclear DNA damage, and in doing so, may reduce the probability of cancer initiation (Reiter, 2001). Physiologically relevant melatonin levels have been reported to upregulate endogenous antioxidant enzyme systems such as glutathione (GSH) peroxidase, γ-glutamylcysteine-synthetase, the rate-limiting enzyme responsible for GSH synthesis as well as GSH levels, and superoxide dismutase (Blask *et al.*, 1997; Hardeland, 2005). In the case of the enzyme for GSH synthesis, this upregulation appears to be mediated via a mechanism mediated by the melatonin receptor (Hardeland, 2005). Not only do physiological concentrations of melatonin markedly elevate total GSH concentrations in MCF-7 human breast cancer cells, but adequate intracelluar levels of GSH appear to be an absolute requirement for the oncostatic action of melatonin in these cells *in vitro*. Furthermore, ER– HS578T human breast cancer cells that are ordinarily insensitive to the oncostatic action of physiological melatonin concentrations can be coerced into responding to melatonin by raising intracellular GSH levels (Blask *et al.*, 1997). Paradoxically, physiological levels of melatonin have been shown to actually enhance the production and release of reactive oxygen species into the incubation medium by human monocytes co-cultured with human cancer cell lines. This resulted in increased lethality to the cancer cells, indicating a beneficial pro-oxidant effect for melatonin (Morrey *et al.*, 1994).

4.2.2 *Circadian genes and cancer: possible mechanisms*

(a) Genetic determinants of circadian rhythms

Although the daily oscillation of physiological and behavioural processes in plants and animals were observed thousands of years ago, it wasn't until the 1960s that such oscillating rhythms were found to be regulated genetically (Pittendrigh, 1967). The first circadian gene, *Period*, was cloned from fruitflies in the mid-1980s (Bargiello *et al.*, 1984; Reddy *et al.*, 1984). Since then, rapid advances in the field of circadian biology have revealed that these clocks are operated by numerous gene products that function in interacting feedback loops in all species studied. Biological clocks provide organisms with a survival advantage, by organizing their behaviour and physiology around cyclic changes in the environment.

At the time of writing, nine core circadian genes have been identified: *Clock* (King *et al.*, 1997), casein kinase I epsilon (*CSNK1E*) (Takano *et al.*, 2000), cryptochrome 1 (*CRY1*), cryptochrome 2 (*CRY2*) (Hsu *et al.*, 1996), Period 1 (*PER1*), Period 2 (*PER2*), Period 3 (*PER3*) (Shearman *et al.*, 1997; Tei *et al.*, 1997), neuronal *PAS* domain protein 2

(*NPAS2)* (Reick *et al.*, 2001), and aryl hydrocarbon receptor nuclear translocator-like (*ARNTL*) (also referred to as brain and muscle Arnt-like protein-1, *BMAL1*) (Hogenesch *et al.*, 1998; Honma *et al.*, 1998). The three *PER* genes encode PER–ARNT–Single-minded protein (*PAS*)-domain proteins that function as surfaces allowing heterodimerization among different clock proteins. The *CLOCK* and *BMAL1* genes encode basic–helix–loop–helix (*bHLH*)-*PAS* transcription factors. *NPAS2* is a paralogue of the transcription factor *CLOCK*, which is a major player in the SCN. The human *CRY* genes encode proteins similar to plant blue-light receptors within class I photolyases. A common feature of these circadian genes is that the levels of mRNAs and proteins that they code for, with the exception of those coded for by *CLOCK* and *CSNK1E*, oscillate throughout a 24-hour period (Reppert & Weaver 2001).

(b) Circadian genes and clock control

The circadian system is divided into two parts, the central pacemaker and the peripheral clocks. The mammalian circadian clock contains three components: input pathways, the central pacemaker, and output pathways. The input pathways transmit information from environmental cues to the central pacemaker. The central pacemaker synchronizes with the environment to generate endogenous rhythms. The output pathways convert the instructions from the central pacemaker into daily oscillations in various physiological and behavioural processes (Hastings, 2000; Hastings & Herzog, 2004; Fu & Lee, 2003). The central pacemaker in mammals resides in the SCN of the anterior hypothalamus. The SCN is composed of multiple, single-cell circadian oscillators that can generate coordinated circadian outputs when synchronized (Welsh *et al.*, 1995; Liu *et al.*, 1997).

A model of transcription-translation feedback loops of circadian genes has been proposed to explain the molecular clockwork of the mammalian central pacemaker (Reppert & Weaver, 2001, 2002; Young & Kay, 2001). At the molecular level, the circadian clock is organized as positive and negative feedback loops based on transcription-translation. The positive components of the loops are CLOCK (or NPAS2) and BMAL1, which form a heterodimer that regulates the expression of genes containing E-box regulatory segments in their promoter regions (Reppert & Weaver 2001; Fu *et al.*, 2002). This heterodimer directly induces the genes coding for the *PERs* and *CRYs*, which constitute the major components of the negative feedback loop. An additional level of regulation within the positive feedback loop is provided by *REV-ERBα*, which controls cyclic *BMAL1* expression (Preitner *et al.*, 2002). The CLOCK–(or NPAS2–)BMAL1 complex also regulates the expression of multiple other clock-controlled genes, either directly or indirectly.

Similar interacting loops of core circadian gene products regulate circadian rhythms in peripheral tissues. The “peripheral clocks” are regulated by the SCN pacemaker, through both the autonomic nervous system and neuroendocrine systems (Bartness *et al.*, 2001; Kalsbeek & Buijs 2002). The rhythmic expression of core circadian genes is observed in most peripheral tissues (Zylka *et al.*, 1998), and can be induced in cultured

fibroblasts (Balsalobre *et al.*, 1998). Ablation of the SCN has been shown to abolish circadian gene oscillation in peripheral tissues as well (Balsalobre *et al.*, 1998; Sakamoto *et al.*, 1998). These findings suggest that the peripheral clocks are either driven or synchronized by the SCN pacemaker. Both the SCN central clock and peripheral tissue clocks regulate cell functions by affecting the expression of clock-controlled genes. Studies have indicated that 2–10% of all mammalian genes are clock-controlled genes (Le Minh *et al.*, 2001; Duffield *et al.*, 2002; Storch *et al.*, 2002).

Recent data also reveals that microRNAs play a key role as regulators of the circadian-timing process. *miR-219–1* is a clock-controlled gene that plays a role in regulating the length of the circadian rhythm. *miR-132* is light-inducible and modulates the phase-shifting capacity of light. Both microRNAs potentially regulate both clock periodicity and clock entrainment (Cheng *et al.*, 2007).

Time information from the central oscillator to the peripheral oscillators is transmitted by neural and humoral stimuli (Schibler *et al.*, 2003; Buijs & Kalsbeek, 2001), which are currently not well characterizedbut among which a secretory product of the pineal gland, melatonin, is thought to play a prominent role. The central oscillator in turn is kept in step ("synchronized") with theperiodic surrounding by the light–dark alteration of the astronomical calendar day. The oscillators in the peripheral tissues are also subject to the entraining (synchronizing) effects of social routine, physical exercise, and food uptake. These secondary synchronizers determining the phase setting of many peripheral oscillators may compete with the lighting regimen, acting over the central oscillator in the SCN in a multifactorial way (Challet & Pévet, 2003). In some tissues, like the liver, the time of food uptake may become the dominant synchronizer and determine the staging of the metabolic rhythms in this organ (Stokkan *et al.*, 2001; Hara *et al.*, 2001). In daily life, circadian rhythms determine the rhythmically varying degree of cognitive functioning and physical strength and dexterity, resulting in predictable timing of best and worst work performance and efficiency. Optimal function of the human body requires a certain sequential and phase-related ordering of the many circadian rhythms extending from the molecular to organismic level.

(c) Circadian gene polymorphisms and circadian disturbance in humans

A limited number of epidemiological studies have examined genetic polymorphisms in clock-related genes and phenotypes such as morning/evening preference and depressive symptoms (Johansson *et al.*, 2003). The T3111C variation of the *CLOCK* gene was first reported by Katzenberg *et al.* (1998) to be associated with morning/evening preference as assessed by the Horne-Ostberg scale (Horne & Ostberg, 1976). A single nucleotide polymorphism located in the 3′ flanking region of the human *CLOCK* gene was demonstrated to be a predictor of diurnal preference in a population-based random sample of 410 normal adults. A smaller study of 105 subjects, however, did not confirm this association (Robilliard *et al.*, 2002). In addition, associations of *PER3* polymorphisms with delayed sleep phase syndrome or diurnal preference have recently been reported (Ebisawa *et al.*, 2001; Archer *et al.*, 2003; Johansson *et al.*, 2003). Archer

et al. (2003) used the Horne-Ostberg scale to examine a *PER3* length polymorphism in which the longer allele was associated with 'morningness' and the shorter allele with 'eveningness'. The shorter allele was also strongly related to delayed sleep phase syndrome, and they reported allele frequencies to be 68% for the shorter allele and 32% for the longer allele. A recent study found that the homozygous *PER3* longer allele (5/5) had a considerable effect on sleep structure and waking performance (Viola *et al.*, 2007). Rapid eye movement (REM) sleep was increased in *PER3* (5/5) compared to *PER3* (4/4) individuals. In addition, the decrement of cognitive performance in response to sleep loss was significantly greater in the *PER3* (5/5) individuals. By contrast, the circadian rhythms of melatonin, cortisol, and peripheral *PER3* mRNA expression were not affected. These findings show that this polymorphism in *PER3* predicts individual differences in the sleep-loss-induced decrement in performance, and the differential susceptibility may be mediated by its effects on sleep homeostasis. Johansson *et al.* (2003) examined a single nucleotide polymorphism in the *PER3* gene (*647 Val/Gly*) in a Swedish population and their results showed a significant association between this *PER3* genetic variation and diurnal preference.

(d) Circadian genes: potential tumour suppressors

A novel role of circadian genes in tumorigenesis comes from discoveries demonstrating that the circadian clock may function as a tumour suppressor at the systemic, cellular and molecular levels through its involvement in cell proliferation, apoptosis, cell cycle control, and DNA-damage response.

(i) *Regulation of cell cycle and apoptosis*

The cell cycle is regulated by an internal circadian clock. In cells of peripheral tissues, the circadian clock controls cell proliferation and apoptosis by regulating the expression of circadian-controlled genes. The circadian clock mechanism is directly involved in the regulation of cell division (Reddy *et al.*, 2005; Lee, 2005; Gery *et al.*, 2006). Studies have shown that about 7% of all clock-controlled genes identified in rodents regulate either cell proliferation or apoptosis (Kornmann *et al.*, 2001; Akhtar *et al.*, 2002; Duffield *et al.*, 2002; Panda *et al.*, 2002). These clock-controlled genes include c-*Myc* and *Mdm2*, the tumour-suppressor genes *Tp53* and *Gadd45a*, as well as genes that encode the caspases, cyclins, transcription factors, and ubiquitin-associated factors that are involved in regulating the cell cycle and apoptosis. In humans, the rhythmic expression of several cyclins and the tumour-suppressor p53 are also regulated by the circadian clock (Bjarnason *et al.*, 1999). Moreover, the expression patterns of these clock-controlled genes are synchronized with the circadian oscillation patterns of *PER1* and *BMAL1* expression in the same tissue (Bjarnason *et al.*, 2001). The *Per2* gene may also play an important role in tumour suppression by inducing apoptotic cell death by enhanced pre-apoptotic signalling and attenuated anti-apoptotic processes (Hua *et al.*, 2006).

(ii) *Modulation of cell proliferation*

In addition to controlling the expression of cell-cycle genes and tumour-suppressor genes at the transcriptional and post-transcriptional levels, the core circadian genes are also involved directly in modulating the intracellular signalling pathways that regulate cell proliferation. It has been shown that a core circadian regulator, *CSNK1E* also functions in promoting cell proliferation by stabilizing β-catenin (Lee *et al.*, 2001). β-Catenin can interact with transcription factors of the T-cell-specific transcription factor/lymphoid enhancer factor-1 family to regulate transcription (van de Wetering *et al.*, 2002), and promote tumorigenesis (Morin, 1999).

(iii) *Control of the cell-cycle checkpoint*

Whether the circadian clock and the cell-cycle clock are connected *in vivo* was subject to debate until a recent study of a mouse model demonstrated that apoptosis induced by γ-radiation is dependent on circadian time in both wild-type and *Per2*-mutant thymocytes (Fu *et al.*, 2002). Specifically, when irradiated at the early stage of the active phase or at the early stage of resting phase, *Per2*-mutant thymocytes show a G2/M-specific resistance to radiation-induced apoptosis. Therefore, the circadian clock not only regulates the expression of cell-cycle genes but could also be involved in controlling cell-cycle checkpoint function.

(iv) *Response to DNA damage*

Studies from animal models have also shown that the core circadian genes can respond directly to γ-radiation. However, disruption of the *Per2* gene stops the response of all core circadian genes to γ-radiation (Fu *et al.*, 2002), suggesting that the molecular clock itself can be modulated by genotoxic stress in peripheral tissues. The ability of circadian genes to mediate the DNA-damage response seems to be cell autonomous, since *Per2*-mutant thymocytes have been shown to attenuate p53-induction in response to γ-radiation *in vitro*. *Per2*-mutant mice also show altered cell division, increased sensitivity to ionizing radiation with impaired DNA repair, and development of malignancies (Fu *et al.*, 2002; Matsuo *et al.*, 2003). Besides γ-radiation, it has also been shown that the clock genes can respond to low levels of ultraviolet irradiation in cultured human keratinocytes (Kawara *et al.*, 2002). *Per1* also plays an important role in regulating growth and DNA-damage control, and it interacts with proteins in the cell-cycle pathway (Gery *et al.*, 2006).

The findings that circadian genes are involved in cancer-related biological pathways such as cell-cycle control and DNA repair support the assumption that disturbances in circadian oscillator functions may increase the risk of carcinogenesis in a variety of tissues. Animal experiments also suggest the genetic circadian oscillator system may be involved in carcinogenesis. These reports have justifiably raised widespread health concerns.

(e) Loss of circadian gene functions in tumorigenesis

In animal models, mice with disruptions in the core circadian gene *Per2* have recently been shown to display salivary-gland hyperplasia and develop spontaneous lymphoma (Fu *et al.*, 2002). It is likely that deregulation of multiple molecular pathways contribute to the cancer-prone phenotype of the *Per2*-mutant mice. Deregulation of the *Myc*-mediated growth-regulatory pathway is proposed to be one possible mechanism by which disruption of the circadian clock could promote tumour formation. Zheng *et al.* (1999) constructed a mouse in which there was a deletion mutation in *Per2*, resulting in a shorter circadian period (~22 hours). Fu *et al.* (2002) reported that this mouse was also more susceptible to radiation-induced tumours, and showed reduced apoptosis in thymocytes. This mouse showed temporal deregulation of *cyclin D1*, *cyclin A*, and c-*Myc*. Moreover, the disruption of circadian rhythms in mice is associated with accelerated growth of malignant tumours, suggesting that the host circadian clock may play an important role in endogenous control of tumour progression (Filipski *et al.*, 2002).

In humans, direct evidence has demonstrated an association between the loss of human PERIOD (hPER1 and hPER2 and hPER3) function and human breast and human endometrial cancer. One study showed that ~95% of breast tumours (53 out of 55 specimens) displayed no or deregulated levels of PER1, PER2 or PER3 proteins in the breast tumour cells when compared to the adjacent normal tissue (Chen *et al.*, 2005). In another study, it was also observed that the loss of PER1 protein was common in human endometrial carcinoma but not in the adjacent normal cells (Yeh *et al.*, 2005). Chen *et al.* (2005) further suggested that the loss of clock-gene expression was linked to DNA-methylation of clock-gene promoters rather than genetic mutations of the clock genes (see paragraph below). A recent study also showed a downregulation of PER1 in human breast and lung cancer tissue (Gery *et al.*, 2006). It was suggested that altered PER expression, resulting in the disruption of normal circadian clock control, may benefit the survival of cancer cells and promote carcinogenesis.

(f) Epigenetic alterations of circadian genes in cancer tissue

The expression level of a gene can be dramatically influenced by the methylation status of its promoter region, and alterations in global methylation patterns have been associated with cancer development. Similarly, changes in circadian gene methylation patterns have also been observed in cancer tissue. One study revealed disturbances in the expression of the three period genes in over 95% of breast cancer cells when compared to non-cancerous cells (Chen *et al.*, 2005). Promoter methylation of *PER1*, *PER2*, and/or *CRY1* was detected in one-third of endometrial cancers compared to one-fifth of non-cancerous endometrial tissues (Shih *et al.*, 2006). The expression levels of *PER1*, *PER2*, *PER3*, *CRY1*, *CRY2* and *BMAL1* were also significantly impaired for those having chronic myeloid leukaemia, and the promoter region of *PER3* was found to be methylated in all of these leukaemia patients (Yang *et al.*, 2006). Microarray analysis also identified *PER1* as being expressed at lower levels in non-small cell lung cancer tissue compared to

normal tissue, and artificially induced expression of *PER1* in non-small cell lung cancer cell lines resulted in a significant reduction in growth. It is believed that DNA hypermethylation and histone H3 acetylation are potential mechanisms for this silencing of *PER1* expression (Gery *et al.*, 2007).

(g) Evidence from genetic association studies in humans

The human *PER*3 gene was the first circadian gene to be linked to increased risk of breast cancer in a genetic association study (Zhu *et al.*, 2005). The *PER*3 gene, which is a central component of the clockwork mechanism, contains a polymorphic repeat region comprised of four or five copies of a 54 bp repetitive sequence in exon 18. This length variation results in the insertion/deletion of 18 amino acids and has been found to be associated with delayed sleep phase syndrome and diurnal preference (Ebisawa *et al.*, 2001; Archer *et al.*, 2003). A case–control study found that the variant genotypes (heterozygous + homozygous 5-repeat alleles) were associated with an increased risk of breast cancer among premenopausal women (OR, 1.70; 95% CI: 1.00–3.0) (Zhu *et al.*, 2005).

NPAS2, the largest circadian gene, is a member of the basic helix–loop–helix-PAS class of transcription factors. *NPAS2* forms heterodimers with *BMAL1*, which transcriptionally activates *PER* and *CRY* expression, which are required for maintaining biological rhythms in many organisms (Vitaterna *et al.*, 1994; Bunger *et al.*, 2000). The *NPAS2* gene is very conserved, with only one missense mutation (SNP database accession No. rs2305160, *Ala394Thr* located in alternative exon 22), listed in the NCBI SNP database. A recent breast cancer case–control study found that women with the heterozygous *Ala394Thr* genotype had a significantly reduced breast cancer risk compared to those with homozygous *Ala394Ala* (OR, 0.61; 95%CI: 0.46–0.81) (Zhu *et al.*, 2008). Furthermore, this protective role was more evident in premenopausal women (OR, 0.44; 95%CI: 0.27–0.77) than in postmenopausal women (OR, 0.65; 95% CI: 0.49–0.91). This is the first piece of evidence demonstrating an association between *NPAS2* and human breast cancer.

The same polymorphism (rs2305160, *Ala394Thr*) in the *NPAS2* gene has also been genotyped in another population-based case–control study of non-Hodgkin lymphoma (Zhu *et al.*, 2007). These results demonstrated that risk of non-Hodgkin lymphoma was significantly reduced among individuals with the heterozygous Ala/Thr genotype (OR, 0.69; 95%CI: 0.53–0.90), the homozygous variant *Thr/Thr* genotype (OR, 0.55; 95%CI: 0.36–0.85), and both variant *Thr* genotypes combined (*Ala/Thr* & *Thr/Thr*) (OR, 0.66; 95%CI: 0.51–0.85), when compared to those with the homozygous *Ala/Ala* genotype. Similar reduced risks were detected for B-cell lymphoma and its two major subtypes: B-cell chronic lymphocytic leukaemia/prolymphocytic leukaemia/small lymphocytic lymphoma, and follicular lymphoma. Previous studies have shown that disruption of circadian rhythm may cause disordered immune responses such as aberrant immune cell trafficking and abnormal cell proliferation cycles (Mormont & Lévi, 1997; Vgontzas & Chrousos, 2002). Given the established association between immune

dysregulation and non-Hodgkin lymphoma (Filipovich *et al.*, 1992), the observed role of the circadian genes in lymphomagenesis could be explained by their impacts on immune activity.

(h) Expression of circadian genes

Mammalian circadian oscillators were originally believed to exist only in neurons of the SCN (Ralph *et al.*, 1990). However, with the identification of the mammalian clock and clock-controlled genes, this view has changed dramatically. Circadian oscillators have been uncovered in both central and peripheral tissues, with the SCN presumed to coordinate cyclic gene expression in the periphery by neural and/or humoral signals (Balsalobre *et al.*, 2000; Kramer *et al.*, 2001; Le Minh *et al.*, 2001; McNamara *et al.*, 2001; Cheng *et al.*, 2002). Robust daily oscillations in gene expression could be detected in almost all investigated tissues (Schibler *et al.*, 2003). These daily cycles were believed to be the result of cyclic humoral or neuronal signalling from the SCN. However, the autonomy of peripheral oscillators is now under debate as peripheral tissues explanted and maintained in culture demonstrate continued oscillation of *Per2* for up to 20 days, and SCN lesioning does not abolish this circadian oscillation (Yoo *et al.*, 2004). Moreover, the mechanisms of regulation of peripheral clocks and indeed, their function, remain largely obscure. Furthermore, disturbances in the expression of the three *PER* genes (*PER*1, *PER*2, and *PER*3) have been detected in human breast cancer cells in comparison with nearby non-cancerous cells (Chen *et al.*, 2005). Because the circadian clock controls expression of cell-cycle-related genes, it was suggested that altered *PER* gene expression may result in the disruption of the control of the normal circadian clock, hence benefit the survival of cancer cells, and promote carcinogenesis.

(i) Light exposure and circadian gene expression

Light is the most powerful circadian synchronizer among all environmental cues (Lucas *et al.*, 2001; Wright & Czeisler, 2002). The molecular mechanisms involved in synchronization to light have been demonstrated in previous experiments. For example, both *Per1* and *Per2* could be induced in SCN tissue by light exposure in mice (Albrecht *et al.*, 1997). In the SCN of wild-type mice, light exposure also evoked a transient interaction between Protein Kinase C α and Per2 proteins that affects Per2 stability and nucleocytoplasmic distribution (Jakubcakova *et al.*, 2007). Using oral mucosa samples, a recent study showed that the induction of human *PER*2 expression was stimulated by exposing subjects to 2 hours of light in the evening (Cajochen *et al.*, 2006). The increase in *PER*2 expression relative to a non-light control condition was statistically significant after exposure to light at 460 nm (blue), but not after exposure to light at 550 nm (green). The authors concluded that the non-image-forming visual system is involved in human circadian gene expression (Cajochen *et al.*, 2006).

(j) The human time structure and its alteration by phase shift

The temporal organization of the human body has to be understood to appreciate the impact of night work and shiftwork upon worker health and well-being. The human body has not only a structure in space, as expressed by its gross and microscopic anatomy, but it has a structure in time, as expressed by rhythms of numerous frequencies superimposed upon linear trends associated with development and aging (Touitou & Haus, 1992). The rhythmic variations encountered vary in period from milliseconds, e.g. in individual nerve cells, to minutes or hours (ultradian rhythms) to 24 hours (circadian rhythms), and to longer periods, such as the menstrual cycle in women, and yearly cycles (circannual rhythms) in both men and women (Haus & Touitou, 1992; Hildebrandt *et al.*, 1998).

Rhythms of a person, synchronized to diurnal activity by the ambient light–dark cycle and social routine, must undergo phase readjustment when forced to adhere to a new activity–sleep schedule due, for example, to night work or geographic displacement across several time zones. The central and peripheral oscillators will follow the new schedule, not immediately however, but over a certain number of transient cycles, to adapt to the changed phase of the environmental synchronizer. During this time of adaptation, disruption of the usual sequence and biological order of the numerous rhythmic events takes place with some clock genes responding faster than others. The result is an internal phase desynchronization within the oscillator mechanism (Sakamoto & Ishida, 2000; Nagano *et al.*, 2003; Nakamura *et al.*, 2005). The circadian oscillators in the anterior region of the SCN undergo a faster time adaptation than those in the posterior portion (Nagano *et al.*, 2003; Nakamura *et al.*, 2005). During the re-adjustment period, desynchronization occurs within the oscillators as well as among different oscillatory tissues and brain regions that re-adjust their phases at different rates (Stokkan *et al.*, 2001; Abe *et al.*, 2002; Nagano *et al.*, 2003). Within the oscillators, after a shift in the light–dark regimen, there is a faster shift of *Per1* and *Per2* oscillator genes and a slower shift of *Cry1*, another component of the oscillator mechanism (Reddy *et al.*, 2002). In the molecular oscillator mechanism, as in the organism as a whole, there is a difference in response with different directions of the phase shift. Phase advances (earlier timing) of the lighting schedule lead to a more prolonged desynchronization within the SCN than do phase delays (Nakamura *et al.*, 2005). Also *Per1* and *Per2* genes have been found to behave differently during advancing and delaying phase shifts (Yan & Silver, 2002; Albrecht *et al.*, 1997). Moreover, the phase-shifting kinetics of circadian rhythms in transcriptional activity show region-specific differences (Nagano *et al.*, 2003; Nakamura *et al.*, 2005), with different tissues exhibiting different resetting behaviour than the SCN or behavioural rhythms (Abe *et al.*, 2002). The adaptation of the peripheral oscillators is independent – in part – of the hypothalamic control (Stokkan *et al.*, 2001). Thus, during the phase-resetting process, internal desynchronization is manifested within the individual oscillators and simultaneously also between central and peripheral oscillators. In the absence of hypothalamic control and synchronization, peripheral oscillators of diverse tissues cycle with different periods; thus, during the process of adaptation, they express

different phases and changed phase relations. The unique circadian phase and period values expressed by each tissue suggest that the quantitative properties of the circadian oscillators in each tissue are unique and tissue-specific (Yoo *et al.*, 2004) and/or may be the expression of different synchronizing mechanisms acting upon different tissue oscillators (Lakatua *et al.*, 1975, 1983, 1988). The overall effect of a phase shift of this nature is alteration at several hierarchical levels of the internal time organization during the transitional duration of adjustment. For example, the top physical efficiency that is typically observed in the afternoon becomes delayed into the night time. The propensity to sleep, which is the expression also of a circadian rhythm, may be high during the environmental time that requires alertness and efficiency, and it may be low during the time reserved for rest, resulting in insomnia and non-restorative sleep. During adaptation, this external and internal desynchronization of the human organism leads to a functional disturbance of the time organization ("dyschronism"), with loss in performance efficiency plus the expression of a set of symptoms, similar to those of jet lag (Hildebrandt *et al.*, 1974; Harris, 1977; Ribak *et al.*, 1983; Folkard & Akerstedt, 2004; Folkard & Lombardi, 2004).

In this context, it is important to understand that a circadian phase shift: (1) affects all metabolizing and proliferating cells in the organism; (2) leads to transient internal desynchronization on a molecular basis within the individual cellular oscillators; (3) results in desynchronization among the cellular oscillators in the SCN and peripheral tissues; (4) is not immediate but requires time (days) for complete adjustment, occurring over several transient cycles; and (5) varies by variable and function in the amount of time required for phase adaptation and, with regard to cell and tissue proliferation, may extend over several weeks' time.

A circadian phase shift exerts its effects upon molecular cell and tissue physiology and occurs over an extended period during which the time sequence of the biological rhythms of many variables is different from that found in day–night-adapted individuals, i.e. the circadian time organization which is thought to be linked to optimal function (Touitou & Haus, 1992, Winget *et al.*, 1992; Monk, 1992; Mormont & Waterhouse, 2002). Changes in the neuroendocrine web, controlling cell and tissue proliferation during the internally desynchronized span of phase adaptation, may permit or even promote growth of abnormal cell proliferation in target tissues that find themselves out of phase with their usual controlling influences.

(k) Summary

Exposure to artificial light during the night may disrupt circadian gene function in the SCN, which in turn may alter circadian-regulated biological pathways, such as cell-cycle regulation and DNA repair. The impact of artificial light on the circadian pacemaker might be modified by genetic variants of the core circadian genes, although such gene–environment interactions have yet to be explored. Given the roles of circadian genes in tumorigenesis, the light-mediated dysfunction of circadian genes may provide a possible

mechanism for the putative carcinogenic effect of light, which may or may not involve melatonin.

4.2.3 *Melatonin as part of the neuroendocrine immune axis*

Pineal melatonin plays an important part in the neuro-immune-endocrine web regulating mammalian immune defenses. Immune functions in different species of mammals, including man, show circadian and seasonal variations with enhancement during short days, which correlates with the prolonged duration of the daily secretion of melatonin (Nelson & Drazen 2000).

However, in addition to the circadian and seasonally periodic pineal melatonin, the recent observations on the synthesis of melatonin by immune-competent cells in different parts of the immune system suggest a role for locally produced melatonin in the regulation of the immune response. The presence of melatonin and the mechanisms for melatonin-synthesis in many peripheral tissues raises questions about the function of the peripherally produced and/or stored melatonin. There are questions about potential release of this peripheral melatonin into circulation and about its potential participation in circadian system regulation. The relationship of the peripherally formed melatonin to the circadian timekeeping system and its disruptions has not been widely explored, but will be of interest since the same immune-competent cells carry the circadian oscillator genes, and are subject to multifrequency time regulation.

(a) Observations in animals

(i) *Pinealectomy – surgical and functional*

Surgical and functional pinealectomy by continuous bright light exposure led to abnormal development of the immune organs of mammals and birds (Vaughan *et al.*, 1987; Janković *et al.*, 1994). Impairment of different aspects of the immune response after pinealectomy was reported in rats (Liebmann *et al.*, 1996; Molinero *et al.*, 2000; Beskonakli *et al.*, 2001), in mice (Maestroni *et al.*, 1986; del Gobbo *et al.*, 1989; Vermeulen *et al.*, 1993; Mocchegiani *et al.*, 1996;), other rodents (Haldar *et al.*, 2001), and birds (Rosołowska-Huszcz *et al.*, 1991; Moore *et al.*, 2002; Moore & Siopes, 2003). These defects in immune function could be reversed by the administration of melatonin.

In studies on male Wister rats, constant light which suppresses pineal function and melatonin production induced a 30% depression of the phagocytic ability of blood neutrophils throughout the whole 24-hour cycle without altering its circadian oscillations. It was deduced that the daily dark span serves as synchronizer, and the rhythmic melatonin secretion is involved in the maintenance of the level of phagocytosis and the timing of its circadian rhythm, but does not cause the circadian oscillation as such (Hriscu *et al.*, 2002).

Pharmacological inhibition of melatonin synthesis in mice by the β-receptor antagonist propanolol was shown to be associated with suppressed humoral and cellular

immunological responses (Liebmann *et al.*, 1996). Given before onset of the daily dark span, propanolol markedly decreased primary and secondary antibody formation in Balb/c mice injected with sheep red blood cells (Maestroni *et al.*, 1986; Maestroni & Conti, 1996).

(ii) *Relation to length of daily photoperiod*

The relationship between the photoperiod and various aspects of immune function is stronger with short day lengths (light spans) in diurnal as well as in nocturnal species (Nelson, 2004). There is a correlation between the elevated night time (dark span) melatonin concentrations with the number and response of immunocompetent cells in humans, and in several rodent species (Giordano *et al.*, 1993; Haldar *et al.*, 2001; Prendergast *et al.*, 2003).

(b) Melatonin receptors in immune-competent cells

(i) *Observations in animals*

Immune-competent cells, including splenocytes, lymphocytes and monocytes carry membrane-bound and nuclear receptors. The membrane-bound MT1 high affinity receptor is coupled to G-protein. The lower affinity MT2 receptor binding sites are not bound to G-protein and have a different pharmacological profile. The melatonin actions in the immune system are mainly mediated by the MT1 receptor. The nuclear receptors found belong to the retinoid-related (retinoid Z receptor/retinoid-related orphan receptors) superfamily of nuclear receptors (Dubocovich, 1995; Dubocovich & Markowska, 2005; Nosjean *et al.*, 2000).

(ii) *Observations in humans*

Specific membrane and nuclear receptors were found in peripheral blood lymphocytes and monocytes (Lopez-Gonzalez *et al.*, 1992; Pozo *et al.*, 2004). The Kd values of these receptors suggest that they can recognize physiological concentrations of melatonin in circulating blood at night and endogenous melatonin generated locally by the immune system (Carrillo-Vico *et al.*, 2005).

4.2.4 *The immunomodulatory response to exogenous melatonin*

(a) Observations in animals

Melatonin administration in animals leads to immuno-enhancement at several levels of the immune system ,and in several immune-system-related functions. These actions of melatonin are most pronounced when the animal's immune system is suppressed, e.g. by light exposure or by corticosteroid suppression (Haldar *et al.*, 2004).

Melatonin administration increased the proliferative capacity of mouse splenocytes (Demas & Nelson, 1998) and rat lymphocytes (Martins *et al.*, 1998), and led to an increase in tissue mass of thymus and spleen (Vaughan & Reiter, 1971; Vaughan *et al.*,

1987; Rai & Haldar, 2003). The enhancement by melatonin of mouse splenocytes in response to the T-cell mitogen concanavalin A was blocked by the administration of luzindole, a high-affinity melatonin receptor antagonist. Luzindole also reduced the ability of splenocytes to proliferate during the daily dark span (night) when endogenous melatonin concentrations are naturally high. This effect was not observed during daytime (light span) when melatonin concentrations are low (Drazen *et al.*, 2001). The authors suggested that melatonin enhancement of splenocyte proliferation was mediated directly by melatonin receptors on splenocytes and also that the circadian rhythm in splenocyte proliferation was mediated by splenic melatonin receptors (Drazen *et al.*, 2001). Melatonin also acts upon the non-specific immune response and leads to an increase in the number of natural killer (NK) cells and monocytes in the bone marrow (Currier *et al.*, 2000), and enhances the antibody-dependent cellular cytotoxicity (Giordano *et al.*, 1993).

Melatonin *in vivo* modulates several cytokines active in immune responses via the regulation of their gene expression and production. Among those that are in mice in splenic and/or peritoneal macrophages: the production of tumour necrosis factor α (TNFα), interleukin-1 (IL-1), major histocompatibility complex-II (MHC-II), macrophage-colony stimulating factor (M-CSF), transforming growth factor β (TGFβ), interferon gamma (IFNγ) and IL-10 (Pioli *et al.*, 1993; Liu *et al.*, 2001; Raghavendra *et al.*, 2001a,b). In rats, melatonin increases the generation of thymosin-α1 via an increase in pro-thymosin-α gene expression (Molinero *et al.*, 2000). Interaction between the effects of melatonin upon the immune system with the opiatergic system have been suggested, as in some studies, naltrexone, a specific opioid antagonist, prevented the immune-stimulatory effects of melatonin. Similar effects were observed with the administration of β-endorphin and dynorphin (Maestroni *et al.*, 1988a, Maestroni, 2001).

(b) Observations in humans

In humans, exogenous melatonin acts upon NK-cell activity (Lissoni *et al.*, 1986) in a biphasic pattern. In diurnally active subjects, resting during the night, melatonin given in the afternoon (15:00) led to a stimulation of NK-cell activity during the first 4 hours, followed by a phase of apparent inhibition, suggesting an ultradian periodicity.

4.2.5 *Retinal/pineal/hypothalamic/pituitary/adrenal interaction*

The relation between the hypothalamic-pituitary-adrenal (Hth-Pit-Adr) axis and the retinal-hypothalamic-pineal (Ret-Hth-Pin) axis are characterized by variables that are rhythmic in several frequencies in each one of these organs (for a review, see Haus, 2007). The optimal function of the mammalian organism depends upon certain time relations between rhythmic variables. In animal experiments, the adrenocorticotropic hormone (ACTH) will elicit a strong adrenal response if given at certain stages of the circadian adrenal cycle in responsiveness when activation of the gland is expected. The response will be substantially less when it is given at other circadian stages both *in vivo* (Haus, 1964) and *in vitro* (Ungar & Halberg, 1962; Sánchez de la Peña, 1993). In this

regard, the extent of the response of the Hth-Pit-Adr axis to stress (e.g. handling of an animal or saline injection) may be out of phase with the activation of the adrenal gland directly by ACTH due to temporal differences in the cycles of responsiveness of the adrenal and of superimposed controls (Haus, 1964). The rhythmic interactions among hormonal stimuli, rhythmic receptor activity, and target organ response imply that a study of an endocrine and neuroendocrine interaction at a certain (single) time represents a snapshot characterizing only that certain time point. Furthermore, the interactions between the variables studied may be quite different quantitatively and even qualitatively a few hours earlier or later. This is the case in environmentally synchronized organisms and much more so during a phase shift of the organism when different variables have a different time course in phase adaptation (Haus & Halberg, 1969; Fève-Montange *et al.*, 1981). The rhythmicity in the variables studied without a chronobiological experimental design has led to many publications that are difficult to interpret or even contradictory. Studies without such an experimental design have to be qualified as valid only for that specific time and constellation of rhythms of the variables studied.

(a) Melatonin receptors in human central nervous system and pituitary

The MT1 melatonin receptor is widely distributed in the human hypothalamus and pituitary. In addition to the SCN, MT1 immunoreactivity was found in numerous sites including the paraventricular nucleus, periventricular nucleus, supraoptic nucleus, and others. The MT1 receptor was colocalized with some vasopressin neurons in the SCN, and with vasopressin and oxytocin neurons in the paraventricular nucleus, and with parvocellular corticotropin-releasing hormone (CRH) neurons in the paraventricular nucleus (Wu *et al.*, 2006).

The colocalization of MT1 and CRH suggest that melatonin might directly modulate the Hth-Pit-Adr axis in the paraventricular nucleus suggesting cross-modulation between the systems at the hypothalamic level, which may have implications for stress reactions and other conditions (Wu *et al.*, 2006).

In the pituitary, strong MT1 expression was observed in the *pars tuberalis* while only weak staining was found in the anterior and posterior pituitary (Wu *et al.*, 2006).

(b) Animal studies on pineal-adrenal interaction

Both the *N*-acetyltransferase activity in the pineal glandwhich is the rate limiting step in melatonin synthesis, as well as adrenal activity are under sympathetic control (Buijs *et al.*, 1999). The rat pineal gland expresses glucocorticoid receptors in a density comparable to the liver (Ballard *et al.*, 1974; Ferreira *et al.*, 2005). The receptors are functional and participate in glucocorticoid-induced effects upon the pineal, which are blocked by the high-affinity glucocorticoid receptor antagonist mifepristone (Gagne *et al.*, 1985). Melatonin binding sites have been identified in the adrenal in rats (Persengiev, 1992), suggesting the existence of a direct interaction between pineal melatonin and adrenal cortex steroid production (Persengiev & Kanchev, 1991).

Glucocorticoids *in vitro* were reported to decrease the norepinephrine-stimulated melatonin secretion in the rat pineal gland (Fève-Montange & Abou-Samra 1983), and to participate in lowering pineal *N*-acetyltransferase activity and melatonin production during stress (Joshi *et al.*, 1986).

In perifusion studies on adult rat pineal glands, corticosterone and dexamethasone, but not deoxycorticosterone, decreased melatonin production in pharmacological doses. Lower concentrations had no effect, regardless of the circadian stage (Zhao & Touitou, 1993). Torres-Farfan *et al.* (2003) studied MT1 melatonin receptors in the adrenal glands of the capuchin monkey, and through sampling at a single time point found inhibition of ACTH-stimulated cortisol production by melatonin. This effect was reversed by the MT1/MT2 antagonist luzindole.

In studying the interaction of the pineal gland with pituitary and adrenal glands *in vitro*, Sánchez de la Peña *et al.* (1983a,b) found in a chronobiological study design that the effect of aqueous pineal gland extracts and of melatonin upon production of corticosterone in the mouse adrenal gland did depend critically upon the circadian stage in which the adrenal glands were harvested. In LD12:12-synchronized B6D2F1 mice, pineal gland extracts harvested at one circadian stage and ACTH 1–17, (an analogue of the natural ACTH pituitary hormone), added *in vitro* to adrenal glands harvested at six different circadian stages showed that, depending upon the circadian stage, when the adrenal glands were obtained, the pineal gland extract or melatonin either stimulated or inhibited or had no effect on adrenal corticosterone production stimulated by ACTH 1–17 (Sánchez de la Peña *et al.*, 1983a, b). The effect of the pineal gland extract or melatonin did depend upon the circadian cycle of responsiveness of the target organ both quantitatively and in direction. The circadian-stage-dependent effect of the pineal gland on the adrenalgland may explain many of the controversial results reported in the literature.

The adrenal androgen dehydroepiandrosterone sulfate (DHEA-S) stimulated melatonin production and secretion by 50–80% in perifused isoproterenol-stimulated rat pineal glands which had been removed during the light phase, while in pineals obtained during the dark span, only the highest doses of DHEA-S increased melatonin secretion, and by only 25% (San Martin & Touitou, 2000). No such effect was observed from dehydroepiandrosterone (DHEA) which is also secreted by the adrenal gland.

In in-vivo studies, a direct inter-relation between the pineal gland and the Hth-Pit-Adr axis could be shown in some models but not in others. DHEA-S, given as single injection in pharmacological doses (500 μg), induced a significant increase in nocturnal pineal gland melatonin content and an increase in *N*-acetyltransferase in Wistar rats, both young and old. DHEA-S or DHEA at lower doses (50 and 250 μg administered acutely) and at doses of 100 μg administered daily over 8 days had no effect (Djeridane & Touitou, 2004). In a strain of mice with the enzymatic mechanisms to produce DHEA, melatonin stimulated DHEA production in ex-vivo adrenal incubates at all stages of the circadian rhythm (Haus *et al.*, 1996). The administration of tryptophan in rats caused a marked rise

in plasma melatonin but had no effect upon corticosterone concentrations (Hajak *et al.*, 1997).

The acute and longer-lasting exposure of rats to stress led to a significant rise in adrenal corticosterone secretion but had no effect upon circulating melatonin levels (Hajak *et al.*, 1997). Some in-vivo models of stress which increase corticosterone secretion such as immobilization (Lynch *et al.*, 1977), forced swimming (Wu *et al.*, 1988) and insulin-induced hypoglycaemia (Tannenbaum *et al.*, 1987) did increase daytime levels of melatonin, and attenuate nocturnal light-pulse inhibition in melatonin synthesis (Funk & Amir, 1999).

In a model of chronic inflammation in rats exposed to Bacillus Calmette-Guérin (BCG), Ferreira *et al.* (2005) reported in Wistar rats kept on an LD12:12 lighting regimen and sampled at the early part of the light span (09:00–11:00) that corticosterone potentiated noradrenaline-induced melatonin and *N*-acetylserotonin production in pineal organ culture in a bell-shaped curve through the action of the glucocorticoid receptor. Glucocorticoids exerted a positive control on the secretion of melatonin by the pineal gland in animals undergoing a chronic inflammation process (Ferreira *et al.*, 2005).

When mice were exposed to competing synchronizers (e.g. light versus time-limited meal feeding), the circadian rhythm in corticosteroids tended to counteract the internal desynchronization between central and peripheral oscillators, and tended to stabilize the internal circadian time organization (Le Minh *et al.*, 2001).

In the more complex models, often both the Ret–Hth–Pin and the Hth–Pit–Adr axes react concomitantly. Inconsistencies and controversial results reported in the literature often may be due to the variable constellations seen in one- or two-point snapshots of two or more high-amplitude rhythmic systems.

(c) Human studies on pineal-adrenal interaction

Glucocorticoid secretion was not modified by either acute or chronic melatonin administration in close to physiological doses (Wright *et al.*, 1986; Waldhauser *et al.*, 1987). No correlation was found between the nocturnal urinary excretion of melatonin and cortisol, either among healthy subjects or among patients with panic disorder (with increased excretion of cortisol) or in insomnia patients (with a high incidence of low melatonin secretion) (Hajak *et al.*, 1997).

The circadian rhythms of cortisol and melatonin are related in their timing within the framework of the day–night-synchronized human time organization with activity during the day, and in free-running blind subjects (Skene *et al.*, 1999). The plasma melatonin concentration begins to rise (melatonin onset) when the cortisol concentration is at its lowest, and peaks when the cortisol concentration begins to rise, it then begins to drop (melatonin offset) when the cortisol concentration reaches its peak (Arendt, 1988; Rivest *et al.*, 1989). In case of a rapid phase shift in shiftwork or travel over time zones, melatonin rapidly follows the light–dark and sleep–wakefulness pattern while cortisol

phase-shifts only slowly over a large number of transient cycles (Fève-Montange *et al.*, 1981).

In clinically healthy men, in samples collected every 30 minutes over 24 hours, the ultradian rhythms of cortisol and melatonin followed ultradian periods of about 8 hours and 5.5 hours, respectively (Rivest *et al.*, 1989), suggesting an intrinsic difference in the mechanism controlling their secretion. Similarly, the cortisol and melatonin response to 24 hours of complete bed rest under dim light was also different.

Cagnacci *et al.* (1995b) administered a high pharmacological dose of melatonin (100 mg) or placebo at 08:00 on two consecutive days to a group of young women (22–32 year of age) in early follicular phase and a group of postmenopausal women (54–62 years of age), and observed gender and age differences in melatonin and cortisol blood concentrations over 48 hours. The postmenopausal group had higher cortisol concentrations than the young group during the daytime (especially at lunch time and early in the evening).

In pituitary- and adrenal-dependent Cushing syndrome with hypercortisolemia patients, the circadian rhythm of melatonin was abolished, and the nocturnal melatonin levels and the integrated 24-hour secretion were significantly lower than in controls (Werner *et al.*, 1981; Soszyński *et al.*, 1989).

In human subjects, melatonin concentrations were markedly reduced after the administration of a low dose (1 mg) of dexamethasone at 22:00 (Beck-Friis *et al.*, 1985). Similar results were reported by Demisch *et al.* (1988). However, a higher dose of dexamethasone (4 mg given during 1 day in a dosage of 1 mg orally at 08:00, 12:00, 18:00 and 00:00) had no significant effect on melatonin concentration (Beck-Friis *et al.*, 1983).

The inhibition of cortisol synthesis with the use of metyrapone resulted in an increase in melatonin urinary excretion (Brismar *et al.*, 1985). No significant difference in cortisol was found during a propanolol-induced decrease in melatonin (Beck-Friis *et al.*, 1983, 1984).

The Hth–Pit–Adr and the Ret–Hth–Pin axes are two major branches of the human time-keeping system and provide time information to peripheral tissues. The two axes behave differently during phase shift and phase adaptation. A direct interaction is suggested by the presence of functional receptors for melatonin in the central nervous system, the pituitary gland, and the adrenal gland. However, these interactions, if they are truly functional, may vary with the circadian stage and the responsiveness of the target tissues. At the time of writing, a consistent relationship has not yet been established and many of the studies reported suffer from a lack of a chronobiological study design, which may be required to obtain meaningful results.

4.2.6 *Melatonin and the neuroendocrine reproductive axis*

Melatonin, as the messenger of darkness in diurnally and nocturnally active species, plays a major role in directing the activity of the reproductive system. It provides input on

the length of the daily dark span, thus indicates the season to the species' neuroendocrine system in the parts of the northern and southern hemisphere where seasonal changes in luminosity occur.

The majority of mammals are seasonal breeders. The role of the pineal gland and of melatonin in controlling mammalian reproduction among seasonal breeders is now well established (e.g. Goldman, 2001). There are differences among different species in the mechanisms elicited by melatonin stimulus, e.g., in the hamster, the reproductive system is inhibited by short photoperiods with a prolonged melatonin signal leading to an anestrous effect in females, and testicular regression in males (Hoffman, 1973; Carter *et al.*, 1982). The anti-gonadal effect of the short photoperiod is prevented by pinealectomy (Reiter 1972, 1980) while gonadal inhibition can be achieved even during long days by the daily injection of melatonin (Stetson *et al.*, 1976). In species like the ewe, the mechanism is different with suppression of the estrous cycle during spring and summer with fertility resumed during autumn and winter (Goldman, 1999, 2001). In this species, there is a different response to the prolonged melatonin signal, leading to a release of gonadotropin (Bittman *et al.*, 1983). Interspecies differences have to be kept in mind if the results of animal experiments are to be applied to humans.

The melatonin effects on the reproductive system in humans and animals appear to take place at several locations, and appear to be receptor-mediated. Melatonin has been shown to exert its reproductive effects at the level of the central nervous system where the presence of melatonin receptors and responsive neurons has been widely demonstrated. Melatonin directly inhibits hypothalamic GnRH pulses (Bittman *et al.*, 1983), and suppresses the pituitary response to GnRH (Martin *et al.*, 1980). However, peripheral actions at the level of the gonads have also been reported. The ovary in experimental animals and humans takes up circulating [3H]melatonin more effectively than most other tissues (Wurtman *et al.*, 1964; Cohen *et al.*, 1978).

(a) Central mechanisms in animal studies

Melatonin exerts its regulatory effects on the reproductive axis predominantly through actions upon the central nervous system (e.g. Glass & Lynch 1981; Lawson *et al.*, 1992; Goldman, 2001). Melatonin binding sites have been demonstrated in numerous areas in the hypothalamus, which are involved in reproductive functions (Migaud *et al.*, 2005; Vaněcek, 1988; Weaver *et al.*, 1989) together with the *pars tuberalis* of the pituitary gland (Morgan, 2000). In sheep, the pre-mammillary hypothalamus was identified as the site where melatonin regulates seasonal reproduction (Malpaux *et al.*, 2001; Lincoln, 2002). In times of reproductive quiescence induced by short photoperiods or melatonin treatment, the pituitary gland remains responsive to exogenous GnRH (Robinson *et al.*, 1986) favouring a mechanism located in the hypothalamus rather than the pituitary gland. Animal experiments have shown that the action of melatonin may be mediated by way of regulating gonadotropin release through effects upon hypothalamic monoamines and GnRH (Martin & Sattler, 1982; Arendt, 1986; Reiter, 1991), and by action at the level of the pituitary gland through cAMP- and Ca2+-dependent mechanisms leading to inhibition

of the pituitary response to GnRH (Martin & Klein, 1976; Vanecek, 1995; Vanecek & Klein, 1995). Control of seasonal prolactin operates via the MT1 receptors of the *pars tuberalis* (Lincoln, 2002, 2006a, b; Lincoln *et al.*, 2003).

In the Syrian hamster, neurons expressing melatonin receptors in the dorsomedial nucleus of the hypothalamus are implicated in the regulation of gonadotropin secretion and gonadal activity (Maywood *et al.*, 1996). In LSH/SsLaK female hamsters, melatonin treatment given approximately one hour before light-off in an L14:D8 regimen decreased significantly the weight of the uterine and pituitary glands, FSH, LH, and prolactin (Lawson *et al.*, 1992). In ovariectomized virgin animals of the same strain, melatonin (25 µg/day subcutaneously) given at the same circadian phase reduced the number of cells expressing estrogen receptor immunoreactivity in the medial preoptic area (Lawson *et al.*, 1992).

At the level of the pituitary gland, melatonin acts in sheep and other photoperiodic animals via MT1 receptors in the *pars tuberalis* to control seasonal prolactin secretion (Morgan, 2000; Lincoln & Clarke, 1994; Hazlerigg *et al.*, 2001). In the *pars tuberalis*, it appears that circadian clock genes provide a molecular mechanism by which melatonin duration is decoded (Lincoln *et al.*, 2002; Lincoln, 2006a). The ovine *pars tuberalis* expresses the core clock genes with a 24-hour rhythm in mRNA levels distinct for each gene and different in timing and amplitude from the clock-gene profiles of the SCN (Lincoln *et al.*, 2002; Hazlerigg *et al.*, 2004). In the *pars tuberalis*, but not in the SCN, the timing of the clock gene rhythms is markedly modulated by photoperiod and manipulation of melatonin (Hazlerigg *et al.*, 2004; Johnston *et al.*, 2006). *Cry1* is controlled in sheep and also in rodents via the MT1 receptor (Hazlerigg *et al.*, 2004; von Gall *et al.*, 2005; Johnston *et al.*, 2005, 2006) with a low amplitude circadian rhythm remaining after melatonin suppression by exposing animals to constant light (Johnston *et al.*, 2006). Under constant light conditions, melatonin was effective at all times in activating *Cry1* expression, but suppressed RNA levels for the other clock genes measured (*Bmal1*, *Per1*, *Per2*, *Rev-erbα*) only at the times when endogenous gene expression was increased (Johnston *et al.*, 2006). A phase-dependence of melatonin action upon the stage of the endogenous rhythms at the level of the target organ may explain many controversial resultsMelatonin onset at dusk activates *Cry1* gene expression (the dusk oscillator) and melatonin offset at dawn activates *Per1* gene expression (the dawn oscillator), and the interval between these events corresponds to the night length, and thus varies with the seasons. The *Per/Cry* interval dictates the level of Per/Cry protein complexes in the *pars tuberalis* cell nucleus achieved during each circadian cycle, and governs the functional output of the *pars tuberalis* (Lincoln, 2006a, b).

(b) Interactions of estrogen with melatonin at the level of the target organs in animal studies

Estrogens stimulate the growth of ER+ breast cancer cells by stimulating the transcription of cell-cycle progression genes, and downregulating the expression of genes that block cell-cycle progression (Métivier *et al.*, 2003; Stossi *et al.*, 2006). Chromatin

remodelling mediated by the estrogen receptor α (Erα) has been suggested as constituting an essential part of mammary tumorigenesis (Sahar & Sassone-Corsi, 2007). Cyclin D1 stimulates mammary growth and in its overexpression leads to mammary tumorigenesis associated with Erα, and enhances its activity by antagonizing the repressor *BRCA1* (Wang *et al.*, 2005). Since cyclin D1 is under clock control (Fu *et al.*, 2002), a direct relation between cell proliferation and circadian regulation or dysregulation may play a role in mammary gland cell proliferation and carcinogenesis. Also *CLOCK* and other linked circadian regulators appear to play a role in cell-cycle regulation, and DNA repair. Actions of *CLOCK* in its enzymatic functions as enzyme histone acetyletransferase may be involved in chromatin remodelling in response to estrogens in a circadian manner (Sahar & Sassone-Corsi, 2007), and in the case of disrupted circadian rhythms, may lead to alterations in cell proliferation and cancer.

In addition to its central regulatory functions, melatonin has been shown to interfere with the proliferation of human breast cancer cells *in vitro* (Blask & Hill, 1986; Hill & Blask, 1988). The local inhibitory and anti-estrogenic effects of melatonin have been studied largely in human breast cancer cells of the ER+ and estrogen responsive MCF-7 cell line. Melatonin was shown to downregulate the ER expression in MCF-7 cells, and its anti-proliferative effects appeared to be mediated through the estrogen response pathway (Hill *et al.*, 1992). The melatonin anti-proliferation effect upon breast cancer cells is limited to ERα+ MCF-7 cells and is not found in ERα– (MDA-MB-231) breast cancer cells (Hill *et al.*, 1992). There is substantial literature supportive of an anti-proliferative action of melatonin in physiological concentrations corresponding to peak night time and daytime serum values found in humans, which directly inhibit the MCF-7 cell line *in vitro* (Blask & Hill, 1986; Hill *et al.*, 1992; Hill & Blask, 1988; Cos & Sánchez-Barceló, 1995). In a recent study, it was shown in a human breast cancer xenograft rodent model that melatonin-rich human blood obtained during night time reduced tumour proliferation while melatonin-depleted blood obtained during daytime or following exposure to bright polychromatic light at night enhanced human breast cancer xenograft proliferative activity (Blask *et al.*, 2005b).

With regard to mechanisms, melatonin suppresses both ERα protein and *ERα* RNA in a time- and dose-dependent manner (Molis *et al.*, 1994) but does not compete with E2 for binding to the ERα (Molis *et al.*, 1994). In MCF-7 cells, melatonin pretreatment significantly reduced E2-induced *ERα* transactivation and ERα estrogen-responsive-element-binding activity (Kiefer *et al.*, 2002). Melatonin also inhibited the E2-induced elevation of cAMP levels; melatonin, in this model, acting as biological modifier to affect ERα transcriptional activity (Kiefer *et al.*, 2002).

(c) Prenatal exposure to melatonin in animals

Throughout fetal development, expression of the melatonin receptor exhibits considerable plasticity. During early stages of development, melatonin receptors are transiently expressed in multiple neural and endocrine tissues (Davis, 1997). Expression of MT1 receptors is subject to developmental and circadian control, which may modulate

the physiological actions of melatonin. In studies with cloned regions of the ovine *MT1* promoter and studies of the rat promoter, Johnston *et al.* (2007) suggested a model in which the melatonin expression in the mammalian pituitary gland during development is determined by the changing balance between stimulating and inhibiting transcription factors. In these studies, the authors also suggested that the circadian variation in *MT1* gene expression does not depend upon the direct action of circadian clock genes (Johnston *et al.*, 2003a,b, 2006).

In rats, the maternal pineal gland and melatonin (which passes the placental barrier) are necessary for normal sexual maturation. Prenatal melatonin treatment was shown to produce delayed sexual maturation (Díaz López *et al.*, 2005), and hyperprolactinemia in 30-days-old offspring. Melatonin treatment during pregnancy was shown to influence the ontogeny of the hypothalamus–pituitary–gonadal (Hth–Pit–Gnd) axis that begins during intrauterine life, and leads to alterations in gonadotropin and prolactin secretion of both female and male rats during sexual development (Díaz López *et al.*, 2005). The feedback of E2 on LH secretion by the pituitary gland was altered in the female offspring exposed to melatonin in utero, resulting in precocious initiation of puberty. In the male offspring, both the LH and FSH feedback mechanism were delayed. Modification of the fetal endocrine environment caused by prenatal melatonin administration induced changes in the sensitivity of gonadotropin regulation and the prolactin feedback response to exogenous androgens indicative of a delayed sexual development of the male offspring (Díaz López *et al.*, 2005). Increased exposure to melatonin during intrauterine life resulted in an inhibitory effect on postnatal androgen biosynthesis (Díaz Rodríguez *et al.*, 1999). Both maternal pinealectomy and melatonin treatment led to alterations of oocyte development in the female offspring (Fernández *et al.*, 1995).

In the fetus of mother capuchin monkeys (90% of gestation), the MT1 receptor and the clock genes *Bmal1*, *Per2*, *Cry2* and *Clock* showed circadian changes in the SCN and adrenal gland, and a rhythm of DHEA-S concentration was found in plasma (Torres-Farfan *et al.*, 2006). Maternal melatonin suppression by a constant light exposure changed the expression of *BMAL1*, *Per2* and MT1 in the fetal SCN. These effects were reversed by maternal melatonin replacement. In contrast to the SCN, maternal melatonin suppression nor its replacement had an effect on the clock genes or MT1 expression in the fetal adrenal gland or the circadian rhythm of fetal plasma DHEA-S. The authors suggested that maternal melatonin is a zeitgeber (synchronizer) for the fetal SCN but probably not for the adrenal gland (Torres-Farfan *et al.*, 2006).

(d) Melatonin effects at the level of the ovary in human studies

The uptake of melatonin in animal and human ovarian tissue has been reported (Wurtman *et al.*, 1964; Cohen *et al.*, 1978). High levels of melatonin which undergo circadian and seasonal variations are foundin human pre-ovulatory follicular fluid (Yie *et al.*, 1995a; Rönnberg *et al.*, 1990). In human granulosa-luteal cells, melatonin binding sites have been detected (Yie *et al.*, 1995b), and a stimulation of progesterone production by melatonin has been shown (Brzezinski *et al.*, 1992; Webley & Luck, 1986). Several

forms of melatonin receptor genes are expressed in human granulosa-luteal cells (Niles *et al.*, 1999). Woo *et al.* (2001) identified the melatonin receptor subtypes MT1-R and MT2-R. Cloning and sequence analysis revealed that these receptors were identical to their brain counterparts. Treatment of these cells with melatonin significantly increased the *LH* receptor mRNA levels without any effect on the expression of the FSH receptor gene. After melatonin treatment, both GnRH and *GnRH* receptor mRNA were significantly decreased to 61% and 45% of control levels, respectively. In the same study, melatonin itself had no effect upon basal progesterone production, but enhanced human chorionic gonadotropin (hCG) stimulated progesterone production. There appeared to be a complex receptor-mediated direct melatonin action upon ovarian steroidogenesis involving the *LH* and *GnRH* receptor gene expression in the steroid-producing human granulosa-luteal cells. These peripheral actions of melatonin complement its central actions and can conceivably lead to an alteration of the gonadal steroid balance (Woo *et al.*, 2001).

(e) Melatonin during puberty in humans

Serum night time melatonin concentrations are high in children, and drop by 75% from childhood (1–5 years) to young adulthood (Waldhauser *et al.*, 1984; Waldhauser & Dietzel, 1985). The morning values are uniformly low without change over different ages. The night time melatonin concentration were negatively correlated with the Tanner Stages of sexual development. In contrast, the aMT6s excretion in children and adults was similar in per day amount (Tetsuo *et al.*, 1982; Bojkowski *et al.*, 1987b). It appears that the amount of melatonin secreted by the pineal gland from childhood to young adulthood remains about the same, but as it is distributed over a larger body volume, the serum concentration is lower.

(f) Melatonin during the menstrual cycle in humans

Conflicting results have been reported in studies of the circadian melatonin rhythm during the menstrual cycle. Some studies reported increased melatonin levels during the luteal phase (Wetterberg *et al.*, 1976; Arendt 1978, 1988; Webley & Leidenberger, 1986; Brun *et al.*, 1987) or no difference between the phases (Brzezinski *et al.*, 1988; Wright *et al.*, 2001).

Brzezinski *et al.* (1988) found no significant change of plasma melatonin during the normal menstrual cycle in 14 clinically healthy normally cycling women (± 36 years of age (range 19–34)) studied at 2-hour intervals over a 24-hour span during early follicular, periovulatory, and luteal phase of the menstrual cycle. Circadian phase, amplitude, and total amount of melatonin secreted were consistent among the three profiles.

Studying the relations of melatonin to FSH and LH in 79 healthy women of different ages, Fernández *et al.* (1990) found a significant correlation of melatonin with FSH and E_2 in menstruating women during the follicular phase, while during the luteal phase, a negative correlation was found between melatonin, progesterone, and E_2. During the perimenopausal period, there was no significant correlation between the serum hormone

concentrations. In menopause, as during the follicular phase, melatonin and FSH were negatively correlated.

Exposure to bright light at night appears to have some effects upon the regulation of the menstrual cycle (Dewan, 1967; Lin *et al.*, 1990). A response of menstrual cycle length to nocturnal light exposure (100 W bulb with 235 lux) has been reported in women with long and irregular menstrual cycles (Lin *et al.*, 1990). Nocturnal light may also have effects upon the menstrual cycle phase (Putilov *et al.*, 2002).

There is no direct evidence that either endogenous, nocturnal circulating levels of melatonin or the administration of exogenous doses of melatonin mimicking circulating physiological concentrations exert any influence on pituitary gonadotrophins, prolactin, or gonadal steroids in humans. However, exposure of normal menstrual cycling women to continuous light (500–800 lux measured at eye level) during the night suppressed nocturnal circulating melatonin and prolactin concentrations while elevating FSH concentrations; no clear-cut effects were observed on LH levels when compared to control subjects maintained in the dark (Miyauchi *et al.*, 1991). This same group later reported that the incidence of menstrual irregularities in a cohort of 766 women who worked in various occupations was highest in nurses (24.9%), factory workers (36.8%), and barmaids (40.0%) when compared to teachers (13.1%) and office personnel (14.9%); the incidence of menstrual irregularities were significantly higher in those working during the night versus the day. In a small subset of nurses, those working during the night ($n = 5$) had significantly lower blood concentrations of melatonin and prolactin (sampling at 22:00 and 02:00) versus nurses resting in their quarters ($n = 6$); however, no differences were observed in plasma LH or FSH levels (Miyauchi *et al.*, 1992). In a study of 53 healthy women exposed to light during the night, circulating melatonin levels during the night were suppressed while there was no point for point changes in matching mesures of circulating E2 levels regardless of whether women were in the follicular or luteal phases of the menstrual cycle. Furthermore, in women who chronically secrete low or high levels of melatonin during the night (area under the curve range) had similar E2 blood levels (Graham *et al.*, 2001). This was also true in nude female rats exposed to increasing intensities of white, fluorescent light during the dark phase (0, 0.02, 0.05, 0.06, 0.08 and 345 μW/cm2) of an LD12:12 regimen – a dose-dependent suppression of the nocturnal amplitude of blood melatonin levels was observed while circulating levels of E2 were unchanged (Blask *et al.*, 2005b)

Disruption of circadian rhythms is associated with disturbances in menstrual function. Female shiftworkers compared to non-shiftworkers are more likely to report menstrual irregularity, and longer menstrual cycles (Baker & Driver, 2007).

Menstrual cycle irregularities have been reported in female airplane crew members, which may be the result of frequently repeated phase shift, light exposure at times unusual for their circadian cycle, or other causes specific to air travel (Iglesias *et al.*, 1980). The frequent phase shift in airline personnel has also been reported to lead to cognitive deficits (Cho *et al.*, 2000) and even associated with organic changes in the temporal lobe area

(Cho, 2001). No observations on reproductive axis dysregulation were mentioned in these reports

(g) Seasonal variations of pineal-ovarian relations in humans

In human subjects, the availability and exposure to artificial illumination appears to decrease the seasonal differences in environmental daily light–dark span, and the associated changes in pineal–gonadal relation. However, in Northern countries with strong seasonal variation in luminosity, melatonin also seems to contribute to the seasonal control of reproductive function in humans. During the dark months of the year, the activity of the pituitary-ovarian axis (Ronkainen *et al.*, 1985) on the conception rate (Timonen *et al.*, 1964; Sandahl, 1978) is decreased.

Studying serum melatonin as the likely messenger of the length of the daily dark span, Kivelä *et al.* (1988) found that the serum melatonin concentrations on menstrual cycle Days 2 and 10 of 12 clinical healthy, diurnally active women were 27% and 49%, respectively, higher in the winter than in the summer. Night time serum LH levels at mid-cycle were 76% higher in the summer than in the winter. The high levels of melatonin in the winter may have had an inhibiting effect upon serum LH levels (Kivelä *et al.*, 1988).

Kauppila *et al.* (1987) found that the area-under-the-curve of 24-hour melatonin profiles obtained by 2-hourly serum sampling during the dark (winter) season in 11 normally cycling women were significantly larger than during the light season. The duration of the nocturnal melatonin pulse during the dark season was lengthened whereas the mean serum E2 concentration was significantly decreased at the time of ovulation and during the luteal phase of the cycle in spite of increased gonadotropin concentration, indicating lowered ovarian responsiveness. The concentration of free testosterone was also lower during the dark season.

(h) Aging of the pineal-gonadal axis in the rat

In middle-aged female rats (11-months-old) with irregular estrous cycles and lowered gonadotropin surge during proestrus (perimenopausal in human equivalent), melatonin enhanced the amount of LH, FSH, and prolactin released during the surge at the proestrus day and restored the afternoon preovulatory surge in LH, FSH, and prolactin to values equivalent to those found in young rats. E2 concentrations were markedly increased in the treated animals on the day of proestrus which preceded the FSH, LH, and prolactin surges in the afternoon (Díaz *et al.*, 1999). Melatonin administration in middle-aged female rats regulated the activity of the hypothalamo-pituitary unit, and particularly improved gonadotropin secretion in response to the luteinizing-hormone-releasing hormone (Díaz López *et al.*, 2005; Díaz *et al.*, 1999, 2000).

In acyclic 23–25-months-old rats, melatonin reduced the elevated LH and FSH concentrations and increased the prolactin concentration (Diaz *et al.*, 2000). The responsiveness of the pituitary to the luteinizing-hormone-releasing hormone *in vivo* was increased by melatonin treatment, which in aging animals restored the pituitary

responsiveness to levels similar to that seen in young rats (Díaz *et al.*, 1999; Fernández Alvarez *et al.*, 1999). This is in contrast with in-vitro findings in the neonatal pituitary gland (Martin & Klein, 1976). Therefore, the effect of melatonin changes with the age of the animals.

(i) Menopause in humans

Under controlled 'constant routine' conditions, there was no significant difference in the amplitude of the salivary melatonin circadian rhythm between healthy middle-aged premenopausal (age 42 ± 4 years) and postmenopausal (55 ± 2 years) women (Walters *et al.*, 2005). In this respect, this study agrees with the findings of Zeitzer *et al.* (1999), which showed no age-related difference in melatonin amplitude when subjects were studied under constant routine conditions (although the age difference of the groups in this study was small).

There was a significant advance of the timing of the melatonin acrophase in the postmenopausal compared to the premenopausal women (1.1 ± 0.5 hours versus 2.3 ± 0.3 hour clock time in decimals, respectively) (Walters *et al.*, 2005). This result is in agreement with the studies of Cagnacci *et al.* (1995b), Duffy *et al.* (2002) and Yoon *et al.* (2003) while other investigators reported a phase delay (Sharma *et al.*, 1989), or no change in timing (Youngstedt *et al.*, 2001).

The correlation between melatonin and LH and melatonin and FSH was negative in perimenopausal and menopausal women before treatment with melatonin. After 6 months of treatment with 3 mg of melatonin at bedtime, a significant decrease in plasma LH was found only in the younger women (43–49 years of age) and not in the older women (50–62 years of age). There was a significant decrease of FSH especially in women with low basal overnight melatonin levels. In the same study, the women treated with melatonin had a significant increase in concentrations of total thyroid hormones, triiodothyronine (T_3), and thyroxine (T_4) in comparison to the women treated with placebo, without concomitant changes in the thyroid-stimulating hormone (TSH) on single-time-point sampling (Bellipanni *et al.*, 2001).

(j) Melatonin in disorders of the human hypothalamic–pituitary–gonadal axis

(i) *Women athletes with functional hypothalamic amenorrhoea*

Women athletes have abnormalities of the hypothalamic–pituitary–ovarian (Hth–Pit–Ova) (Veldhuis *et al.*, 1985; Loucks *et al.*, 1989) and hypothalamic–pituitary–adrenal (Hth–Pit–Adr) axes (Loucks *et al.*, 1989; Ding *et al.*, 1988). The changes in the Hth–Pit–Ova axis resemble those of women with functional hypothalamic amenorrhoea who do not exercise (Berga *et al.*, 1989; Suh *et al.*, 1988) in whom the magnitude and duration of nocturnal melatonin secretion is increased. Elevated daytime plasma concentrations of melatonin were observed in cycling and in amenorrhoeic women athletes compared to sedentary women. In contrast, nocturnal melatonin concentrations in sedentary and

cycling athletic women were indistinguishable while the amenorrhoeic athletic women had a marked increase in nocturnal peak amplitude and delay in melatonin offset leading to a 2-fold amplification of the nocturnal melatonin secretion (Laughlin *et al.*, 1991). Neither opioidergic (naloxone) nor dopaminergic (metoclopramide) blockade changed melatonin secretion in any of the three groups. The mechanisms of the amenorrhoea in the athletes appeared to be similar to that of sedentary functionally amenorrhoeic women. These mechanisms seemed related to a common hypothalamic dysregulation rather than to athleticism which was accompanied by daytime elevated values of melatonin, and not by the characteristic elevation seen in the amenorrhoeic subjects during night time (Laughlin *et al.*, 1991).

(ii) *Functional hypothalamic amenorrhoea*

Plasma melatonin concentrations in seven women with functional hypothalamic amenorrhoea (aged 22–35 years, mean 28.4), measured in 2-hourly sampling over a 24-hour span (daytime and night time), were significantly higher than in concomitantly studied healthy controls observed during three stages of their menstrual cycle (Brzezinski *et al.* 1988). Similar results were reported by Berga *et al.* (1988) in seven women with the same condition sampled at 30-minute intervals over a 24-hour span. While the daytime melatonin levels were undetectable in both groups, the integrated night-time levels were three times greater in the amenorrhoeic women than in the matched controls. The rise was due both to an increased peak amplitude and an extended duration of melatonin secretion towards morning, in spite of a comparable light–dark regimen. In a further study by Okatani & Sagara (1994), 20 women with functional hypothalamic amenorrhoea had significantly higher nocturnal melatonin concentrations than 11 matched controls. Negative correlations between the cumulative melatonin concentration (between 20:00 and 08:00) and serum E_2, and between the peak serum melatonin values and serum E_2 were observed. Intravenous administration of conjugated estrogen (Premarin 20 mg) significantly suppressed nocturnal melatonin secretion.

Five women with endometriosis and a low estrogen state induced by a GnRH agonist treatment had an increase in nocturnal melatonin secretion which was similar to that of the women with hypothalamic amenorrhea. This observation suggests that melatonin does not alter gonadotropin responses in humans to GnRH (Weinberg *et al.*, 1980; Fideleff *et al.*, 1976).

(iii) *Hth–Pit–Gnd disorders in the male*

Hypogonadotropic hypogonadism and delayed puberty are based on GnRH deficiency. Both of these conditions in young males resulted in a marked increase in nocturnal melatonin concentrations and integrated nocturnal melatonin secretion values (area-under-the-curve) when compared to normal pubertal male controls (Luboshitzky *et al.*, 1995). There was no correlation between melatonin and LH or between melatonin and prolactin concentrations, suggesting that circulating sex steroids rather than LH modulate melatonin secretion in a reverse fashion (Luboshitzky *et al.*, 1995). This nocturnal

increase in melatonin secretion was corrected using a testosterone treatment resulting in the melatonin concentrations returning to normal levels (Luboshitzky *et al.*, 1996a).

In contrast, untreated males with hypergonadotropic hypogonadism, due to untreated Klinefelter syndrome and sampled overnight, all had elevated FSH, LH, and E_2 concentrations. Klinefelter syndrome patients with low testosterone concentrations had significantly lower melatonin nocturnal concentrations and area-under-the-curve profiles when compared to Klinefelter syndrome patients with normal testosterone levels, and controls. No correlations between the melatonin concentration and LH, FSH, or E_2 levels were observed (Luboshitzky *et al.*, 1996b).

In male and female patients with central precocious puberty with elevated sex steroid levels, serum melatonin levels were lower than normal subjects (Waldhauser *et al.*, 1991, 1993) indicating that in general, in conditions in which sex hormones are lower with decreased or normal gonadotropin concentrations, melatonin was found to be elevated, and vice-versa. (Berga *et al.*, 1988; Brzezinski *et al.*, 1988; Laughlin *et al.*, 1991; Tortosa *et al.*, 1989; Okatani & Sagara 1994; Puig-Domingo *et al.*, 1992).

4.2.7 *Time organization in the normal and abnormal human breast*

(a) Periodicity in the normal human breast

Periodicities in the normal human breast were studied non-invasively by measuring the skin temperature above the mammary gland by ambulatory thermography monitoring. Thermography methods study both the metabolic activity of the gland and the blood flow in the overlying tissue. In some studies, the thermography readings over the breast were related to simultaneously monitored skin temperatures obtained at other sites or to oral temperature allowing to partly separate these two components, and obtain a corrected "breast-specific temperature" (Simpson *et al.*, 1989). Circadian (about 24-hour), circaceptan (about 7-day), and circamenstrual (about 28–32 day) rhythms were identified (Gautherie & Gros, 1977). The breast temperature in clinically healthy diurnally active women exhibited a circadian rhythm similar to that of the oral or the core temperature with a peak (acrophase) in the evening (Mansfield *et al.*, 1973; Gautherie & Gros, 1977). The circamenstrual rhythm in breast temperature included changes in the circadian rhythm parameters in mean amplitude, and a characteristic periovulatory rise with a peak occurring approximately 24 hours after ovulation (Phillips *et al.*, 1981; Wilson *et al.*, 1983). In large numbers of breast biopsies taken from women in different phases of the menstrual cycle, Anderson *et al.* (1982) found the highest incidence of epithelial mitoses to occur before the onset of the menstrual period.

(b) Time of initiation of breast cancer

The initiation of breast cancer may occur many years before the clinical manifestation of the tumour. In many instances, a breast cancer may begin to develop in the early premenopausal period (Simpson *et al.*, 1988). Findings concerning the influence of age at

first pregnancy (MacMahon *et al.*, 1970) and the relation of the time of radiation exposure to the appearance of the tumour (Howe, 1984) support the concept that the predominant environmental initiation of breast cancer occurs in the premenopausal period during the reproductive lifespan. This is when the epithelium is proliferating and biologically vulnerable to carcinogenic agents interfering with the circadian periodicity of cell proliferation (Simpson *et al.*, 1988).

An increased cancer incidence in shiftworkers may be related both to initiation of the tumour and to events occurring during the period of promotion of the malignancy, until it becomes clinically manifest.

(c) Circadian time structure and risk to develop breast cancer

Gautherie and Gros (1980) reported on a large series of women who received routine breast examination, including a breast thermogram. Of these, 1245 were followed up for a period of 12 years because of a questionable abnormal thermal pattern. During the follow-up period, 501 of these developed breast cancer.

In a group of 106 women with apparently healthy breast and no family history of related medical conditions, but with an abnormal thermal pattern, 27.2% developed breast cancer. In a group of 31 women with family history for breast cancer and an abnormal thermogram, 11 women (35.8%) developed breast cancer when compared to only 3.9% of 486 women with a normal thermogram. The abnormal thermal pattern preceded the clinical diagnosis of cancer in the majority of cases by 4 to 5 years, but in some instances beyond 5 years, but usually less than 10 years (Gautherie, 1983; Amalric *et al.*, 1981).

Rhythm alterations in the circadian timing of 12 hormonal variables were reported in women with a high risk (epidemiologically determined) of developing breast cancer (Ticher *et al.*, 1996). A total of 24 clinically healthy, diurnally active non-obese American women of three age groups (adolescent 17 ± 2 yr, $n = 8$; young adult 33 ± 1 yr, $n = 10$; and postmenopausal 56 ± 7 yr, $n = 8$) were studied. The women were characterized as high risk ($n = 12$) or low risk ($n = 12$) of developing breast cancer according to the epidemiological index criteria. Risk assessment followed a scale based upon the epidemiological data presented by MacMahon *et al.* (1973), Farewell *et al.* (1977), and Choi *et al.* (1978), which are similar to another review of this topic (Gail *et al.*, 1989). No subjects with a family history of *BRCA1* or *BRCA2* mutations were included. A family history of first degree relatives with (sporadic) breast cancer was the primary distinction, as it applied to all age groups. No medications known to affect prolactin secretion, including oral contraceptives, were allowed 6 months before the start of the study until its completion.

Most subjects were sampled throughout a series of four 24-hour spans during a single year, once each season, and at a different menstrual stage. There were no seasonal differences in the incidence of the different stages of the menstrual cycle. The total number of time series analysed was 44 for the cohort of high-risk subjects (31 in regularly adult menstruating women and 14 in postmenopausal women) and 41 for the cohort of low-risk subjects (26 in regularly non-menopausal menstruating women and 15 in

postmenopausal women). The number of time series analysed per season was as follows: $n = 21$ spring, $n = 20$ summer, $n = 20$ autumn, $n = 24$ winter. Blood for cortisol and prolactin was collected every 100 minutes over each 24-hour span, and blood for the other variables (aldosterone, cortisol, DHEA-S, E2, insulin, LH, 17-hydroxyprogesterone, TSH, thyroxine, and triiodothyronine) every 100 minutes. The data for each subject were analysed for each variable by the single cosinor test (Nelson *et al.*, 1979) yielding a calculated peak time (acrophase), an amplitude, and a circadian-rhythm-corrected mean value (MESOR). The differences and similarities between the high- and low-risk groups and the age groups in the dispersion of the set of acrophases and the ratio of amplitude over MESOR were analysed by a multiple Pearson correlation test and the resulting correlation matrix was used for cluster analysis. Two main profiles of acrophase dispersion were detected according to the level of breast cancer risk. The circadian time organization was similar in women with a high risk to develop breast cancer, irrespective of age, and different from the pattern in women with a low risk. In contrast, the amplitude/MESOR ratio was characteristic for the age group, and unrelated to breast cancer risk (Ticher *et al.*, 1996).

In the same study, Lewy *et al.* (2007) compared the distribution of circadian and ultradian (in the range of 4–18 hours) rhythms in low-risk and high-risk patients sampled during the four seasons for prolactin and cortisol. The high-risk and low-risk patients expressed different rhythmic output patterns in both variables, also suggesting that the genetic background as defined by the risk state to develop breast cancer was related to differences in the circadian time structure including the ability to change the subjects' predominant rhythm periods as a function of season. The low-risk patients exhibited a statistically significant change in the rhythm periods of both variables with a shift from the circadian to an ultradian rhythmicity as a function of the season while the high-risk patients did not.

Rhythm alteration in the menstrual temperature rhythm of patients at high risk to develop breast cancer was described by Simpson *et al.* (1989). The high-risk state in this study was defined by previous excision of an ipsilateral or contralateral breast tumour. While the basic breast-specific temperature in the women at usual risk of breast cancer showed the usual variation characteristic for the menstrual period with a sustained rise after ovulation and high values during the luteal phase, the high-risk patients had three temperature peaks separated by 7 and 6 days, respectively, the largest (first peak), preceding the salivary progesterone peak by about 6 days, the second and the third peaks appearing 2 days and 8 days after the salivery progesterone peak, respectively (progesterone peak appearing 8 days after the ovulation).

These data indicate significant changes in the circadian and menstrual (possibly adaptive) characteristics in the human time structure related to the risk state to develop breast cancer.

4.2.8 *Sleep deprivation – impact upon the neuroendocrine and immune system*

The most prevalent health problem for the night worker and shiftworker is the quantity and quality of sleep. The night worker, but also the early-morning shiftworker, sleeps about >2 hours less than the average day worker, and often with decreased sleep efficiency and sleep quality. Sleep deprivation impacts heavily upon the entire neuroendocrine-immune system complex regulating several biological functions, including cell proliferation, immune defence and adaptation, and defence to everyday stresses.

(a) Sleep deprivation and the immune system

The immune system in all its components is closely integrated in two-way communication and feedback loops with the nervous and the endocrine system, forming a web of biological regulation, which functions rhythmically in multiple frequencies. In the circadian frequency range, the immune system is subject to the central hypothalamic oscillator in the SCN with peripheral oscillators in immunocompetent cells and organs. It is kept in pace by neural as well as neuroendocrine and endocrine messengers and synchronizers. Some of the multifrequency periodic neuroendocrine variables (e.g. prolactin, melatonin) enhance immune reactions, while other variables (e.g. cortisol) keep them in check and control their intensity, or if these variables are overexpressed, they might suppress the immune response.

Immune reactions taking place in mammalian organisms (including humans) exert feedback effects upon the regulatory centres. The immunocompetent cells involved in an immune reaction produce humoral messengers that act on the neuroendocrine system signalling the occurrence of damage and/or of an ongoing immunodefence reaction. The feedback mechanism from the peripheral cells to the centre elicits a neuroendocrine response, which in turn regulates the peripheral cellular response to the stimulus encountered. While cortisol acts as an immunosuppressor, melatonin enhances IFNγ and IL-1 production (Maestroni *et al.*, 1986; Caroleo *et al.*, 1992; Colombo *et al.*, 1992; Morrey *et al.*, 1994), and antagonizes the immunosuppressive effect of cortisol (Maestroni *et al.*, 1988a, b). There is a bidirectional link between sleep and the immune system, in which cytokines such as IL-1, IL-2, interferon, and TNF induce sleep (Krueger & Obál, 1993).

In addition to cytokines, human peripheral leukocytes, e.g. infected by a virus or exposed to endotoxin will synthesize immunoreactive ACTH, and endorphins. The immunoreactive ACTH produced by the immunocompetent cells appears to be identical to pituitary ACTH, and acts upon the same receptors in the target tissues and shows a steroidogenic response in mice. The production of ACTH, both by pituitary cells and by leukocytes in response to synthetic corticotropin-releasing factor (CRF), is suppressed by dexamethasone *in vitro* and *in vivo* suggesting that the production of ACTH and endorphins by leukocytes is controlled by the CRF (Smith *et al.*, 1986). CRF in itself has anti-inflammatory effects that are independent of the pituitary and adrenal glands (Kiang

et al., 1987; Gao *et al.*, 1991; Wei & Gao 1991; Serda & Wei 1992). CRF is produced in the hypothalamus in a cyclic fashion, and also in response to a wide variety of environmental stimuli as a stress response and in response to pro-inflammatory cytokines such as IL-1 (Anderson *et al.*, 1993; Rivier, 1993). In animal experiments, elimination of cyclicity by exogenous CRF leads to altered response patterns after challenge (e.g. by bacterial endotoxin) (Linthorst *et al.*, 1997).

The alternation of sleep and wakefulness is a fundamental part of the organization of circadian time and coordinates numerous neuroendocrine variables. Several immunologically active hormones and peptides influence the sleep–wake cycle of the brain and are involved in a bidirectional or multidirectional communication between neuroendocrine, immune, and central nervous system functions. Most of those possess circadian rhythmicity, and some are influenced by environmental factors acting as synchronizers or as masking agents. IL-1 and other cytokines play a regulatory role on the sleep–wake cycle (Opp *et al.*, 1992), and interact in this process with various immunologically active neuroendocrine substances (Krueger *et al.*, 1990a,b). In the physiological regulation of the sleep–wake rhythm, the natural sleep-promoting or wakefulness-promoting substances require a specific constellation of multiple variables that in part is determined by their circadian rhythms and in part by environmental and behavioural conditions (Moldofsky, 1994). Periods of predisposition to sleepiness are separated by periods of resistance to sleep (Lavie & Weller, 1989).

Sleep deprivation in experimental animals and in human subjects leads to an impairment in immune function which, if prolonged, will lead to the death of the animals and of the human subjects (fatal familial insomnia syndrome) (Everson, 1993; Portaluppi *et al.*, 1994). Sleep deprivation in rodents, even for a brief 7-hour period, leads to a downregulation in immune defence against viral infection, and after challenge, to significantly decreased antibody titres (Brown *et al.*, 1989a, b). With more prolonged sleep deprivation, Everson (1993) reported in rats a breakdown in immune defences with a systemic infection by pathogenic organisms, leading to the death of the animals.

Phase shifts, as they are encountered in shiftworkers or after transmeridian flights or rhythm disturbances under irregular work schedules, lead to internal desynchronization of immune-related circadian rhythms, and to the impairment of immune functions. In studies on shiftworkers, Nakano *et al.* (1982) reported lower proliferative responses in lymphocytes when compared to regular daytime workers. As shiftwork is usually accompanied by a certain degree of sleep deprivation, it is unclear whether the impairment of immune function in shiftworkers is a consequence of circadian desynchronization, of sleep deprivation, or of both. In night shiftworkers, a short daytime sleep isa consequence of circadian desynchronization as a result of the misalignment of the circadian rhythm in sleep propensity of the worker with the time for sleep allowed by the work schedule.

(i) *Total sleep deprivation*

Unfortunately, many of the studies in this area have limited their sampling to single or very few time points per day, which, in view of the high amplitude circadian rhythms of immunocompetent cells and their responsiveness to stimulation, raises questions as to their interpretation since they often do not allow a distinction between an actual change in level of the variable studied or a shift in circadian phase (Haus, 1996; Haus & Smolensky, 1999). This problem is compounded by different sampling times used in different studies. In prolonged studies of sleep deprivation (e.g. 64 hours) with measurements of circulating immunocompetent cells limited to single time points at a given clock hour only, biphasic or other reaction patterns may be an expression of circadian phase alteration level changes or masking. These sampling limitations in much of the published literature are a likely explanation of the many contradictory results obtained by different investigators.

After 48 hours of sleep deprivation, with blood sampling at single time point at 08:00 before and after 24 and 48 hours of sleep deprivation, and 24 hours after recovery sleep, Ozturk *et al.* (1999) found a decrease in the proportion of NK cells during sleep deprivation with return to normal after recovery sleep. In contrast, Dinges *et al.* (1994) sampled blood daily at 22:00 in 20 healthy young adults of both genders over a 64-hour span of total sleep deprivation and at 22:00 in the pre-deprivation day and on the first recovery day. They reported during total sleep deprivation an increase in the number of circulating white blood cells, including granulocytes, monocytes, and NK cells as well as an increase in NK-cell activity, and increased response of lymphocytes to phytohaemagglutinin, a T-cell mitogen. On the basis of their observations, Dinges *et al.* (1994) assumed that an activation of these branches of the immune system occurred with 64 hours of total steep deprivation.

Seventy-seven hours of total sleep deprivation in eight clinically healthy women led to reduced phagocytosis by polymorphonuclear granulocytes, increased interferon production by lymphocytes, and increased the plasma cortisol concentration (Palmblad *et al.*, 1976). Sampling was limited to a single time point at 12:30, and after 28 and 76 hours of total sleep deprivation. The experimental design included a stressful surrounding during sleep deprivation with simulated battlefield environment.

Also using a single time point of measurement in 12 healthy young men after 48 hours of total sleep deprivation and in-vitro phytohaemagglutinin stimulation of their lymphocytes, Palmblad *et al.* (1979) reported a decreased lymphocyte blastogenesis.

These differences in the outcome of single-time point studies of variables with high amplitude circadian rhythms emphasize the need for studies at more than one circadian stage, or the use of a marker rhythm (Haus *et al.*, 1988) when studying conditions like shiftwork in which circadian phase alterations are to be expected.

(ii) *Partial sleep deprivation*

In contrast to prolonged total sleep deprivation, partial sleep deprivation with wakefulness either during the first part or the latter part of the night corresponds more closely to the situation encountered by the shiftworker.

Irwin and colleagues (1994) studied NK-cell activity in 23 healthy adult men (22–61 years of age) with sampling at a single clock hour (between 07:00 and 09:00) after one night of late night partial sleep deprivation, with no sleep from 03:00 to 07:00 following three baseline nights of regular sleep, and again after a recovery night of sleep. The late night sleep deprivation was associated with a decreased NK-cell activity in 18 of the 23 subjects with an average reduction in lytic activity of 28%.

In a similar study of early night of partial sleep deprivation with no sleep until 03:00, Irwin *et al.* (1996) found in 42 clinically healthy men after a single night by single-time point sampling at the same clock hour (between 07:00 and 09:00), a reduction of the natural immune response as expressed by a decrease in NK-cell activity, NK activity per number of NK cells, decrease in lymphokine-activated killer cell number and activity, and lymphokine-activated killer activity per number of lymphokine-activated killer precursors. IL-2 production stimulated by concanavalin-A was also suppressed. After one night of recovery, sleep NK-cell activity had returned to baseline levels while IL-2 production remained suppressed. These data indicate that even a modest disturbance of sleep produces a reduction in natural immune responses and T-cell cytokine production.

(iii) *Sleep deprivation and cytokine balance*

The immune system is organized in a two-branch model. The pro-inflammatory Type 1 T-helper1 (Th1) cytokines (IL-2IFNγ and IL-12) produced by immunocompetent peripheral blood mononuclear cells is counterbalanced by the anti-inflammatory group of Type 2 T-helper2 (Th2) cytokines (IL-4 and IL-10) (Lucey *et al.*, 1996). In diurnally active human subjects, the Type 1 immunodefence pattern predominates during night hours (Petrovsky, 2001; Dimitrov *et al.*, 2004a). The Type 1 cytokines support the cellular aspects of immune response and are moderated in their pro-inflammatory action by the Type 2 cytokines. Maintenance of this balance is essential since excessive production of one or the other type of cytokines leads to immune disturbances with either inflammation and tissue damage or with susceptibility to infection and allergy (Lucey *et al.*, 1996). The balance among the cytokine groups is maintained in the healthy organism by cross-inhibition and by superimposed neuroendocrine control (Romagnani, 1996), which in its time organization is directed by the SCN, and the related circadian clock mechanisms.

Sleep is an integral part of the circadian time structure and plays a vital role in the regulation of the immune system (Bryant *et al.*, 2004). There is a sleep-associated shift towards Type 1 cytokine activity in T-cells (Dimitrov *et al.*, 2004a). Sleep deprivation leads to alterations in the cytokine balance. A shift towards Type 2 activity has been reported for sleep deprivation in otherwise healthy subjects, in insomnia, under stress, and in the aged (Dimitrov *et al.*, 2004b; Sakami *et al.*, 2002–2003; Glaser *et al.*, 2001). Elevation of sympathetic tone during the night also contributes to a reduction of cellular immunity, e.g. in psychological stress situations (Irwin *et al.*, 1990a; Irwin *et al.*, 1991).

Covering an entire 24-hour span with frequent sampling and sleep permitted from 23:00 to 07:00, and a second 24-hour span without sleep in the same subjects at least

4 weeks apart, Lange *et al.* (2006) studied by flow cytometry IL-12- and IL-10-producing monocytes, representing messengers of the Th1 and Th2 pattern, respectively. During sleep, there was an increase in the number of IL-12- producing monocytes and a concurrent decrease of IL-10-producing monocytes, leading to a circadian rhythm in these cells with a peak at 02:20 and 11:30, respectively. These apparently rhythmic temporal variations were absent during continuous wakefulness. Monocytes are a major contributor to pro-inflammatory cytokine production in the peripheral blood. Nocturnal sleep shifts monocyte cytokine production to Type 1 cytokines, which is regarded as a prerequisite for sleep-associated predominance of Th1-mediated adaptive immune defence (Lange *et al.*, 2006). The human monocytes are regarded as direct precursors of antigen-presenting cells, and can be directly assessed by flow cytometry in blood samples (Geissmann *et al.*, 2003). The study of Lange *et al.* (2006) shows a dependence of the cytokine rhythm on sleep and its apparent absence during continuous wakefulness. The circadian variation in monocyte-derived IL-12 and IL-10 production, and the respective Type 1/Type 2 cytokine balance, which are induced primarily by sleep, are vulnerable to sleep disturbances and sleep deprivation.

With regard to mechanisms, growth hormone and prolactin shift the Type 1/Type 2 balance towards Type 1, whereas cortisol and norepinephrine shift it towards Type 2 (Dimitrov *et al.*, 2004a, b; Elenkov & Chrousos, 2002). Both prolactin and growth hormone rhythms are altered during sleep deprivation (Lange *et al.*, 2006). There was a positive correlation between the prolactin level and IL-12+ monocyte numbers, and between norepinephrine and IL-10+ monocyte numbers, and a negative correlation between the cortisol level and IL-12+ monocyte numbers (Lange *et al.*, 2006; Petrovsky & Harrison, 1998). *In vitro*, studies of prolactin and cortisol effects support the assumption of a direct hormonal action upon IL-12+ monocytes (Petrovsky & Harrison, 1998; Visser *et al.*, 1998; Petrovsky, 2001; Elenkov & Chrousos, 2002; Lange *et al.*, 2006). A direct effect of growth hormone on the immunocompetent cells is less well documented (Elenkov & Chrousos, 2002; Lange *et al.*, 2006). Melatonin also stimulates Type 1 activity (Petrovsky, 2001), and nocturnal suppression of melatonin may counteract this shift.

Irwin *et al.* (2006) studied in 30 diurnally active healthy adult men (n = 17) and women (n = 13) the monocyte intracellular pro-inflammatory cytokine production across 3 days of baseline testing, and after 1 day of partial sleep deprivation with wakefulness from 23:00 to 03:00. Sampling occurred at 08:00, 12:00, 16:00, 20:00 and 23:00. In the morning after sleep loss, but not at the other times of sampling, the monocyte production of IL-6 and TNFα was significantly greater when compared to the same time (08:00) following uninterrupted sleep. Sleep loss apparently led to an activation of these pro-inflammatory cytokine genes with a more than 3-fold increase in transcription of *IL-6* mRNA, and a 2-fold increase in *TNFα* mRNA. This change was the expression of a functional difference in the monocytes and did not relate to any difference in the numbers of cells. Global gene expression profiling in leukocyte total RNA by high density oligonucleotide assay in five subjects before and after sleep deprivation revealed a set of

22 genes that were significantly upregulated after partial sleep deprivation. These included the circadian clock gene *Per1*, several epidermal-growth-factor-related genes, and multiple inflammatory response genes. The complex ensemble of functional genomic alterations induced by sleep loss included multiple immediate early response genes, and signal transduction mediators. The remodelling of leukocyte gene expression by sleep and its alteration by sleep loss may point to molecular sites of action in the immune system, and also more generally in cellular physiology and pathology.

(b) Sleep deprivation and the neuroendocrine system

(i) *Prolactin and sleep*

Prolactin plasma concentrations show pulsatile episodic hormone secretion patterns superimposed upon ultradian rhythms as well as circadian oscillation. The prolactin 24-hour profile reflects both tonic and intermittent hormone release (Veldhuis *et al.*, 1992). The normal secretory pattern of prolactin consists of a series of daily pulses, occurring every 2–3 hours, which vary in amplitude. The bulk of the hormone is secreted during REM sleep. In diurnally active human subjects, REM sleep occurs predominantly during the latter half of the nightly sleep phase, so that the highest plasma prolactin concentrations usually occur late during the night (Sassin *et al.*, 1972, 1973). In men and non-pregnant and non-lactating women, REM sleep is the dominant organizer of prolactin secretion. It has been shown that, in turn, prolactin infusion increases REM activity in the electroencephalogram (Obál *et al.*, 1994; Roky *et al.*, 1995). In lactating women, the reflex elevation of prolactin and oxytocin by nipple stimulation during nursing becomes the predominant controller of circulating prolactin concentrations (Leake *et al.*, 1983).

Sleep onset is associated with an increase in prolactin secretion also during daytime naps, irrespective of the time of the day, but the amplitude of the prolactin rise during daytime sleep is usually less than during nocturnal sleep. Conversely, modest elevations in prolactin concentration may occur at the time of the usual sleep onset even when one remains awake. Thus, prolactin plasma concentrations appear to be regulated by a circadian rhythm and superimposed pulsatile secretions modulated by the sleep-wakefulness pattern, with maximal secretion when sleep and circadian rhythmicity are in phase (Spiegel *et al.*, 1994, 1999; Waldstreicher *et al.*, 1996). Shallow and fragmented sleep, prolonged awakening, and interrupted sleep patterns, as frequently seen in the elderly, are associated with a dampening of the nocturnal prolactin rise, decreased amplitude of the nocturnal prolactin pulses (van Coevorden *et al.*, 1991; Greenspan *et al.*, 1990), and decreased prolactin concentrations (Spiegel *et al.*, 1995).

Prolactine secretion in man is normally restrained by the action of dopamine, which is secreted from the hypothalamus. Prolactin is the only pituitary hormone that is secreted at unrestrained high levels when completely isolated from any tropic influences of the hypothalamus. However, a variety of stimulatory prolactin secretagogues have been identified including steroids (estrogen), hypothalamic peptides, vasoactive intestinal peptide, and oxytocin, and growth factors such as epidermal growth factor, and fibroblast

growth factor-2. Numerous medications used in everyday clinical practice elevate prolactin secretion, and this can mask physiological rhythmicity and occasionally may even lead to symptomatic hyperprolactinaemia. These agents include commonly used antidepressants, antiemetics, and narcotics, which antagonize dopamine action or elevate serotonin or endorphin bioactivity (Ben-Jonathan, 1994). Hypnotics like benzodiazepines (e.g. triazolam) and imidazopyridines (e.g. zolpidem) taken at bedtime (concordant with the tendency of the daily prolactin rise) may lead to substantial rises of serum prolactin concentrations into the range regarded as abnormal (Copinschi *et al.*, 1990, 1995). Melatonin itself acutely stimulates prolactin release in humans (Wright *et al.*, 1986; Waldhauser *et al.*, 1987). Endogenous estrogens play a role in the differential regulation of prolactin in relation to age and sex. Mean prolactin concentrations, pulse amplitude, and pulse frequency are all higher in normally cycling young women than in either postmenopausal women or in men (Katznelson *et al.*, 1998). Blunting of the nocturnal rise is not specific and is found also in other medical conditions, including breast cancer.

(ii) *Prolactin and the immune system*

The effects of prolactin in the human body are manyfold. Of importance is the regulatory role it plays on the immune system. Prolactin receptors are found on most immune-precursor and -effector cells in each of the major haematopoietic and lymphopoietic organs, such as the bone marrow, spleen, and thymus. However, the action of prolactin upon the immune system is complex, and depends upon the stage of both the circadian timing of the prolactin rhythm and its time relations to the circadian rhythms of immune-related functions in the target organs (Cincotta *et al.*, 1995).

In laboratory experiments, prolactin restores immune competence in hypophysectomized animals (Gala, 1991). Inhibition of prolactin secretion by bromocriptine results in immunosuppression (Hiestand *et al.*, 1986; Bernton *et al.*, 1988; Berczi, 1989). Prolactin antagonizes the immunosuppressive effects of glucocorticoids (Bernton *et al.*, 1992). While lowered prolactin concentration leads to immunodeficiency, and exogenous prolactin in short-term experiments produces immunoenhancement, persistently elevated prolactin levels, due to a variety of medical conditions, are associated with immunosuppression (Karmali *et al.*, 1974; Jungers *et al.*, 1982; Gerli *et al.*, 1987; Lavalle *et al.*, 1987; Nicoletti *et al.*, 1989; McMurray *et al.*, 1991; Vidaller *et al.*, 1986, 1992).

Some of the discordant results of investigations pertaining to the effects of prolactin on the immune system may be due to the pronounced circadian variation in its regulatory action (Cincotta *et al.*, 1995), and the marked time-dependent difference of immunocellular responses. In the male BALB/c mouse, the immunostimulatory activity of prolactin was restricted to only an 8-hour daily interval, from 4–12 hours after light on in animals kept on an LD12:12 regimen. Prolactin administration outside this sensitive interval was occasionally associated with immunosuppressive effects both in the one-way mixed lymphocyte reaction and in the hapten-specific delayed-type hypersensitivity responses. Reducing endogenous levels of prolactin with bromocriptine inhibited immune

functions only when the medication was administered during this daily interval of immunoregulatory sensitivity to the hormone (Cincotta *et al.*, 1995). This observation is similar to that of Bernton *et al.* (1992) who found that the effect of the prolactin inhibitor cysteamine (a dopamine β-hydroxylase inhibitor) on splenocyte mitogenic response was circadian-time-dependent.

A chronobiological explanation of the interaction of the rhythms in human prolactin secretion and in target cell responsiveness, however, has not been reported. It appears that in the immunoregulatory action of prolactin, the overall level of plasma prolactin is of less importance than the circadian rhythmicity of prolactin and that of the apparently circadian periodic responses of the immunocompetent target cell systems. The phase relation between the circadian rhythm in prolactin and that of the rhythms in immunocellular response may be the determining factor for the prolactin effect upon the immune system. Circadian rhythm disruption or phase shifts of either of these rhythms may be associated with immunological dysfunction, which may be of interest for shiftwork and transmeridian flights, and in the elderly, circadian rhythm and sleep disturbances.

Prolactin effects on human immune activity and immunological disorders, including lupus erythematosus and the postpartum exacerbation of rheumatoid arthritis, have been reported (Vidaller *et al.*, 1986; Gerli *et al.*, 1987; Lavalle *et al.*, 1987; Nicoletti *et al.*, 1989; Gala, 1991).

(iii) *Hypothalamic–pituitary–thyroid axis and sleep*

The hypothalamic–pituitary–thyroid (Hth–Pit–Thy) axis possesses an intricate time structure with rhythmic variations of multiple frequencies found at all levels of the system, from the hypothalamic neurons to the cells of the peripheral target tissues. The frequencies observed include pulsatile secretions and ultradian, circadian, and circannual rhythms. The time-dependent rhythmic (and non-rhythmic) variations of the Hth–Pit–Thy system interact with, and are modulated by, similar time-dependent variations of other neuroendocrine, metabolic, and immune functions.

The thyrotropin-releasing hormone is a tripeptide neurotransmitter that exerts multiple actions in the central nervous system and beyond (Metcalf & Jackson, 1989; Nicolau & Haus, 1992). It is produced also in peripheral tissues, including the immune system (Simard *et al.*, 1989). In addition to its capacity to stimulate the release of TSH from the anterior pituitary, it also stimulates prolactin.

TSH is secreted from the pituitary gland in a series of discrete pulses with an average pulse frequency of 9 pulses/24 hours (range 7–12) in normal men and women (Brabant *et al.*, 1990; Nicolau & Haus, 1992). These pulses are not equally distributed, but cluster during the evening and night hours when fusion of the pulses and an increase in amplitude leads to the nightly increase of TSH concentration, forming the circadian rhythm of this hormone with a maximum in day–night-synchronized subjects occurring usually between 02:00 and 04:00 (Brabant *et al.*, 1990; Samuels *et al.*, 1990). The relatively high peak values of individual TSH pulses during sleep have to be kept in mind, as the values reached may be slightly above the usually accepted normal range.

The pulse pattern may be necessary for normal thyroid gland function due to the better response of the pituitary thyrotrops to intermittent rather than continuous thyrotropin-releasing hormone stimulation (Spencer *et al.*, 1980). Loss of the usual nocturnal variation in TSH and pulse amplitude may be sufficient to cause clinical hypothyroidism (Samuels *et al.*, 1990).

Sleep deprivation and sleep fragmentation result in a marked decrease in the mean 24-hour TSH secretion as well as a lowering of pulse amplitude also without change in peak frequency (Behrends *et al.*, 1998; Brabant *et al.*, 1990; Spiegel *et al.*, 1999).

(iv) *Growth hormone and sleep*

The 24-hour profile of growth hormone (GH) in adult subjects consists of stable low values interrupted by secretory pulses. There is a marked sexual dimorphism of the secretory pattern. In men, the highest pulse, amounting to about 70% of the secretory output per 24 hours, occurs shortly after sleep onset with the first phase of slow-wave sleep (Van Cauter *et al.*, 1998). In normally cycling women, there is a wider distribution of GH pulses throughout the day. The sleep-onset-associated pulse is still found in most women, but accounts only for a smaller fraction of the total 24-hour secretory product (Ho *et al.*, 1987). The linkage of a major GH pulse to sleep onset leads to an immediate shift in the circadian rhythm in GH with any change of the sleep–wake cycle, e.g. in shiftworkers and after transmeridian travel over several times zones. This linkage also leads to alterations of GH secretion in the case of sleep irregularities (Van Cauter *et al.*, 1998). The mechanism of this association is based on the hypothalamic relationship of the GH releasing hormone to areas of the brain involved in the regulation of sleep (Krueger & Obál, 1993). Inhibition of endogenous GH releasing hormone action by a specific antagonist or by immunoneutralization inhibits both sleep and GH secretion (Ocampo-Lim *et al.*, 1996). On the other hand, substances which promote sleep also lead to increases in nocturnal GH secretion (Gronfier *et al.*, 1996; Van Cauter *et al.*, 1997).

Total sleep deprivation with absence of recovery sleep leads to a markedly decreased growth hormone secretion (Van Cauter *et al.*, 1992; Weibel *et al.*, 1997). Recovery from total sleep deprivation irrespective of the time of day when recovery sleep occurs leads to a robust increase in GH secretion. When bedtime is acutely delayed by a few hours, nocturnal GH levels remain low as long as the subject is awake, and rebound as soon as sleep is initiated (Van Cauter *et al.*, 1998). Semichronic partial sleep deprivation more closely resembles the condition experienced by shiftworkers. Spiegel *et al.* (2000) studied 11 clinically healthy men after 6 nights of restricted bedtimes (01:00 to 05:00) and after 7 nights of extended bedtimes (21:00 to 09:00). After 1 week of sleep extension to 12 hours, the major GH peak occurred at the same time as the usual 8-hour sleep time after onset of sleep. After 1 week of bedtime reduced to 4 hours, the GH secretory rate exhibited a biphasic pattern with a large pulse occurring during waking around the usual time of sleep onset on a standard 8-hour bedtime schedule, an expression of the circadian rhythm in GH secretion, followed by a second sleep-induced pulse after onset of the (shortened) sleep span. The state of subchronic partial sleep deprivation (sleep debt) was

associated with a markedly different temporal association of GH secretion. The biphasic nature of the GH secretory pattern during sleep restriction resulted in a longer exposure of peripheral tissues to elevated GH concentrations (4 hour 12 minute ± 25 minute vs 3 hour 25 minute ± 33 minute during sleep extension). This biphasic pattern represents an adaptive process to the subchronic sleep deprivation as it was not found in studies with acute sleep deprivation (Van Cauter & Copinschi, 2000). The prolonged exposure of the peripheral tissues to GH may have played a role in the marked deterioration of glucose tolerance that was found in these subjects after 1 week of subchronic sleep restriction (Spiegel *et al.*, 1999). In relation to this study, the question can be raised if a curtailment of sleep by a phase advance due to earlier rising rather than delayed bedtime may avoid the biphasic secretion, and lead to a different adaptive response, possibly with less or different side-effects.

(v) *The Hth–Pit–Adr axis and sleep*

The corticotropic axis with the CRH, the ACTH of the pituitary, and cortisol from the adrenal cortex is, in addition to the direct effects upon multiple systems, a major messenger of time information in the circadian regulatory system. In addition, CRH is synthesized and produced in multiple peripheral tissues with likely involvement in the regulation of energy balance, metabolism, and immune response (Richard *et al.*, 2000; Baigent, 2001). CRH in the rat brain is produced in the arcuate and paraventricular nuclei of the hypothalamus (Sawchenko & Swanson, 1985), and receives time information from SCN neurons. As a neurotransmitter, CRH acts within the brain to elicit changes in neuroendocrine, autonomic and behavioural activity similar to those observed after stress. Centrally administered CRH induces suppression of NK-cell cytotoxicity (Irwin *et al.*, 1988), an action which appears to be mediated through sympathetic activation as it can be counteracted by adrenergic-receptor blockade (Irwin *et al.*, 1990b). Stress-induced suppression of NK activity appears to be mediated by CRH, and can be antagonized by the central immunoneutralization of CRH (Irwin *et al.*, 1990a). The immunoregulatory role of CRH is not associated with the activation of the pituitary-adrenal axis (Irwin *et al.*, 1990a).

The corticotropic axis receives time information through inputs from oscillator neurons in the SCN to the CRH-ergic neurons in the paraventricular and arcuate nucleus, which release CRH into the hypophyseal portal vein, in a periodic and pulsatile pattern leading to the characteristic periodic and pulsatile ACTH release which is followed by corresponding pulses of cortisol secretion. The clinically manifest activity of the axis reflects the interaction of cycles of hormone secretion and of responsiveness of the endocrine target organs (pituitary and adrenal), and of the corticoid responsive peripheral tissues to the stimulation.

The rhythmicity of the corticotropic axis is quite stable and not rapidly altered in its circadian peak by minor changes of the sleep–wakefulness pattern, light, and other environmental stimuli. The normal circadian rhythm of the hypothalamic-pituitary-adrenal axis that is regarded as the major transducer of stress, is primarily regulated by the

circadian oscillator system, and is only minimally modulated by sleep. Sleep onset is associated with an acute inhibition of cortisol secretion (Born *et al.*, 1988; Weibel *et al.*, 1995). Awakening during the night, and especially in the morning, is followed by secretory cortisol pulses (Pruessner *et al.*, 1997; Späth-Schwalbe *et al.*, 1991). These changes are absent if a person is prevented from sleeping.

Chronic insomniacs with difficulty falling or staying asleep, with less than 6.5 hours sleep time and a sleep efficacy of less than 80%, exhibited a significantly higher 24-hour ACTH and cortisol secretion than a matched control population with greatest differences in plasma concetrations in the evening and during the first half of the night (Vgontzas *et al.*, 2001). The circadian rhythm in ACTH and cortisol as such was maintained.

In clinically healthy diurnally active young men, partial sleep deprivation (sleep from 04:00 to 08:00) or total sleep deprivation for one night led on the following day to an elevation of plasma cortisol concentration during the evening (18:00 to 23:00), and the onset of the daily quiescent period in plasma cortisol was delayed (Leproult *et al.*, 1997).

In a study of semichronic sleep deprivation in 11 young men whose sleep time was restricted to 4 hours per night (01:00 to 05:00) for 6 nights, Spiegel *et al.* (1999) found similar changes in the 24-hour profile of plasma cortisol in comparison to the circadian profile of the same subjects studied after a 6-day recovery period. The changes observed after semichronic sleep deprivation also consisted of a shortened quiescent period (537 ± 44 minute versus 634 ± 24 minute) due largely to a delay in its onset of nearly 1.5 hours and raised cortisol concentrations in the afternoon and early evening (Spiegel *et al.*, 1999).

Some studies of sleep loss did not find evidence of a stress reaction in urinary cortisol and catecholamine excretion (Kant *et al.*, 1984) or plasma cortisol (Akerstedt *et al.*, 1980; Davidson *et al.*, 1991; Follenius *et al.*, 1992; Lange *et al.*, 2006; Vgontzas *et al.*, 2004), which, in part, may be due to the relatively short time span in which a deviation from the usual cortisol concentrations can be recognized. These studies suggest that sleep loss does not constitute an acute stimulus for the Hth-Pit-Adr axis, i.e. a “stressor.”

The Hth-Pit-Adr axis possesses powerful and far reaching immunoregulatory activity. CRH directing the characteristic rhythmicity of this system also inhibits endotoxin-stimulated production of IL-1 and IL-6 by human monocytes. ACTH suppresses IFNγ production by human lymphocytes (Johnson *et al.*, 1984).

The glucocorticoids exert an extensive and multifaceted immunoregulatory activity. They are powerful anti-inflammatory agents inhibiting inflammatory mediators including cytokines, phospholipid products, proteases, and oxygen metabolites. They downregulate cytokine expression of IL-1, Il-2, IL-3, IL-6, IL-4, IL-8, IFNγ, and TNFα (for a review, see Petrovsky, 2001). In contrast to the downregulation of cell-mediated immunity, glucocorticoids enhance immunoglobulin production (Cooper *et al.*, 1979) and also induce the macrophage migration inhibitory factor, a pro-inflammatory cytokine which counteracts and moderates the anti-inflammatory effects of glucocorticoids (Calandra *et al.*, 1995), maintaining a balance between the pro-inflammatory and anti-inflammatory components of the system. By stimulating the production of IL-4, IL-10 and IL-13,

glucocorticoids favour the Th2 mode of the immune system (Ramírez *et al.*, 1996). The changes in the immune system found in sleep deprivation and shiftwork may in part be related to the circadian rhythm alterations in the Hth–Pit–Adr system experienced during these conditions.

Sleep loss, similar to aging, may slow down the rate of recovery of the corticotropic axis response following a challenge, and may facilitate the development of central and peripheral disturbances associated with glucosteroid excess. Especially elevated cortisol concentrations at the time of the normal daily quiet period may, in the long run, result in undesirable side-effects, such as memory deficits, insulin resistance, and osteoporosis (Dallman *et al.*, 1993; McEwen, 1998; Dennison *et al.*, 1999; Plat *et al.*, 1999).

In circadian phase shift, as may be experienced in shiftwork or under the effect of competing synchronizers between the light-directed SCN and peripheral stimuli like the time of food uptake, the rhythmic reaction of glucocorticoids inhibits the uncoupling of peripheral circadian oscillators from the central pacemaker (Le Minh *et al.*, 2001). This may counteract the internal circadian desynchronization and favour maintenance of the circadian time organization, and, if a phase shift takes place, determine in part the time of phase adaptation.

(c) Sleep deprivation and metabolism

Numerous studies over the last decade have consistently reported, with cross-sectional as well as with prospective design, an inverse relation between the numbers of hours of sleep and body weight in both children and adults with some age and gender differences noted (Vioque *et al.*, 2000; Sekine *et al.*, 2002; Cournot *et al.*, 2004; Hasler *et al.*, 2004; Patel *et al.*, 2004; Taheri *et al.*, 2004; Reilly *et al.*, 2005). Obesity in shiftworkers has been associated with a short duration of sleep (van Amelsvoort *et al.*, 1999; Moreno *et al.*, 2006). The incidence and degree were related to the duration of the shiftwork. A significant increase in the waist:hips ratio was found in workers after 2–5 years' involvement in shiftwork, and in the body mass index after more than 5 years in shiftwork (van Amelsvoort *et al.*, 1999). A causal relationship between sleep restriction and weight gain is supported by metabolic studies.

Spiegel *et al.* (1999, 2004b) studied 24-hour hormone and metabolic profiles in 11 young adult men after 6 days of sleep deprivation (4 hours' bedtime, 01:00 to 05:00) and 1 week of recovery. After 6 days of sleep deprivation, the mean circadian leptin concentration and the circadian amplitude of leptin were decreased, and ghrelin concentrations were increased together with increased hunger and appetite (Spiegel *et al.*, 2004a, b). The leptin concentrations were similar to the values found after calorie restriction (Chin-Chance *et al.*, 2000) in spite of adequate calorie intake. Similar findings of short sleep duration associated with reduced leptin, elevated ghrelin sampled at a single time point in the morning and increased body mass index was reported by Taheri *et al.* (2004). In animal experiments, a marked increase in food uptake was found in sleep-deprived rats (Rechtschaffen & Bergmann, 1995). It appears that sleep deprivation alters the regulation of leptin and ghrelin production, and, accordingly, the feedback on the

energetic needs and appetite control to the brain, which may lead to an increase in food uptake and represent a risk factor for obesity.

Estimations of the sympathovagal balance derived from recordings of heart-rate variability were significantly higher during sleep restriction (Spiegel *et al.*, 1999). The higher sympathetic activity may be related to metabolic changes (e.g., insulin-resistance) and other metabolic and cardiovascular changes. In sleep deprivation and during sleep-debt conditions, an impairment of carbohydrate tolerance develops with a slower rate of glucose clearance, with a decrease in glucose effectiveness, and a lower acute insulin response to glucose (Spiegel *et al.*, 1999) leading to conditions found in natural aging (Kahn *et al.*, 1993), and close to findings in non-insulin-dependent diabetics (Bergman, 1989) or gestational diabetes (Catalano *et al.*, 1993). Decreased carbohydrate tolerance and increased sympathetic tone are risk factors for the development of insulin resistance, obesity, and hypertension (Reaven *et al.*, 1996), corresponding to the condition described as "metabolic syndrome." It appears likely that some endemic disorders of the modern society like diabetes and obesity are in part a consequence of chronic sleep deprivation (Sekine *et al.*, 2002; Taheri *et al.*, 2004; Cizza *et al.*, 2005; Gangwisch *et al.*, 2005; Taheri, 2006). This includes the increased incidence of obesity in shiftworkers (van Amelsvoort *et al.*, 1999; Gangwisch *et al.*, 2005; Moreno *et al.*, 2006), which again, may be related to an increased cancer risk in these workers.

The high intake of dietary fat at night by rotating shiftworkers (40% of total calories) (Lennernäs *et al.*, 1994) leads to marked postprandial increases in triacylglycerols and non-esterified fatty acids such as linoleic acid (Holmbäck *et al.*, 2002). Linoleic acid provides a robust stimulatory signal for cancer growth via its mutagenic metabolite, 13-hydroxyoctadecadienoic acid (13-HODE). Elevated physiological nocturnal melatonin levels in the blood of human premenopausal women have the capacity to inhibit the uptake of linoleic acid, and its metabolism to 13-HODE, and tumour proliferative activity in (estrogen receptor negative/progesterone receptor negative (ER–/PgR–) and ER+/PgR+ tissue in isolated breast cancer xenografts perfused *in situ*. Exposure of these subjects to bright white light at night suppresses melatonin production resulting in substantially increased linoleic acid uptake, 13-HODE formation, and tumour proliferative activity in human breast cancer xenografts perfused *in situ*, with this melatonin-depleted blood. These results suggest that nocturnal circadian melatonin levels in women may protect against the breast cancer growth-promoting effects of increased dietary linoleic acid levels ingested at night (Blask *et al.*, 2005b).

4.3 Mechanistic arguments

Melatonin has been shown to have antiproliferative effects on human cancer cells cultured *in vitro*. These oncostatic effects have been observed at physiological concentrations, and include reduction of cell-cycle progression by increasing the expression of the tumour suppressor gene *TP53*, and inhibition of DNA synthesis. In addition, melatonin reduces the invasive and metastatic properties of human cancer cells *in vitro*, and increases intercellular communication between these cells. There is evidence

from animal models that melatonin inhibits or reduces the induction of DNA damage by free radicals. Pinealectomized rats showed a higher level of DNA damage in response to treatment with a carcinogen than did pineal-intact rats. Melatonin has also been shown to upregulate anti-oxidant enzyme systems.

Epidemiological studies on genetic polymorphisms in clock-related genes and phenotypes such as morning/evening preference and depressive symptoms, have shown a significant association between a single-nucleotide polymorphism in the *PER2* gene and diurnal preference. In a wider sense, the circadian clock may function as a tumour suppressor at the systemic, cellular, and molecular levels. Clock-controlled genes involved in cell-cycle control include *c-MYC*, *MDM*2, *TP*53 and *GADD45*a, as well as caspases, cyclins, and various transcription factors. In transgenic mice, a deletion in *Per2* results in a shorter circadian period, a higher susceptibility to radiation-induced tumours, and reduced apoptosis in thymocytes. The disruption of the circadian rhythm in mice is associated with the accelerated growth of malignant tumours.

Functional loss of the *Period* genes has been observed in various human tumours, and is probably based on epigenetic changes, i.e. the modulation of the methylation pattern in the promoter region. The loss of the clock protein function and the aberrant methylation of *PER1*, *PER2*, *PER3*, *CRY1* and *CRY2* promoters has been found in tumours of the breast, endometrium, lung, and in leukaemia. Artificially induced expression of *PER1* in non-small lung cancer cells *in vitro* results in a significant reduction in growth.

The human circadian gene *PER3* is linked to breast cancer risk. A polymorphic repeat region in this gene results in a PER3 protein of different length, which is associated with delayed sleep-phase syndrome, and diurnal preference. The variant genotypes are associated with an increased breast cancer risk in premenopausal women.

4.4 References

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5. Summary of Data Reported

5.1 Exposure data

Several types of shift systems exist, described according to several main characteristics: permanent or rotating, continuous (all days of the week are covered) or discontinuous (interruption at the weekend or on Sunday), or with or without night work. Other important organizational factors that may have an impact on health are: length of the shift cycle, duration of shifts, number of alternating workers/crews, start and finish time of the duty periods, speed and direction (clockwise or anticlockwise) of shift rotation, number and position of rest days and regularity/irregularity of the shift schedules.

The amount of night work in any shift period is the most important factor to be considered in the disruption of biological functions. The amount of sleep of the shiftworker decreases both in terms of quantity and quality, both on night shifts (due to circadian and environmental reasons) and on early-morning shifts.

Shiftwork, that includes night work, is estimated to involve about 15–20% of the total working population, although reliable and comparable statistics are not available in most countries. In Europe, large differences have been recorded among countries (from 6.4 to 30%), and between self-employed (5.7%) and employees (19.8%); in the USA, the average prevalence of shiftwork that includes night work is 14.8% (16.7% in men and 12.4% in women). Shiftwork is most prevalent among workers in the health care, transportation, communication, leisure and hospitality sectors (above 30%), and in the service, mining and industrial manufacturing sectors (20–30%). The prevalence of shiftwork is more common in work schedules of younger workers but decreases with the age of the workers, from more than 20% in the youngest decades of life to approximately 10% after 55 years of age.

At the time of writing, there is no known biomarker of exposure for shiftwork. However, because of the importance of melatonin in the relation to the activity in the circadian rhythm, levels of melatonin could be useful biomarkers of circadian disruption. Melatonin can be measured in the blood, saliva, or urine. The measurement of melatonin concentration in plasma at regular intervals (e.g. hourly) can identify the onset, offset and duration of melatonin secretion, the time at which peak secretion occurred and the total amount of melatonin secreted. Salivary melatonin concentration is a good alternative measure as it is highly correlated with serum concentrations. The primary urinary metabolite of melatonin, 6-sulfatoxymelatonin, may also be a useful biomarker.

The disruptive effects of night work on the biological functions and social life have been recognized by some regulators both at the national and international levels, i.e. the

International Labour Organization, the European Union, and the Federal Aviation Administration.

5.2 Human carcinogenicity data

Female breast cancer

Eight studies from various geographic regions have been designed to assess the relationship between breast cancer and shiftwork that involves night work. Six of these eight studies, including two prospective cohort studies in nurses, have consistently pointed towards a modestly increased risk of breast cancer among long-term employees who performed night shiftwork, defined in different ways. Most studies reported this increased risk after controlling for potential confounders. Two of the eight studies, one of which appeared to be hampered by important limitations in design, were not supportive of an association between shiftwork and breast cancer. There were a relatively limited number of studies (most focused on a single profession, i.e. nurses), some potential for confounding by unknown risk factors, and inconsistent and inaccurate exposure assessments of shiftwork, which may have biased the results towards the null.

Another occupational group of shiftworkers is flight cabin crew personnel, who also experience circadian disruption due to the crossing of time zones. The incidence of breast cancer has been studied in eight cohorts of female flight attendants, all but one consistently reported an increased risk for breast cancer which was greater after a longer duration of employment. Limitations of these studies included the potential for detection bias among female cabin crew due to a higher prevalence of breast cancer screening in this occupational group, proxy measures of exposure used in dose–response relationships, and potential confounding by reproductive factors and cosmic radiation.

The Working Group concluded that the evidence for an association with breast cancer and shiftwork that involves night work was consistent in the studies that were specifically designed to address this question. The studies of cabin crews provided additional support.

Other cancers

Few studies have investigated the association between shiftwork and cancers at other organ sites. Increased risks of cancers of the prostate, colon, and endometrium have been reported. The earliest studies of airline pilots also showed a markedly elevated incidence of prostate cancer compared with national reference levels, but limitations of these studies included the potential for detection bias due to a higher prevelance of screening for prostate cancer in this occupational group.

5.3 Animal carcinogenicity data

Animal models have been used extensively to test the impact of the circadian system (central circadian pacemaker in the suprachiasmatic nuclei and the pineal gland/melatonin-generating system) and its disruption (i.e. phase shifts, light during the dark period, melatonin suppression) on tumour development and growth at all stages of oncogenesis.

Two studies examined the impact of continuous high-intensity light versus low-intensity light on tumour development in mice. One study demonstrated clear increases in the incidence of lung adenocarcinomas, leukaemias and lymphomas combined. The second study showed an increase in the incidence of and mortality from mammary tumours in one substrain that had normal vision, and no increase in a substrain of the same strain that had retinal degeneration due to genetic predisposition. A third study showed no effects.

All of the remaining experimental studies used initiation–promotion protocols or tumour growth models following the transplantation of syngeneic tumour fragments, cells, or human cancer xenografts. The species used in these studies included both sexes of rats, mice and hamsters, all of which yielded positive results in at least one study. The types of rodent model systems studied included mammary adenocarcinoma/fibroadenoma, cancers of the peripheral nervous system and kidney, hepatocarcinoma, pancreatic adenocarcinoma, colon adenocarcinoma, prostate adenocarcinoma, squamous-cell carcinoma and fibrosarcoma, osteosarcoma and carcinosarcoma, melanoma, neuroblastoma, and undifferentiated neoplasms.

The model systems used to study the role of the central circadian function and its disruption on cancer development and/or growth encompassed the exposure of animals to chronic alterations in the light–dark environment (i.e. constant bright light, constant darkness, altered light–dark schedules, intermittent light during darkness, single light pulse during darkness). Other model systems used more focused experimental manipulations that included phase-shifting central circadian activity only (i.e. exposure to experimental chronic jet lag), suppression or ablation of the nocturnal circadian melatonin signal (i.e. pinealectomy or exposure to dim light during darkness), ablation of the central circadian activity and of melatonin production (i.e. induction of lesions in suprachiasmatic nuclei), clock gene mutations (i.e. mPer2 knockouts) and the impact of carcinogen administration at different circadian times on tumorigenesis. A specialized model system evaluated the acute proliferative activity of tissue-isolated melatonin-receptor-positive murine or human tumours perfused *in situ* with different physiological levels of melatonin from natural diurnal blood changes and artificial manipulation.

The major patterns of light–dark environments that have an impact on cancer development and/or growth (i.e. stimulation) are constant light exposure (two positive of three studies, five positive of six initiation–promotion studies, five positive of five tumour-growth studies), dim light during darkness (five positive of five studies), experimental chronic jet lag (two positive of two studies), and circadian timing of

carcinogens (four positive of four studies). Two conditions that produced no clear effects or even slowed tumour growth were light pulses during the dark period (two of two studies), and constant darkness (two of two studies). Mechanistically oriented animal studies specifically aimed at investigating the role of the pineal gland (i.e. pinealectomy-induced stimulation of cancer development and/or growth) and the nocturnal melatonin profile (i.e. inhibition of cancer proliferative activity) also had a major impact on cancer (18 positive of 26 studies). Furthermore, a limited number of studies on suprachiasmatic nuclei or clock genes yielded important results with respect to increased tumorigenesis (two positive of three studies).

5.4 Other relevant data

The evidence that relates laboratory investigations and mechanistic considerations to shiftwork-induced carcinogenesis can be divided into two basic fields: disturbance of the circadian system due to light at night with alteration of the sleep–activity pattern leading to potential melatonin suppression and circadian gene alterations; and sleep deprivation that results from the need to sleep when it is not readily possible and misaligned with the surrounding active daytime social environment.

The disturbance of the circadian system is studied at the level of the molecular circadian oscillation. Genes that are responsible for maintaining circadian rhythms have been identified, and may function as transcriptional factors and regulate expression of genes in cancer-related pathways, such as cell cycle, DNA repair, and apoptosis. Animal studies have shown that knockout of the circadian *Period* gene, *Per2*, promotes tumour development. Some evidence in humans links genetic polymorphisms in circadian genes to breast cancer and non-Hodgkin lymphoma, and functional loss of the *PERIOD* genes has been observed in various human tumours. Exposure to artificial light during the night has been demonstrated to disrupt circadian gene expression in mice and humans, which in turn, may alter circadian-regulated biological pathways. Because of their possible roles in tumorigenesis, the light-mediated dysfunction of circadian genes may provide a possible mechanism for the putative carcinogenic effect of light that may or may not involve melatonin.

The light-induced alteration of the circadian system is in part linked to the suppression of melatonin, which is secreted by the pineal gland and acts throughout the organism as a time signal. The suppression of melatonin leads to changes in the gonadotropic axis that specifically involves estrogens and androgens in experimental animals, and may be stimulatory or inhibitory depending on the species and the situation. In humans treated with low pharmacological doses of melatonin, few melatonin-induced changes were documented except a stimulation of prolactin. In animal studies, melatonin in the target sites interferes with the metabolism of estrogen through several metabolic pathways. No data clearly link nocturnal blood levels of endogenous melatonin with endogenous production of estradiol in women.

The decrease in endogenous melatonin may lead to diminished free radical scavenging that may induce local tissue damage, the extent and importance of which is not entirely clear at present.

Melatonin is a direct and indirect immunostimulant; its suppression leads to a state of immunodeficiency that is aggravated by the pronounced effects of sleep deprivation upon the immune system. Prolactin, a strong immunostimulant, is decreased during sleep deprivation.

Direct inhibitory effects of melatonin on tumour cell proliferation have been shown in several animal models not only at pharmacological but also at physiological concentrations.

Sleep deprivation is a common feature in most forms of shiftwork that involves night and/or early morning hours. Changes in the immune system have been shown to occur in partial (early or late night) sleep deprivation and comprise changes in the cytokine pattern that favours the Th2 group of cytokines and decreases Th1 cytokines (e.g. interferon γ) which act in cellular immune defence and in immune surveillance to counteract tumour growth. In the majority of studies of sleep deprivation, suppression of natural-killer-cell activity has been shown, and this also leads to a decrease in anti-tumour surveillance.

The evidence in support of shiftwork-induced carcinogenesis thus links events at the cellular level that affect cell proliferation and endocrine changes with hormonal constellations that promote endocrine-dependent cancers with defects in the immune surveillance that enhance tumour development and growth.

None of these changes stands in isolation; they are all linked to the disruption of the circadian system of shiftworkers and, in combination, may alter the risk of cancer through both tumour induction and promotion.

The experimental data from animal studies in several inter-related physiological systems are strongly suggestive of a causal link between circadian disruption and all its consequences and the development of malignant tumours. Human studies are suggestive of physiological effects that are possibly relevant to carcinogenesis.

6. Evaluation and Rationale

6.1 Cancer in humans

There is *limited evidence* in humans for the carcinogenicity of shiftwork that involves night work.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of light during the daily dark period (biological night).

6.3 Overall evaluation

Shiftwork that involves circadian disruption is *probably carcinogenic to humans (Group 2A)*.

LIST OF ABBREVIATIONS

13-HODE	13-hydroxyoctadecadienoic acid
15-min TWA	15-minute time-weighted average
ACGIH	American Conference Of Government Industrial Hygienists
ACTH	Adrenocorticotropic hormone
aMT6s	6-sulfatoxymelatonin
ARNTL	Aryl hydrocarbon receptor nuclear translocator-like
BCG	Bacillus Calmette-Guérin
BEI	Biological Exposure Index
bHLH	Basic–helix–loop–helix
BMAL1	Brain and muscle Arnt-like protein-1
cAMP	Cyclic adenosine monophosphate
CEI	Cumulative exposure index
CH2=CHCHO	Acrolein
CH4	Methane
CI	Confidence interval
CO	Carbon monoxide
CO2	Carbon dioxide
CRF	Corticotropin-releasing factor
CRH	Corticotropin-releasing hormone
CRY1	Cryptochrome 1
CRY2	Cryptochrome 2
CSNK1E	Casein kinase I epsilon
CYP	Cytochrome P450
DEGME	2-(2-Methoxyethoxy)ethanol
DEGEE	2-(2-Ethoxyethoxy)ethanol
DEGBE	2-(2-Butoxyethoxy)ethanol
PGME	1-Methoxy-2-propanol
PGBE	1-Butoxy-2-propanol
DPGME	1-(2-Methoxy-1-methylethoxy)-2-propanol
DHEA	Dehydroepiandrosterone
DHEA-S	Dehydroepiandrosterone sulfate
DMBA	9,10-Dimethyl-1,2-benzanthracene
E2	Estradiol

EBCLIS	Electromagnetic Fields and Breast Cancer on Long Island Study
EC	European Community
EGEEA	Ethylene glycol monoethyl ether acetate
ELISA	Enzyme-linked immunosorbant assay
EPA	The Federal Environmental Protection Agency
ER/PgR	Estrogen receptor/progesterone receptor
ERK1/2	Extracellular signal-related kinase
Erα	Estrogen receptor α
EU	European Union
FEV1	Forced Expiratory Volume in 1 Second
FSH	Follicle-stimulating hormone
FVC	Force Vital Capacity
GC-MS	Gas chromatography-mass spectrometry
GH	Growth hormone
GnRH	Gonadotropin-releasing hormone
GSD	Geometric standard deviation
GSH	Glutathione
GST	Glutathione-S-transferase
HAZMAT	Hazardous materials
HCDBD	Heptachlorodibenzodioxin
hCG	Human chorionic gonadotropin
HCl	Hydrochloric acid
HCN	Hydrogen cyanide
HDI	1,6-Hexamethylene diisocyanate
Hth-Pit-Adr	Hypothalamic-pituitary-adrenal
Hth-Pit-Gnd	Hypothalamus-pituitary-gonadal
Hth-Pit-Ova	Hypothalamic-pituitary-ovarian
Hth-Pit-Thy	Hypothalamic-pituitary-thyroid
HVLP	High-volume low-pressure
IAFF	International Association of Fire Fighters
IDR	Incidence density ratio
IL-10	Interleukin-10
ILO	International labour organization
IMO	International Maritime Organization
IOELV	Indicative Occupational Exposure Limit Values
ISIC	International Standard Industrial Classification
JEM	Job exposure matrix
LC-MS/MS	Liquid chromatography tandem mass spectrometry
LD12:12	12 Hours of light and 12 hours of darkness
LH	Luteinizing hormone
MDCSS	Metropolitan Detroit Cancer Surveillance System
MEK	Extracellular signal-regulated kinase kinase

MESOR	Circadian-rhythm-corrected mean value
MM1	Melanotic Melanoma No. 1
MOR	Mortality odds ratio
ns	Not significant
NAFTA	North American Free Trade Agreement
NCI	National Cancer Institute
NCO	Free isocyanate groups
ND	Not detected
NPAS2	Neuronal PAS domain protein 2
NFPA	National Fire Protection Association
NG	Not given
NHS	Nurses' Health Study cohorts
NJ	New Jersey;
NK	Natural killer
NOx	Nitrogen oxides
NR	Not reported
NZCR	New Zealand Cancer Registry
OCISS	Occupational Cancer Incidence Surveillance System
RAEB	Refractory anaemia with excess blasts
OEL	Occupational exposure limit
OEM	Original equipment manufacturer
p.o.	Per oral
PAH	Polycyclic aromatic hydrocarbon
PAS	PER–ARNT–single-minded protein
PCB	Polychlorinated-biphenyls
PCBs	Polychlorinated biphenyls
PCBz	Polychlorobenzenes
PCDDs	Polychlorinated-dibenzodioxins
PCDF	Polychlorinated-dibenzofurans
PCMR	Proportionate cancer mortality ratios
PEI	Protective Effectiveness Index
PEL	Permissible Exposure Limit
Per1	Period 1
Per2	Period 2
Per3	Period 3
PMR	Proportional mortality ratio
PRR	Proportionate risk ratio
PUR	Polyurethane
PVC	Polyvinyl chloride
REM	Rapid eye movement
Ret-Hth-Pin	Retinal-hypothalamic-pineal
RIA	Radioimmunoassay
RR	Rate ratio or relative risk

SCE	Sister chromatid exchanges
SCN	Suprachiasmatic nuclei
SCOEL	Scientific Committee on Occupational Exposure Limits
SD	Standard deviation
SE	Standard Error
SEER	Surveillance, Epidemiology and End Results
SEM	Standard error of the mean
SES	Socioeconomic status
SIR	Standardized incidence ratio
SMOR	Standardized morbidity odds ratios
SMR	Standardized mortality ratio
SO2	Sulfur dioxide
SOP	Standard operating procedures
SPMRs	Standardized proportional mortality ratios
STEL	Short-term exposure limit
SVOC	Semivolatile organic compound
TCDD	2,3,7,8-tetrachlorodibenzodioxin
TEQ	2,3,7,8-tetrachlorodibenzodioxin equivalent
Th1	Type 1 T-helper1
Th2	Type 2 T-helper2
TLV	Threshold limit value
TSH	Thyroid stimulating hormone
TWA	Time-weighted average
UV	Ultraviolet
VOC	Volatile organic compound

SUPPLEMENTARY CORRIGENDA TO VOLUMES 1–97

Volume 97

p. 93, first paragraph, line 7: *replace* 0.84 (95% CI, 0.74–0.85) *by* 1.64 (95% CI, 0.85–2.87). This error has already been corrected in the online version of Volume 97.

CUMULATIVE CROSS INDEX TO *IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS*

The volume, page and year of publication are given. References to corrigenda are given in parentheses.

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List of IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*

Volume 1
Some Inorganic Substances, Chlorinated Hydrocarbons, Aromatic Amines, *N*-Nitroso Compounds, and Natural Products
1972; 184 pages (out-of-print)

Volume 2
Some Inorganic and Organo-metallic Compounds
1973; 181 pages (out-of-print)

Volume 3
Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds
1973; 271 pages (out-of-print)

Volume 4
Some Aromatic Amines, Hydrazine and Related Substances, *N*-Nitroso Compounds and Miscellaneous Alkylating Agents
1974; 286 pages (out-of-print)

Volume 5
Some Organochlorine Pesticides
1974; 241 pages (out-of-print)

Volume 6
Sex Hormones
1974; 243 pages (out-of-print)

Volume 7
Some Anti-Thyroid and Related Substances, Nitrofurans and Industrial Chemicals
1974; 326 pages (out-of-print)

Volume 8
Some Aromatic Azo Compounds
1975; 357 pages (out-of-print)

Volume 9
Some Aziridines, *N*-, *S*- and *O*-Mustards and Selenium
1975; 268 pages (out-of-print)

Volume 10
Some Naturally Occurring Substances
1976; 353 pages (out-of-print)

Volume 11
Cadmium, Nickel, Some Epoxides, Miscellaneous Industrial Chemicals and General Considerations on Volatile Anaesthetics
1976; 306 pages (out-of-print)

Volume 12
Some Carbamates, Thio-carbamates and Carbazides
1976; 282 pages (out-of-print)

Volume 13
Some Miscellaneous Pharmaceutical Substances
1977; 255 pages

Volume 14
Asbestos
1977; 106 pages (out-of-print)

Volume 15
Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals
1977; 354 pages (out-of-print)

Volume 16
Some Aromatic Amines and Related Nitro Compounds—Hair Dyes, Colouring Agents and Miscellaneous Industrial Chemicals
1978; 400 pages

Volume 17
Some *N*-Nitroso Compounds
1978; 365 pages

Volume 18
Polychlorinated Biphenyls and Polybrominated Biphenyls
1978; 140 pages (out-of-print)

Volume 19
Some Monomers, Plastics and Synthetic Elastomers, and Acrolein
1979; 513 pages (out-of-print)

Volume 20
Some Halogenated Hydrocarbons
1979; 609 pages (out-of-print)

Volume 21
Sex Hormones (II)
1979; 583 pages

Volume 22
Some Non-Nutritive Sweetening Agents
1980; 208 pages

Volume 23
Some Metals and Metallic Compounds
1980; 438 pages (out-of-print)

Volume 24
Some Pharmaceutical Drugs
1980; 337 pages

Volume 25
Wood, Leather and Some Associated Industries
1981; 412 pages

Volume 26
Some Antineoplastic and Immunosuppressive Agents
1981; 411 pages (out-of-print)

Volume 27
Some Aromatic Amines, Anthraquinones and Nitroso Compounds, and Inorganic Fluorides Used in Drinking-water and Dental Preparations
1982; 341 pages (out-of-print)

Volume 28
The Rubber Industry
1982; 486 pages (out-of-print)

Volume 29
Some Industrial Chemicals and Dyestuffs
1982; 416 pages (out-of-print)

Volume 30
Miscellaneous Pesticides
1983; 424 pages (out-of-print)

Volume 31
Some Food Additives, Feed Additives and Naturally Occurring Substances
1983; 314 pages (out-of-print)

Volume 32
Polynuclear Aromatic Compounds, Part 1: Chemical, Environmental and Experimental Data
1983; 477 pages (out-of-print)

Volume 33
Polynuclear Aromatic Compounds, Part 2: Carbon Blacks, Mineral Oils and Some Nitroarenes
1984; 245 pages (out-of-print)

Volume 34
Polynuclear Aromatic Compounds, Part 3: Industrial Exposures in Aluminium Production, Coal Gasification, Coke Production, and Iron and Steel Founding
1984; 219 pages (out-of-print)

Volume 35
Polynuclear Aromatic Compounds, Part 4: Bitumens, Coal-tars and Derived Products, Shale-oils and Soots
1985; 271 pages

Volume 36
Allyl Compounds, Aldehydes, Epoxides and Peroxides
1985; 369 pages

Volume 37
Tobacco Habits Other than Smoking; Betel-Quid and Areca-Nut Chewing; and Some Related Nitrosamines
1985; 291 pages (out-of-print)

Volume 38
Tobacco Smoking
1986; 421 pages

Volume 39
Some Chemicals Used in Plastics and Elastomers
1986; 403 pages (out-of-print)

Volume 40
Some Naturally Occurring and Synthetic Food Components, Furocoumarins and Ultraviolet Radiation
1986; 444 pages (out-of-print)

Volume 41
Some Halogenated Hydrocarbons and Pesticide Exposures
1986; 434 pages (out-of-print)

Volume 42
Silica and Some Silicates
1987; 289 pages

Volume 43
Man-Made Mineral Fibres and Radon
1988; 300 pages (out-of-print)

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Alcohol Drinking
1988; 416 pages

Volume 45
Occupational Exposures in Petroleum Refining; Crude Oil and Major Petroleum Fuels
1989; 322 pages

Volume 46
Diesel and Gasoline Engine Exhausts and Some Nitroarenes
1989; 458 pages

Volume 47
Some Organic Solvents, Resin Monomers and Related Compounds, Pigments and Occupational Exposures in Paint Manufacture and Painting
1989; 535 pages (out-of-print)

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Some Flame Retardants and Textile Chemicals, and Exposures in the Textile Manufacturing Industry
1990; 345 pages

Volume 49
Chromium, Nickel and Welding
1990; 677 pages

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Pharmaceutical Drugs
1990; 415 pages

Volume 51
Coffee, Tea, Mate, Methylxanthines and Methylglyoxal
1991; 513 pages

Volume 52
Chlorinated Drinking-water; Chlorination By-products; Some Other Halogenated Compounds; Cobalt and Cobalt Compounds
1991; 544 pages

Volume 53
Occupational Exposures in Insecticide Application, and Some Pesticides
1991; 612 pages

Volume 54
Occupational Exposures to Mists and Vapours from Strong Inorganic Acids; and Other Industrial Chemicals
1992; 336 pages

Volume 55
Solar and Ultraviolet Radiation
1992; 316 pages

Volume 56
Some Naturally Occurring Substances: Food Items and Constituents, Heterocyclic Aromatic Amines and Mycotoxins
1993; 599 pages

Volume 57
Occupational Exposures of Hairdressers and Barbers and Personal Use of Hair Colourants; Some Hair Dyes, Cosmetic Colourants, Industrial Dyestuffs and Aromatic Amines
1993; 428 pages

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Beryllium, Cadmium, Mercury, and Exposures in the Glass Manufacturing Industry
1993; 444 pages

Volume 59
Hepatitis Viruses
1994; 286 pages

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Some Industrial Chemicals
1994; 560 pages

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Schistosomes, Liver Flukes and *Helicobacter pylori*
1994; 270 pages

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Wood Dust and Formaldehyde
1995; 405 pages

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Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals
1995; 551 pages

Volume 64
Human Papillomaviruses
1995; 409 pages

Volume 65
Printing Processes and Printing Inks, Carbon Black and Some Nitro Compounds
1996; 578 pages

Volume 66
Some Pharmaceutical Drugs
1996; 514 pages

Volume 67
Human Immunodeficiency Viruses and Human T-Cell Lymphotropic Viruses
1996; 424 pages

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Silica, Some Silicates, Coal Dust and *para*-Aramid Fibrils
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Polychlorinated Dibenzo-*para*-Dioxins and Polychlorinated Dibenzofurans
1997; 666 pages

Volume 70
Epstein-Barr Virus and Kaposi's Sarcoma Herpesvirus/Human Herpesvirus 8
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Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide
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Hormonal Contraception and Post-menopausal Hormonal Therapy
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Some Chemicals that Cause Tumours of the Kidney or Urinary Bladder in Rodents and Some Other Substances
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Surgical Implants and Other Foreign Bodies
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Ionizing Radiation, Part 1, X-Radiation and γ-Radiation, and Neutrons
2000; 492 pages

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Some Antiviral andAntineoplastic Drugs, and Other Pharmaceutical Agents
2000; 522 pages

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Some Industrial Chemicals
2000; 563 pages

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2001; 595 pages

Volume 79
Some Thyrotropic Agents
2001; 763 pages

Volume 80
Non-Ionizing Radiation, Part 1: Static and Extremely Low-Frequency (ELF) Electric and Magnetic Fields
2002; 429 pages

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Man-made Vitreous Fibres
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Some Traditional Herbal Medicines, Some Mycotoxins, Naphthalene and Styrene
2002; 590 pages

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Tobacco Smoke and Involuntary Smoking
2004; 1452 pages

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Some Drinking-Water Disinfectants and Contaminants, including Arsenic
2004; 512 pages

Volume 85
Betel-quid and Areca-nut Chewing and Some Areca-nut-derived Nitrosamines
2004; 334 pages

Volume 86
Cobalt in Hard Metals and Cobalt Sulfate, Gallium Arsenide, Indium Phosphide and Vanadium Pentoxide
2006; 330 pages

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Inorganic and Organic Lead Compounds
2006; 506 pages

Volume 88
Formaldehyde, 2-Butoxyethanol and 1-tert-Butoxypropan-2-ol
2006; 478 pages

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Smokeless Tobacco and Some Tobacco-specific N-Nitrosamines
2007; 626 pages

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Human Papillomaviruses
2007; 670 pages

Volume 91
Combined Estrogen-Progestogen Contraceptives and Combined Estrogen-Progestogen Menopausal Therapy
2007; 528 pages

Volume 92
Some Non-heterocyclic Polycyclic Aromatic Hydrocarbons and Some Related Exposures
2010; 853 pages

Volume 93
Carbon Black, Titanium Dioxide, and Talc
(in preparation)

Volume 94
Ingested Nitrate and Nitrite, and Cyanobacterial Peptide Toxins
2010; 450 pages

Volume 95
Household Use of Solid Fuels and High-temperature Frying
2010; 430 pages

Volume 96
Alcohol Consumption
(in preparation)

Volume 97
1,3-Butadiene, Ethylene Oxide and Vinyl Halides (Vinyl Fluoride, Vinyl Chloride and Vinyl Bromide)
2008; 510 pages

Volume 98
Painting, Firefighting, and Shiftwork
2010; 806 pages

Supplement No. 1
Chemicals and Industrial Processes Associated with Cancer in Humans (*IARC Monographs*, Volumes 1 to 20)
1979; 71 pages (out-of-print)

Supplement No. 2
Long-term and Short-term Screening Assays for Carcinogens: A Critical Appraisal
1980; 426 pages (out-of-print)
(updated as IARC Scientific Publications No. 83, 1986)

Supplement No. 3
Cross Index of Synonyms and Trade Names in Volumes 1 to 26 of the *IARC Monographs*
1982; 199 pages (out-of-print)

Supplement No. 4
Chemicals, Industrial Processes and Industries Associated with Cancer in Humans (*IARC Monographs*, Volumes 1 to 29)
1982; 292 pages (out-of-print)

Supplement No. 5
Cross Index of Synonyms and Trade Names in Volumes 1 to 36of the *IARC Monographs*
1985; 259 pages (out-of-print)

Supplement No. 6
Genetic and Related Effects: An Updating of Selected *IARC Monographs* from Volumes 1to 42
1987; 729 pages (out-of-print)

Supplement No. 7
Overall Evaluations of Carcinogenicity: An Updating of *IARC Monographs* Volumes1–42
1987; 440 pages (out-of-print)

Supplement No. 8
Cross Index of Synonyms and Trade Names in Volumes 1 to 46of the *IARC Monographs*
1990; 346 pages (out-of-print)