IARC MONOGRAPHS

WELDING, MOLYBDENUM TRIOXIDE, AND INDIUM TIN OXIDE

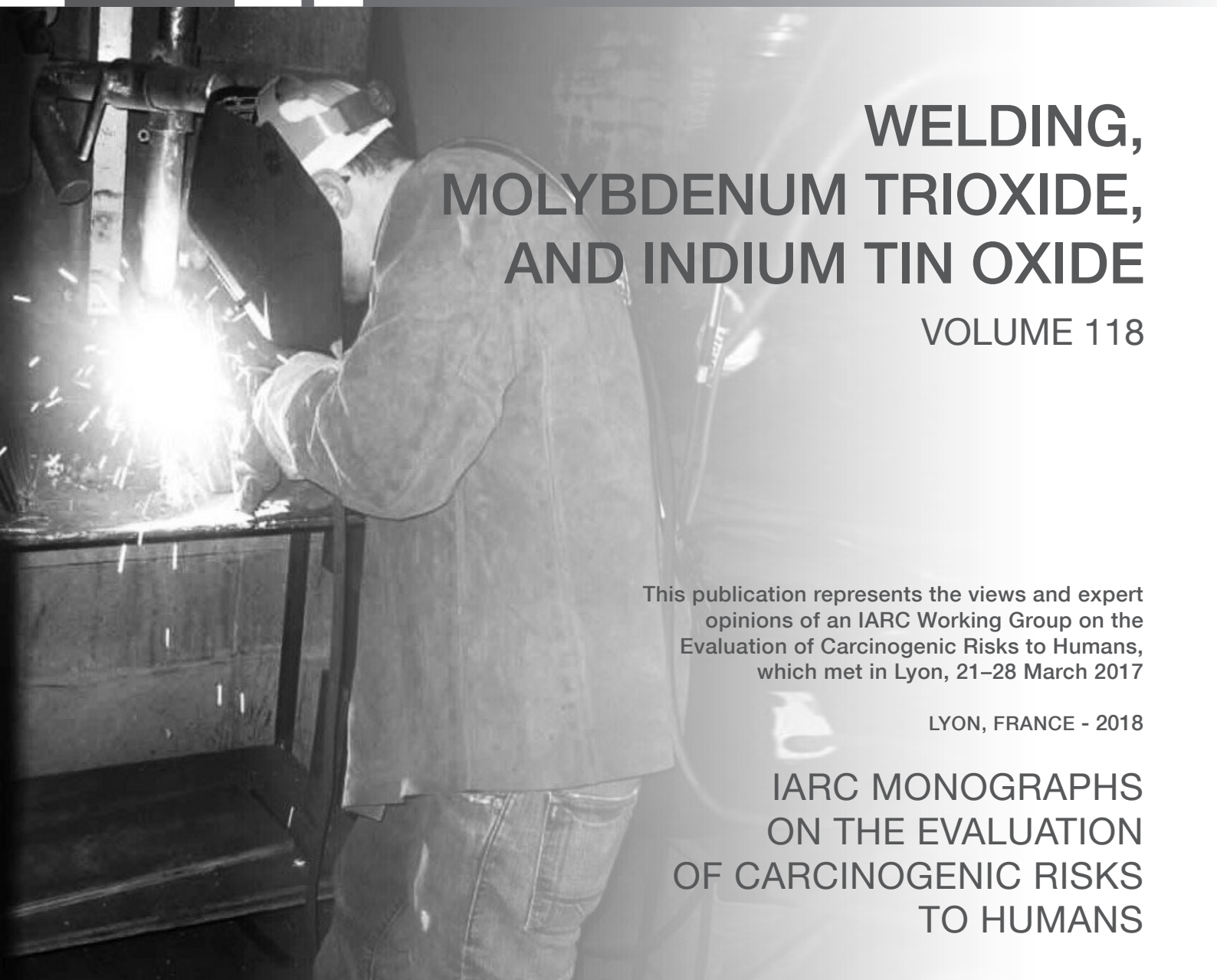
VOLUME 118

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

IARC MONOGRAPHS



WELDING, MOLYBDENUM TRIOXIDE, AND INDIUM TIN OXIDE

VOLUME 118

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 21–28 March 2017

LYON, FRANCE - 2018

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

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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 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 European Commission Directorate-General for Employment, Social Affairs, and Inclusion, initially by the Unit of Health, Safety and Hygiene at Work, and since 2014 by the European Union Programme for Employment and Social Innovation "EaSI" (2014–2020) (for further information please consult: http://ec.europa.eu/social/easi). Support has also been provided 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 United States National Cancer Institute, the United States National Institute of Environmental Health Sciences, the United States Department of Health and Human Services, or the European Commission.

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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. 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. Similarly, identification of cancer sites with *sufficient evidence* or *limited evidence* in humans should not be viewed as precluding the possibility that an agent may cause cancer at other sites.

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.

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[3] Each Observer agreed to respect the Guidelines for Observers at *IARC Monographs* meetings. Observers did not serve as Meeting Chair or Subgroup Chair, draft any part of a Monograph or participate in the evaluations. They also agreed not to contact participants before the meeting, not to lobby them at any time, not to send them written materials, and not to offer them meals or other favours. IARC asked and reminded Working Group Members to report any contact or attempt to influence that they may have encountered, either before or during the meeting.

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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 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 web site (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

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

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

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

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

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 web site (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 web site (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.

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, before 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 web site 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:

Exposure data

Studies of cancer in humans

Studies of cancer in experimental animals

Mechanistic and other relevant data

Summary

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 several 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.

First, 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.

Second, 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.

Third, 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.

Several 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 first 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 nonlinearity 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 web site (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, 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.

References

Bieler GS, Williams RL (1993). Ratio estimates, the delta method, and quantal response tests for increased carcinogenicity. *Biometrics*, 49:793–801. doi:10.2307/2532200 PMID:8241374

Breslow NE, Day NE (1980). Statistical methods in cancer research. Volume I - The analysis of case-control studies. *IARC Sci Publ*, 32:5–338. PMID:7216345

Breslow NE, Day NE (1987). Statistical methods in cancer research. Volume II–The design and analysis of cohort studies. *IARC Sci Publ*, 82:1–406. PMID:3329634

Buffler P, Rice J, Baan R, et al. (2004). Workshop on mechanisms of carcinogenesis: contributions of molecular epidemiology. Lyon, 14–17 November 2001. Workshop report. *IARC Sci Publ*, 157:1–27. PMID:15055286

Capen CC, Dybing E, Rice JM, Wilbourn JD (1999). Species differences in thyroid, kidney and urinary bladder carcinogenesis. Proceedings of a consensus conference. Lyon, France, 3–7 November 1997. *IARC Sci Publ*, 147:1–225. PMID:10627184

Cogliano V, Baan R, Straif K, et al. (2005). Transparency in IARC Monographs. *Lancet Oncol*, 6:747. doi:10.1016/S1470-2045(05)70380-6

Cogliano VJ, Baan RA, Straif K, et al. (2004). The science and practice of carcinogen identification and evaluation. *Environ Health Perspect*, 112:1269–1274. doi:10.1289/ehp.6950 PMID:15345338

Dunson DB, Chen Z, Harry J (2003). A Bayesian approach for joint modeling of cluster size and subunit-specific outcomes. *Biometrics*, 59:521–530. doi:10.1111/1541-0420.00062 PMID:14601753

Fung KY, Krewski D, Smythe RT (1996). A comparison of tests for trend with historical controls in carcinogen bioassay. *Can J Stat*, 24:431–454. doi:10.2307/3315326

Gart JJ, Krewski D, Lee PN, et al. (1986). Statistical methods in cancer research. Volume III–The design and analysis of long-term animal experiments. *IARC Sci Publ*, 79:1–219. PMID:3301661

Greenland S (1998). Meta-analysis. In: Rothman KJ, Greenland S, editors. Modern epidemiology. Philadelphia: Lippincott Williams & Wilkins, pp. 643–673.

Greim H, Gelbke H-P, Reuter U, et al. (2003). Evaluation of historical control data in carcinogenicity studies. *Hum Exp Toxicol*, 22:541–549. doi:10.1191/0960327103ht394oa PMID:14655720

Haseman JK, Huff J, Boorman GA (1984). Use of historical control data in carcinogenicity studies in rodents. *Toxicol Pathol*, 12:126–135. doi:10.1177/019262338401200203 PMID:11478313

Hill AB (1965). The environment and disease: Association or causation? *Proc R Soc Med*, 58:295–300. PMID:14283879

Hoel DG, Kaplan NL, Anderson MW (1983). Implication of nonlinear kinetics on risk estimation in carcinogenesis. *Science*, 219:1032–1037. doi:10.1126/science.6823565 PMID:6823565

Huff JE, Eustis SL, Haseman JK (1989). Occurrence and relevance of chemically induced benign neoplasms in long-term carcinogenicity studies. *Cancer Metastasis Rev*, 8:1–22. doi:10.1007/BF00047055 PMID:2667783

IARC (1977). IARC Monographs Programme on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Preamble (IARC Intern Tech Rep No. 77/002).

IARC (1978). Chemicals with sufficient evidence of carcinogenicity in experimental animals – IARC Monographs Volumes 1–17 (IARC Intern Tech Rep No. 78/003).

IARC (1979). Criteria to select chemicals for IARC Monographs (IARC Intern Tech Rep No. 79/003).

IARC (1982). Chemicals, industrial processes and industries associated with cancer in humans (IARC Monographs, volumes 1 to 29). *IARC Monogr Eval Carcinog Risk Chem Hum Suppl*, 4:1–292. Available from: http://publications.iarc.fr/136 PMID:6963265

IARC (1983). Approaches to classifying chemical carcinogens according to mechanism of action (IARC Intern Tech Rep No. 83/001).

IARC (1987). Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1 to 42. *IARC Monogr Eval Carcinog Risks Hum Suppl*, 7:1–440. Available from: http://publications.iarc.fr/139 PMID:3482203

IARC (1988). Report of an IARC Working Group to Review the Approaches and Processes Used to Evaluate the Carcinogenicity of Mixtures and Groups of Chemicals (IARC Intern Tech Rep No. 88/002).

IARC (1991). A consensus report of an IARC Monographs Working Group on the Use of Mechanisms of Carcinogenesis in Risk Identification (IARC Intern Tech Rep No. 91/002).

IARC (2004). Some drinking-water disinfectants and contaminants, including arsenic. *IARC Monogr Eval Carcinog Risks Hum*, 84:1–477. Available from: http://publications.iarc.fr/102 PMID:15645577

IARC (2005). Report of the Advisory Group to Recommend Updates to the Preamble to the IARC Monographs (IARC Intern Rep No. 05/001).

IARC (2006). Report of the Advisory Group to Review the Amended Preamble to the IARC Monographs (IARC Intern Rep No. 06/001).

McGregor DB, Rice JM, Venitt S (1999). The use of short-and medium-term tests for carcinogens and data on genetic effects in carcinogenic hazard evaluation. Consensus report. *IARC Sci Publ*, 146:1–18. PMID:10353381

Montesano R, Bartsch H, Vainio H, et al., editors (1986). Long-term and short-term assays for carcinogenesis—a critical appraisal. *IARC Sci Publ*, 83:1–564. PMID:3623675

OECD (2002). Guidance notes for analysis and evaluation of chronic toxicity and carcinogenicity studies (Series on Testing and Assessment No. 35), Paris: OECD.

Peto R, Pike MC, Day NE, et al. (1980). Guidelines for simple, sensitive significance tests for carcinogenic effects in long-term animal experiments. *IARC Monogr Eval Carcinog Risk Chem Hum Suppl*, 2(Suppl):311–426. PMID:6935185

Portier CJ, Bailer AJ (1989). Testing for increased carcinogenicity using a survival-adjusted quantal response test. *Fundam Appl Toxicol*, 12:731–737. doi:10.1016/0272-0590(89)90004-3 PMID:2744275

Sherman CD, Portier CJ, Kopp-Schneider A (1994). Multistage models of carcinogenesis: an approximation for the size and number distribution of late-stage clones. *Risk Anal*, 14:1039–1048. doi:10.1111/j.1539-6924.1994.tb00074.x PMID:7846311

Stewart BW, Kleihues P, editors (2003). World cancer report, Lyon: IARC.

Tomatis L, Aitio A, Wilbourn J, Shuker L (1989). Human carcinogens so far identified. *Jpn J Cancer Res*, 80:795–807. doi:10.1111/j.1349-7006.1989.tb01717.x PMID:2513295

Toniolo P, Boffetta P, Shuker DEG, et al. (1997). Proceedings of the workshop on application of biomarkers to cancer epidemiology. Lyon, France, 20–23 February 1996. *IARC Sci Publ*, 142:1–318. PMID:9410826

Vainio H, Magee P, McGregor D, McMichael A (1992). Mechanisms of carcinogenesis in risk identification. IARC Working Group Meeting. Lyon, 11–18 June 1991. *IARC Sci Publ*, 116:1–608. PMID:1428077

Vainio H, Wilbourn JD, Sasco AJ, et al. (1995). [Identification of human carcinogenic risks in IARC monographs.] *Bull Cancer*, 82:339–348. [French] PMID:7626841

Vineis P, Malats N, Lang M et al., editors (1999). Metabolic polymorphisms and susceptibility to cancer. *IARC Sci Publ*, 148:1–510. PMID:10493243

Wilbourn J, Haroun L, Heseltine E, et al. (1986). Response of experimental animals to human carcinogens: an analysis based upon the IARC Monographs programme. *Carcinogenesis*, 7:1853–1863. doi:10.1093/carcin/7.11.1853 PMID:3769134

GENERAL REMARKS

This one-hundred-and-eighteenth volume of the *IARC Monographs* contains evaluations of the carcinogenic hazard to humans of welding (welding fumes and ultraviolet radiation from welding), molybdenum trioxide, and indium tin oxide. Welding and indium tin oxide were accorded high priority for evaluation in the *IARC Monographs* programme by an Advisory Group that met in 2014 (Straif et al., 2014).

Welding fumes were classified as *carcinogenic to humans* (Group 1) by the present Working Group, an upgrade from the earlier classification of fumes as *possibly carcinogenic to humans* (Group 2B) in 1989 (IARC, 1990). Ultraviolet radiation from welding was also evaluated for the first time and classified as *carcinogenic to humans* (Group 1), in line with previous evaluations of ultraviolet radiation as a human carcinogen (*IARC Monographs*, Volume 100D; IARC, 2012). Molybdenum trioxide and indium tin oxide had not been previously evaluated by the *IARC Monographs* programme.

A summary of the findings of this volume appears in *The Lancet Oncology* (Guha et al., 2017).

Indium tin oxide

Indium tin oxide is used in the production of liquid crystal displays, touch screens, solar panels and photovoltaics (NTP, 2009). Exposure primarily occurs in occupational settings where indium tin oxide is produced or processed, or where elemental indium is recycled and recovered from indium tin oxide. Indium tin oxide became an occupational exposure of interest in the early 2000s, when a series of case reports from Japanese workers with interstitial pulmonary disease and pulmonary fibrosis related to indium exposure appeared in the literature (Homma et al., 2003; Taguchi & Chonan, 2006; Omae et al., 2011). Currently no data are available to estimate the number of people exposed to indium tin oxide, and there are no published observational epidemiological studies of cancer associated with exposure to indium tin oxide. However, the use, recycling, and disposal of electronics continues to increase worldwide.

Studies in vivo and in vitro have suggested that the generation of indium from the solubilization of particles (for example, indium tin oxide and indium phosphide), as well as the sintering of indium tin oxide, contribute to the lung toxicity and perhaps carcinogenicity of these particles. In a previously reported 2-year inhalation study, indium phosphide particles were carcinogenic to the lung and other tissues in male and female mice and rats, even at the lowest concentration tested (0.03 mg/m^3) and with a short exposure duration (22 weeks for 0.1 and 0.3 mg/m^3) (Volume 86; IARC, 2006). The increased potency of indium phosphide compared with indium

tin oxide particles with regard to toxicity and carcinogenicity may be due in part to the greater breakdown of indium phosphide to generate 'free' indium.

In the 2-year studies of inhalation with indium tin oxide, the lowest exposure concentration tested was 0.01 mg/m^3, which was one order of magnitude lower than the occupational exposure limit established by the American Conference of Governmental Industrial Hygienists (ACGIH) and the recommended exposure limit established by the National Institute for Occupational Safety and Health (NIOSH) for indium. In the 2-year studies with indium phosphide, 0.01 mg/m^3 was not tested. Despite this low exposure concentration for indium tin oxide, 0.01 mg/m^3 induced malignant tumours of the lung in male and female rats. Also, exposure to indium tin oxide at the highest concentration (0.1 mg/m^3) was only for a short duration (26 weeks), but induced malignant tumours of the lung in male and female rats.

References

Guha N, Loomis D, Guyton KZ, Grosse Y, El Ghissassi F, Bouvard V, et al.; International Agency for Research on Cancer Monograph Working Group (2017). Carcinogenicity of welding, molybdenum trioxide, and indium tin oxide. *Lancet Oncol*, 18(5):581–2. doi:10.1016/S1470-2045(17)30255-3 PMID:28408286

Homma T, Ueno T, Sekizawa K, Tanaka A, Hirata M (2003). Interstitial pneumonia developed in a worker dealing with particles containing indium-tin oxide. *J Occup Health*, 45(3):137–9. doi:10.1539/joh.45.137 PMID:14646287

IARC (1990). Chromium, nickel and welding. *IARC Monogr Eval Carcinog Risks Hum*, 49:1–648. Available from: http://publications.iarc.fr/67 PMID:2232124

IARC (2006). Cobalt in hard metals and cobalt sulfate, gallium arsenide, indium phosphide and vanadium pentoxide. *IARC Monogr Eval Carcinog Risks Hum*, 86:1–294. Available from: http://publications.iarc.fr/104 PMID:16906675

IARC (2012). Radiation. *IARC Monogr Eval Carcinog Risks Hum*, 100D:1–437. Available from: http://publications.iarc.fr/121 PMID:23189752

NTP (2009). Chemical information profile for indium tin oxide [CAS No. 50926-11-9]. Research Triangle Park, (NC), USA: National Toxicology Program, National Institute of Environmental Health Sciences, National Institutes of Health, United States Department of Health and Human Services.

Omae K, Nakano M, Tanaka A, Hirata M, Hamaguchi T, Chonan T (2011). Indium lung–case reports and epidemiology. *Int Arch Occup Environ Health*, 84(5):471–7. doi:10.1007/s00420-010-0575-6 PMID:20886351

Straif K, Loomis D, Guyton K, Grosse Y, Lauby-Secretan B, El Ghissassi F, et al. (2014). Future priorities for the IARC Monographs. *Lancet Oncol*, 15(7):683–4. doi:10.1016/S1470-2045(14)70168-8

Taguchi O, Chonan T (2006). [Three cases of indium lung.] *Nihon Kokyuki Gakkai Zasshi*, 44(7):532–6. [Japanese] PMID:16886812

WELDING

1. EXPOSURE DATA

1.1 Description of major welding processes and materials

Welding is a broad term for the process of joining metals through coalescence (AWS, 2010). Welding techniques tend to be broadly classified as arc welding or gas welding. Arc welding uses electricity to generate an arc, whereas gas or oxyfuel welding (ISO 4063:2009 process numbers 3, 31, 311, 312, and 313) uses fuel gases such as acetylene or hydrogen to generate heat. Welding results in concurrent exposures including welding fumes, gases, and ionizing and non-ionizing radiation, and coexposures from other sources such as asbestos and solvents (Table 1.1).

Welding fumes are produced when metals are heated above their melting point, vapourize and condense into fumes. The fumes consist of predominantly fine solid particles with an aerodynamic diameter of less than 1 μm, and are a complex mixture of particles from the wire or electrode, base metal, or any coatings on the base metal. They consist mainly of metal oxides, silicates, and fluorides. Exposure to various gases also occurs during welding, such as nitrogen oxides (NO_x), carbon monoxide (CO), or ozone (O_3). Welding fumes and welding gases are distinct in that fumes contain solid particles that are temporarily suspended in the air due to a solid material being heated (such as metals), whereas gases are molecules in a gaseous state in the ambient air that have been generated by or are used as part of the welding process (e.g. the shielding gas) (ISO, 2009).

While there are many welding processes routinely employed in occupational settings, the most common arc welding processes are manual metal arc (MMA, ISO No. 111), gas metal arc (GMA, ISO No. 13), flux-cored arc (FCA, ISO Nos 114 and 136), gas tungsten arc (GTA, ISO No. 14), and submerged arc (SA, ISO No. 12) (Table 1.2 and Table 1.3). Electric resistance welding (ER, ISO Nos 21 and 22) is also commonly used for spot or seam welding, and uses electric currents and force to generate heat. In occupational settings, these processes are most commonly used to weld mild steel (MS, low carbon) or stainless steel (SS). Flame cutting (ISO No. 81), the process of using oxygen (O) and a fuel to cut a metal, is a closely related process that is often grouped occupationally with welding (ISO, 2009). Other processes closely related to welding, and often performed by welders, include gouging, brazing, carbon arc or plasma arc cutting, and soldering (broadly described by ISO Nos 8 and 9) (Burgess, 1995). An overview of all welding and allied processes is given in ISO standard 4063 (ISO, 2009).

1.1.1 History of welding processes

With epidemiological studies of welders spanning the 20th and 21st centuries, a brief mention of how welding has changed during this period and when welding processes became used commercially is warranted. A carbon arc torch was patented in 1881, and gas welding and

Table 1.1 Occupational exposures of welders that have been evaluated by the *IARC Monographs*

Agent	Evidence for carcinogenicity		Overall evaluation	Most recent volume (year)	Occurrence	Welding types	Organ sites (sufficient or limited evidence in humans)
	Humans	Animals					
Arsenic and inorganic arsenic compounds	Sufficient	Sufficient	1	100C (2012)	Impurity in some mild SS welding fumes	All	Lung, skin, urinary bladder, prostate, kidney, liver
Asbestos	Sufficient	Sufficient	1	100C (2012)	Insulation material and in heat-protective equipment of welders and the weld	Shipyard welding	Mesothelioma, larynx, lung, ovary, pharynx, stomach, colon, rectum
Beryllium and beryllium compounds	Sufficient	Sufficient	1	100C (2012)	Hardening agent in copper, magnesium, aluminium alloys and electrical contacts	GMA, GTA	Lung
Cadmium and cadmium compounds	Sufficient	Sufficient	1	100C (2012)	Platings on base metals, SS containing cadmium	All	Lung, kidney, prostate
Chromium VI compounds	Sufficient	Sufficient	1	100C (2012)	Alloy in SS, also in welding rods	All SS	Lung, nasal sinuses, nose
Electric fields, extremely low frequency	Inadequate	No relevant data	3	80 (2002)	Electrical currents from welding processes	All (more with processes using higher currents, such as resistance welding)	
Formaldehyde	Sufficient	Sufficient	1	100F (2012)	Metal coatings, degreasing solvents	All	Nasopharynx, nasal sinuses, leukaemia,
Inorganic lead compounds	Limited	Sufficient	2A	87 (2006)	In solder, brass, and bronze alloys; welding on lead-containing or -coated materials	GMA, GTA	Stomach
Magnetic fields, extremely low frequency	Limited	Inadequate	2B	80 (2002)	Electrical currents from welding processes	All (more with processes using higher currents, such as resistance welding)	Childhood leukaemia
Nickel compounds	Sufficient	Sufficient	1	100C (2012)	Alloy in SS, also in welding rods	All SS	Lung, paranasal sinuses, nasal cavity
Silica dust or crystalline, in the form of quartz or cristobalite	Sufficient	Sufficient	1	100C (2012)	Some welding fluxes contain silica	GMA, FCA, GTA	Lung
Titanium dioxide	Inadequate	Sufficient	2B	93 (2010)	Found in SMA (MMA) electrodes	SMA (MMA)	

Table 1.1 (continued)

Agent	Evidence for carcinogenicity		Overall evaluation	Most recent volume (year)	Occurrence	Welding types	Organ sites (sufficient or limited evidence in humans)
	Humans	Animals					
Ultraviolet radiation	Sufficient	Sufficient	1	100D (2012)	Arcs from welding guns	All	Ocular melanoma
Iron oxides (evaluation specific to iron and steel founding)	Sufficient	Inadequate	1	100F (2012)	Main component of steel	All	Lung
Vanadium pentoxide	Inadequate	Sufficient	2B	86 (2006)	Alloy in SS	All SS	
Outdoor air pollution ($PM_{2.5}$)	Sufficient	Sufficient	1	109 (2016)	$PM_{2.5}$ generated from all welding processes	All	Lung
Welding fume	Limited	Inadequate	2B	49 (1990)	Generated from welding processes	All	Lung

FCA, flux cored arc; GMA, gas metal arc; GTA, gas tungsten arc; MMA, manual metal arc; PM, particulate matter; SMA, shielded metal arc; SS, stainless steel

Table 1.2 Welding processes, materials, and uses

Welding type	Primary exposures encountered	Common industrial uses	Most common base metals welded	References
Oxyfuel	NO_2	Repair/maintenance	MS[a], AS	Weman (2003), Moniz & Miller (2010)
MMA	Metals, silicates, fluoride, asbestos[b], UV radiation, ELF-EMF	Steel fabrication, construction	MS[a], SS, AS	Burgess (1995), Weman (2003)
GMA	Metals, O_3, NO_2, CO, chlorinated HC, UV radiation, ELF-EMF	Various metal fabrication	MS[a], SS, AS, Al	Burgess (1995), Weman & Lindén (2006)
FCA	Metals, CO_2, UV radiation, ELF-EMF	Equipment repair, shipbuilding	MS[a], SS, AS	Spiegel-Ciobanu (2010)
GTA	O_3, NO, NO_2, metals, chlorinated HC, UV radiation, ELF-EMF	Aerospace, bicycle manufacturing, various metal fabrication	MS, SS[a], AS, Al	Burgess (1995), Weman (2003)
SA	Fluorides, UV radiation, ELF-EMF	Steel fabrication, shipbuilding	MS[a], SS, AS	Burgess (1995), Weman (2003)
ER	Metals, UV radiation, ELF-EMF	Aerospace, automobile, shipbuilding	MS, SS, AS, Al	Weman (2003), Moniz & Miller (2010)
Brazing/soldering	Metals, UV radiation	Metal arts, plumbing, electric components	All metals/steels	Moniz & Miller (2010)
Cutting/gouging	Metals, O_3, NO_2, UV radiation	Fabrication, construction, shipbuilding	All metals/steels	Weman (2003), Moniz & Miller (2010)

[a] Most common type welded

[b] Used historically as an insulating material in ships, to insulate covered rod electrodes, in cylinders holding acetylene gas, and in heat-protective equipment of welders and the weld

Metals include but are not limited to: Fe, Mn, Al, Ni, Cr, K, Ba, Ca, F, Ti, Co, Zn, Mo, Pb, Mg, and As. These will vary by composition of base metal

Al, aluminium alloys; AS, alloyed steel; CO, carbon monoxide; CO_2, carbon dioxide; ELF-EMF, extremely low-frequency electromagnetic fields; ER, electric resistance; FCA, flux cored arc; GMA, gas metal arc; GTA, gas tungsten arc; HC, hydrocarbon; MMA, manual metal arc; MS, mild steel; NO, nitric oxide; NO_2, nitrogen dioxide; O_3, ozone; SA, submerged arc; SS, stainless steel; UV, ultraviolet

Compiled by the Working Group

Table 1.3 Type of welding and material welded by both welders and non-welders reporting welding activities, as included in the ECRHS II study

Type of welding or metal	Proportion associated with various processes/metal welded	
	Welders (n = 27 job periods held during 1969–2001, 23 subjects) (%)	Non-welders (n = 388 job periods held during 1962–2001, 340 subjects) (%)
Type of welding		
MMA	70.4	66.2
GMA	81.5	48.7
GTA	40.7	20.0
SA	11.1	5.2
FCA	25.9	16.0
Other (includes oxyfuel)	10.1	19.6
Type of metal		
Stainless steel	55.6	33.5
Mild steel	85.2	63.9
Galvanized steel	74.1	60.0
Aluminium	48.1	17.5
Painted metal	40.7	47.2
Other	3.7	21.6

FCA, flux-cored arc; GMA, gas metal arc; GTA, gas tungsten arc; MMA, manual metal arc; SA, submerged arc
Compiled by the Working Group from the ECRHS study (described in Lillienberg et al., 2008)

cutting were developed soon after with resistance welding as the common joining process. MMA welding technology was introduced in the late 1800s and achieved commercial status in the early 1900s. Various types of electrodes were developed and used during the 1920s and 1930s, but covered electrodes dominated after the 1930s as better welds could be achieved. Research into the use of shielding gas began in the 1920s, which led to the development of GTA welding. GTA welding began to be used commercially in the early 1940s, with GMA welding processes being developed and used commercially in the late 1940s. The use of consumable electrodes with carbon dioxide as a shielding gas was introduced in the late 1950s, which led to the development of FCA welding. Dual-shield FCA welding was introduced in the late 1950s, and a few years later inner-shield FCA welding was introduced (Cary, 1998; Weman, 2003). New or modified methods of welding continue to be developed to meet the needs of industry. Notably, laser welding and cutting are becoming popular and prevalent, although this type of welding is frequently carried out by robots (Klein et al., 1998).

1.1.2 Description of welding processes

See Table 1.2

(a) Gas welding

(i) Oxyfuel gas welding (ISO Nos 3, 31, 311, 312, and 313)

Oxyfuel gas welding includes oxyacetylene welding, oxypropane welding, and oxyhydrogen welding. The process uses heat from the combustion of oxygen mixed with a fuel gas, such as acetylene, methylacetylene-propadiene (MAPP), propane, hydrogen, or propylene. Oxyacetylene is the most commonly used oxyfuel welding process, and can also be used for cutting metals (flame cutting, ISO No. 81). Oxyfuel gas welding can be performed with or without a filler metal

and is very portable and flexible; it is therefore encountered in all metalworking industries. It is most commonly used for maintenance and repair work on light sheet metal, for tack welding pieces that are to be arc welded, or in locations where no electricity is available (Weman, 2003; Moniz & Miller, 2010).

(b) Arc welding

(i) Manual metal arc welding (ISO No. 111)

MMA welding is also referred to as shielded metal arc welding, stick welding, electrode welding, or flux shielded arc welding. The process draws an electric arc between a consumable electrode (welding rod) covered with a flux, and the base metal, melting the metals together and leaving a joint of molten metal. As the weld is laid the flux disintegrates from the electrode, the vapours of which serve as a shielding gas. When the weld has cooled, a slag cover is left behind which is a mixture of the flux and impurities; this is typically removed using a chipper or grinder. The MMA welder will go through many electrodes while laying a weld, with an electrode replacement required every few minutes. MMA welding is most commonly used to weld steels of varying thicknesses (mild, alloyed, and stainless steels), making it popular in construction and fabrication of steel structures. Typically, the welding rod or electrode is of a similar metal alloy to the base metal, with a variety of different flux coatings including rutile (25–35% TiO_2), calcium fluoride, cellulose, and iron powder (Burgess, 1995; Weman, 2003).

(ii) Gas metal arc welding (ISO No. 13)

GMA welding is also called metal inert gas welding, metal active gas welding, and gas-shielded metal arc welding. It is the most common industrial welding process due to its versatility, speed, relatively low cost, and adaptability to robotic welding. GMA welding forms an electric arc between a consumable wire electrode fed through the welding gun, and the base metal, creating enough heat to melt and join the metals together. A shielding gas is also fed through the welding gun, protecting the weld from contaminant and eliminating slag. While the addition of the shielding gas makes GMA welding a difficult welding process to perform outdoors or in areas with heavy ventilation, no additional grinding or chipping of slag is required to reveal the completed weld. The shielding gas is typically helium, argon, carbon dioxide, nitrogen, or a blend of these gases, and is chosen according to the base metal being welded and the specifics of the process. GMA welding can be used to weld aluminium, copper, magnesium, nickel alloys, titanium, and steel alloys, making it a very versatile welding process that is popular for metal fabrication in a variety of (mostly indoor) settings (Burgess, 1995; Weman & Lindén, 2006).

(iii) Flux-cored arc welding (ISO Nos 132, 136, and 114)

FCA welding, also known as self-shielded tubular cored arc welding, uses the same equipment as for GMA welding. It is rapidly becoming a popular and prevalent welding process worldwide due to the fact it can be used in all welding positions, is a quick process, requires less pre- and post-cleaning of the base metal and weld, and requires less skill to achieve good-quality welds. FCA welding uses a continuously fed automatic or semi-automatic consumable electrode containing a flux and a voltage to lay a weld. Dual-shield FCA welding uses an externally supplied shielding gas to protect the weld, in addition to a powder flux in the centre of the electrode. The common external shielding gases are carbon dioxide and argon, or a mixture of the two. Inner-shield or self-shielding FCA welding (ISO No. 114) does not require a separate shielding gas, as the flux core in the consumable electrode can generate a shielding gas. This makes dual-shield FCA welding ideal for outdoor or windy conditions. FCA welding is generally used to weld thicker materials with a single pass,

such as in equipment repair or the shipbuilding industry, and can be performed on carbon steels, cast iron, nickel-based alloys, and some types of SS (Burgess, 1995; Moniz & Miller, 2010).

(iv) Gas tungsten arc welding (ISO No. 14)

GTA welding, also known as tungsten inert gas welding, uses a tungsten electrode to produce the weld. Due to the high melting point of tungsten, the electrode does not melt during the welding process. Further, a shielding gas (Ar or He) is used to protect the weld and a consumable filler metal is added to make the joint. GTA welding is commonly used for welding on thin pieces of SS, aluminium, magnesium, and copper alloys, but it can be used on nearly all metals except zinc. The process can utilize a variety of filler metals since the weld metal is not transferred across the electric arc; this allows the filler and base metal to be matched, leading to reduced corrosion and cracking. GTA welding is therefore considered a high-quality weld, requiring a higher level of skill to master. It is commonly employed in the aerospace and bicycle industries, in machinery production for the food industry, in maintenance and repair work, and for spot welding (Burgess, 1995; Weman, 2003).

(v) Submerged arc welding (ISO No. 12)

SA welding uses a bare wire electrode as the filler metal, and a granular flux to protect the weld which is fed onto the base metal before the arc path. Typically, SA welding is a fully automated process; the operator does not handle the weld, but is only involved in setting up and monitoring. The flux typically contains oxides of manganese, silicon, titanium, aluminium, or calcium fluoride. SA welding can be used for welding straight, thick sections on carbon steels, low alloy steels and, less commonly, on SS and nickel-based alloys. It is commonly used in shipyards or for other large steel fabrication projects. SA welding allows for quick and deep welds, and can be performed in both indoor and outdoor environments (Burgess, 1995; Weman, 2003).

(c) Other processes

(i) Electric resistance welding (ISO Nos 21 and 22)

ER welding, also called resistance spot welding, spot welding, resistance seam welding, and seam welding, is a group of seam or spot welding processes that produce a weld at a faying surface. The heat for the weld is generated from the electrical resistance of the material; small pools of molten metal are created by passing an electrical current through the metal workpiece. ER welding methods are typically used with thin materials, and it is a popular welding process in aerospace or automobile manufacturing. As for SA welding, ER welding is generally a fully automated process with the operator only responsible for setting up and monitoring the welding (Weman, 2003; Moniz & Miller, 2010).

(ii) Other hot work processes (brazing/soldering, cutting, gouging) (ISO Nos 8 and 9)

Welders routinely perform other hot work processes, such as brazing, soldering, cutting, and gauging. Brazing and soldering are similar, although brazing is conducted at a higher temperature and can therefore use stronger filler metals. Unlike welding, where the two metals being joined typically need to be similar and are melted to join them together, soldering and brazing involve using a filler metal with a melting temperature below the metals being joined; they can therefore be used to join dissimilar metals. Welded joints are stronger than brazed joints, which are in turn stronger than soldered joints. Brazing and soldering are both common in metal arts, jewellery making, plumbing, or for electric components. While soldering historically used lead as a filler metal, this is now less common in more developed countries and gold, silver,

copper, brass, tin alloys, and iron are generally used (Weman, 2003; Moniz & Miller, 2010).

There are many types of cutting that welders may routinely perform. Plasma arc cutting removes molten metal with a jet of ionized gas (plasma). The superheated plasma can conduct an electric arc, which melts the base metal. Plasma arc cutting is typically used to cut aluminium, SS, brass, and copper and uses a tungsten electrode similar to that for GTA welding. While plasma arc cutting can be carried out manually, computer-assisted cutters are commonly used which can make complex shapes and cuts. Air carbon arc cutting heats and cuts metal using a carbon arc, while the molten metal is removed with a blast of air. This method can be used to cut SS, aluminium, copper, magnesium, and carbon steels. It can also be used to gouge metals, which is the removal of metal from a surface to prepare it for welding (Weman, 2003; Moniz & Miller, 2010). Table 1.2 lists the exposures common to the welding and hot work processes described here, and their typical uses in industry.

1.1.3 Welding materials

See Table 1.2

The majority of welding in occupational settings is performed on MS and SS. All steel is an alloy of iron and other elements, primarily carbon, with MS containing small amounts of manganese (typically < 1.6%) in addition to carbon (typically < 0.3%) and iron (Jones & Ashby, 2005). SS contains at least 12% chromium, making it more resistant to corrosion than MS (Verhoeven, 2007). Depending on the grade of SS, it may contain up to 25% chromium, 7% nickel, and 4% molybdenum, with the levels of these metals varying to achieve particular characteristics (Bringas, 2004; Outokumpu, 2013). MS that is galvanized (coated with zinc) or painted (typically with primers) is also welded.

Alloy steels contain specific amounts of alloying elements other than carbon, such as additional manganese, chrome, nickel, molybdenum, silicon, titanium, copper, vanadium, or aluminium. The specific elements and their proportions determine the weldability, resistance to corrosion, strength, ductility, or magnetic properties of the steel (Verhoeven, 2007).

Welding is also performed on cast iron (alloys of iron, carbon, silicon) and nonferrous metals (such as alloys of nickel, copper, aluminium, magnesium, and titanium), which may contain other metals over a range of concentrations to achieve particular characteristics (Moniz & Miller, 2010; Table 1.1).

1.1.4 People exposed to welding fumes or welding worldwide

See Table 1.4

It is challenging to quantify the number of welders worldwide. Such estimates typically come from a population census or survey; however, variability in sampling and coding methods, inclusion and exclusion criteria, year of data collection, and language of results combine to make it difficult to meaningfully compare and combine data from various countries for a worldwide estimate. Acknowledging these limitations, the Working Group used the Integrated Public Use Microdata Series, International (IPUMS-International) data system to gather census microdata from 60 countries that had an occupational census between 1973 and 2015 (Minnesota Population Center, 2015). These data, representing the percentage of the economically active population which the job designations represent in 60 countries over a 40-year period, are listed in Table 1.4. Assuming that historical estimates are reflective of current estimates, it can be estimated that over 6 million people worldwide may have the occupational title of welder either full-time or part-time (Minnesota Population Center, 2015).

In the countries included in Table 1.4, the Working Group calculated that the average

Table 1.4 Estimates of number of welders worldwide based on publicly available population data[a]

Country	Census year	Occupational designation	Number	Welding proportion of population[b] (%)
China	1990	Welders	1 798 300	0.27
USA	2010	Welding, soldering, and brazing workers	727 122	0.40
India	2004	Welders and flame cutters	499 219	0.14
Viet Nam	2009	Metal moulders, welders, sheet metal workers, structural metal preparers, and related workers	339 106	0.71
Brazil	2010	Welders and flame cutters	292 365	0.34
Spain	2001	Welders, laminators, metal structure assemblers, blacksmiths, toolmakers, and similar	262 620	1.61
UK	2001	Metal forming, welding and related trades	227 044	0.55
Mexico	2010	Welders and flame cutters	191 819	0.45
Nigeria	2010	Welders and flame cutters	190 637	0.27
Philippines	2000	Metal moulders, welders, and sheet metal workers	185 060	0.32
Iran (Islamic Republic of)	2006	Welders and flame cutters	150 439	0.87
Indonesia	2005	Welders and flame cutters	142 572	0.16
South Africa	2007	Metal moulders, welders, sheet metal workers, structural metal preparers, and related trades workers	121 635	0.99
Germany (West)	1987	Welder	110 040	0.39
Canada	2006	Welder	103 000	0.61
Egypt	2006	Metal moulders, welders, sheet metal workers, structural metal preparers, and related trades workers	99 070	0.49
Thailand	2000	Metal moulders, welders, sheet metal workers, structural metal preparers, and related trades workers	97 626	0.20
Australia[c]	2011	Structural steel and welding trades workers	86 400	0.77
Morocco	2004	Moulders, welders, and sheet metal workers	85 320	0.91
Romania	2002	Welders and flame cutters	80 460	0.95
Portugal	2011	Sheet and structural metal workers, moulders and welders, and related workers	76 580	1.55
Netherlands[d]	1996	Welders	75 000	1.21
Venezuela (Bolivarian Republic of)	2001	Mould-press workers, welders, laminators, boilermakers, assemblers of metal structures, and similar	70 170	0.31
Malaysia	2000	Metal moulders, welders, sheet metal workers, structural metal preparers, and related trades workers	43 400	0.53
Cuba	2002	Moulders, welders, panel beaters, and assemblers	39 710	0.92
Ecuador	2010	Sheet and structural metal workers, moulders, welders, and related workers	37 640	0.64

Table 1.4 (continued)

Country	Census year	Occupational designation	Number	Welding proportion of population[b] (%)
Peru	2007	Plumbers and pipe fitters, welders and flame cutters, sheet metal workers, and structural metal preparers and erectors	37 350	0.36
France	2011	Skilled metal welders	36 164	0.14
Senegal	2002	Metal moulders, welders, sheet metal workers, structural metal preparers, and related trades workers	25 550	0.80
Bolivia (Plurinational State of)	2001	Moulders, welders, laminators, boilermakers, assemblers of metal structures, and similar	22 090	0.27
Panama	2010	Moulders, welders, boilermakers, fitters of metallic structures, and related workers	21 550	1.53
Cameroon	2005	Sheet and structural metal workers, moulders, welders, and related workers	19 940	0.40
El Salvador	2007	Metal moulders, welders, sheet metal workers, structural metal preparers, and related trades workers	17 930	0.91
Guinea	1996	Metal moulders, welders, sheet metal workers, structural metal preparers, and related trades workers	17 070	0.50
Kenya	1989	Welder	15 680	0.21
Mozambique	2007	Metal moulders, welders, sheet metal workers, structural metal preparers, and related trades workers	14 490	0.18
Malawi	2008	Plumbers, welders, sheet metal and structural metal preparers and erectors	14 240	0.34
Costa Rica	2000	Moulders, welders, locksmiths, boilermakers, metal structure builders, and similar	13 810	1.06
Mali	2009	Welder	12 860	0.23
Zambia	2010	Metal moulders, welders, sheet metal workers, structural metal preparers, and related trades workers	12 620	0.32
Pakistan	1973	Welders and flame cutters	12 353	0.07
Nicaragua	2005	Metal moulders, welders, sheet metal workers, structural metal preparers, and related trades workers	12 040	0.69
Greece	2001	Welders and flame cutters	11 330	0.27
Jamaica	2001	Metal moulders, welders, sheet metal workers, structural metal preparers, and related trades workers	11 263	1.17
Ireland	2006	Welders and steel erectors	10 090	0.41
Ethiopia	1994	Welders, metal moulders, and related trades workers	9 297	0.04
Haiti	2003	Metal moulders, welders, sheet metal workers, structural metal preparers, and related trades workers	7 990	0.38
Uruguay	2006	Metal moulders, welders, sheet metal workers, structural metal preparers, and related trades workers	7 553	0.58
Uganda	2002	Welders, sheet metal workers, and metal moulders	7 380	0.10

Table 1.4 (continued)

Country	Census year	Occupational designation	Number	Welding proportion of population[b] (%)
Kyrgyzstan	1999	Welders and flame cutters	7 220	0.42
Cambodia	2008	Sheet and structural metal workers, moulders, welders, and related workers	6 650	0.10
Puerto Rico	2010	Welding, soldering, and brazing workers	5 220	0.33
Armenia	2011	Sheet and structural metal workers, moulders, welders, and related workers	4 930	0.45
Iraq	1997	Welders and flame cutters	4 320	0.11
Fiji	2007	Metal workers	3 240	1.34
Switzerland	2000	Welders and flame cutters	2 670	0.07
Rwanda	2002	Workers for metal smelting, foundry, welding, metal sheet work, boiler making, metal frames for houses and buildings, and assimilated	2 390	0.07
Mongolia	2000	Metal moulders, welders, sheet metal workers, structural metal preparers, and related trades workers	1 810	0.23
Paraguay	1982	Oxyfuel cutters, welders, soldering by hand or machine, electric welders, and blowtorch welding	1 460	0.15
Jordan	2004	Metal moulders, welders, sheet metal workers, structural metal preparers, and related trades workers	1 050	0.10

[a] Unless otherwise specified, data compiled from Minnesota Population Center (2015)
[b] Percent of the economically active population for each country that the number of persons employed in the occupational designation represents
[c] Data from Australia compiled from Australian Bureau of Statistics (2012)
[d] Data from the Netherlands compiled from Simmelink (1996)
Compiled by the Working Group

percentage of job designations including welder represented in the economically active population was 0.31%. Applying these percentages to the International Labour Organization's 2010 estimate of the worldwide economically active population (3.5 billion), the Working Group estimated there may be 11 million welders worldwide (ILO, 2010). However, it must be acknowledged that the variability in how the job of welding was coded between censuses could lead to uncertainty in any estimates generated from these data. Some occupational designations (e.g. Spain) include jobs where not every worker welds, which would overestimate the number of welders for a country. At the same time, however, a census would not capture workers performing welding without the official job title of welder; for example, construction or agricultural workers might weld intermittently but would not be classified as welders (see additional discussion in Section 1.1.5).

Separate from this analysis, the German Welding Society estimated that over 1.1 million people have full-time positions in the field of welding in 19 European countries. This figure only includes welders, welding supervisors, welding inspectors, welding researchers, welding trainers, and robot operators (Von Hofe, 2009).

1.1.5 Non-welder occupations performing welding

In addition to workers with the job title of welder, other occupations routinely or intermittently weld. Table 1.5 lists occupational categories where workers weld, as reported in the European Community Respiratory Health Follow-up Survey (ECRHS) (ECRHS II, 2017) and the Canadian general population job-exposure matrix (CANJEM) (CANJEM, 2017).

The ECRHS II (Janson et al., 2001) prospectively assessed the relationship between welding at work and respiratory symptoms. Subjects participating in ECRHS II held 10 016 job periods (e.g. time periods defined in the study where a subject was employed in a particular job) during 1962–2001, 415 of which involved some welding activities. Table 1.5 lists the percentage of job periods for which workers reported performing welding, stratified by broad occupational category. For the 415 job periods associated with welding activities, Table 1.3 lists the processes which were used and the metals which were welded separately for the welder and non-welder occupations. The ECRHS II survey found that only 7% of workers performing welding actually had the job title of welder or flame cutter, showing that many more workers weld and are potentially exposed to welding fumes than those with the job title of welder (Lillienberg et al., 2008). The ECRHS II also found that almost 30% of the individuals who responded positively to the question "Have you carried out welding, at work or at home?" only welded at home. Of the professional welders, 3% also indicated welding at home (ECRHS II, 2017).

CANJEM (2017) covers 258 agents developed from expert assessments and informed by structured occupational interviews (Lavoue et al., 2014; Zeng et al., 2017). The matrix comprises information for 31 780 jobs held during 1921–2005 by 6222 Canadian men and 2563 Canadian women. Table 1.5 lists the proportion of job periods during which workers were exposed to any type of welding fumes (gas, arc, soldering) by occupational category (same definition as in Lillienberg et al., 2008), as calculated by CANJEM. From this analysis of CANJEM, only 12% of job periods during which workers were exposed to welding fumes corresponded to the occupation of welder (as per ISCO 1988). In addition, among the exposed jobs the median duration of exposure was 40 hours per week for welders, with 70% exposed full-time. For non-welders, the median duration of exposure was 5 hours per week, with 24% exposed full-time [calculation performed by the Working Group].

Table 1.5 Number and proportion of job periods during which workers were exposed to welding fumes for each occupational category, by study

Occupational categories	ECRHS II		CANJEM	
	Number	Proportion (%)	Number	Proportion (%)
Miscellaneous (artist, firefighters)	5	80	950	9
Sheet metal and metalworkers	30	70	305	69
Welders and flame cutters	42	64	310	98
Blacksmiths and toolmakers	26	62	314	27
Motor vehicle, agricultural, and industrial mechanics and fitters	124	50	965	44
Building workers (frame and finisher)	216	37	1316	28
Electrical and electronic equipment mechanics and fitters	50	36	329	52
Agricultural workers	34	35	604	1
Plant and machine operators	142	32	3172	9
Painters and building structure cleaners	18	33	227	5
Production and general managers	58	29	2194	3
Engineers and engineering science technicians	127	23	3184	5
Drivers and truck operators	93	22	2183	2
Service labourer workers	117	8	1394	2
Armed forces	17	6	–	–
Teaching professionals	191	5	521	3
Secretaries	135	4	2229	2
Others (not working, unknown, student)	232	3	–	–
Occupations with no welding activities reported	8359	0	–	–

[a] Proportion of job periods associated with welding activities in the ECRHS study (assessed using self-reports of welding)
[b] Proportion of job periods in the CANJEM population that were deemed exposed to either gas, arc, or soldering welding fumes (assessed using expert judgment of job exposures)
Compiled by the Working Group from data from the ECRHS study (described in Lillienberg et al., 2008), and the CANJEM job exposure matrix (CANJEM, 2017; Lavoue et al., 2014)

For some occupational titles there are differences between CANJEM and ECRHS II data, some of which can be explained by classification; ECRHS II tends to have a higher proportion of workers exposed to welding fumes than CANJEM for most occupational categories. CANJEM relied on an expert assessment of job exposures, while workers self-reported welding activities in ECRHS II. [The Working Group noted that ECRHS II was likely able to identify more job titles that include infrequent welding, which might not have been picked up by expert assessment. Additionally, CANJEM and ECRHS II used different occupational coding systems when originally assigning job titles (Lillienberg et al., 2008; Lavoue et al., 2014; CANJEM, 2017). The Working Group therefore estimated that the number of people exposed to welding fumes might be 10 times higher than the number of people with the occupational title of welder. This would indicate that the number of people exposed to welding fumes worldwide could approach 110 million workers (3% of the worldwide economically active population).]

Table 1.6 Methods for the analysis of welding-related exposures

Sample matrix	Agent	Assay procedure	Limit of detection	Standard/method/reference
Air	Total dust	Gravimetric	0.03 mg/sample	ISO 10882-1:2011, NIOSH 0500
	Respirable dust	Gravimetric	0.03 mg/sample	NIOSH 0600
	Metals in dust	ICP-AES	1 µg/sample	NIOSH 7300
	CO	Electrochemical sensor	1 ppm	EN ISO 10882-2:2000, NIOSH 6604
	NO_2	UV-VIS	1 µg/sample	EN ISO 10882-2:2000, NIOSH 6014
	NO	UV-VIS	1 µg/sample	EN ISO 10882-2:2000, NIOSH 6014
	O_3	IC/UV-VIS	3 µg/filter	EN ISO 10882-2:2000, OSHA ID-214
Urine	Metals	ICP-AES	0.1 µg/sample	NIOSH 8310
Whole blood	Metals	ICP-AES	1 µg/100 g blood	NIOSH 8005
NA	UV	Direct measurement		Tenkate (2008); Vecchia et al. (2007)
NA	EMF	Direct measurement		IEC 61786-1:2013

CO, carbon monoxide; EMF, electromagnetic fields; IC, ion chromatography; ICP-AES, inductively coupled plasma atomic emission spectrometry; IEC, International Electrochemical Commission; ISO, International Organization for Standardization; NA, not applicable; NIOSH, National Institute for Occupational Safety and Health; NO, nitric oxide; NO_2, nitrogren dioxide; O_3, ozone; OSHA, Occupational Safety and Health Administration; UV, ultraviolet; UV-VIS, ultraviolet visible spectrophotometry
Compiled by the Working Group

1.2 Measurement and analysis

This section reviews the methodologies of sampling and analysis for exposures related to welding in ambient air, as well as biomonitoring of exposure.

1.2.1 Detection and quantification of welding-related exposures

Exposure to welding fumes predominantly occurs via inhalation. Welding fumes in the air are generally measured by sampling of the respirable fraction (Table 1.6), which is highly correlated with sampling of the inhalable fraction (Lehnert et al., 2012). Metals in welding fumes, such as iron, chromium, copper, nickel, manganese, aluminium, titanium, molybdenum and zinc, are often analysed individually. In addition to welding fumes, gases (such as O_3, CO, and NO_x) arising from welding activities are monitored. A range of analytical methods is available, as listed in Table 1.6.

Internal exposure to specific elements in welding fumes can be determined in urine and blood samples (Table 1.6). Biomonitoring has been primarily focused on chromium and nickel, but other metals, including aluminium, cadmium and manganese, have also been frequently monitored.

Assessment of exposure to ultraviolet (UV) radiation is generally performed using radiometric, spectroradiometric or personal dosimetry techniques (Vecchia et al., 2007; Tenkate, 2008).

The International Electrochemical Commission (IEC) standard for measuring extremely low frequency electromagnetic fields (ELF-EMF) is described in IEC 61 786-1:2013 (IEC, 2013).

1.2.2 Measurement strategies

(a) Welding fumes and gases

High variability in exposure, both between and within workers, is inherent in welding due to the different base metals, different types of welding, and varying circumstances. Determinants of exposure should therefore be recorded along with personal air monitoring, including details related to the welding techniques used, base metal, duration of welding tasks and related activities (preparation, clean-up,

breaks, etc.), the position of the welder, presence of local exhaust ventilation or general ventilation, or whether a helmet with clean air supply was used. In addition to the welding procedure and material used, the welders' level of experience may also influence the particles generated from welding fumes (Chang et al., 2013). It has been suggested that the quality of the welding performance influences exposure to welding fumes, implying increased exposure for apprentice welders or welders with minimal training (Graczyk et al., 2016). Repeated measurements among the same workers may provide information about the variability between and within (temporal) workers.

Personal exposure measurements are typically performed in the breathing zone to best represent the exposure of the individual worker. With welding processes it is critical to take into account the position of the monitoring device relative to the face shield, as it may physically deflect the welding fumes away from the breathing zone (ISO 10 882-2:2000). The concentration of particles inside the plume is 10–100 times higher than outside the plume (Lidén & Surakka, 2009). Personal sampling should therefore be performed behind the welder's face shield and as close to the mouth as possible (within 10 cm) (ISO 10 882-1:2011).

Welders should wear equipment that enables the sampler to stay in position throughout the sampling period (ISO 10 882-1:2011), for example, the headset-mounted minisampler described by Lidén & Surakka (2009) or the in-visor sampler from the Health and Safety Laboratory (2009). The position of such a sampler is not affected by the position of the face shield or helmet. This means that if the face shield or helmet is raised or completely removed during the sampling period, the sampler will stay in place.

For gases, samplers should also be positioned in the breathing zone at a maximum distance of 5 cm from the mouth. Badges for personal sampling of exposure to gases might be unsuitable for sampling behind a welder's face shield, due to limited air movement (ISO 10 882-2:2000).

(b) Biomonitoring of metals

Similar data regarding the nature of the welding activities should be collected for biomonitoring of metal exposure, both on the day of sample collection and before (depending on accumulation of the biomarker in the body). While assessment of exposure to welding fumes is primarily focused on the occupational setting, Scheepers et al. (2008) reported that one quarter of the welders in their study were also engaged in welding activities during off-work hours (Scheepers et al., 2008). Although these activities may be more difficult to identify and potentially less monitored, biomonitoring results may also measure these exposures.

(c) Radiation

Arc welding processes can lead to UV radiation exposure of the eyes and skin. Since arc welding procedures emit radiation with fluctuation and instability, and due to interference by electromagnetic radiation, it can be complicated to obtain accurate radiometric and spectroradiometric results (Tenkate, 2008). The geometrical aspects of exposure to UV radiation must be considered, including the diameter of aperture of the detector if the irradiance profile is heterogeneous, and the field of view of the detector (Vecchia et al., 2007). The "arc time" (i.e. the time for which the arc is actually struck) will affect the overall exposure during a working day (Tenkate, 2008), as well as eye and skin protection used. As well as the actual workers performing the welding tasks, their coworkers (bystanders) may also be exposed to UV radiation (Vecchia et al., 2007).

Exposure to UV radiation is usually expressed in terms of irradiance (power per unit area, W/m2) or radiant exposure (J/m^2), the amount of energy received per unit area accumulated

over a time interval. As different wavelengths are associated with different biological impact, an "efficient" exposure rate is calculated as a weighted average across the whole UV spectrum (Vecchia et al., 2007; ACGIH, 2013). Both the American Conference of Governmental Industrial Hygienists (ACGIH) and the International Commission on Non-Ionizing Radiation Protection (ICNIRP) propose an occupational exposure limit of 3 mJ/cm^2 (effective radiant energy). In practice, effective irradiance is measured in the field and the time required to reach the permissible radiant energy is calculated (ICNIRP, 2004; ACGIH, 2013).

Electric welding techniques may result in exposure to ELF-EMF. The overall exposure will be affected by the source of exposure (e.g. vicinity and position in relation to welding devices, and distance to power cables) and the total welding time (Hansson Mild et al., 2009).

1.3 Occurrence and exposure

1.3.1 Exposure to welding fumes and gases

Welding fumes are produced when metals are heated above their melting point, vapourize, and condense into fumes with predominantly fine solid particles of diameter less than 1 μm. These fumes are a complex mix of particles from the wire or electrode, the base metal, and any coatings on the base metal (paint, metalworking fluid, platings, etc.) (Hewett, 1995a; Warner, 2014). Most commonly, they are composed of metal oxides (mainly iron oxides, depending on the base metal), silicates (from coated electrodes and fluxes), and fluorides (when fluoride-containing electrode coatings/fluxes are used). A variable proportion of the metal elements can also be found in the form of magnetite-like spinels, that is, multimetal oxides where the metal ions share oxygen atoms instead of the various metal-specific oxides. Fumes from SS welding contain chromium and nickel, whereas these two exposures are much lower in MS welding fumes. Welding gases are generated from the shielding gases used, the decomposition of fluxes, and interactions between UV radiation and/or high temperatures with gases found in the air (e.g. N in the air combining with heat to produce NO_2, or O interacting with the welding arc to produce O_3). Common gases encountered during welding include: shielding gases such as carbon dioxide, argon, or helium; fuel gases such as acetylene, butane, or propane; and gases produced from the welding processes such as carbon monoxide, ozone, nitrogen oxides, and hydrogen fluoride (Burgess, 1995; Antonini, 2003). The distinction between welding fumes and welding gases is that fumes contain solid particles that are temporarily suspended in the air due to a solid material being heated (such as metals), whereas gases are molecules in a gaseous state in the ambient air that have either been generated by or are used in the welding process.

Table 1.1 and Table 1.7 outline some of the common exposures encountered by welders in the complex mixtures of welding fumes and gases, and the type of welding in which the exposures are most likely to be encountered. Many of these exposures have previously been evaluated by the *IARC Monographs* (Table 1.1); common exposures that have not been evaluated by the *IARC Monographs* are listed separately (Table 1.7).

Table 1.8 summarizes the concentrations of welding fumes generated from various welding processes. Fumes from welding on SS ranged from less than 1 mg/m^3 to more than 25 mg/m^3. The lowest average concentrations are generated from GTA welding (two studies: means, 0.16 and 0.98 mg/m^3), whereas MMA welding produces the highest average concentrations (range of means, 3.0–5.4 mg/m^3).

As for SS welding, MS welding is associated with concentrations of fumes ranging from less than 1 mg/m^3 to more than 50 mg/m^3; the highest average concentration is found in MMA (range of means, 0.63–11.9 mg/m^3) or FCA

Table 1.7 Additional occupational exposures of welders that have not been evaluated by *IARC Monographs*

Agent	Occurrence	Welding types
Aluminium	Aluminium component of some alloys, welding on aluminium	GMA, GTA
Copper	Alloys such as brass, bronze, small amounts in SS and MS, some welding rods	All
Fluorides	Electrode coating and flux material for low- and high-alloy steels	All
Manganese	Found in varying amounts in most steels	All
Molybdenum	Found in varying amounts in most steels	All
Zinc	Galvanized and painted metal	All
Carbon monoxide	Formed in welding arc	GMA (when shielded with CO_2)
Hydrogen fluoride	Decomposition of rod coatings	SMA (MMA), SA
Nitrogen oxides	Formed by welding arc	All arc welding
Ozone	Formed by welding arc	Plasma arc cutting, GMA, GTA
Oxygen deficiency	Welding in confined spaces, air displacement form shielding gas	Shipbuilding, other confined space welding

CO_2, carbon dioxide; GMA, gas metal arc; GTA, gas tungsten arc; MMA, manual metal arc; MS, mild steel; SA, submerged arc; SMA, shielded metal arc; SS, stainless steel
Compiled by the Working Group

welding (one study: mean, 8.97 mg/m^3; range, 1.17–55.4 mg/m^3), and the lowest average concentration is reported in a study of GMA fabrication welders (mean, 0.51 mg/m^3). A study of welding apprentices reported very low exposures to welding fumes from gas (oxyfuel) welding, with an arithmetic mean of 0.0052 mg/m^3 (Baker et al., 2016). In this cohort of apprentice welders, oxyfuel exposures were comparable to exposures from GTA-MS and GTA-SS welding (arithmetic mean, 0.0055 mg/m^3), but nearly 7 times lower than MMA-MS welding (arithmetic mean, 0.035 mg/m^3) and 5.5 times lower than GMA-MS welding (arithmetic mean, 0.029 mg/m^3) (Baker et al., 2016). [The Working Group noted that exposures at this apprentice welding school are lower than those measured in general industry. However, as this was the only exposure assessment that could be found representing just oxyfuel welding, the Working Group included this value.]

As for all particles, the toxicological profile of welding fumes is not only dependent on the material and concentration, but also on the particle size distribution and surface characteristics; these differ by welding process and base metal. In a laboratory-based study of fumes generated from GMA and MMA welding of SS and MS, Hewett (1995a) found that GMA produced welding fumes with greater bulk density and specific surface area, and consisted of a greater quantity of smaller particle sizes, compared with MMA (although the majority of welding fumes for both processes and base metals contained particles of diameter less than 1 μm). These differences were mostly attributable to process (MMA vs GMA) as opposed to base metal (MS vs SS). In a further analysis of these laboratory-generated fumes, Hewett (1995b) found that GMA welding fumes had a 60% greater total lung deposition than MMA welding fumes, regardless of base metal, with the majority of fumes from both welding processes depositing in the alveoli. Given the differences in specific surface area between GMA and MMA, and the greater deposition of GMA, Hewett estimated that, for an equal exposure, GMA welding delivers three times the particle

Table 1.8 Occupational exposure to welding fumes

Reference	Location, collection date	Occupation description	Sampling matrix, approach, *N*, duration	Exposure level[a] (mg/m³)	Exposure range (mg/m³)	Comments/additional data
Knudsen et al. (1992)	Denmark, 1987	GMA-SS welder	Total particulate, personal, 10, full shift	1.01	NR	MCE filters placed inside the welders' face shields
		GTA-SS welder	Total particulate, personal, 40, full shift	0.98	NR	
Matczak & Chmielnicka (1993)	Poland, 1987–1990	MMA-SS welder, Plant A	Respirable, personal, 5, 7 h	9.0	2.8–23.4	Respirable samples taken behind the face shield of welders at four different industrial plants. Two-stage personal air sample with respirable fraction collected on membrane filter and glass fibre filter. Total respirable particulate adjusted to 8 h TWA
		MMA-SS welder, Plant B	Respirable, personal, 13, 7 h	3.2	NR	
		MMA-SS welder, Plant C	Respirable, personal, 31, 7 h	3.5	1.0–9.1	
		Welding assistants, Plant C	Respirable, personal, NR, 7 h	0.8	0.2–1.9	
		MMA-SS welder, Plant D	Respirable, personal, 22, 7 h	1.3	NR	
Karlsen et al. (1994)	Norway, NR	MMA-SS welder, shipyard (inside ship section)	Total particulate, personal, 48, full shift	5.4	0.3–29	12 welders were monitored for 4–5 consecutive workdays; MCE filters attached outside the welders' face shields
		MMA-SS welder, shipyard (inside the module)	Total particulate, personal, 30, full shift	3.0	1.0–5.8	Personal samples on unspecified number of welders taken over 2 weeks; MCE filters attached outside the welders' face shield
		MMA-SS welder, shipyard (welding shops)	Total particulate, personal, 42, full shift	2.0	0.5–6.6	
		MMA-SS welder, shipyard (grinding)	Total particulate, personal, 34, full shift	11	3.1–51	

Table 1.8 (continued)

Reference	Location, collection date	Occupation description	Sampling matrix, approach, *N*, duration	Exposure level[a] (mg/m³)	Exposure range (mg/m³)	Comments/additional data
Karlsen et al. (1994) (cont.)		MMA-SS welder, shipyard (grinding)	Total particulate, environmental, NR, full shift	2.0	0.4–3.0	Area samples placed near aerosol generation but not directly in plume; filter cassettes placed 1.5 m above floor, at least 5 m from nearest welding or grinding site, cassette inlets faced downwards
		MMA-SS welder, shipyard (welding shops)	Total particulate, environmental, NR, full shift	0.7	0.2–2.2	
		MMA-SS welder, shipyard (inside the module)	Total particulate, environmental, NR, full shift	0.4	0.2–0.5	
Wallace et al. (2001)	USA, NR	GMA-SS, fabrication	Total particulate, personal, 11, NR	1.61	0.49–2.67	Closed-face, 37 mm PVC filters hanging outside face shield; filters were changed periodically throughout the day to prevent overloading, and summed at the end of the day to approximate a full shift sample
		GTA-SS welder, fabrication	Total particulate, personal, 10, NR	0.16	0.06–0.27	
		FCA welder, boilerplate fabrication	Total particulate, personal, 20, NR	8.97	1.17–55.46	
Dryson & Rogers (1991)	New Zealand, NR	GMA-MS welder	Total particulate, personal, 6, 2–4 h	2.56	0.86–4.51	Samples collected inside the face shield
		MMA-MS welder	Total particulate, personal, 4, 2–4 h	2.59	0.35–5.16	
Järvisalo et al. (1992)	Finland, NR	MMA-MS welder, shipyard	Total particulate, personal, 24, NR	11.8	3.4–19.2	Samples collected inside the face shield from 5 welders, with repeat measures for 5 days (1 welder only measured 4 days)
Akbar-Khanzadeh (1993)	England, NR	Various/MS welder, shipyard	Total particulate, personal, 209, 6.5 h (average)	4.39	NR	Samples collected inside the face shield
		Administrative controls, shipyard	Total particulate, environmental, 109, 7.1 h (average)	0.67	NR	Non-welder controls from the shipyard (office workers, joiners, fitters, drivers, staging makers, electricians) had area sampling in their work environment
Woskie et al. (2002)	USA, June 1994–April 1999	Various/MS welder, construction	Inhalable, personal, 22, 6 h	9.325	Max, 21.07	IOM inhalable sampler outside the face shield

Table 1.8 (continued)

Reference	Location, collection date	Occupation description	Sampling matrix, approach, *N*, duration	Exposure level[a] (mg/m³)	Exposure range (mg/m³)	Comments/additional data
Balkhyour & Goknil (2010)	Saudi Arabia, NR	MMA-MS welder, Factory 1	Total particulate, environmental, 10, 2 h	6.3	2.0–15.5	Took 10 area samples from each of 6 factories within 0.5 m of welders' breathing zone; 1–4 samples were collected per shift, each over a period of ~2 h, and were adjusted to 8 h average concentrations
		MMA-MS welder, Factory 2	Total particulate, environmental, 10, 2 h	5.3	3.0–10.5	
		MMA-MS welder, Factory 3	Total particulate, environmental, 10, 2 h	11.3	3.0–24.0	
		MMA-MS welder, Factory 4	Total particulate, environmental, 10, 2 h	6.8	4.5–12.0	
		MMA-MS welder, Factory 5	Total particulate, environmental, 10, 2 h	4.7	1.0–13.0	
		MMA-MS welder, Factory 6	Total particulate, environmental, 10, 2 h	3.0	1.5–4.5	
Schoonover et al. (2011)	USA, NR	MMA-MS welder, fabrication	Total particulate, personal, 7, full shift	GM, 0.630	0.150–2.100	37 mm open-faced cassette attached outside face shield
		GMA-MS welder, fabrication	Total particulate, personal, 6, full shift	GM, 0.510	0.140–1.700	Personal exposure samples collected using 37 mm open-faced cassette; sampled over 5 consecutive Mondays, each worker sampled once; samplers attached outside face mask
		Non-welder controls, fabrication	Total particulate, personal, 22, full shift	GM, 0.060	0.0038–0.370	
Hedmer et al. (2014)	Sweden, NR	GMA-MS welder, Company 1	Respirable, personal, 43, 6.2 h (0.5–9.1 h)	1.5	0.2–6.5	11 companies in south-west Sweden included in the study; Company 1 was visited 3 times for exposure measurements and a total of 16 workers participated; respirable dust sampler placed outside the face shield
		GMA-MS welder, Company 2	Respirable, personal, 30, 6.2 h (0.5–9.1 h)	2.3	0.2–7.7	Company 2 was visited 3 times for exposure measurements and a total of 12 workers participated; respirable dust sampler placed outside the face shield

Table 1.8 (continued)

Reference	Location, collection date	Occupation description	Sampling matrix, approach, *N*, duration	Exposure level[a] (mg/m³)	Exposure range (mg/m³)	Comments/additional data
Hedmer et al. (2014) (cont.)		GMA-MS welder, Company 3	Respirable, personal, 37, 6.2 h (0.5–9.1 h)	2.3	0.3–11.9	Company 3 was visited 3 times for exposure measurements and a total of 14 workers participated; respirable dust sampler placed outside the face shield
		GMA-MS welder, Company 4	Respirable, personal, 12, 6.2 h (0.5–9.1 h)	1.2	0.5–2.3	Company 4 was visited 3 times for exposure measurements and a total of 5 workers participated; respirable dust sampler placed outside the face shield
		GMA-MS welder, Company 5	Respirable, personal, 21, 6.2 h (0.5–9.1 h)	5.7	0.1–38.3	Company 5 was visited 3 times for exposure measurements and a total of 9 workers participated; respirable dust sampler placed outside the face shield
		GMA-MS welder, Company 6	Respirable, personal, 13, 6.2 h (0.5–9.1 h)	3.2	0.5–11.2	Company 6 was visited 3 times for exposure measurements and a total of 5 workers participated; respirable dust sampler placed outside the face shield
		GMA-MS welder, Company 7	Respirable, personal, 21, 6.2 h (0.5–9.1 h)	3.0	1.2–10.5	Company 7 was visited 3 times for exposure measurements and a total of 9 workers participated; respirable dust sampler placed outside the face shield
		GMA-MS welder, Company 8	Respirable, personal, 28, 6.2 h (0.5–9.1 h)	3.1	0.7–8.3	Company 8 was visited 3 times for exposure measurements and a total of 11 workers participated; respirable dust sampler placed outside the face shield
		GMA-MS welder, Company 9	Respirable, personal, 29, 6.2 h (0.5–9.1 h)	0.4	0.1–1.8	Company 9 was visited 3 times for exposure measurements and a total of 14 workers participated; respirable dust sampler placed outside the face shield
		GMA-MS welder, Company 10	Respirable, personal, 12, 6.2 h (0.5–9.1 h)	1.4	0.1–6.1	Company 10 was visited 3 times for exposure measurements and a total of 6 workers participated; respirable dust sampler placed outside the face shield
		GMA-MS welder, Company 11	Respirable, personal, 18, 6.2 h (0.5–9.1 h)	1.6	0.4–3.3	Company 11 was visited 3 times for exposure measurements and a total of 7 workers participated; respirable dust sampler placed outside the face shield
Matczak & Gromiec (2002)	Poland, NR	GMA-Al welder, Plant I and II	Total particulate, personal, 34, 6–7 h	6	0.8–17.8	Samples collected with 37 mm filters for total dust and adjusted to 8 h TWA concentrations; not specified whether inside or outside of face shield; Plant 1 had AM concentration 8.8 mg/m³ and Plant II had AM concentration of 5.0 mg/m³
		GMA-Al welder, Plant II	Respirable, personal, 12, 6–7 h	2.6	0.7–6.0	Samples collected with cyclones for respirable dust and adjusted to 8 h TWA concentrations; not specified whether inside or outside of face shield

Table 1.8 (continued)

Reference	Location, collection date	Occupation description	Sampling matrix, approach, *N*, duration	Exposure level[a] (mg/m^3)	Exposure range (mg/m^3)	Comments/additional data
Matczak & Gromiec (2002) (cont.)		Turner and crane operator, Plant I	Total particulate, personal, 3, 6–7 h	1.4	1.3–1.6	For non-welders working in the same room as GMA-Al welders; 37 mm filters for total dust adjusted to 8 h TWA concentrations; not specified whether inside or outside of face shields
		GTA-Al welder, Plant III	Total particulate, personal, 13, 6–7 h	0.69	0.25–1.36	Samples collected with 37 mm filters for total dust and adjusted to 8 h TWA concentrations; not specified whether inside or outside of face shield
		GTA-Al welder, Plant III	Respirable, personal, 5, 6–7 h	0.79	0.32–1.85	Samples collected with cyclones for respirable dust and adjusted to 8 h TWA concentrations; not specified whether inside or outside of face shield

[a] Exposure level expressed as arithmetic mean unless indicated otherwise

Al, aluminium; AM, arithmetic mean; FCA, flux cored arc; GM, geometric mean; GMA, gas metal arc; GTA, gas tungsten arc; h, hour(s); IOM, Institute of Occupational Medicine; MCE, mixed cellulose ester; MMA, manual metal arc; MS, mild steel; NR, not reported; PVC, polyvinyl chloride; SS, stainless steel; TWA, time-weighted average

surface area to the respiratory system compared with that of MMA.

The concentration of welding fumes which a welder is exposed to depends on several factors, including welding process, welded metal, presence of coatings, arc time, and workplace and personal characteristics. Kromhout et al. (2004) created a database of welding fumes consisting of over 1200 measurements from 10 individual studies conducted during 1983–2003 in the Netherlands. The authors had information on welding process (GMA, GTA, MMA, other), ventilation (general or local), and whether the welder wore an improved helmet to provide cleaner air. Fitting a mixed model with these fixed effects, including random effects for worker and factory, the authors found that these determinants explained 18% of the variability between factories and 16% of the variability between workers within the same factory. The type of metal welded did not have an apparent effect in the model when considering total welding fumes. When including background concentration of welding fumes on a subset of workers for which this was known, 36% of the total variance was explained.

Liu et al. (2011) compiled over 2000 individual total particulate measurements from welders to assess sources of variability, with the major factors related to exposure being country (higher exposure levels in Finland and the USA, and lower exposure levels in Canada, the United Kingdom, and New Zealand), industry (highest levels in manufacturing and lowest levels in automobile industries), trades (highest exposures for boilermakers, and lowest exposures for pipe and welder fitters), type of ventilation (lowest exposures with mechanical and local exhaust ventilation), and type of welding process (highest exposures in MMA, followed by GMA, GTA, and ER welding). Exposures to welding fumes had not changed over the 40-year period. Creely et al. (2007) found similar results when analysing the database of welding fumes previously described by Kromhout et al. (2004); it was noted that, while exposure to welding fumes had decreased by 4% per year during 1983–2003, this was a lower rate of reduction than for other chemicals in the same geographic region.

Hobson et al. (2011) summarized 28 articles describing particulate exposure to welding fumes in field studies, and found that welding process and degree of enclosure explained 76% of the variability in mean particulate exposures. Lehnert et al. (2012) investigated determinants of exposure to particle size specific welding fumes and, as for Hobson et al. (2011), Liu et al. (2011), and Kromhout et al. (2004), found welding process, use of ventilation, and degree of enclosure to be the major determinants of exposure. Lehnert et al. (2012) found that FCA generated the highest concentration of welding fumes, followed by GMA and MMA. While GTA generated the lowest concentration of welding fumes, this welding process did have the highest number of small particles including ultrafine particles (UFP), which are less than 0.1 μm in diameter. In GTA welders, Graczyk et al. (2016) found 92% of the particle counts were of UFP type.

Suarthana et al. (2014) used the exposure models developed by Kromhout et al. (2004), Liu et al. (2011), and Lehnert et al. (2012) to estimate exposure to UFP in Canadian apprentice welders. Comparing estimates from the three models (which were developed using measurements of inhalable, total particulate, and respirable welding fumes) to measured concentrations of UFP, Suarthana et al. found low R^2 correlations ranging from 0.11 to 0.22. However, R^2 correlations between the Kromhout, Liu, and Lehnert models were higher, ranging from 0.41 to 0.74, showing that they correlated better with each other than any of the three models correlated with the measured concentrations of UFP. [The Working Group noted that this perhaps shows that particle size and nature of work (apprentice welder vs skilled welder) are other relevant

Table 1.9 Occupational exposures to chromium and nickel within the stainless steel and mild steel welding industries by process and industry

Reference (country)	Welding process	Industry	Total Cr (μg/m³)[a]	Cr(VI) (μg/m³)[a]	Ni (μg/m³)[a]
Stainless steel welding processes					
Åkesson & Skerfving (1985) (Sweden)	MMA (high Ni alloy, 75% Ni)	Fabrication	101 (26–220)	–	440 (70–970)
Angerer & Lehnert (1990); Angerer et al. (1987) (Germany)	MMA	Shipbuilding	4[b] (< 1–50)	–	72 (< 50–260)
Angerer et al. (1987); Angerer & Lehnert (1990) (Germany)	GMA	Shipbuilding	10[b] (< 1–80)	–	100 (< 50–320)
Bonde (1990) (Denmark)	GTA	Fabrication	14.8; SD, 11.4	3.6; SD, 2.8	-
Knudsen et al. (1992) (Denmark)	GMA	NR	14.7; SD, 6.2	–	11.6; SD, 9.2
Knudsen et al. (1992) (Denmark)	GTA	NR	27.7; SD, 60.4	–	15.2; SD, 17.3
Matczak & Chmielnicka (1993) (Poland)	MMA	NR	(5–991)	50 (5–842)	20 (10–150)
Karlsen et al. (1994) (Norway)	MMA, shipyard	Shipyard	230 (8.3–1000)	140 (3.6–640)	50 (2.8–150)
Karlsen et al. (1994) (Norway)	MMA, offshore module	Fabrication	30 (4.7–87)	6.2 (< LOD–18)	11 (1.6–41)
Karlsen et al. (1994) (Norway)	MMA, welding shops	Fabrication	50 (< LOD–270)	12 (< LOD–84)	14 (5.5–39)
Karlsen et al. (1994) (Norway)	Grinding, small shop	Fabrication	1100 (270–4300)	< LOD (< LOD–0.9)	250 (79–650)
Edmé et al. (1997) (France)	MMA	Fabrication	201 (16–1328)	86 (1–649)	-
Edmé et al. (1997) (France)	GMA	Fabrication	185 (13–1200)	3.7 (1–65)	-
Edmé et al. (1997) (France)	GTA	Fabrication	52 (1–308)	2.4 (1–16	-
Wallace et al. (2001) (USA)	GMA	Fabrication	GM, 89.67 (SD, 64.62)	–	GM, 44.84 (SD, 31.32)
Wallace et al. (2001) (USA)	GTA	Fabrication	GM, 2.74 (SD, 0.86)	–	GM, 1.57 (SD, 0.54)
Stridsklev et al. (2004) (Norway)	FCA	NR	200 (2.4–2.744)	11.3 (< 0.2–151.3)	50.4 (< 2.0–416.7)
Ellingsen et al. (2006) (the Russian Federation)	MMA	Fabrication and shipyard	57 (5–976)	–	34 (3–240)
Ellingsen et al. (2006) (the Russian Federation)	GMA	Fabrication and shipyard	73 (7–387)	–	28 (2–270)
Ellingsen et al. (2006) (the Russian Federation)	FCA	Fabrication and shipyard	9 (3–18)	–	7 (2–25)
Mild steel welding processes					
Dryson & Rogers (1991) (New Zealand)	GMA	NR	< LOD	–	(< LOD–0.002)
Dryson & Rogers (1991) (New Zealand)	MMA	NR	< LOD	–	< LOD
Bonde (1990) (Denmark)	MMA, GMA	Fabrication	3.0 (SD, 1.8)	2 (SD, 1.2)	–

Table 1.9 (continued)

Reference (country)	Welding process	Industry	Total Cr (µg/m³)[a]	Cr(VI) (µg/m³)[a]	Ni (µg/m³)[a]
Wallace et al. (2001) (USA)	FCA, boilerplate[c]	Fabrication	GM, 12.61 (SD, 15.86)	–	GM, 11.76 (SD,13.78)
Schoonover et al. (2011) (USA)	MMA	Fabrication	1.8 (0.051–1.90)		0.36 (0.14–2.5)
Schoonover et al. (2011) (USA)	GMA	Fabrication	0.46 (0.14–1.6)		0.29 (0.11–1.2)

[a] Arithmetic mean unless otherwise specified, range in parentheses
[b] Median
[c] Defined as carbon steel with no further information, but defined separately from stainless steel in the article
Cr, chromium; Cr(VI), hexavalent chronium; FCA, flux-cored arc; GM, geometric mean; GMA, gas metal arc; GTA, gas tungsten arc; LOD, limit of detection; MMA, manual metal arc; Ni, nickel; NR, not reported; SD, standard deviation

considerations when characterizing exposures to welding fumes.]

1.3.2 Exposure to chromium and nickel

Airborne exposures to chromium and nickel compounds are summarized in Table 1.9 for both SS and MS welding processes. For total chromium exposures, the ranges of mean concentration for MMA-SS and GMA-SS welding were 4–230 μg/m³ (Angerer & Lehnert, 1990; Karlsen et al., 1994; Edmé et al., 1997) and 10–185 μg/m³ (Angerer & Lehnert, 1990; Knudsen et al., 1992; Edmé et al., 1997), respectively. The mean concentrations from two FCA-SS welding studies were 200 μg/m³ and 9 μg/m³ (Stridsklev et al., 2004; Ellingsen et al., 2006). GTA-SS welding was observed to result in lower mean total chromium exposures, ranging from 14.8 to 52 μg/m³ (Bonde, 1990; Knudsen et al., 1992; Edmé et al., 1997).

Chromium VI exposures tended to be highest for MMA-SS welders (range of means, 50–140 μg/m³) (Matczak & Chmielnicka, 1993; Karlsen et al., 1994; Edmé et al., 1997). Considering only SS welders again, nickel exposures were lowest in two studies of GTA welding (means, 15.2 and 1.57 μg/m³) (Knudsen et al., 1992; Wallace et al., 2001), and concentrations varied in studies of MMA (range of means, 11–440 μg/m³) (Åkesson & Skerfving, 1985; Karlsen et al., 1994; Ellingsen et al., 2006), FCA (means, 7 and 50.4 μg/m³) (Stridsklev et al., 2004; Ellingsen et al., 2006), and GMA welding (range of means, 11.6–100 μg/m³) (Angerer & Lehnert, 1990; Knudsen et al., 1992; Wallace et al., 2001; Ellingsen et al., 2006).

Airborne exposures to chromium and nickel compounds could be 10 times lower for MS processes (Dryson & Rogers, 1991; Schoonover et al., 2011).

In the WELDOX study, Weiss et al. (2013) characterized determinants of exposure to both airborne and urinary chromium and nickel. They found that metal content in electrodes or base material and the welding process explained most of the variability in air measurements; SS welding demonstrated much higher concentrations of both chromium and nickel in air than MS welding. In urine, chromium and nickel concentrations were higher when welding was performed in a confined space or with poor ventilation. The use of respiratory protection was associated with a decrease in urinary chromium and nickel concentrations.

Persoons et al. (2014) investigated determinants of exposure to chromium and nickel as measured in the urine of GMA-SS welders. They found that welding by the more experienced, in a confined space, or for a longer time during the previous working week resulted in higher concentrations of chromium in urine, whereas welding of MS (as opposed to SS) and using mechanical ventilation resulted in lower concentrations of urinary chromium. Urinary nickel concentrations were found to be highest for welders with greater experience and who had performed grinding, and lowest for welders of MS. The metal content of the consumable electrode did not influence urinary chromium or nickel in this model. As in the models of welding fumes described by Kromhout et al. (2004), Hobson et al. (2011), Liu et al. (2011), and Lehnert et al. (2014), when assessing determinants of exposure to urinary chromium and nickel, the use of ventilation resulted in reduced exposures, confined space welding resulted in higher exposures, and there were differences in measured exposure due to type of welding or base metal used.

1.3.3 Exposures from aluminium welding

GMA and GTA processes can be used for welding aluminium and aluminium alloys (which often include beryllium, Be), which can present additional exposures to fumes and gases. Higher levels of ozone and UV exposure can also be generated from aluminium welding due

to the high currents and pure argon shielding gas used (Faggetter et al., 1983). Typically, exposures to aluminium experienced by welders are measured in urine or plasma. However, airborne aluminium was measured in a study of 52 GMA and 18 GTA aluminium welders; mean aluminium concentrations of 2.1 mg/m^3 (range, 0.1–7.7 mg/m^3) and 0.17 mg/m^3 (range, 0.07–0.50 mg/m^3) were measured in GMA and GTA welding fumes, respectively (Matczak & Gromiec, 2002).

1.3.4 Exposure to welding gases

Table 1.10 provides a summary of exposures to welding gases. Only one study was found that quantified exposures to gases related to SS welding. Among GTA-SS welders, measured nitrogen dioxide and nitric oxide exposures ranged from less than 0.3 to 21.2 ppm, and from less than 0.04 to 13.8 ppm, respectively (Dryson & Rogers, 1991).

Gases such as carbon monoxide, nitrogen oxides, or ozone are also generated during MS welding processes. Carbon monoxide exposures as high as 1.5 ppm for GMA and MMA welders have been reported (Dryson & Rogers, 1991; Golbabaei et al., 2012). Oxides of nitrogen (NO_2 and NO) were highest for GMA (mean NO_2, 3.29 ppm; mean NO, 0.54 ppm) and GTA (mean NO_2, 3.54 ppm; mean NO, 0.41 ppm) welding operations in the Islamic Republic of Iran (Azari et al., 2011).

1.3.5 Exposure to radiation

(a) UV

In addition to exposures to welding fumes and gases, welders of all types in all industries are exposed to UV radiation from the welding arc. Arc welding produces UV radiation over the full spectrum (UVA, UVB, and UVC), with demonstrated harmful effects on exposed skin and the eyes (Vecchia et al., 2007; ACGIH, 2013).

The exposure of welders to UV radiation has been well characterized in the literature, and is summarized in Table 1.11. Compared with outdoor UV radiation exposure, arc welding UV radiation exposures are very intense within a few metres of the arc; exposure guidelines can be exceeded in a matter of seconds to minutes. This is compatible with the frequent occurrence of skin erythema (sunburn) and photokeratoconjunctivitis ("welder's flash") as reported in the literature (Kimlin & Tenkate, 2007). Despite welders typically wearing UV protective face shields or goggles when arcing, relevant exposure can still occur. Unprotected bystanders can also be exposed to UV radiation (Tenkate & Collins, 1997).

Exposure to UV radiation is higher when: the welder works close to the arc; arc energy, duration, or electrical current are increased; aluminium is being welded (because of the higher energy required); or argon is being used as the shielding gas. UV radiation emission is greatest in GMA, followed by MMA and then GTA welding, although this order can vary depending on current and other parameters (IARC, 1990; American Welding Society, 2014). UV radiation emissions from oxyfuel (gas) welding are generally much lower, but could be associated with less-frequent use of eye protection (Burgess, 1995). Peng et al. (2007) monitored UV radiation exposure during experimental MMA welding scenarios to compare with ACGIH UV exposure guidelines. The effective irradiance at 50 cm from the arc was in the range 0.03–0.3 mW/cm^2 (median, 0.155 mW/cm^2), and reported permissible exposure times ranging from 9.6 to 90.6 seconds (average, 19.4 seconds). In comparison, measurements taken behind a protective mask corresponded to approximately 6 minutes of permissible exposure time (Peng et al., 2007). A similar analysis for GTA welding of aluminium alloys found an effective irradiance at 50 cm from the arc in the range 0.1–0.9 mW/cm^2, reporting a permissible exposure

Table 1.10 Occupational exposures to gases within the stainless steel and mild steel welding industries by process and industry

Reference (country)	Welding process	Industry	CO (ppm)[a]	NO_2 (ppm)[a]	NO (ppm)[a]	F (mg/m³)[a]	O_3 (ppm)[a]
Stainless steel welding processes							
Dryson & Rogers (1991) (New Zealand)	GTA	NR	–	(< 0.3–21.2)	(< 0.04–13.8)	–	–
Mild steel welding processes							
Dryson & Rogers (1991) (New Zealand)	GMA	NR	1.5 (1.2–1.8)	(< 0.01–0.7)	(< 0.01–0.17)	–	–
Dryson & Rogers (1991) (New Zealand)	MMA	NR	–	(< 0.1–4.4)	(< 0.07–1.6)	–	–
Akbar-Khanzadeh (1993) (UK)	Various	Shipyard	1.1 (SD, 0.5)	0.06 (SD, 0.03)	0.25 (SD, 0.27)	–	–
Wallace et al. (2001) (USA)	FCA, boilerplate	Fabrication	10 (single grab sample)	ND	–	–	ND
Woskie et al. (2002) (USA)	MS	Construction	–	–	–	0.73 (SD, 1.13)	–
Schoonover et al. (2011) (USA)	MMA	Fabrication		0.064 (0.052–0.22)			0.0047 (< LOD–0.020)
Schoonover et al. (2011) (USA)	GMA	Fabrication		0.038 (0.037–0.061)			0.012 (< LOD–0.037)
Hedmer et al. (2014) (Sweden)	GMA	Fabrication	–	–	–	–	GM, 0.03 (< 0.01–0.66)
Azari et al. (2011) (Islamic Republic of Iran)	GTA	Fabrication	–	3.54 (SD, 0.65)	0.41 (SD, 2.7)	–	0.21 (SD, 0.12)
Azari et al. (2011) (Islamic Republic of Iran)	GMA	Fabrication	–	3.29 (SD, 0.60)	0.54 (SD, 3.2)	–	0.37 (SD, 0.22)
Golbabaei et al. (2012) (Islamic Republic of Iran)	MMA	Fabrication	1.8 (SD, 1.40)	0.397 (SD, 0.35)	–	–	0.018 (SD, 0.02)

[a] Arithmetic mean unless otherwise specified, range in parentheses

CO, carbon monoxide; F, fluoride; FCA, flux-cored arc; GM, geometric mean; GMA, gas metal arc; GTA, gas tungsten arc; LOD, limit of detection; MMA, manual metal arc; MS, mild steel; ND, not determined; NO, nitric oxide; NO_2, nitrogen dioxide; NR, not reported; O_3, ozone; ppm, parts per million; SD, standard deviation

Compiled by the Working Group

Table 1.11 Occupational exposures to non-ionizing radiation within the welding industry by process and industry

Reference (country)	Welding process	Distance (cm)	Industry	ELF-EMF (μT)[a]	UV (μW/cm²)[a]
Peng et al. (2007) (China)	MMA	50	Experimental		Median, 154.9 (33.1–311)
	MMA	100	Experimental		Median, 39.3 (14.2–76.2)
	MMA	200	Experimental		Median, 5.0 (0.2–16.6)
	MMA	300	Experimental		Median, 2.0 (0.0–12.1)
Nakashima et al. (2016) (Japan)	GTA, aluminium	50	Experimental		(91–910)
Okuno et al. (2001) (Japan)	GMA with CO_2 shielding gas	100	Experimental		(28–785)
Wolska (2013) (Poland)	GTA, MMA	60–34			Mean range, 779–3760
Skotte & Hjøllund (1997) (Denmark)	MMA direct current		Shipyard	Workday, 21.2 (range of means, 5.3–43)	
	GMA alternating current		Shipyard	Workday, 2.3 (range of means, 0.59–4.9)	
Dasdag et al. (2002) (Turkey)	MMA		Fabrication	(100–250)	

[a] Range in parentheses

CO_2, carbon dioxide; ELF-EMF, extremely low frequency electromagnetic fields; GMA, gas metal arc; GTA, gas tungsten arc; MMA, manual metal arc; UV, ultraviolet

Compiled by the Working Group

time of 3.3–33 seconds. UV emissions caused by GTA aluminium welding were about one tenth of the emissions by GMA aluminium welding, based on previous results (Nakashima et al., 2016). Wolska (2013) reported on UV radiation exposure measurements at 13 workstations involving GTA and MMA welding with varying process parameters. Mean effective irradiance varied from 0.7 to 3.7 mW/cm², corresponding to a permissible exposure time in the range 1.7–75 seconds. It was not possible to distinguish patterns of higher exposure for GTA or MMA welding due to variations in other parameters such as current.

UV radiation associated with arc welding is generally much higher than for other artificial UV radiation generating processes (e.g. germicidal lamps, photocuring, tanning lamps); exposure concentrations are typically orders of magnitude higher than natural sunlight (Tenkate & Collins, 1997).

(b) ELF-EMF

Welders are also exposed to ELF-EMF, and measured exposures are summarized in Table 1.11. While the number of publications assessing the exposure of welders to EMF is limited, Stern (1987) reported that welders operate devices using a direct, alternating, or pulsing current in the range 100–100 000 A. These currents create magnetic flux densities of 100–10 000 μT at distances of 0.2–1 m from the weld device (Stern, 1987). The arc time of welders typically occupies 30–50% of the working day and welders can work in close proximity to other welders; Stern (1987) calculated that the cumulative EMF exposure for welders can exceed that of the general population by a factor of 2–200.

Skotte & Hjøllund (1997) measured the exposure to ELF-EMF of 50 metalworkers and 15 shipyard welders, who reported welding activity for 5.8 and 56% of the workday, respectively. The personal exposure metres worn by the workers recorded a measurement every 10 seconds for the metalworkers, and every 4 seconds for the shipyard welders. For the metalworkers, the mean ELF-EMF exposure for the workday (calculated using all measurements from all metalworkers) was 0.50 μT, and the maximum of the workday mean exposures (the maximum mean calculated for all of the 50 metalworkers) was 9.73 μT. For the shipyard welders, the mean ELF-EMF exposure for the workday was 7.22 μT and the maximum of the workday mean exposures was 27.5 μT. Higher ELF-EMF exposures were found for MMA direct current welders (workday arithmetic mean, 21.2 μT) than for GMA alternating current welders (workday arithmetic mean, 2.3 μT). During welding-only time, mean exposure was 65 μT for MMA direct current welders and 7 μT for the GMA alternating current welders (Skotte & Hjøllund, 1997). Resistance welders may experience the highest exposures to ELF-EMF compared with other welding processes, as the former involves electric currents up to 100 000 A, resulting in peak ELF-EMF exposures in the millitesla range (Håkansson et al., 2002).

The United States National Institute for Occupational Safety and Health (NIOSH) reports average ELF-EMF daily median and exposure ranges for a variety of workers. Of the workers listed, welders have the highest average daily median exposure of 8.2 milligauss [0.82 μT] and largest range of exposures of 1.7–96 milligauss [0.17–9.6 μT]. As a comparison, electric line workers have an average daily median exposure of 2.5 milligauss [0.25 μT] over the range 0.5–34.8 milligauss [0.05–3.48 μT], and clerical workers experience a median exposure of 1.2 milligauss [0.12 μT] over the range 0.5–4.5 milligauss [0.05–45 μT] (NIOSH, 1996).

(c) Thorium-232

Tungsten electrodes used for GTA welding usually contain 1–4% thorium oxide, added to facilitate arc starting, increase arc stability, reduce weld metal contamination, and improve the current-carrying capacity. Thorium-232 (^{232}Th) is a major radioactive isotope of thorium and an emitter of α particles with a very long decay half-life (1.4×10^{10} years) (Saito et al., 2003). Exposure to ionizing radiation may occur during grinding of the electrode before and after welding, and during welding. In three studies monitoring air sampled in the breathing zone of workers performing welding and grinding, radioactivity was measured within the range 0.1–100 mBq/m^3; this corresponds to estimated yearly effective doses which are mostly below the current general population limit set by the International Commission on Radiological Protection (Ludwig et al., 1999; Gäfvert et al., 2003; Saito et al., 2003). Exposure tended to be higher when alternating current was used, since it is associated with a higher electrode consumption rate (Ludwig et al., 1999).

1.3.6 Coexposures (asbestos, solvents)

A historical exposure related to welding is asbestos, as it was commonly used as an insulating material in ships, in the material covering rod electrodes, in the cylinders holding acetylene gas, and in the heat-protective equipment of welders and blankets to slow cooling of the weld. As asbestos fibres are not stable at the high temperatures used for welding, during such processes they are more likely to aerosolize (Kendzia et al., 2013). Exposure to asbestos in shipyards is most commonly assessed via questionnaire or expert (industrial hygienist) opinion based on historic job duties and tasks. In one cohort study performed by NIOSH at a US shipyard, cumulative exposure to asbestos was determined through a combination of historic asbestos air samples (n = 915) collected from

Table 1.12 Limit values for welding fumes (8 hours)

Country	Limit value (mg/m³)
Australia	5[a]
Austria	5 (respirable aerosol)
Belgium	5
Canada – Québec	5
France	5
Ireland	5
Latvia	4
New Zealand	5[a, b]
People's Republic of China	4[c]
Singapore	5
Republic of Korea	5
Spain	5
Netherlands	1[d]

[a] Not otherwise classified
[b] A range of airborne contaminants are associated with gas and arc welding. The type of metal being welded, the electrode employed and the welding process will all influence the composition and amount of fumes. Gaseous products such as nitrogen oxides, carbon monoxide, and ozone may also be produced. In the absence of toxic elements such as chromium, and where conditions do not support the generation of toxic gases, the concentration of fumes inside the welder's helmet should not exceed 5 mg/m³
[c] Inhalable fraction
[d] Until 1 April 2010, the legal limit value was 3.5 mg/m³
Adapted from GESTIS International Limit Values, Update: March 2017 (GESTIS, 2016)

the 1940s to the 1990s and informed by an industrial hygiene panel. The majority (852) of asbestos samples fell below the limit of detection (< 0.004 fibres/mL) with the remaining 63 samples ranging from 0.004 to 25.0 fibres/mL; that is, 6% of welders were considered to have experienced high exposures to asbestos (Seel et al., 2007).

The use of chlorinated solvents, such as trichloroethylene (TCE) or tetrachloroethylene, for cleaning coated metal in tandem with welding may result in exposures to hydrogen chloride and possibly phosgene (Burgess, 1995). The Working Group could not find reported exposure levels to these solvents for welders. Among job periods exposed to any welding fumes in CANJEM, 15% were also deemed exposed to chlorinated solvents. Among welder occupations (sheet metal workers, mechanics, welders), 10–20% of the job periods were deemed exposed to both chlorinated solvents and welding fumes. Higher proportions of coexposure (30%) were found in occupations related to electric/electronic maintenance.

Benzene has historically been used in solvents for metal cleaning. Among CANJEM job periods exposed to any welding fumes, 11% were also deemed exposed to benzene (4% after 1980) (CANJEM, 2017).

1.4 Regulations and guidelines

Limit values for occupational exposure to welding fumes are generally set at 5 mg/m³; exceptions are in the People's Republic of China (limit value of 4 mg/m³) and the Netherlands where, on 1 April 2010, a limit value of 1 mg/m³ over 8 hours came into force. In most countries the size fraction of welding fumes has not been defined but, given the process during which the fumes are generated, it is assumed that the welding fumes fall into the respirable aerosol size range (Table 1.12). No short-term limit values exist.

A range of airborne contaminants are associated with gas and arc welding. The type of metal being welded, the electrode employed, and the welding process all influence the composition and amount of fumes. Gaseous products such as nitrogen oxides, carbon monoxide, and ozone may also be produced. Some countries no longer have an exposure limit for welding fumes, but instead use limits for specific metals in welding fumes or respirable dust (e.g. Germany, the United Kingdom, and the USA) (BG-Regel, 2006; OSHA, 2013; HSE, 2017). In the United Kingdom a generic exposure limit to welding fumes of 5 mg/m³ as total inhalable particulate (TIP) was withdrawn in 2005 (Garrod & Ball, 2005), as the limit was not considered to be protective of health.

The World Health Organization has recommended the use of personal protective equipment for welders and helpers and the use of engineering controls (e.g. "light-tight" cabinets and enclosures, UV-absorbing glass, plastic shielding, baffles) to protect non-involved staff in the welding workplace (ICNIRP, 2007).

1.5 Exposure assessment of epidemiological studies

Table 1.13, Table 1.14, and Table 1.15 provide an overview of the exposure assessment methods used in the key epidemiological studies that were evaluated by the Working Group. The strengths and the weaknesses of each study were assessed, as well as the potential effects of these on the interpretation of the risk estimates.

Some studies used the job title "welder" as a measure of exposure (Tucker et al., 1985; Schoenberg et al., 1987; Holly et al., 1996; Kogevinas et al., 2003; Reulen et al., 2008; Pukkala et al., 2009; Kendzia et al., 2013; 't Mannetje et al., 2016; MacLeod et al., 2017). Job title alone does not provide information on different tasks and circumstances; since these influence the level and frequency of exposure to welding fumes, job title does not specifically characterize exposure to welding fumes. Additionally, workers with job titles other than welder may also perform welding tasks (see Table 1.3). Some of the studies using job titles separately classified welders and "occasional welders" (Kendzia et al., 2013; Matrat et al., 2016; MacLeod et al., 2017). Definitions of occasional welder vary between studies and have been based on job titles judged by study authors to involve welding tasks, for example plumbers and sheet metal workers. The exact definition will affect the level of exposure misclassification, so both classifications (regular welders and occasional welders) should always be assessed separately. The reference group should not include either welders or occasional welders when calculating risk estimates in epidemiological studies.

Exposure assessment in several studies on ocular melanoma relied on self-reported UV radiation exposure (Seddon et al., 1990; Ajani et al., 1992; Vajdic et al., 2004); although this is more informative than job title alone, it may be prone to recall bias.

Several studies used general job-exposure matrices (JEMs) (Pesch et al., 2000; Guénel et al., 2001; Lutz et al., 2005), with some based on monitoring data (Simonato et al., 1991; Sørensen et al., 2007; Yiin et al., 2007; Siew et al., 2008). However, Yiin et al. (2007) acknowledged that scarcity of data on welding fumes was a complicating factor in the quantitative assessment. Since JEMs are a standardized method of assessing exposures, any misclassification is likely to be non-differential and the assessment process is transparent. On the other hand, standardization negatively affects the possibility of accounting for between-worker variations, since workers with the same job title will all be assigned the same exposure.

Exposure to welding fumes can also be determined from welding-specific questionnaires, either through case-by-case expert assessment (e.g. industrial hygienists) or directly reporting on specific tasks performed by the respondent (Siemiatycki, 1991; van Loon et al., 1997; Gustavsson et al., 1998; Jöckel et al., 1998a, b; Gustavsson et al., 2000; 't Mannetje et al., 2012; Vallières et al., 2012). The assessment can therefore incorporate all available information (job title, type and name of the company, what was being produced in the department, time period, welding type and material, control measures) and account for between-worker variations within the same job. These assessment methods also have their limitations, because they rely on the reported work histories and welding characteristics. Self-reported occupational information is susceptible to recall bias, but this bias is minimized when exposure assessment is based on reported tasks rather than specific exposures.

Occupational information collected from proxy respondents is not very useful for assessing exposure to welding fumes, as spouses or other relatives will not be able to provide details on specific welding tasks and materials.

Several studies have reported good inter-rater agreement analyses in the exposure assessment of welding fumes. Seel et al. (2007) found good concordance (78%) for estimating intensity of exposure to welding fumes and excellent concordance (98%) for frequency estimates, defined as the number of 8-hour working days per year at the estimated intensity (Seel et al., 2007). Benke et al. (1997) also reported good agreement between raters for welding fumes (κ = 0.57). 't Mannetje et al. (2012) reported a κ of 0.9 for agreement between experts in assessing exposures to welding fumes in a multicentre study on lung cancer. [The Working Group noted that high agreement between experts does not necessarily relate to correct assessments of exposure.]

[The main strengths of most of the case–control studies listed in Table 1.14 are that full job histories were assessed. The cohorts listed in Table 1.13 do not have full job histories of the subjects, which might have led to underestimation of exposure to welding fumes.]

1.5.1 *Summary exposure assessment quality of epidemiological studies*

In summary, the cohort studies with the strongest exposure assessment are those that applied a "welding exposure matrix" (Simonato et al., 1991; Sørensen et al., 2007), followed by studies that applied either case-by-case expert assessment (van Loon et al., 1997) or general JEMs (Yiin et al., 2005; Meguellati-Hakkas et al., 2006; Yiin et al., 2007; Siew et al., 2008). Studies that only looked at job titles (Gerin et al. 1984; Kjuus et al. 1986; Pukkala et al., 2009; MacLeod et al., 2017) are considered less informative.

Taking into account all available information, exposure assessments based on welding-specific questionnaires in the case–control studies of cancer of the lung are considered the most informative on exposure to welding fumes (Siemiatycki, 1991; Jöckel et al., 1998a, b; 't Mannetje et al., 2012; Vallières et al., 2012; Matrat et al., 2016). Caution is warranted when interpreting studies based on information (partly) collected from proxy respondents, since they will often be unfamiliar with the detailed technical and workplace characteristics needed for welding-specific questionnaires. Exposure assessment based on job titles alone (Kendzia et al., 2013) provides no information on the level of exposure to welding fumes. Studies that only reported ever versus never welder (Schoenberg et al., 1987), or were based predominantly on data collected from proxy respondents (Hull et al., 1989; Gustavsson et al., 2000), are considered to be least informative regarding the characterization of exposure to welding fumes.

The case–control studies of ocular melanoma applying a JEM (Guénel et al., 2001; Lutz et al., 2005) are the most informative regarding exposure to UV radiation, followed by self-reported eye burns (Guénel et al., 2001; Vajdic et al., 2004) and self-reported exposure from specific welding types (Vajdic et al., 2004), although caution is advised with regards to recall bias. The studies assessing exposure to welding fumes (Siemiatycki, 1991) and ever exposure to welding arcs (Seddon et al., 1990; Ajani et al., 1992) as a proxy for UV radiation exposure are less informative. Studies reporting on ever versus never welders alone provide the least information on UV radiation exposure (Tucker et al., 1985; Holly et al., 1996).

For the case–control studies on other cancer types, assessment of exposure to welding fumes based on expert judgement (Siemiatycki, 1991) or on a JEM (Pesch et al., 2000) is preferred over assessments based on job title alone (Kogevinas et al., 2003; Reulen et al., 2008; 't Mannetje et al., 2016).

Table 1.13 Exposure assessment in key epidemiological studies of welders: cohort studies

Exposure assessment method	Description	Strengths	Limitations	Reference	Exposure metrics reported
Welding exposure matrix	Cohort study of male metal workers employed for at least 1 yr at 1 or more Danish SS or MS industrial companies Ever welders, who started work in 1960 or later, were included for analyses Information on lifetime occupational exposures was collected during a questionnaire in 1986; for deceased workers, proxy respondents were interviewed	Exposure to welding fumes assessed specifically Quantitative exposure assessment, based on measurement data Standardized assessment by JEM; any exposure misclassification therefore likely to be non-differential Details on individual welding tasks taken into account	Retrospective recall of details of the welding process has questionable accuracy No full job histories	Sørensen et al. (2007)	Exposure to welding fumes up to baseline, expressed as mg/m^3-yr
Welding exposure matrix	Multicentre cohort study of male welders from 135 companies in 9 European countries Exposure histories were constructed for each cohort member, including employment dates, base metal welded, welding process used, work environment, and changes in exposure over time	Exposure to welding fumes assessed specifically Quantitative exposure assessment based on expert judgment and measurement data Standardized assessment by JEM; any exposure misclassification therefore likely to be non-differential Detailed job information, accounting for welding material and process	No full job histories In some cases company information was used to complete individual exposure histories	Simonato et al. (1991); Gérin et al. (1993)	Years since first exposure to welding fumes (0–9, 10–19, 20–29, ≥ 30) and duration of employment in years (< 9, ≥ 10) were assigned Welders were classified by type of welding: shipyards, MS only, ever SS, predominantly SS Level of exposure was expressed in units of mg/m^3; cumulative exposure to welding fumes was then derived by multiplying level by duration and expressed as mg/m^3-yr

Table 1.13 (continued)

Exposure assessment method	Description	Strengths	Limitations	Reference	Exposure metrics reported
Expert assessment	Prospective cohort study, men and women aged 55–69 yr in September 1986 Job history was obtained via self-administered questionnaire, collecting data on job title, company, department, and period	Exposure to welding fumes assessed specifically Blinded exposure assessment; any exposure misclassification therefore likely to be non-differential All available information used (job title, type, name of the company, what was being produced in the department, time period) Final re-evaluation round performed to minimize miscategorization of exposures	No quantitative data on welding fumes Job histories only up to start of follow-up, so may have missed up to 10 yr of the end of career	van Loon et al. (1997)	Probability of exposure to welding fumes (particularly SS), classified into four categories (no exposure; possible exposure, < 30%; probable exposure, 30–90%; nearly certain exposure, > 90%), given the weights 0, 0.15, 0.6, and 0.95, respectively Cumulative probability of exposure was assigned based on the combination of probability weight and duration in years
JEM	Cohort study of men and women employed at the Portsmouth Naval Shipyard for at least 1 day between 1 January 1952 and 31 December 1992, who were monitored for radiation Detailed computerized work histories collected from personnel records	Exposure to welding fumes assessed specifically Expert assessment by panel of industrial hygienists who were familiar with shipyard operations Standardized assessment by JEM; any exposure misclassification therefore likely to be non-differential	No full job histories No quantitative data on welding fumes	Yiin et al. (2005)	Exposure to welding fumes (0, none; 1, possible; 2, probable) was assigned to each job title/shop combination by an expert panel Cumulative exposure score was calculated as the sum of the duration of exposed jobs (in years) multiplied by the exposure probability score Cumulative exposure to welding fumes was then classified into three categories: 0, > 0–5, and > 5

Table 1.13 (continued)

Exposure assessment method	Description	Strengths	Limitations	Reference	Exposure metrics reported
JEM	Cohort study of workers in technical branch of the telephone company on 1 January 1978 and newly hired up to 31 December 1994 Individual job histories since start of employment in the company were obtained from company records Occupations were classified into six groups, as well as into seven sectors; start and end date of each occupation was recorded	Exposure to welding fumes assessed specifically Standardized assessment by JEM; any exposure misclassification therefore likely to be non-differential	No full job histories No quantitative data on welding fumes	Meguellati-Hakkas et al. (2006)	Exposure to arc welding fumes was expressed by duration in years
JEM	Cohort study of men and women employed at the Portsmouth Naval Shipyard for at least 1 day between 1 January 1952 and 31 December 1992, who were monitored for radiation Detailed computerized work histories collected from personnel records, including job titles, shop assignment, and employment dates	Exposure to welding fumes assessed specifically Quantitative exposure assessment based on expert judgement Standardized assessment by JEM; any exposure misclassification therefore likely to be non-differential	No full job histories Scarcity of monitoring data on welding fumes hindered quantitative assessment based on data	Yiin et al. (2007)	Intensity and frequency of exposure to welding fumes (as Fe_2O_3 fumes) were assessed Cumulative exposure (mg-days/m^3) was assigned to each subject
JEM	Cohort study of all economically active Finnish men born during 1906–1945 Occupations were obtained from the 1970 population census; jobs were coded according to ISCO-1958 and FIN-JEM was applied	Exposure to welding fumes assessed specifically Quantitative exposure assessment, based on measurement data Standardized assessment by JEM; any exposure misclassification therefore likely to be non-differential	No full job history	Siew et al. (2008)	Level of exposure to welding fumes in mg/m^3; any occupation with more than 5% of workers exposed was considered potentially exposed

Table 1.13 (continued)

Exposure assessment method	Description	Strengths	Limitations	Reference	Exposure metrics reported
Job title	Census-based cohort study of male workers aged 24–74 in 1991 in Canada Occupation in week before census or the longest-held job in the previous year was asked for	Both welders and occasional welders identified	No full job histories, only occupation at one point in time Exposure to welding fumes was not assessed specifically Number of occasional welders overestimated since many occupations were classified as such	MacLeod et al. (2017)	Employment as welder or occasional welder vs non-welders
Job title	Census-based cohort study, men and women aged 30–64 yr in the 1960, 1970, 1980/81, and/or 1990 censuses in the Nordic countries Occupation and industry were recorded in the census	Standardized classification of jobs across countries (ISCO-1958)	Only ever vs never employment as welder Exposure to welding fumes was not assessed specifically Workers may be performing welding tasks and/or be exposed to welding fumes without having the job title "welder" No full job histories	Pukkala et al. (2009)	Ever vs never employment as welder

Fe_2O_3, iron oxide; FIN-JEM, Finnish job-exposure matrix; ISCO, International Standard Classification of Occupations; JEM, job-exposure matrix; MS, mild steel; SS, stainless steel; vs, versus; yr, year(s)

Table 1.14 Exposure assessment in key epidemiological studies of welders: cancer of the lung case–control studies

Exposure assessment method	Description	Strengths	Limitations	Reference	Exposure metric reported/notes
Expert assessment	Two lung cancer case–control studies Detailed job histories were obtained by interview; case-by-case expert assessment was used to assess exposures	Exposure to welding fumes assessed specifically Full job histories All available information used (job title, tasks, materials used, company, department, protective equipment) Separated by arc welding and gas welding fumes Welding-specific questionnaire, also administered to other job titles if indicating welding tasks Blinded exposure assessment; any exposure misclassification therefore likely to be non-differential	No quantitative data on welding fumes Information for ~23% of the subjects was collected via proxy respondents, who may not be aware of the specific tasks and working conditions of the case or control under study	Vallières et al. (2012)	Confidence of exposure occurrence (possible, probably, definite) Intensity of exposure (non-exposed, low, medium, high) Frequency of exposure (low, 1–5% of time; medium, 5–30%; high, > 30%) Ever exposed to gas welding fumes, arc welding fumes vs never exposed to welding fumes
Expert assessment	Case–control study on lung cancer (1998–2001) in 6 central and eastern European countries and in the UK Questionnaire assessing occupations held for more than 1 yr, including questions on welding or gas cutting and if any welding or gas cutting was done near the subject; a specialized questionnaire on welding was administered when the general questionnaire indicated employment as a welder; case-by-case expert assessment was used to assess exposures	Exposure to welding fumes assessed specifically Full job histories All available information used (job title, tasks, materials used, company, department, protective equipment) Separated by arc welding and gas welding fumes Welding-specific questionnaire, also administered to other job titles if indicating welding tasks Blinded exposure assessment; any exposure misclassification therefore likely to be non-differential Standardization through yearly training of experts and use of manual for assessment; high agreement ($\kappa = 0.9$) between experts for welding fumes	No quantitative data on welding fumes Expert's ability to assess the level of exposure to welding fumes was limited	't Mannetje et al. (2012)	Confidence of exposure occurrence (possible, probably, definite) Intensity of exposure (non-exposed, low, medium, high) Frequency of exposure (low, 1–5% of time; medium, 5–30%; high, > 30%) Ever exposed to gas welding fumes, arc welding fumes vs never exposed to welding fumes

Table 1.14 (continued)

Exposure assessment method	Description	Strengths	Limitations	Reference	Exposure metric reported/notes
Expert assessment	Case–control study for several cancer sites Detailed job histories were obtained by interview; case-by-case expert assessment was used to assess exposures	Exposure to welding fumes assessed specifically Full job histories All available information used (job title, tasks, materials used, company, department, protective equipment) Separated by arc welding, gas welding, and soldering fumes Welding-specific questionnaire, also administered to other job titles if indicating welding tasks Blinded exposure assessment; any exposure misclassification therefore likely to be non-differential	No quantitative data on welding fumes Information for 29% of the subjects was collected via proxy respondent, who may not be aware of the specific tasks and working conditions of the case or control under study	Siemiatycki (1991)	Intensity of exposure (non-exposed, low, medium, high) Frequency of exposure (low, 1–5% of time; medium, 5–30%; high, > 30%)
Welding-specific questionnaire	Case–control study on cancers of the respiratory tract in France (2001–2007) Face-to-face interviews using standardized questionnaires Lifetime occupational history, including the start and end dates, industry and tasks, and a job-specific questionnaire for welding, brazing, or metal cutting	Full job histories Job-specific questionnaire on welding for anyone who indicated being exposed to welding, including information on the welding process, type of metals welded, type of coating covering the metal, treatments applied before welding and the use of protective clothing Both regular welders and occasional welders defined	Exposure to welding fumes was not assessed specifically Self-reported occupational information susceptible to recall bias; however, reporting tasks probably less prone to recall bias	Matrat et al. (2016)	Ever regular welder, ever occasional welder vs never welder Ever gas, arc, spot, or other welding vs never welding Frequency of welding (≤ 5%, > 5%) Total duration of exposure to welding activity (≤ 10, > 10 yr) Time since last exposure (≤ 35, > 35 yr) Time since last exposure (0, 0–10, 10–20, 20–30, 30–40, > 40 yr)

Table 1.14 (continued)

Exposure assessment method	Description	Strengths	Limitations	Reference	Exposure metric reported/notes
Welding-specific questionnaire	Case–control study on lung cancer in Germany (1988–1993) A structured questionnaire was used to obtain information on job history (for jobs held for at least 6 mo) and occupational exposures; supplemental questionnaires were used for exposure to welding fumes	Full job histories Job-specific questionnaire on welding, including type of welding, metals welded, coating on metals, working conditions, and time dimensions For each individual possibly using welding devices (based on job history), the welding-specific supplementary questionnaire was administered	No quantitative data on welding fumes Self-reported occupational information susceptible to recall bias. However, reporting tasks probably less prone to recall bias	Jöckel et al. (1998a, b)	Ever vs never exposed Lifetime hours of welding oxyacetylene or MMA welding, or both (non-exposed, ≤ 1000, > 1000 to ≤ 6000, > 6000 h)
Job title	Pooled analysis of lung cancer case–control studies Full job histories were collected, including all jobs held for at least 1 yr; start and end year was recorded for each job	Standardized classification of jobs (ISCO-1968) and industries (ISIC revision 2) across studies Full job histories Taking into account workers without the job title welder who may be performing welding tasks and/or exposed to welding fumes	Exposure to welding fumes was not assessed specifically No information on welding process available	Kendzia et al. (2013)	Ever vs never employment as welder Ever vs never employment as occasional welder Longest-held occupation as welder or occasional welder vs never
Welding-specific questionnaire	Lung cancer case–control study among white male welders in Los Angeles County (1972–1987) Interviews collecting information on occupational exposures to specific welding processes, metals welded, asbestos, and confined-space welding	Full job histories Information on type of welding and welding material	Information was largely collected via proxy respondents, who may not be aware of the specific tasks and working conditions of the case or control under study	Hull et al. (1989)	Ever vs never exposed Ever MMA, SS, MS, high-alloy steel welding, confined-space welding, shipyard welding Ever exposed for > 5 yr

Table 1.14 (continued)

Exposure assessment method	Description	Strengths	Limitations	Reference	Exposure metric reported/notes
Job title	Pooled analysis of lung cancer case–control studies Full job histories were collected, including all jobs held for at least 1 yr; start and end year was recorded for each job	Standardized classification of jobs (ISCO-1968) and industries (ISIC revision 2) across studies Full job histories Taking into account workers without the job title welder who may be performing welding tasks and/or exposed to welding fumes	Exposure to welding fumes was not assessed specifically No information on welding process available	Kendzia et al. (2013)	Ever vs never employment as welder Ever vs never employment as occasional welder Longest-held occupation as welder or occasional welder vs never
Job title	Case–control study on lung cancer in New Jersey (1980–1981) Personal interviews of the subjects or their next of kin; information was also obtained on each full-time or part-time job held for 3 mo or more since 12 yr of age Information recorded: name and address of employer; type of business; job title; duties performed; materials handled; exposure to solvents, fumes, or dust; and time period of employment For shipbuilding workers, supplemental questions on employment in specific shipyard trades were also asked	Full job histories	Exposure to welding fumes was not assessed specifically No information on welding process available Workers without the job title welder may be performing welding tasks and/or be exposed to welding fumes	Gerin et al. (1984); Kjuus et al. (1986); Schoenberg et al. (1987)	Ever welder or burner

Table 1.14 (continued)

Exposure assessment method	Description	Strengths	Limitations	Reference	Exposure metric reported/notes
Expert assessment	Case–control study on lung cancer in Sweden (1985–1990) Postal questionnaire recording start and end date, job title, job tasks, and company for each job held for more than 1 yr Case-by-case expert assessment was used to assess exposures; probability and intensity of exposure to a range of occupational exposures, including welding fumes, was assigned	Exposure to welding fumes assessed specifically Full job histories Blinded exposure assessment; any exposure misclassification therefore likely to be non-differential All available information used (work tasks were taken into account in addition to job titles) Only one expert conducted the assessments, enhancing uniform assignments	Information was mostly collected via proxy respondents, who may not be aware of the specific tasks and working conditions of the case or control under study Proxy respondents more often used for cases, possibly resulting in differential misclassification Only one expert conducted the assessments, hindering evaluation of the quality of assessments No quantitative data on welding fumes	Gustavsson et al. (2000)	Exposure to welding fumes was assessed as low, medium, or high, with category averages assigned as 1, 5, and 15 units, respectively, where 15 units corresponded to full-time employment as a MMA welder Probability of exposure (0%, 20%, 50%, or 85%) Cumulative exposure for each factor was calculated as the product of the intensity, the probability, and the duration of the exposure, summed over all work periods in the person's occupational history

h, hour(s); ISCO, International Standard Classification of Occupations; ISIC, International Standard Industrial Classification; mo, month(s); MMA, manual metal arc; MS, mild steel; SS, stainless steel; vs, versus; yr, year(s)

Table 1.15 Exposure assessment in key epidemiological studies of welders: ocular melanoma (ultraviolet radiation)

Exposure assessment method	Description	Strengths	Limitations	Reference	Exposure metrics reported/notes
JEM	Case–control study on ocular melanoma in France Interviews collecting detailed description of each job held for at least 6 mo, using open-ended questions; for selected work tasks (including welding), details on work procedures (e.g. type of welding process) and materials were obtained from a specific questionnaire Jobs were coded with ISCO-1968 and a study-specific JEM was applied	Full job histories Artificial and solar UV radiation assessed separately Ever eye burn from welding recorded Interviewer not aware of research questions and coders blinded Standardized assessment by JEM; any exposure misclassification therefore likely to be non-differential	No quantitative data on artificial UV radiation JEMs do not take into account variability in exposure between people with the same job	Guénel et al. (2001)	Exposure to artificial UV radiation Exposure probability, i.e. estimated proportion of workers exposed within job (< 20% exposed workers, 20–50%, > 50%) Exposure frequency (occasional, several days per month, several days per week, daily) Exposure intensity (high, medium, low) Summary score was the product of probability, frequency, and intensity
JEM	Pooled analysis of case–control studies on ocular melanoma Interviews collecting occupational histories, including each job held for at least 6 mo Jobs were coded with ISCO-1968 and a study-specific JEM was applied	Full job histories Artificial and solar UV radiation separately assessed Standardized assessment by using JEM; any exposure misclassification therefore likely to be non-differential	Short intense exposures may have been missed; information on eye burns due to welding not included No quantitative data on artificial UV radiation JEMs do not take into account variability in exposure between people with the same job	Lutz et al. (2005)	Exposure to artificial UV radiation Exposure probability, i.e. estimated proportion of workers exposed within job (< 20% exposed workers, 20–50%, > 50%) Exposure frequency (occasional, several days per month, several days per week, daily) Exposure intensity (high, medium, low) Summary score was the product of probability, frequency, and intensity

Table 1.15 (continued)

Exposure assessment method	Description	Strengths	Limitations	Reference	Exposure metrics reported/notes
Self-report	Case–control study on ocular melanoma in Australia Telephone interview with structured questions about use of welding equipment Ever welder or exposure to others arc welding < 5 m away, and further detailed questions about exposure	Artificial UV radiation exposure assessed specifically, including bystander exposure Welding either at work or at home Information on type of welding, wearing of goggles/mask, and number of eye burns due to welding	No quantitative data on artificial UV radiation Self-reported exposure susceptible to recall bias	Vajdic et al. (2004)	Lifetime hours of exposure (based on years, usual frequency, and duration of exposure) Exposed to own welding (ever, never) Type of welding (none, arc and oxy, arc only, oxy only, electric/spot only, other) Welding at work (ever, never) Exposed to others welding (ever, never)
Expert assessment	Case–control study for several cancer sites, including ocular melanoma, in Canada Case-by-case expert assessment was used to assess exposures	Full job histories All available information used (job title, tasks, materials used, company, department, protective equipment) Welding-specific questionnaire, administered to other job titles also if indicating welding tasks Blinded exposure assessment; any exposure misclassification therefore likely to be non-differential	Exposure assessment focused on (arc) welding fumes, not UV radiation from welding No quantitative data Assessment of many (293) substances overall, creating a large burden on the assessors Information for about 12% of the subjects was collected via proxy respondent, who may not be aware of the specific tasks and working conditions of the case or control under study	Siemiatycki (1991)	Exposure to welding fumes Intensity of exposure (low, medium, high) Frequency of exposure (low, 1–5% of time; medium, 5–30%; high, > 30%)

Table 1.15 (continued)

Exposure assessment method	Description	Strengths	Limitations	Reference	Exposure metrics reported/notes
Self-report	Case–control study on uveal melanoma in the USA Telephone interview recording exposure to potential risk factors, including natural and artificial sources of UV, occurring at present or 15 yr before the interview	Sources of artificial and natural UV radiation assessed separately	No full job histories Exposure to welding arcs occurring 15 yr before interview Self-reported exposure susceptible to recall bias Exposure to UV radiation was not assessed specifically No information on duration or intensity of exposure or on eye protection worn	Seddon et al. (1990); Ajani et al. (1992)	Ever vs never exposure to welding arcs
Job title	Case–control study on intraocular melanoma in the USA Interviews were held (controls via telephone), collecting information on occupational history (six longest-held jobs), exposure to chemicals, and sun exposure "Welders" included men who were exposed to welding for at least 3 h/wk for 6 mo or men who worked as welder or cutter, or those in proximity of welding	Including bystander exposure	Exposure to UV radiation was not assessed specifically Short intense exposures may have been missed due to criteria for "welder" Type of welder not taken into account No information on eye protection worn Unclear how workers "exposed to welding by proximity of working conditions" were identified	Holly et al. (1996)	Ever vs never welder Duration of employment (0, ≤ 1, 2–10, ≥ 11 yr)
Job title	Case–control study on intraocular melanoma. Telephone interview recording employment history.	Full job histories	Type of welder not taken into account. Exposure to UV radiation was not assessed specifically. No information on duration or intensity of exposure or eye protection worn.	Tucker et al. (1985)	Ever vs never welder

h, hour(s); ISCO, International Standard Classification of Occupations; JEM, job-exposure matrix; mo, month(s); UV, ultraviolet; vs, versus; wk, week(s); yr, year(s)

References

ACGIH (2013). Documentation on TLV: Ultraviolet radiation. Cincinnati (OH), USA: American Conference of Governmental Industrial Hygienists.

Ajani UA, Seddon JM, Hsieh CC, Egan KM, Albert DM, Gragoudas ES (1992). Occupation and risk of uveal melanoma. An exploratory study. *Cancer*, 70(12):2891–900. doi:10.1002/1097-0142(19921215)70:12<2891::AID-CNCR2820701228>3.0.CO;2-1 PMID:1451071

Akbar-Khanzadeh F (1993). Short-term respiratory function changes in relation to workshift welding fume exposures. *Int Arch Occup Environ Health*, 64(6):393–7. doi:10.1007/BF00517944 PMID:8458654

Åkesson B, Skerfving S (1985). Exposure in welding of high nickel alloy. *Int Arch Occup Environ Health*, 56(2):111–7. doi:10.1007/BF00379382 PMID:4055066

American Welding Society (2010). Standard welding terms and definitions including terms for adhesive bonding, brazing, soldering, thermal cutting, and thermal spraying. ANSI/AWS A3.0M/A3.0:2010. Miami (FL), USA: American Welding Society.

American Welding Society (2014). Safety and health fact sheet No. 26: Arc viewing distance. Available from: http://www.aws.org.

Angerer J, Amin W, Heinrich-Ramm R, Szadkowski D, Lehnert G (1987). Occupational chronic exposure to metals. I. Chromium exposure of stainless steel welders–biological monitoring. *Int Arch Occup Environ Health*, 59(5):503–12. doi:10.1007/BF00377845 PMID:3653996

Angerer J, Lehnert G (1990). Occupational chronic exposure to metals. II. Nickel exposure of stainless steel welders–biological monitoring. *Int Arch Occup Environ Health*, 62(1):7–10. doi:10.1007/BF00397842 PMID:2295525

Antonini JM (2003). Health effects of welding. *Crit Rev Toxicol*, 33(1):61–103. doi:10.1080/713611032 PMID:12585507

Australian Bureau of Statistics (2012). 3223 Structural steel and welding trades workers. Australian and New Zealand Standard Classification of Occupations, First Edition. Australian Workforce Development Agency. Canberra, Australia: Department of Industry, Innovation and Science. Available from: https://industry.gov.au/Office-of-the-Chief-Economist/SkilledOccupationList/Documents/2014SOLOccupationalSummarySheets/3223StructuralSteelandWeldingTradesWorkers.pdf, accessed May 2018.

Azari MR, Esmaeilzadeh M, Mehrabi Y, Salehpour S (2011). Monitoring of occupational exposure of mild steel welders to ozone and nitrogen oxides. *Tanaffos*, 10(4):54–9. PMID:25191389

Baker MG, Stover B, Simpson CD, Sheppard L, Seixas NS (2016). Using exposure windows to explore an elusive biomarker: blood manganese. *Int Arch Occup Environ Health*, 89(4):679–87. doi:10.1007/s00420-015-1105-3 PMID:26589320

Balkhyour MA, Goknil MK (2010). Total fume and metal concentrations during welding in selected factories in Jeddah, Saudi Arabia. *Int J Environ Res Public Health*, 7(7):2978–87. doi:10.3390/ijerph7072978 PMID:20717553

Benke G, Sim M, Forbes A, Salzberg M (1997). Retrospective assessment of occupational exposure to chemicals in community-based studies: validity and repeatability of industrial hygiene panel ratings. *Int J Epidemiol*, 26(3):635–42. doi:10.1093/ije/26.3.635 PMID:9222790

BG Regel (2006). Welding fumes. Federation of Institutions for Statutory Accident Insurance and Prevention. Available from: https://www.bghm.de/fileadmin/user_upload/Arbeitsschuetzer/Fachinformationen/Schweissen/BGR_220_englisch.pdf.

Bonde JP (1990). Semen quality and sex hormones among mild steel and stainless steel welders: a cross sectional study. *Br J Ind Med*, 47(8):508–14. PMID:2118383

Bringas JE (2004). Handbook of comparative world steel standards: Third edition. ASTM International. Available from: http://kmcenter.rid.go.th/kcresearch/MANUAL_OUT/MAEN0006.pdf.

Burgess WA (1995). Recognition of health hazards in industry: a review of materials and processes. New York (NY), USA: John Wiley and Sons.

CANJEM (2017). CANJEM Occupational Exposure Information System. Available from: www.canjem.ca.

Cary HB (1998). Modern welding technology, 4th ed. Upper Saddle River (NJ), USA: Prentice Hall.

Chang C, Demokritou P, Shafer M, Christiani D (2013). Physicochemical and toxicological characteristics of welding fume derived particles generated from real time welding processes. *Environ Sci Process Impacts*, 15(1):214–24. doi:10.1039/C2EM30505D PMID:24592438

Creely KS, Cowie H, Van Tongeren M, Kromhout H, Tickner J, Cherrie JW (2007). Trends in inhalation exposure–a review of the data in the published scientific literature. *Ann Occup Hyg*, 51(8):665–78. PMID:17932083

Dasdag S, Sert C, Akdag Z, Batun S (2002). Effects of extremely low frequency electromagnetic fields on hematologic and immunologic parameters in welders. *Arch Med Res*, 33(1):29–32. doi:10.1016/S0188-4409(01)00337-X PMID:11825628

Dryson EW, Rogers DA (1991). Exposure to fumes in typical New Zealand welding operations. *N Z Med J*, 104(918):365–7. PMID:1891137

ECRHS II (2017). European Community Respiratory Health Survey. Available from: http://www.ecrhs.org/.

Edmé JL, Shirali P, Mereau M, Sobaszek A, Boulenguez C, Diebold F, et al. (1997). Assessment of biological chromium among stainless steel and mild steel welders in relation to welding processes. *Int Arch Occup Environ Health*, 70(4):237–42. doi:10.1007/s004200050213 PMID:9342623

Ellingsen DG, Dubeikovskaya L, Dahl K, Chashchin M, Chashchin V, Zibarev E, et al. (2006). Air exposure assessment and biological monitoring of manganese and other major welding fume components in welders. *J Environ Monit*, 8(10):1078–86. doi:10.1039/b605549d PMID:17240914

Faggetter AK, Freeman VE, Hosein HR (1983). Novel engineering methods for ozone reduction in gas metal arc welding of aluminum. *Am Ind Hyg Assoc J*, 44(5):316–20. doi:10.1080/15298668391404897

Gäfvert T, Pagels J, Holm E (2003). Thorium exposure during tungsten inert gas welding with thoriated tungsten electrodes. *Radiat Prot Dosimetry*, 103(4):349–57. doi:10.1093/oxfordjournals.rpd.a006152 PMID:12797558

Garrod A, Ball E (2005). Welding fume – limit-less exposure? British Occupational Hygiene Society. *BOHS newsletter insert*, 20(2):1–2.

Gérin M, Fletcher AC, Gray C, Winkelmann R, Boffetta P, Simonato L (1993). Development and use of a welding process exposure matrix in a historical prospective study of lung cancer risk in European welders. *Int J Epidemiol*, 22(Suppl 2):S22–8. doi:10.1093/ije/22.Supplement_2.S22 PMID:8132388

Gerin M, Siemiatycki J, Richardson L, Pellerin J, Lakhani R, Dewar R (1984). Nickel and cancer associations from a multicancer occupation exposure case-referent study: preliminary findings. *IARC Sci Publ*, 53(53):105–15. PMID:6532976

GESTIS (2016). Welding fumes. GESTIS Substance Database. Sankt Augustin, Germany: IFA (Institut für Arbeitsschutz). Available from: http://www.dguv.de/ifa/gestis/gestis-stoffdatenbank/index-2.jsp, accessed 29 December 2016.

Golbabaei F, Hassani H, Ghahri A (2012). Risk assessment of exposure to gases released by welding processes in Iranian natural gas transmission pipelines industry. *IJOH*, 4(1):6–9.

Graczyk H, Lewinski N, Zhao J, Concha-Lozano N, Riediker M (2016). Characterization of tungsten inert gas (TIG) welding fume generated by apprentice welders. *Ann Occup Hyg*, 60(2):205–19. doi:10.1093/annhyg/mev074 PMID:26464505

Guénel P, Laforest L, Cyr D, Févotte J, Sabroe S, Dufour C, et al. (2001). Occupational risk factors, ultraviolet radiation, and ocular melanoma: a case-control study in France. *Cancer Causes Control*, 12(5):451–9. doi:10.1023/A:1011271420974 PMID:11545460

Gustavsson P, Jakobsson R, Johansson H, Lewin F, Norell S, Rutkvist LE (1998). Occupational exposures and squamous cell carcinoma of the oral cavity, pharynx, larynx, and oesophagus: a case-control study in Sweden. *Occup Environ Med*, 55(6):393–400. doi:10.1136/oem.55.6.393 PMID:9764099

Gustavsson P, Jakobsson R, Nyberg F, Pershagen G, Järup L, Schéele P (2000). Occupational exposure and lung cancer risk: a population-based case-referent study in Sweden. *Am J Epidemiol*, 152(1):32–40. doi:10.1093/aje/152.1.32 PMID:10901327

Håkansson N, Floderus B, Gustavsson P, Johansen C, Olsen JH (2002). Cancer incidence and magnetic field exposure in industries using resistance welding in Sweden. *Occup Environ Med*, 59(7):481–6. doi:10.1136/oem.59.7.481 PMID:12107298

Hansson Mild K, Alanko T, Decat G, Falsaperla R, Gryz K, Hietanen M, et al. (2009). Exposure of workers to electromagnetic fields. A review of open questions on exposure assessment techniques. *Int J Occup Saf Ergon*, 15(1):3–33. doi:10.1080/10803548.2009.11076785 PMID:19272237

Health and Safety Laboratory (2009). In visor testing. RR733 Research Report. Buxton, England: Health and Safety Laboratory, Health and Safety Executive.

Hedmer M, Karlsson J-E, Andersson U, Jacobsson H, Nielsen J, Tinnerberg H (2014). Exposure to respirable dust and manganese and prevalence of airways symptoms, among Swedish mild steel welders in the manufacturing industry. *Int Arch Occup Environ Health*, 87(6):623–34. doi:10.1007/s00420-013-0896-3 PMID:23979145

Hewett P (1995a). The particle size distribution, density, and specific surface area of welding fumes from SMAW and GMAW mild and stainless steel consumables. *Am Ind Hyg Assoc J*, 56(2):128–35. doi:10.1080/15428119591017150 PMID:7856513

Hewett P (1995b). Estimation of regional pulmonary deposition and exposure for fumes from SMAW and GMAW mild and stainless steel consumables. *Am Ind Hyg Assoc J*, 56(2):136–42. doi:10.1080/15428119591017169 PMID:7856514

Hobson A, Seixas N, Sterling D, Racette BA (2011). Estimation of particulate mass and manganese exposure levels among welders. *Ann Occup Hyg*, 55(1):113–25. doi:10.1093/annhyg/meq069 PMID:20870928

Holly EA, Aston DA, Ahn DK, Smith AH (1996). Intraocular melanoma linked to occupations and chemical exposures. *Epidemiology*, 7(1):55–61. doi:10.1097/00001648-199601000-00010 PMID:8664402

HSE (2017). Welding health and safety. UK: Health and Safety Executive. Available from: http://www.hse.gov.uk/welding/index.htm.

Hull CJ, Doyle E, Peters JM, Garabrant DH, Bernstein L, Preston-Martin S (1989). Case-control study of lung cancer in Los Angeles county welders. *Am J Ind Med*, 16(1):103–12. doi:10.1002/ajim.4700160111 PMID:2750746

IARC (1990). Chromium, nickel and welding. *IARC Monogr Eval Carcinog Risks Hum*, 49:1–648. Available from: http://publications.iarc.fr/67 PMID:2232124

ICNIRP (2007). Protecting workers from ultraviolet radiation. International Commission on Non-Ionizing Radiation Protection (ICNIRP) in collaboration with International Labour Organization and World Health Organization. ICNIRP 14/2007. Available from: http://www.who.int/uv/publications/Protecting_Workers_UV_pub.pdf?ua=1.

IEC (2013). IEC 61786-1:2013 Measurement of DC magnetic, AC magnetic and AC electric fields from 1 Hz to 100 kHz with regard to exposure of human beings - Part 1: Requirements for measuring instruments. International Electrotechnical Commission. Available from: https://webstore.iec.ch/publication/5906.

ILO (2010). Evolution of the economically active population from 1950 to 1995 and forecasts for the year 2010. Geneva, Switzerland: International Labour Organization. Available from: http://www.ilo.org/global/statistics-and-databases/WCMS_087891/lang--en/index.htm.

International Commission on Non-Ionizing Radiation Protection (2004). Guidelines on limits of exposure to ultraviolet radiation of wavelengths between 180 nm and 400 nm (incoherent optical radiation). *Health Phys*, 87(2):171–86. doi:10.1097/00004032-200408000-00006 PMID:15257218

ISO (2009). Welding and allied processes – nomenclature of processes and reference numbers. International Standard ISO 4063. Fourth edition. Geneva, Switzerland: International Organization for Standardization.

Janson C, Anto J, Burney P, Chinn S, de Marco R, Heinrich J, et al.; European Community Respiratory Health Survey II (2001). The European Community Respiratory Health Survey: what are the main results so far? European Community Respiratory Health Survey II. *Eur Respir J*, 18(3):598–611. doi:10.1183/09031936.01.00205801 PMID:11589359

Järvisalo J, Olkinuora M, Kiilunen M, Kivistö H, Ristola P, Tossavainen A, et al. (1992). Urinary and blood manganese in occupationally nonexposed populations and in manual metal arc welders of mild steel. *Int Arch Occup Environ Health*, 63(7):495–501. doi:10.1007/BF00572116 PMID:1577529

Jöckel KH, Ahrens W, Jahn I, Pohlabeln H, Bolm-Audorff U (1998a). Occupational risk factors for lung cancer: a case-control study in West Germany. *Int J Epidemiol*, 27(4):549–60. doi:10.1093/ije/27.4.549 PMID:9758106

Jöckel KH, Ahrens W, Pohlabeln H, Bolm-Audorff U, Müller KM (1998b). Lung cancer risk and welding: results from a case-control study in Germany. *Am J Ind Med*, 33(4):313–20. doi:10.1002/(SICI)1097-0274(199804)33:4<313::AID-AJIM1>3.0.CO;2-V PMID:9513638

Jones DRH, Ashby MF (2005). Engineering materials 2: an introduction to microstructures, processing and design. Oxford, England: Butterworth-Heinemann.

Karlsen JT, Torgrimsen T, Langård S (1994). Exposure to solid aerosols during regular MMA welding and grinding operations on stainless steel. *Am Ind Hyg Assoc J*, 55(12):1149–53. doi:10.1080/15428119491018222

Kendzia B, Behrens T, Jöckel K-H, Siemiatycki J, Kromhout H, Vermeulen R, et al. (2013). Welding and lung cancer in a pooled analysis of case-control studies. *Am J Epidemiol*, 178(10):1513–25. doi:10.1093/aje/kwt201 PMID:24052544

Kimlin MG, Tenkate TD (2007). Occupational exposure to ultraviolet radiation: the duality dilemma. *Rev Environ Health*, 22(1):1–37. doi:10.1515/REVEH.2007.22.1.1 PMID:17508696

Kjuus H, Skjaerven R, Langård S, Lien JT, Aamodt T (1986). A case-referent study of lung cancer, occupational exposures and smoking. I. Comparison of title-based and exposure-based occupational information. *Scand J Work Environ Health*, 12(3):193–202. doi:10.5271/sjweh.2158 PMID:3749833

Klein RM, Dahmen M, Mohlmann C, Schloms R, Zschiesche W (1998). Workplace exposure during laser machining. *J Laser Appl*, 10(3):99–105. doi:10.2351/1.521834

Knudsen LE, Boisen T, Christensen JM, Jelnes JE, Jensen GE, Jensen JC, et al. (1992). Biomonitoring of genotoxic exposure among stainless steel welders. *Mutat Res*, 279(2):129–43. doi:10.1016/0165-1218(92)90255-X PMID:1375338

Kogevinas M, 't Mannetje A, Cordier S, Ranft U, González CA, Vineis P, et al. (2003). Occupation and bladder cancer among men in Western Europe. *Cancer Causes Control*, 14(10):907–14. doi:10.1023/B:CACO.0000007962.19066.9c PMID:14750529

Kromhout H, Lillienberg L, Zock J-P, et al. (2004). Quantitative estimation of exposure to welding fumes in an international general population study on asthma *Eur Respir J*, 24(Suppl 48):Session 33.

Lavoue J, Labrèche F, Richardson L, Goldberg M, Parent M-É, Siemiatycki J (2014). 0382 CANJEM: a general population job exposure matrix based on past expert assessments of exposure to over 250 agents. *Occup Environ Med*, 71(Suppl 1):A48. doi:10.1136/oemed-2014-102362.149

Lehnert M, Pesch B, Lotz A, Pelzer J, Kendzia B, Gawrych K, et al.; Weldox Study Group (2012). Exposure to

inhalable, respirable, and ultrafine particles in welding fume. *Ann Occup Hyg*, 56(5):557–67. PMID:22539559

Lehnert M, Weiss T, Pesch B, Lotz A, Zilch-Schöneweis S, Heinze E, et al.; WELDOX Study Group (2014). Reduction in welding fume and metal exposure of stainless steel welders: an example from the WELDOX study. *Int Arch Occup Environ Health*, 87(5):483–92. PMID:23719851

Lidén G, Surakka J (2009). A headset-mounted mini sampler for measuring exposure to welding aerosol in the breathing zone. *Ann Occup Hyg*, 53(2):99–116. PMID:19196747

Lillienberg L, Zock JP, Kromhout H, Plana E, Jarvis D, Torén K, et al. (2008). A population-based study on welding exposures at work and respiratory symptoms. *Ann Occup Hyg*, 52(2):107–15. doi:10.1093/annhyg/mem063 PMID:18216372

Liu S, Hammond SK, Rappaport SM (2011). Statistical modeling to determine sources of variability in exposures to welding fumes. *Ann Occup Hyg*, 55(3):305–18. PMID:21355083

Ludwig T, Schwass D, Seitz G, Siekmann H (1999). Intakes of thorium while using thoriated tungsten electrodes for TIG welding. *Health Phys*, 77(4):462–9. doi:10.1097/00004032-199910000-00015 PMID:10492354

Lutz JM, Cree I, Sabroe S, Kvist TK, Clausen LB, Afonso N, et al. (2005). Occupational risks for uveal melanoma results from a case-control study in nine European countries. *Cancer Causes Control*, 16(4):437–47. doi:10.1007/s10552-004-5029-6 PMID:15953986

MacLeod JS, Harris MA, Tjepkema M, Peters PA, Demers PA (2017). Cancer risks among welders and occasional welders in a national population-based cohort study: Canadian Census Health and Environmental Cohort. *Saf Health Work*, 8(3):258–66. doi:10.1016/j.shaw.2016.12.001 PMID:28951802

Matczak W, Chmielnicka J (1993). Relation between various chromium compounds and some other elements in fumes from manual metal arc stainless steel welding. *Br J Ind Med*, 50(3):244–51. PMID:8457491

Matczak W, Gromiec J (2002). Evaluation of occupational exposure to toxic metals released in the process of aluminum welding. *Appl Occup Environ Hyg*, 17(4):296–303. doi:10.1080/10473220252826600 PMID:11942673

Matrat M, Guida F, Mattei F, Cénée S, Cyr D, Févotte J, et al.; Icare Study Group (2016). Welding, a risk factor of lung cancer: the ICARE study. *Occup Environ Med*, 73(4):254–61. doi:10.1136/oemed-2015-102964 PMID:26865654

Meguellati-Hakkas D, Cyr D, Stücker I, Févotte J, Pilorget C, Luce D, et al. (2006). Lung cancer mortality and occupational exposure to asbestos among telephone linemen: a historical cohort study in France. *J Occup Environ Med*, 48(11):1166–72. doi:10.1097/01.jom.0000243357.70143.47 PMID:17099453

Minnesota Population Center (2015). Integrated Public Use Microdata Series, International: Version 6.4. [dataset]. Minneapolis, USA: University of Minnesota; doi:10.18128/D020.V6.4

Moniz BJ, Miller RT (2010). Welding skills. Orland Park (IL), USA: American Technical Publishers.

Nakashima H, Utsunomiya A, Fujii N, Okuno T (2016). Hazard of ultraviolet radiation emitted in gas tungsten arc welding of aluminum alloys. *Ind Health*, 54(2):149–56. doi:10.2486/indhealth.2015-0141 PMID:26632121

NIOSH (1996). EMFs in the workplace. DHHS (NIOSH) Publication Number 96-129. Atlanta (GA), USA: National Institute for Occupational Safety and Health. Available from: https://www.cdc.gov/niosh/docs/96-129/, accessed 16 January 2017.

Okuno T, Ojima J, Saito H (2001). Ultraviolet radiation emitted by CO(2) arc welding. *Ann Occup Hyg*, 45(7):597–601. doi:10.1016/S0003-4878(01)00023-0 PMID:11583661

OSHA (2013). Controlling hazardous fume and gases during welding. [cited 2016 May 5]. Washington (DC), USA: Occupational Safety and Health Administration. Available from: https://www.osha.gov/Publications/OSHA_FS-3647_Welding.pdf.

Outokumpu (2013). Handbook of stainless steel. Espoo, Finland: Outokumpu Oyi. Available from: http://www.outokumpu.com/sitecollectiondocuments/outokumpu-stainless-steel-handbook.pdf.

Peng CY, Liu HH, Chang CP, Shieh JY, Lan CH (2007). Evaluation and monitoring of UVR in shield metal arc welding processing. *Health Phys*, 93(2):101–8. doi:10.1097/01.HP.0000259903.64054.84 PMID:17622813

Persoons R, Arnoux D, Monssu T, Culié O, Roche G, Duffaud B, et al. (2014). Determinants of occupational exposure to metals by gas metal arc welding and risk management measures: a biomonitoring study. *Toxicol Lett*, 231(2):135–41. doi:10.1016/j.toxlet.2014.09.008 PMID:25223250

Pesch B, Haerting J, Ranft U, Klimpel A, Oelschlägel B, Schill W (2000). Occupational risk factors for renal cell carcinoma: agent-specific results from a case-control study in Germany. MURC Study Group. Multicenter urothelial and renal cancer study. *Int J Epidemiol*, 29(6):1014–24. doi:10.1093/ije/29.6.1014 PMID:11101542

Pukkala E, Martinsen JI, Lynge E, Gunnarsdottir HK, Sparén P, Tryggvadottir L, et al. (2009). Occupation and cancer - follow-up of 15 million people in five Nordic countries. *Acta Oncol*, 48(5):646–790. doi:10.1080/02841860902913546 PMID:19925375

Reulen RC, Kellen E, Buntinx F, Brinkman M, Zeegers MP (2008). A meta-analysis on the association between bladder cancer and occupation. *Scand J Urol Nephrol Suppl*, 42(218):64–78. doi:10.1080/03008880802325192 PMID:18815919

Saito H, Hisanaga N, Okada Y, Hirai S, Arito H (2003). Thorium-232 exposure during tungsten inert gas arc welding and electrode sharpening. *Ind Health*, 41(3):273–8. doi:10.2486/indhealth.41.273 PMID:12916759

Scheepers PT, Heussen GA, Peer PG, Verbist K, Anzion R, Willems J (2008). Characterisation of exposure to total and hexavalent chromium of welders using biological monitoring. *Toxicol Lett*, 178(3):185–90. doi:10.1016/j.toxlet.2008.03.013 PMID:18455331

Schoenberg JB, Stemhagen A, Mason TJ, Patterson J, Bill J, Altman R (1987). Occupation and lung cancer risk among New Jersey white males. *J Natl Cancer Inst*, 79(1):13–21. PMID:3474440

Schoonover T, Conroy L, Lacey S, Plavka J (2011). Personal exposure to metal fume, NO2, and O3 among production welders and non-welders. *Ind Health*, 49(1):63–72. doi:10.2486/indhealth.MS1150 PMID:20823632

Seddon JM, Gragoudas ES, Glynn RJ, Egan KM, Albert DM, Blitzer PH (1990). Host factors, UV radiation, and risk of uveal melanoma. A case-control study. *Arch Ophthalmol*, 108(9):1274–80. doi:10.1001/archopht.1990.01070110090031 PMID:2400347

Seel EA, Zaebst DD, Hein MJ, Liu J, Nowlin SJ, Chen P (2007). Inter-rater agreement for a retrospective exposure assessment of asbestos, chromium, nickel and welding fumes in a study of lung cancer and ionizing radiation. *Ann Occup Hyg*, 51(7):601–10. doi:10.1093/annhyg/mem037 PMID:17846032

Siemiatycki J (1991). Risk factors for cancer in the workplace. Boca Raton (FL): CRC Press.

Siew SS, Kauppinen T, Kyyrönen P, Heikkilä P, Pukkala E (2008). Exposure to iron and welding fumes and the risk of lung cancer. *Scand J Work Environ Health*, 34(6):444–50. doi:10.5271/sjweh.1296 PMID:19137206

Simmelink VI (1996). Welding in the Netherlands: sectors and job profiles. [Dutch]. Amsterdam, Netherlands: DIJK 12 Beleidsonderzoek.

Simonato L, Fletcher AC, Andersen A, Anderson K, Becker N, Chang-Claude J, et al. (1991). A historical prospective study of European stainless steel, mild steel, and shipyard welders. *Br J Ind Med*, 48(3):145–54. PMID:2015204

Skotte JH, Hjøllund HI (1997). Exposure of welders and other metal workers to ELF magnetic fields. *Bioelectromagnetics*, 18(7):470–7. doi:10.1002/(SICI)1521-186X(1997)18:7<470::AID-BEM2>3.0.CO;2-# PMID:9338628

Sørensen AR, Thulstrup AM, Hansen J, Ramlau-Hansen CH, Meersohn A, Skytthe A, et al. (2007). Risk of lung cancer according to mild steel and stainless steel welding. *Scand J Work Environ Health*, 33(5):379–86. doi:10.5271/sjweh.1157 PMID:17973064

Spiegel-Ciobanu VE (2010). Welding fume - risk assessment and preventive measures. Proceedings of the 4th International Conference on Innovative Technologies for Joining Advanced Materials, Timişoara, Romania, 10–11 June 2010. Available from: https://www.tib.eu/en/search/id/TIBKAT%3A736729607/Proceedings-The-4th-International-Conference-Innovative/.

Stern RM (1987). Cancer incidence among welders: possible effects of exposure to extremely low frequency electromagnetic radiation (ELF) and to welding fumes. *Environ Health Perspect*, 76:221–9. doi:10.1289/ehp.8776221 PMID:3447902

Stridsklev IC, Schaller K-H, Langård S (2004). Monitoring of chromium and nickel in biological fluids of stainless steel welders using the flux-cored-wire (FCW) welding method. *Int Arch Occup Environ Health*, 77(8):587–91. doi:10.1007/s00420-004-0560-z PMID:15538617

Suarthana E, Debia M, Burstyn I, Kromhout H (2014). Do existing empirical models for welding fumes estimate exposure to ultrafine particles among canadian welding apprentices? *J Occup Environ Med*, 56(4):e9–11. doi:10.1097/JOM.0000000000000134 PMID:24709774

't Mannetje A, Brennan P, Zaridze D, Szeszenia-Dabrowska N, Rudnai P, Lissowska J, et al. (2012). Welding and lung cancer in Central and Eastern Europe and the United Kingdom. *Am J Epidemiol*, 175(7):706–14. doi:10.1093/aje/kwr358 PMID:22343633

't Mannetje A, De Roos AJ, Boffetta P, Vermeulen R, Benke G, Fritschi L, et al. (2016). Occupation and risk of non-Hodgkin lymphoma and its subtypes: a pooled analysis from the InterLymph Consortium. *Environ Health Perspect*, 124(4):396–405. PMID:26340796

Tenkate T (2008). Welding arc time and UV exposure: implications for worker safety. *J Occup Health Saf Aust NZ*, 24:161–6.

Tenkate TSD, Collins MJ (1997). Angles of entry of ultraviolet radiation into welding helmets. *Am Ind Hyg Assoc J*, 58(1):54–6. doi:10.1080/15428119791013099 PMID:9018838

Tucker MA, Shields JA, Hartge P, Augsburger J, Hoover RN, Fraumeni JF Jr (1985). Sunlight exposure as risk factor for intraocular malignant melanoma. *N Engl J Med*, 313(13):789–92. doi:10.1056/NEJM198509263131305 PMID:4033707

Vajdic CM, Kricker A, Giblin M, McKenzie J, Aitken JF, Giles GG, et al. (2004). Artificial ultraviolet radiation and ocular melanoma in Australia. *Int J Cancer*, 112(5):896–900. doi:10.1002/ijc.20476 PMID:15386378

Vallières E, Pintos J, Lavoué J, Parent MÉ, Rachet B, Siemiatycki J (2012). Exposure to welding fumes increases lung cancer risk among light smokers but not among heavy smokers: evidence from two case-control studies in Montreal. *Cancer Med*, 1(1):47–58. doi:10.1002/cam4.6 PMID:23342253

van Loon AJ, Kant IJ, Swaen GM, Goldbohm RA, Kremer AM, van den Brandt PA (1997). Occupational exposure to carcinogens and risk of lung cancer: results from The Netherlands cohort study. *Occup Environ*

Med, 54(11):817–24. doi:10.1136/oem.54.11.817 PMID:9538355

Vecchia P, Hietanen M, Stuck BE, Van Deventer E, Niu S (2007). Protecting workers from ultraviolet radiation. Available from: http://www.who.int/uv/publications/Protecting_Workers_UV_pub.pdf?ua=1.

Verhoeven JD (2007). Steel metallurgy for the non-metallurgist. Ohio, USA: ASM International.

Von Hofe (2009). Determination of the number of people employed in welding technology in Europe. German Welding Society (DSV). DSV Working Group, Economics, N40, Rev. 3E.

Wallace M, Shulman S, Sheehy J (2001). Comparing exposure levels by type of welding operation and evaluating the effectiveness of fume extraction guns. *Appl Occup Environ Hyg*, 16(8):771–9. doi:10.1080/10473220117155 PMID:11504352

Warner C (2014). Lung bioaccessibility of manganese in arc welding fume. University of Washington, USA. [Master of Science thesis].

Weiss T, Pesch B, Lotz A, Gutwinski E, Van Gelder R, Punkenburg E, et al.; WELDOX Group (2013). Levels and predictors of airborne and internal exposure to chromium and nickel among welders–results of the WELDOX study. *Int J Hyg Environ Health*, 216(2):175–83. doi:10.1016/j.ijheh.2012.07.003 PMID:22926021

Weman K (2003). Welding processes handbook. Boca Raton (FL), USA: CRC Press.

Weman K, Lindén G, editors. (2006). MIG welding guide. Sawston, Cambridge: Woodhead Publishing.

Wolska A (2013). [Occupational exposure of welders to ultraviolet and "blue light" radiation emitted during TIG and MMA welding based on field measurements.] *Med Pr*, 64(1):69–82. [Polish] PMID:23650770

Woskie SR, Kalil A, Bello D, Virji MA (2002). Exposures to quartz, diesel, dust, and welding fumes during heavy and highway construction. *AIHA J (Fairfax, Va)*, 63(4):447–57. doi:10.1080/15428110208984733 PMID:12486778

Yiin JH, Schubauer-Berigan MK, Silver SR, Daniels RD, Kinnes GM, Zaebst DD, et al. (2005). Risk of lung cancer and leukemia from exposure to ionizing radiation and potential confounders among workers at the Portsmouth Naval Shipyard. *Radiat Res*, 163(6):603–13. doi:10.1667/RR3373 PMID:15913392

Yiin JH, Silver SR, Daniels RD, Zaebst DD, Seel EA, Kubale TL (2007). A nested case-control study of lung cancer risk and ionizing radiation exposure at the portsmouth naval shipyard. *Radiat Res*, 168(3):341–8. doi:10.1667/RR0843.1 PMID:17705634

Zeng F, Lerro C, Lavoué J, Huang H, Siemiatycki J, Zhao N, et al. (2017). Occupational exposure to pesticides and other biocides and risk of thyroid cancer. *Occup Environ Med*, 74(7):502–10. doi:10.1136/oemed-2016-103931 PMID:28202579

2. CANCER IN HUMANS

2.1 Introduction

Welding is a broad term for the process of joining metals through coalescence (AWS, 1997). Welding processes generate fumes which contain particulate matter formed from the condensation of metal liquefied during the welding process (see Section 1.1 for further details). In the occupational literature, welding is often grouped together with flame-cutting, which is a closely related process where oxygen and a fuel gas are used to cut a metal. Welding involves concomitant exposure to ultraviolet (UV) radiation, fumes, particles, and gases.

There is extensive literature on the risks of cancer from either welding jobs or exposure to welding fumes from both cohort and case–control studies, and also partly from studies of routinely collected data. Since the previous *IARC Monographs* evaluation in 1990 (IARC, 1990), the number of published epidemiological studies has increased substantially; a few cohorts have also extended the follow-up period. For this monograph, the Working Group has focused its review on those studies that report risk estimates associated with occupation as a welder or exposure to welding fumes. Studies or risk estimates of occupations which may involve unspecific and infrequent welding (such as pipefitters, plumbers, and solderers), are excluded from this review; the frequency of welding in these occupations is not normally clear, and the groupings are too broad to meaningfully evaluate exposure as a welder. Studies that reported only broad occupational aggregations, combining welding with related occupations, were also excluded as they lack specificity for welding.

Assessments of exposure to welding fumes were generally based on occupation as a welder or welding as a job task, rather than on quantitative estimates of individual exposures. Several cancer types have been investigated; there has been a special focus on cancer of the lung, but also a variety of other sites including cancers of the respiratory tract and urinary bladder, haematopoietic cancers, and ocular melanoma.

The cohort studies of welders typically focus on specific occupational or industrial settings; some include assessment of exposure to welding fumes at baseline, but may lack information on exposure to potential confounders such as tobacco smoking and asbestos. Some studies also lack information on exposures after baseline and have a limited number of cases other than cancer of the lung during further follow-up.

The majority of case–control studies have a simple and indirect exposure assessment, for example by job type, but some include more detailed assessments based on job-exposure matrices (JEMs), job-specific questionnaires, and/or case-by-case expert assessment. As a particular strength, case–control studies often include a lifelong assessment of welding history as well as potential confounders, both occupational and non-occupational.

Welders are exposed to a complex mixture of chemical compounds that vary by the welding

method and the type of metal to be welded, for example mild steel (MS) versus stainless steel (SS); the latter involves exposure to nickel (Ni) and chromium (Cr) compounds, recognized lung carcinogens (IARC, 2012a). In evaluating the risk of cancer from welding jobs and exposure to welding fumes, it is important to distinguish between exposures which are normally part of the welding environment and those which occur as co-exposures, typically from other working processes not necessarily related to the welding or from non-welding coworkers (e.g. metal grinders in the nearby working environment). In their working environment, welders may be exposed to compounds other than those directly occurring from the welding process which may be considered as potential confounders. Examples of co-exposures that may contribute to the overall occupational exposures of welders, and therefore the potential risk of cancer, include coatings on the welded metal (e.g. paints, grease, and other compounds) as well as compounds used to prepare metal for welding (e.g. trichloroethylene (TCE) or paint strippers). Welders have also been exposed to asbestos as part of heat-protective equipment (including blankets used to cover the weld, in order to prevent abrupt cooling) and as an insulation material in the welding locality, especially in shipyards where asbestos was extensively used.

Tobacco smoking is considered a major potential confounder for certain tobacco-associated cancers observed in welders. Some studies show a higher prevalence of tobacco use in welders compared with the general population (e.g. Dunn et al., 1960; Office of Population Censuses and Surveys, 1978).

In the absence of information on specific co-exposures in studies of cancer of the lung, crude indirect indications of confounding can be considered, for example, the risk of mesothelioma as an indicator of asbestos exposure.

Overall, the Working Group considered the preceding factors in evaluating and comparing study results; heterogeneity in results may partly reflect such differences. The Working Group noted that the studies should ideally include information on material welded, type of welding process, and co-exposure to asbestos and tobacco smoking. Studies that provided this information were considered the most informative for this evaluation. Additionally, exposure–response data were included when they were available in the published reports.

2.2 Ocular melanoma

See Table 2.1 and Table 2.2

Acute overexposure of the eye to UV radiation is common among electric arc welders, and UV radiation is a confirmed cause of ocular melanoma (IARC, 2012b). Because of the rarity of this cancer and the existence of only relatively small cohorts of welders, the association between welding and ocular melanoma has mostly been investigated via case–control studies. The Working Group identified two independent cohort studies (Table 2.1) that included information on welding exposure from cancer registries in the Nordic countries (Siew et al., 2008; Pukkala et al., 2009) and Canada (MacLeod et al., 2017), and less than ten independent case–control studies on ocular melanoma (Table 2.2). Overall, most studies reported an increased risk of ocular melanoma based on dichotomous exposure variables. The welding exposure is self-reported and crude in most studies, and includes job titles such as welder and/or flame-cutter or sheet metalworker; welding tasks are also included in some studies. Most studies did not distinguish between arc welding, which normally involves exposure to UV radiation, and gas welding without UV radiation [including gas welders may attenuate risk estimates]. Most studies specified that they excluded the rare uveal tract melanoma of the iris.

Table 2.1 Population-based cohort studies on cancer and welding or exposure to welding fumes

Reference, location, enrolment period/follow-up	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kromhout et al. (1992) Zutphen, Netherlands Enrolment 1977–1978/follow-up 1977–1985	878 men, 67 lung cancer cases; random sample of men born in 1900–1919 who lived in Zutphen for at least 5 yr. Exposure assessment method: expert judgement; two JEMs: general and population-specific (developed from self-reported exposures)	Lung	Welding fumes General JEM: Population-specific JEM	 NR NR	 1.54 (0.37–6.30) 1.93 (1.05–3.55)	Age, smoking	Strengths: comparison of two methods of exposure assessment for welding and soldering fumes Limitations: small numbers
van Loon et al. (1997b) Netherlands Enrolment September 1986/follow-up September 1986–1990	Case–cohort analysis: 524 lung cancer cases, 1630 men in the subcohort; general population cohort of 58 279 men aged 55–69 yr; study restricted to subjects who reported a complete job history Exposure assessment method: expert judgement from a self-administered questionnaire; assessment of probability of exposure to welding fumes, asbestos, paint dusts, and PAHs Cumulative score calculated as the sum of the duration of exposed jobs, weighted by exposure probability	Lung	Ever exposed to welding fumes Welding fumes: lifetime exposure index in tertiles 0 1st tertile (low) 2nd tertile 3rd tertile (high) Trend test *P* value,	NR 457 17 26 20 0.75	0.86 (0.46–1.58) 1 0.71 (0.31–1.60) 1.49 (0.72–3.07) 1.01 (0.49–2.06)	Age, smoking, other occupational exposures, vitamin C, β-carotene, retinol	General population levels of exposure are probably low Strengths: semi-quantitative assessment of exposure to welding fumes; adjustment for smoking, exposure to asbestos, paints, and PAHs and other potential confounders Limitations: self-administered questionnaire; short follow-up

Table 2.1 (continued)

Reference, location, enrolment period/follow-up	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Zeegers et al. (2004) Netherlands Enrolment 1986/follow-up 1986–1993 Nested case–control	Cases: 830 men with microscopically confirmed incident carcinomas of the prostate identified by cancer registries and Dutch National Database of Pathology Reports Controls: 1525 subcohort men randomly sampled from cohort Exposure assessment method: questionnaire; self-administered questionnaires recording occupational history of each job and jobs held for > 5 yr	Prostate	Welder: ever employed	12 12	1.41 (0.51–3.88) 1.81 (0.62–5.30)	Age Age, fruit, vegetable, dairy, meat, alcohol, smoking, education, family history of prostate cancer, physical activity	Strengths: information on diet and lifestyle confounders; multivariate analysis Limitations: exposure misclassification; no information on occupational co-exposures; multiple comparisons; few exposed cases
		Prostate	Longest-held profession: welder	5 5	1.07 (0.23–4.88) 1.42 (0.27–7.46)	Age Age, fruit, vegetable, dairy, meat, alcohol, smoking, family history of prostate cancer, education, physical activity	

Table 2.1 (continued)

Reference, location, enrolment period/follow-up	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Zeegers et al. (2004) (cont.)		Prostate	Profession at baseline: welder	5 5	0.88 (0.21–3.75) 1.19 (0.25–5.64)	Age Age, fruit, vegetable, dairy, meat, alcohol, smoking, family history of prostate cancer, education, physical activity	
Veglia et al. (2007) Europe (multicentre study, 23 centres, 10 countries) Enrolment 1992–2000/ median follow-up for 6.1 yr	217 055 subjects; 809 lung cancer cases; men and women, mostly aged 35–70 yr at recruitment; restricted to centres with information on occupational history (Denmark, Germany, Greece, Italy, Spain, UK) Exposure assessment method: questionnaire; job titles from questionnaires	Lung	Welder Welding shop	55 72	1.67 (1.20–2.30) 1.55 (1.20–2.10)	BMI, physical activity, education, sex, age, smoking, fruits, vegetable	Strengths: large prospective cohort; detailed information on several possible confounders Limitations: job title analysis; no exposure data

Table 2.1 (continued)

Reference, location, enrolment period/follow-up	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Siew et al. (2008) Finland Enrolment 1970/follow-up 1971–1995	1.2 million men; 30 137 lung cancer cases; all economically active Finnish men born during 1906–1945 who participated in the 1970 population census Exposure assessment method: expert judgement; FINJEM linked to the longest-held job in 1970 to assess exposure to welding fumes, iron fumes, asbestos, SiO_2, Cr, Ni, Pb, B[*a*]P, and smoking; exposure estimates based on the judgment of ~20 experts at the Finnish Institute of Occupational Health	Lung	Welder and flame cutter, SS > 10%	110	0.95 (0.78–1.15)	Age, calendar year	Overlaps with Pukkala et al. (2009) but includes quantitative analysis and further adjustment for smoking and asbestos Strengths: very large cohort; adjustment for smoking and other occupational exposures (including asbestos) Limitations: cross-sectional information on occupation
			Welder, shipyard	26	1.05 (0.69–1.55)		
			Welder, building	24	1.31 (0.84–1.95)		
			Welder, NEC	102	1.39 (1.14–1.69)		
			Cumulative exposure to welding fumes (mg/m^3-yr)			Smoking, asbestos, SiO_2, SES, age, periods of follow-up	
			None	27 192	1		
			Low (0.1–10)	2591	1.09 (1.05–1.14)		
			Medium (10.1–49.9)	287	1.16 (1.03–1.31)		
			High (≥ 50)	67	1.15 (0.90–1.46)		
		Lung (SCC)	Cumulative exposure to welding fumes (mg/m^3-yr)			Smoking, asbestos, SiO_2, SES, age, periods of follow-up	
			None	9275	1		
			Low (0.1–10)	870	1.07 (0.99–1.15)		
			Medium (10.1–49.9)	110	1.26 (1.04–1.53)		
			High (≥ 50)	29	1.55 (1.08–2.24)		

Table 2.1 (continued)

Reference, location, enrolment period/follow-up	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Siew et al. (2008) (cont.)		Lung (small cell/ oat cell)	Cumulative exposure to welding fumes (mg/m^3-yr)			Age, smoking, asbestos, SiO_2, SES, periods of follow-up	
			None	4570	1		
			Low (0.1–10)	479	1.15 (1.04–1.27)		
			Medium (10.1–49.9)	46	1.10 (0.82–1.48)		
			High (≥ 50)	7	0.83 (0.40–1.75)		
		Lung (adenocarcinoma)	Cumulative exposure to welding fumes (mg/m^3-yr)			Smoking, asbestos, SiO_2, SES, age, periods of follow-up	
			None	3379	1		
			Low (0.1–10)	342	1.08 (0.95–1.21)		
			Medium (10.1–49.9)	46	1.42 (1.06–1.91)		
			High (≥ 50)	7	1.14 (0.54–2.40)		

Table 2.1 (continued)

Reference, location, enrolment period/follow-up	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pukkala et al. (2009) Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) Enrolment/ follow-up: Denmark 1971–2003; Finland 1971–2005; Iceland 1982–2004; Norway 1961–2003; Sweden 1961–2005	14.9 million people aged 30–64 yr participating in any computerized population census in 1990 or earlier, still alive and living in the country on January 1 in the year following the census. The date and number of census depend on the country: Denmark 1970; Finland 1970, 1980, 1990; Iceland 1981; Norway 1960, 1970, 1981; Sweden 1960, 1970, 1980, 1990 Exposure assessment method: self-administered questionnaire; information on occupation from the 1st census in which the person participated. Original national occupation codes converted to a common classification with 53 occupational categories. Danish welders are included in the category 'mechanic workers'. Results for welders (2606 women and 74 857 men) limited to Finland, Iceland, Norway, and Sweden	Lung	Welder			Age, calendar year	Overlaps with Siew et al. (2008). Results differed by country, and risk estimates for ocular melanoma were elevated only in Finland. Results for welders excluded Denmark; 91 mesotheliomas in male welders (SIR, 1.79; 95% CI, 1.44–2.20); no mesothelioma in female welders (0.3 expected). Strengths: very large cohort, long follow-up, risk estimates for rare cancers Limitations: information on occupation at one point in time; no adjustment for smoking and other lifestyle factors (partial data to evaluate confounding)
			Men	1798	1.33 (1.27–1.40)		
			Women	25	1.70 (1.10–2.51)		
		Lung (adeno-carcinoma)	Men	408	1.51 (1.37–1.67)		
			Women	5	0.98 (0.32–2.29)		
		Lung (small cell/ oat cell)	Men	237	1.24 (1.09–1.41)		
			Women	7	2.78 (1.12–5.74)		
		Lung (SCC)	Men	590	1.35 (1.24–1.46)		
			Women	4	1.73 (0.47–4.42)		
		Kidney	Men	533	1.25 (1.14–1.36)		
			Women	7	1.12 (0.45–2.31)		
			Both	540	1.24 (1.14–1.35)		
		Kidney (urinary pelvis/UUT)	Men	56	1.39 (1.05–1.80)		
			Women	0.48	0 (0–7.63)		
		Urinary bladder	Men	822	1.06 (0.99–1.13)		
			Women	4	0.80 (0.22–2.04)		
			Both	826	[1.05 (0.98–1.30)]		
		Eye: melanoma	Men	36	1.07 (0.75–1.48)		
			Women	1	1.25 (0.03–6.99)		
		Prostate	Men	2871	1.01 (0.98–1.05)		
		Leukaemia: ICD-7 (code 204)	Men	294	1.09 (0.97–1.23)		
			Women	5	1.08 (0.35–2.52)		
		NHL (CLL): ICD-7	Men	115	0.98 (0.82–1.18)		
			Women	2	1.29 (0.16–4.68)		
		Leukaemia (AML): ICD-7	Men	89	1.23 (0.99–1.52)		
			Women	2	1.23 (0.15–4.45)		
		Nasal cavity and sinuses	Men	29	1.13 (0.76–1.62)		
			Women	0	0 (0–10.33)		

Table 2.1 (continued)

Reference, location, enrolment period/follow-up	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pukkala et al. (2009) (cont.)		Larynx: ICD-7 (code 161)	Men	146	1.14 (0.97–1.34)		
			Women	2	4.93 (0.60–17.81)		
		Mesothelioma	Men	91	1.79 (1.44–2.20)		
			Women	0	0 (0–12.30)		
		Brain	Men	346	0.99 (0.90–1.11)		
			Women	16	1.39 (0.80–2.26)		
		NHL: ICD-7 (code 200, 202)	Men	341	0.91 (0.82–1.01)		
			Women	9	1.12 (0.51–2.13)		
		HL: ICD-7 (code 201)	Men	59	0.98 (0.74–1.26)		
			Women	2	2.17 (0.26–7.85)		
		MM: ICD-7 (code 203)	Men	160	0.95 (0.82–1.11)		
			Women	1	0.34 (0.01–1.91)		
		Pharynx	Men	93	1.05 (0.85–1.28)		
			Women	1	1.28 (0.03–7.14)		
Neasham et al. (2011) Europe, multicentre (23 centres, 10 countries) Enrolment 1992–2000; mean follow-up 9 yr	218 968 subjects; incident cases of NHL (n = 707) and HL (n = 40); EPIC cohort; men and women, mostly aged 35–70 yr at recruitment; restricted to centres with information on occupational history (in Denmark, Germany, Greece, Italy, Spain, and the UK) Exposure assessment method: questionnaire; job titles from questionnaires	NHL	Welder	23	0.88 (0.58–1.35)	Education, sex, age, smoking, alcohol, centre	Strengths: large prospective cohort; detailed information on several possible confounders Limitations: job title analysis; no exposure data
			Welding shop	37	1.16 (0.72–1.88)		
		HL	Welder	1	0.55 (0.07–4.13)		
			Welding shop	3	1.02 (0.23–4.48)		

Table 2.1 (continued)

Reference, location, enrolment period/follow-up	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pesch et al. (2013) Europe, multicentre (23 centres, 10 countries) Enrolment 1992–2000 Nested case–control	Cases: 754 incident cases of transitional cell bladder cancer, histopathologically confirmed according to WHO criteria, follow-up of 521 468 EPIC participants Controls: 833 randomly selected from all cohort members alive and free of cancer at diagnosis of the index case (incidence density sampling); matched to the cases by sex, age at time of enrolment (± 3 yr), study centre, and other factors Exposure assessment method: questionnaire; job titles from questionnaires	Urinary bladder: TCC	Welder Welding shop	43 63	1.39 (0.85–2.27) 1.54 (1.01–2.34)	Smoking, region, age	Strengths: large prospective cohort; detailed information on several possible confounders Limitations: job title analysis; no exposure data
Saberi Hosnijeh et al. (2013) Europe, multicentre (23 centres, 10 countries) Enrolment 1992–2000; mean follow-up 11.2 yr	241 465 subjects; 477 incident cases of myeloid and lymphoid leukaemia; men and women mostly aged 35–70 yr at recruitment; restricted to centres with information on occupational history (in Denmark, Germany, Greece, Italy, Spain, and the UK) Exposure assessment method: questionnaire; job titles from questionnaires	Leukaemia (myeloid) Leukaemia (lymphoid)	Worked in welding shop or as welder Worked in welding shop or as welder	13 17	1.14 (0.63–2.05) 0.99 (0.59–1.65)	Age, sex, smoking, alcohol, country	Strengths: large prospective cohort; detailed information on several possible confounders Limitations: job title analysis; no exposure data

Table 2.1 (continued)

Reference, location, enrolment period/follow-up	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
MacLeod et al. (2017) Canada 1991–2011	1 108 410 men (including 12 845 welders and 87 460 occasional welders); linkage of the 1991 Census with the CCR; restricted to individuals aged 25–74 yr with a valid code for occupation on the census form Exposure assessment method: questionnaire; based on occupation self-reported at census; welders = employed as 'welders and soldering machine operators'; occasional welders = employed in other occupations potentially involving welding (from a list defined a priori)	Lung	*All welders by industry*			Age, region, education	The cohort of 942 905 female workers included only 370 welders, with less than 5 cases for the cancer sites of interest, and was not further analysed Strengths: large numbers; internal analyses; risk estimates for histological types of lung cancer; subgroup analyses Limitations: exposure defined by occupation (self-reported) at one point in time; no data on smoking, asbestos, or other co-exposures; adjustment for education and analyses restricted to blue-collar workers may minimize confounding
			Non-welders (ref.)	NR	1		
			All industries	265	1.16 (1.03–1.31)		
			Machine equipment, appliances manufacturing	60	1.21 (0.93–1.56)		
			Construction	45	1.27 (0.96–1.67)		
			Repair of transport vehicles	35	1.41 (1.03–1.94)		
			Transport vehicles manufacturing	10	1.11 (0.58–2.14)		
			Shipbuilding and repair	10	1.65 (0.91–2.98)		
			Other industries	70	0.99 (0.79–1.25)		
			Occasional welders	1625	1.12 (1.07–1.18)		
		Lung (adenocarcinoma)	*All workers*			Age, region, education	
			Non-welders (ref.)	NR	1		
			Welders	75	1.12 (0.89–1.41)		
			Occasional welders	455	1.07 (0.97–1.18)		
		Lung (large cell cancer)	*All workers*			Age, region, education	
			Non-welders (ref.)	NR	1		
			Welders	50	1.01 (0.76–1.34)		
			Occasional welders	310	1.01 (0.90–1.14)		

Table 2.1 (continued)

Reference, location, enrolment period/follow-up	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
MacLeod et al. (2017) (cont.)		Lung (small cell/ oat cell)	*All workers*			Age, region, education	
			Non-welders (ref.)	NR	1		
			Welders	45	1.54 (1.15–2.07)		
			Occasional welders	220	1.16 (1.01–1.34)		
		Lung (SCC)	*All workers*			Age, region, education	
			Non-welders (ref.)	NR	1		
			Welders	60	1.19 (0.92–1.54)		
			Occasional welders	430	1.33 (1.20–1.47)		
		Lung	*Blue-collar welders*			Age, region	
			Non-welders (ref.)	NR	1		
			All industries	265	1.06 (0.94–1.20)		
			Machine equipment, appliance manufacturing	60	1.13 (0.87–1.46)		
			Construction	45	1.12 (0.84–1.48)		
			Repair of transport vehicles	35	1.28 (0.93–1.76)		
			Transport vehicles manufacturing	10	1.02 (0.53–1.96)		
			Shipbuilding and repair	10	1.45 (0.80–2.63)		
			Other industries	70	0.92 (0.73–1.15)		
			Occasional welders	1625	1.02 (0.96–1.07)		

Table 2.1 (continued)

Reference, location, enrolment period/follow-up	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
MacLeod et al. (2017) (cont.)		Lung (adenocarcinoma)	*Blue-collar welders*			Age, region	
			Non-welders (ref.)	NR	1		
			Welders	75	1.07 (0.84–1.36)		
			Occasional welders	455	1.06 (0.96–1.18)		
		Lung (large cell cancer)	*Blue-collar welders*			Age, region	
			Non-welders (ref.)	NR	1		
			Welders	50	0.94 (0.70–1.26)		
			Occasional welders	310	0.92 (0.81–1.04)		
		Lung (small cell/ oat cell)	*Blue-collar welders*			Age, region	
			Non-welders (ref.)	NR	1		
			Welders	45	1.31 (0.96–1.79)		
			Occasional welders	220	1.02 (0.88–1.18)		

Table 2.1 (continued)

Reference, location, enrolment period/follow-up	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
MacLeod et al. (2017) (cont.)		Lung (SCC)	*Blue-collar welders*			Age, region	
			Non-welders (ref.)	NR	1		
			Welders	60	1.04 (0.80–1.35)		
			Occasional welders	430	1.13 (1.02–1.25)		
		Mesothelioma	*All welders*			Age, region, education	
			Non-welders (ref.)	NR	1		
			Welders	15	1.78 (1.01–3.18)		
			Occasional welders	65	1.74 (1.34–2.26)		
		Mesothelioma	*Blue-collar welders*			Age, region	
			Non-welders (ref.)	NR	1		
			Welders	15	1.54 (0.86–2.78)		
			Occasional welders	65	1.48 (1.13–1.96)		

Reference, location, enrolment period/follow-up	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
MacLeod et al. (2017) (cont.)		Urinary bladder	*All welders*			Age, region, education	
			Non-welders (ref.)	NR	1		
			Welders	100	1.40 (1.15–1.70)		
			Occasional welders	515	0.99 (0.90–1.08)		
		Urinary bladder	*Blue-collar welders*			Age, region	
			Non-welders (ref.)	NR	1		
			Welders	100	1.47 (1.21–1.79)		
			Occasional welders	515	1.03 (0.94–1.13)		
		Kidney	*All welders*			Age, region, education	
			Non-welders (ref.)	NR	1		
			Welders	60	1.30 (1.01–1.67)		
			Occasional welders	315	0.96 (0.85–1.08)		
		Kidney	*Blue-collar welders*			Age, region	
			Non-welders (ref.)	NR	1		
			Welders	60	1.34 (1.04–1.73)		
			Occasional welders	315	0.99 (0.87–1.12)		
		Nasal cavity and sinuses	*All welders*			Age, region, education	
			Non-welders (ref)	NR	1		
			Welders	NR	0 (0–0)		
			Occasional welders	25	1.25 (0.82–1.92)		
		Nasal cavity and sinuses	*Blue-collar welders*			Age, region	
			Non-welders (ref.)	NR	1		
			Welders	NR	0 (0–0)		
			Occasional welders	25	1.15 (0.73–1.82)		

Table 2.1 (continued)

Reference, location, enrolment period/follow-up	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
MacLeod et al. (2017) (cont.)		Eye: melanoma	*All welders*			Age, region, education	
			Non-welders (ref.)	NR	1		
			Welders	5	1.55 (0.64–3.76)		
			Occasional welders	20	0.89 (0.57–1.38)		
		Eye: melanoma	*Blue-collar welders*			Age, region	
			Non-welders (ref.)	NR	1		
			Welders	5	1.66 (0.68–4.09)		
			Occasional welders	20	0.91 (0.56–1.47)		
		Brain	*All welders*			Age, region, education	
			Non-welders (ref.)	NR	1		
			Welders	35	1.16 (0.83–1.63)		
			Occasional welders	190	1.08 (0.93–1.26)		
		Brain	*Blue-collar welders*			Age, region	
			Non-welders (ref.)	NR	1		
			Welders	35	1.17 (0.83–1.65)		
			Occasional welders	190	1.09 (0.93–1.27)		

Table 2.1 (continued)

Reference, location, enrolment period/follow-up	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wong et al. (2017) USA Enrolment 2002–2004/follow-up 2002–2009	53 224; 2311 ever welders; current and former heavy smokers (> 30 pack-years, quit within past 15 yr if former smoker) enrolled in the National Lung Screening Trial (NLST) with occupational history information; subjects from 33 centres, randomized into two arms (CT, chest X-ray) Exposure assessment method: questionnaire; job title, work duration, and PPE; ever worked as welders and/or founder defined as held welding job for ≥ 1 yr; information on demographics, medical history, and smoking also ascertained on questionnaire	Lung	*All workers*			BMI, age, sex, race, smoking, family history, study, screening	Cohort analysis and follow-up of subjects enrolled in a randomized control trial (findings for both arms combined) Strengths: sensitivity statistical analyses; information on lung cancer subtypes; large number of cases; information on previous exposure to asbestos Limitations: limited exposure information on welding and co-exposures during welding such as asbestos; short follow-up; not able to assess risk in nonsmokers
			Never welded/ never foundry (ref.)	1824	1		
			Ever welder, never foundry	101	1.12 (0.91–1.37)		
		Lung: incidence (all subtypes)	*Duration ever worked as a welder (yr)*				
			None (ref.)	1824	1		
			≥ 1 to < 3	12	0.80 (0.50–1.25)		
			≥ 3 to < 10	29	1.43 (1.04–1.96)		
			≥ 10 to < 25	27	1.24 (0.89–1.73)		
			≥ 25	30	1.20 (0.87–1.67)		
			Trend test *P* value, 0.039 (ordinal)				
		Lung (SCC): incidence (all subtypes)	*Duration ever worked as a welder (yr)*				
			None (ref)	1824	1		
			≥ 1 to < 3	3	1.4 (0.69–2.84)		
			≥ 3 to < 10	13	1.74 (0.97–3.11)		
			≥ 10 to < 25	4	1.41 (0.75–2.66)		
			≥ 25	11	1.91 (1.13–3.22)		
			Trend test *P* value, 0.003 (ordinal)				
		Lung (adenocarcinoma)	*Duration ever worked as a welder (yr)*				
			None (ref)	593	1		
			≥ 1 to < 3	5	0.97 (0.46–2.05)		
			≥ 3 to < 10	5	1.07 (0.55–2.08)		
			≥ 10 to < 25	8	0.93 (0.46–1.87)		
			≥ 25	10	1.39 (0.80–2.43)		
			Trend test *P* value, 0.418 (ordinal)				

AML, acute myeloid leukaemia; B[*a*]P, benzo[*a*]pyrene; BMI, body mass index; CCR, Canadian Cancer Registry; CI, confidence interval; CLL, chronic lymphocytic leukaemia; Cr, chromium; CT, computerized tomography; EPIC, European Prospective Investigation into Cancer and Nutrition; FINJEM, Finnish job-exposure matrix; HL, Hodgkin lymphoma; ICD, International Classification of Diseases; JEM, job-exposure matrix; MM, multiple myeloma; NEC, not elsewhere classified; NHL, non-Hodgkin lymphoma; Ni, nickel; NR, not reported; PAH, polycyclic aromatic hydrocarbon; Pb, lead; PPE, personal protective equipment; SCC, squamous cell carcinoma; SES, socioeconomic status; SiO_2, silicon dioxide; SIR, standardized incidence ratio; SS, stainless steel; TCC, transitional cell carcinoma; UUT, upper urinary tract; WHO, World Health Organization; yr, year(s)

Table 2.2 Case–control studies on ocular melanoma and welding or exposure to welding fumes

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Tucker et al. (1986) USA 1974–1979	Cases: 497; participation rate, 89% Controls: 501 patients with detached retina not due to tumours matched by race, age, sex, race, date of diagnosis; participation rate, 85% Exposure assessment method: telephone interview with detailed information about medical history, family history, employment, and exposure to environmental agents and sunlight; details from ophthalmologic examination and medical history from records; interview with next-of-kin for 17% of cases and 14% of controls, half of them with spouses	Ever vs never worked as welder	4	10.9 (2.1–56.5)	Age, eye colour, history of cataract	Strengths: large number of cases and controls; high participation rate in both cases and controls Limitations: few exposed cases; no dose–response calculations; no information on other UV exposures

Table 2.2 (continued)

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Seddon et al. (1990) Massachusetts, USA 1984–1987	Cases: 197 [Series 1 population-based] white patients aged 17–88 yr with clinically or histologically confirmed melanoma of the choroid, ciliary body, or both, identified at local hospital or by mailing to ophthalmologists; diagnosed within previous year Controls: 385 [Series 1 population-based] selected by random digit dialling, matched 2:1 by sex, age, city of residence Exposure assessment method: telephone interview including constitutional factors, ocular, and medical histories, and exposure to environmental factors including natural and artificial sources of UV	Arc welder vs never welder Series 1 Series 2	 18 38	 1.3 (0.5–3.1) 0.9 (0.6–1.5)	Age, sex, eye and skin colour, ancestry, use of sun lamps, eye protection, outside work, florescent lighting, southern residence, years of intense exposure, moles	Series 1: results also reported by Ajani et al. (1992), using the same numbers but with fewer covariates in the logistic regression model Series 2: not population-based, 337 cases and 800 sibling controls 140 of the cases were included in both series Strengths: high participation rates in both cases and controls; some information on exposures to UV radiation Limitations: no dose–response assessment
Siemiatycki (1991) Montreal, Canada 1984–1987	Cases: 16 histologically confirmed incident male cases of uveal melanoma, aged 35–70 yr Controls: 3058; 2525 cancer controls + 533 population controls Exposure assessment method: personal interview and collection of detailed occupational history	Exposed vs not exposed to arc welding fumes	4	8.3 (2.5–27.1)	Age, family income, cigarette index	Total number of eye melanoma cases: 16 (Siemiatycki (1991), table 1); analysis was restricted to French-Canadians and cancer controls used Limitations: no dose–response assessment; no adjustments for UV radiation and sun exposure

Table 2.2 (continued)

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Lutz et al. (2005) Denmark, France, Germany, Italy, Latvia, Portugal, Spain, Sweden, and UK 1995–1996	Cases: 292 incident cases of uveal melanoma, identified from ophthalmologic departments, hospital records, or cancer registries, aged 35–69 yr Controls: 2062 population controls selected from population registers, electoral rolls, or practitioner; frequency-matched by region, sex, and 5-yr birth cohorts; 1094 cancer controls randomly selected from colon cancer patients Exposure assessment method: questionnaire with face-to-face or telephone interview	Worked as a welder or sheet metal worker for ≥ 6 mo			Country, 5-yr age group	Data from France reported in the analysis of Guénel et al. (2001); analysis by occupation used only population controls Strengths: relatively large study size Limitations: only modest participation rate in controls; no assessment of dose–response association; no information on UV radiation or sun exposure; use of colon cancer patients may be problematic (perhaps at higher risk of this cancer due to lack of sun exposure)
		Men	15	2.18 (1.18–4.04)		
		Women	1	0.75 (0.09–6.33)		
		Men and women	16	1.95 (1.08–3.52)		
Guénel et al. (2001) France: 10 administrative areas (départements) 1995–1996	Cases: 50; 29 men, 21 women; patients with uveal melanoma Controls: 479; 321 men, 158 women selected at random from electoral polls after stratification for age, sex, and area Exposure assessment method: questionnaire; estimates of occupational exposure to solar and artificial UV light were made using a JEM	Ever vs never welder or sheet metal worker			Age	Strengths: high participation rate in cases (100%) and modest in controls (76%) Limitations: relatively small study; no adjustments for UV radiation or sun exposure
		Worked for ≥ 6 mo	7	7.3 (2.6–20.1)		
		≤ 20 yr	4	5.7 (1.6–19.8)		
		> 20 yr	3	11.5 (2.4–55.5)		
		Trend test *P* value, 0.0008				
Monárrez-Espino et al. (2002) Germany 1995–1998	Cases: 118 incident cases of uveal melanoma Controls: 475 controls matched by age, sex, and region of residence Exposure assessment method: telephone interviews, exposure status classified based on job history	Welding, brazing, soldering	13	0.90 (0.43–1.76)	Age, region	Overlaps with Lutz et al. (2005)
		Ever welder	<6	1.3 (0.6–2.5)		

Table 2.2 (continued)

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Vajdic et al. (2004) Australia 1996–1998	Cases: 246 white Australian residents, aged 18–79 yr, with histopathologically or clinically diagnosed melanoma originating in the choroid, ciliary body Controls: 893 controls matched 3:1 by age, sex, and residence, selected from electoral rolls Exposure assessment method: self-administered questionnaire and telephone interview regarding sun exposure, sun-protective wear, and quantitative exposure to welding equipment and sunlamps	Ever (own welding) vs never	73	1.2 (0.8–1.7)	Age, sex, place of birth, eye colour, ability to tan, squinting as a child, total personal sun exposure at age 10, 20, 30, and 40 yr	Strengths: extensive information collected on exposure including sun exposure, use of personal protective equipment, eye burns during welding; dose–response assessment for welding Limitations: relatively low participation rate in controls
		Duration (yr)				
		0.1–4.0	15	0.8 (0.4–1.4)		
		4.1–22	23	1.2 (0.7–2.2)		
		> 22	35	1.7 (1.0–2.7)		
		Trend test *P* value, 0.07				
		Lifetime exposure (h)				
		0.1–52.0	20	1.1 (0.6–1.9)		
		52.1–858.0	30	1.4 (0.8–2.3)		
		> 858	23	1.1 (0.6–1.9)		
		Trend test *P* value, 0.69				
		Usual exposure (h/d)				
		0.05–0.50	27	1.3 (0.8–2.1)		
		0.51–2.00	30	1.3 (0.8–2.1)		
		> 2.00	16	1.0 (0.5–1.9)		
		Trend test *P* value, 0.74				
		Age at first use (yr)				
		> 20	41	1.2 (0.8–1.9)		
		≤ 20	32	1.2 (0.7–2.0)		
		Trend test *P* value, 0.59				
		Type of welding				
		Arc and oxy	46	1.6 (1.0–2.4)		
		Arc only	21	0.9 (0.5–1.6)		
		Oxy only	5	1.3 (0.5–3.7)		
		Electric/spot only	0	0 (0–2.1)		
		Frequency of goggle or mask use during welding				
		Always/almost always	67	1		
		Half of the time or less	6	1.7 (0.5–5.4)		

Table 2.2 (continued)

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Vajdic et al. (2004) (cont.)		*Number of eye burns during welding*				
		None	44	1		
		1–2	9	0.4 (0.2–0.9)		
		3–5	6	0.6 (0.2–1.6)		
		> 5	14	1.6 (0.7–3.6)		
		Trend test *P* value, 0.78				
Holly et al. (1996) USA 1978–1987	Cases: 221 male white patients with histologically confirmed uveal melanoma, aged 20–74 yr, residing in 11 states Controls: 447 controls selected by random digit dialling matched 2:1 by age (5-yr age group) and residential area Exposure assessment method: interviewer-administered questionnaire with demographic and phenotypic characteristics, occupational history, exposure to chemicals	Ever vs never welder	40	1.9 (1.2–3.0)	None	Strengths: high participation rate in cases and controls Limitations: no direct assessment of UV radiation or sun exposure
		Ever vs never welder	40	2.2 (1.3–3.5)	Age, naevi, eye colour, tanning or burning, sun exposure	
		Duration (yr)			Age	
		0 (ref.)	181	1		
		≤ 1	6	2.2 (0.7–70)		
		2–10	15	1.80 (0.88–3.60)		
		≥ 11	19	1.9 (1.0–3.6)		

CI, confidence interval; JEM, job-exposure matrix; mo, month; NR, not reported; UV, ultraviolet; vs, versus; yr, year

In a case–control study of ocular melanoma in the USA, Tucker et al. (1986) reported an odds ratio of 10.9 (95% CI, 2.1–56.5) based on 4 cases who ever worked as a welder.

Seddon et al. (1990) conducted a case–control study of ocular melanoma in the USA which included two series of cases with partial overlap; either population or sibling controls were used for the analyses. The magnitude of the odds ratios reported for the association between arc welding and ocular melanoma were weaker than in other studies (described below) and, further, differed in the two series. There was overlap in the reported confidence intervals. One report from Ajani et al. (1992) includes results based on one of the two series of cases and controls already reported by Seddon et al. (1990). [The Working Group noted that this study was limited by the lack of a clear description of the overlap between the two case series.]

A small case–control study of ocular melanoma based in Montreal, Canada, reported an odds ratio (OR) of 8.3 (95% CI, 2.5–27.1; 4 exposed cases), based on an expert assessment of any exposure to arc welding fumes (Siemiatycki, 1991).

Lutz et al. (2005) conducted a multicentre case–control study of rare cancers in nine European countries, which included results for ocular melanoma based on dichotomous variables for men who had worked for 6 months or more as welders/sheet metalworkers. The French and German components of this study were published separately (Guénel et al., 2001; Monárrez-Espino et al., 2002). The French component of this study (Guénel et al., 2001) further presented results by duration of employment as a welder: 20 years or more employment (OR, 5.7; 95% CI, 1.6–19.8); and less than 20 years (OR, 11.5; 95% CI, 2.4–55.5) (*P* for trend, 0.0008). They also report an elevated odds ratio for more than five eye burns not specifically due to welding, but the association disappeared when welding was excluded. There was also a significant exposure–response relationship (*P* for trend, 0.003) for cumulative occupational exposure to artificial UV radiation, which included welding as well as other occupations. Arc welding was assigned the highest intensity level for artificial UV radiation from occupation. Another study including a subset of the German participants reported in the Lutz et al. (2005) paper showed an odds ratio of 1.3 (95% CI, 0.6–2.5; < 6 exposed cases) for ever welders (Monárrez-Espino et al., 2002).

Three studies provided information on the association between duration (years) of welding and risk of ocular melanoma (Holly et al., 1996; Guénel et al., 2001; Vajdic et al., 2004), two of which reported a tendency for increasing risk of ocular melanoma with increasing years of welding exposure (Guénel et al., 2001; Vajdic et al., 2004).

A population-based study from Australia, additionally adjusting for eye colour and sun exposure, observed odds ratios of 0.8 (95% CI, 0.4–1.4), 1.2 (95% CI, 0.7–2.2), and 1.7 (95% CI, 1.0–2.7) respectively, for 0.1–4.0, 4.1–22.0, and more than 22 years of welding performed by the worker. No tendencies for increasing risk by increasing welding hours per day or lifetime welding hours were observed. A subgroup with over five eye burns during welding had an odds ratio of 1.6 (95% CI, 0.7–3.6) compared with welders without eye burns. Compared with wearing goggles always or almost always, wearing goggles or a mask only half the time or less during welding resulted in an odds ratio of 1.7 (95% CI, 0.5–5.4) for 6 exposed cases (Vajdic et al., 2004).

A study from the USA of white men showed an overall increased risk of ocular melanoma for ever versus never welders/welding based on 40 exposed cases, but no trend concerning age-adjusted years of exposure was observed (Holly et al., 1996). [The Working Group noted that only some studies are adjusted for indicators of UV radiation from sunlight (Seddon et al.,

1990; Holly et al., 1996; Vajdic et al., 2004), which is the main risk factor for ocular melanoma and thereby a potential confounder; however, there was no evidence that confounding by sunlight explained the results.]

A meta-analysis based on several of the above-mentioned case–control studies (Tucker et al., 1985; Seddon et al., 1990; Ajani et al., 1992; Holly et al., 1996; Guénel et al., 2001; Vajdic et al., 2004), including 1137 cases in total, estimated an overall summary odds ratio of 2.05 (95% CI, 1.20–3.51) (Shah et al., 2005). [The Working Group noted that the meta-analyses included the overlapping cases (n = 197) reported by Seddon et al. (1990) and Ajani et al. (1992); this attenuates the overall association because these two studies have odds ratios of 1.3 and 1.0, respectively, which are weaker than the overall pooled result and are counted twice.]

2.3 Mesothelioma

Several studies reported on the association between welding and mesothelioma. These studies are an indicator of exposure to asbestos.

2.3.1 Case–control studies

The association between welding and mesothelioma was investigated in a French population-based case–control study including 371 male cases and 732 male population controls (Rolland et al., 2010). A lifelong occupational history of all occupations with a duration of at least 6 months was obtained in face-to-face interviews; each job period was coded by industrial hygienists who were blinded for case–control status according to standard classifications of occupations and industries. In an ever versus never comparison, the odds ratio for the occupational group welders and flame-cutters was 4.64 (95% CI, 2.04–10.56) based on 19 exposed cases. Thirteen of these were employed in shipbuilding and repair, manufacture of structural metal products, or manufacture of fabricated metal products. [The Working Group noted that the observed risk was probably due to asbestos exposure, as all occupations that appeared to be associated with elevated odds ratios in this study are known to entail asbestos exposure (e.g. manufacture of asbestos products, pipe fitters, and sheet metal and shipyard workers). This is a particular set of welders exposed to high concentrations of asbestos, so the results should not be generalized to the exposure of all welders.]

2.3.2 Cohort studies

Cohort studies investigated mortality or the incidence of cancer in welders and reported risk estimates for mesothelioma or cancer of the pleura. A population-based cohort study pooling data from four Nordic countries observed a standardized incidence ratio (SIR) of 1.79 (95% CI, 1.44–2.20) for cancer of the pleura in male welders based on 91 cases (Pukkala et al., 2009). Another population-based cohort study in Canada observed 15 cases in welders, which corresponded to an adjusted hazard ratio (HR) of 1.54 (95% CI, 0.86–2.78) (MacLeod et al., 2017). In this study, the risk of mesothelioma among welders in construction was 2.5 times greater compared with non-welders. A cancer mortality study among arc welders exposed to fumes containing chromium and nickel resulted in a standardized mortality ratio (SMR) of 11.80 (95% CI, 4.73–24.31) based on 7 cases (Becker, 1999). A historical cohort study of mortality among shipyard workers in Genova, Italy, reported a statistically significant standardized mortality ratio (3.77) of cancer of the pleura in arc welders based on 3 cases, and a non-significant standardized mortality ratio (1.69) in gas welders based on a single case (Puntoni et al., 2001; see Table 2.3). [The Working Group noted that the observed risks of mesothelioma or cancer of the pleura among welders in these cohort studies is probably due to asbestos exposure.]

2.4 Cohort studies

The increased risks of cancer associated with exposure to welding fumes have been studied in industrial (Section 2.4.1) and population-based cohorts (Section 2.4.2). Both types of study have reported cancer mortality or incidence for either exposure to welding fumes or occupation as a welder. Studies of cumulative exposure to welding fumes typically had more detailed exposure information at the individual level compared with studies of occupation as a welder, and were therefore considered to be more informative (from an exposure assessment point of view).

Almost all studies reported on mortality or incidence of cancer of the lung for welders or exposure to welding fumes. Due to the high rates of mortality/low rates of survival from cancer of the lung, mortality studies probably capture most of the cancer of the lung cases; however, it should be noted that diagnosis based on death certificate may not be as accurate as incidence data. When studying the association between welding and cancer of the lung, the major potential confounders are tobacco smoking and exposure to asbestos (especially in shipyards). In the absence of data on asbestos exposure, mesothelioma occurrence can be used as a crude indicator. SS welders are exposed to higher concentrations of the established lung carcinogens hexavalent chromium (Cr(VI)) and nickel compounds compared with MS welders.

Risk estimates for other cancer sites of interest including larynx, sinus/nasal cavity, brain, urinary bladder, kidney and lympho-haematopoietic system are reported in Table 2.1 and Table 2.3.

2.4.1 Industrial cohorts

See Table 2.3

Many of the industrial cohort studies of welders reported only on cancer of the lung; the reasons for not reporting on other cancers include the small population numbers or the limited power of the study groups to evaluate other common cancers. Almost all of the studies reported cancer risks for occupation as a welder, and a few studies reported risks for cumulative exposure to welding fumes. Two studies from the same population reported findings only for exposure to welding fumes (Yiin et al., 2005, 2007), and two studies (of overlapping populations) reported findings for occupation as a welder in addition to exposure to welding fumes (Simonato et al., 1991; Sørensen et al., 2007). Related studies are grouped and discussed together, and the description of cohort studies is divided into: (a) the IARC multicentre cohort and studies of contributing national subcohorts; (b) cohort studies of welders at shipyards; (c) cohort studies of welders in other industries; (d) studies considered to be less informative, due to low specificity for exposure to welding fumes or inadequate reference population; and (e) studies reporting on other cancer sites but not the lung.

(a) The IARC multicentre cohort study

See Table 2.3 and Table 2.4

A large multicentre cohort study of welders was coordinated by the International Agency for Research on Cancer (Simonato et al., 1991). Several national subcohorts were updated after the IARC study, and these analyses (Moulin et al., 1993; Milatou-Smith et al., 1997; Becker, 1999; Sørensen et al., 2007) are also reviewed (see Table 2.4). An analysis of the Finnish subcohort (Tola et al., 1988) was published before the IARC study, but is not reviewed separately because the IARC study captures all the relevant findings from this population. In addition, the Working Group suspected that two studies of Italian shipyard welders may overlap with the IARC Italian subcohort, although this was not explicitly stated in the publications. These studies are discussed in the shipyard section (Section 2.4.1(b)(ii)) since there was no clear documentation about the overlap.

(i) IARC cohort

The IARC multicentre cohort study comprised 11 092 welders employed in 135 companies in eight European countries (Denmark, England, Finland, France, Germany, Italy, Norway, Scotland, and Sweden) (Simonato et al., 1991). The cohort included welders from different types of industries, welding different types of metals, and using different welding processes. A specific matrix for welding fumes was developed, relating 13 combinations of welding process and metals welded to average exposure levels for total welding fumes, total chromium, hexavalent chromium, and nickel (Gérin et al., 1993). Welders were assigned to three mutually exclusive groups according to type of welding: shipyards welders, only MS welders, or ever SS welders. [The Working Group noted that type of welding was based on information collected at baseline. The number of workers in each group was not reported.] The latter category included a group of predominantly SS welders that was also considered separately. National reference rates were used to compute standardized mortality and incidence ratios. Mortality analysis of the total cohort (Simonato et al., 1991) showed elevated SMRs for cancers of the lung (SMR, 1.34; 95% CI, 1.1–1.6), larynx (SMR, 1.48; 95% CI, 0.59–3.04), bladder (SMR, 1.91; 95% CI, 1.07–3.15), and kidney (SMR, 1.39; 95% CI, 0.72–2.43), and for lymphosarcoma (SMR, 1.71; 95% CI, 0.63–3.71) [lymphosarcoma is now referred to as non-Hodgkin lymphoma or NHL]. No clear increase in standardized mortality ratios with time since first employment was found for any of these cancer sites.

The standardized mortality ratios for cancer of the lung were elevated by type of welding: 1.26 (95% CI, 0.88–1.74) for shipyard welders, 1.78 (95% CI, 1.27–2.43) for MS welders, 1.28 (95% CI, 0.91–1.75) for ever SS welders, and 1.23 (95% CI, 0.75–1.90) for predominantly SS welders. Analyses of mortality from cancer of the lung were conducted by duration of employment and time since first exposure (employment as a welder) in the four subgroups. A positive relationship was observed with time since first exposure for MS and SS welders, which was more evident for predominantly SS welders, but there was no clear positive trend with duration of employment. No association between mortality from cancer of the lung and cumulative exposure to total welding fumes was reported, but data were not shown (Simonato et al., 1991). An analysis restricted to the two groups of ever SS welders and predominantly SS welders (potentially exposed to more Cr(VI) and Ni over time), with at least 5 years of employment and 20 years since first exposure, also failed to demonstrate a dose–response relationship.

The results for incidence of cancer at several other sites (buccal cavity and pharynx, oesophagus, stomach, intestine, rectum, larynx, prostate, bladder, leukaemia, and other lymphatic neoplasms) were available for the Nordic subcohorts (68% of the total cohort); elevated standardized incidence ratios were reported for cancers of the lung (SIR, 1.37; 95% CI, 1.11–1.68), prostate (SIR,1.46; 95% CI, 1.02–2.02), bladder (SIR,1.21; 95% CI, 0.76–1.84), and buccal cavity and pharynx (SIR, 1.60; 95% CI, 0.95–2.53), and for leukaemia (SIR, 1.26; 95% CI, 0.63–2.25).

Smoking habits were available for the Finnish and Norwegian components of the cohort and were similar to that of the general population. [The Working Group noted that this suggests that smoking alone is unlikely to explain the excess cases of cancer of the lung. The finding of five deaths from mesothelioma indicates that the study population experienced exposure to asbestos. The five cases were distributed across all subgroups (one shipyard welder, two MS welders, and two SS welders) and across all categories of duration and time since first employment.]

[The Working Group noted that the strengths of the study included the large number of welders and the grouping of welders by welded material

Table 2.3 Industrial cohort studies on cancer and welding or exposure to welding fumes

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Simonato et al. (1991) Europe, multicentre (Denmark, England, Finland, France, Germany, Italy, Norway, Scotland, Sweden) Enrolment and follow-up different between countries Cohort	11 092 welders (164 077 person-yr); workers employed as shipyard, MS, or SS welders by 135 companies; different inclusion criteria for each national cohort Exposure assessment method: expert judgement; welding process exposure matrix developed to estimate exposure levels for total welding fumes, total Cr, Cr(VI), and Ni (described in Gérin et al. (1993))	Lung	*Incidence*			Age, calendar period	Type of welding: shipyards, MS only, ever SS, predominantly SS SIR data are only from cohort subjects of Denmark, Finland, Norway, and Sweden
			Welders	92	1.37 (1.11–1.68)		
		Lung	Years since first exposure				
			0–9	14	1.65 (0.90–2.77)		
			10–19	27	1.22 (0.81–1.78)		
			20–29	41	1.42 (1.02–1.93)		
			≥ 30	34	1.24 (0.86–1.73)		
			Total	116	1.34 (1.10–1.60)		
		Lung	Years since first exposure: shipyard welders				
			0–9	5	5.08 (1.65–11.85)		
			10–19	6	1.41 (0.52–3.06)		
			20–29	17	1.61 (0.94–2.57)		
			≥ 30	8	0.63 (0.27–1.23)		
			Total	36	1.26 (0.88–1.74)		
		Lung	Years since first exposure: MS welders				
			0–9	4	1.35 (0.37–3.45)		
			10–19	11	1.62 (0.81–2.90)		
			20–29	11	1.86 (0.93–3.33)		
			≥ 30	14	2.07 (1.13–3.48)		
			Total	40	1.78 (1.27–2.43)		
		Lung	Years since first exposure: SS ever welders				
			0–9	5	1.04 (0.34–2.43)		
			10–19	12	1.07 (0.55–1.86)		
			20–29	13	1.32 (0.70–2.26)		
			≥ 30	9	1.94 (0.89–3.69)		
			Total	39	1.28 (0.91–1.75)		

Table 2.3 (continued)

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Simonato et al. (1991) (cont.)		Lung	Years since first exposure: predominantly SS welders				
			0–9	2	0.64 (0.08–2.32)		
			10–19	5	0.88 (0.29–2.06)		
			20–29	7	1.26 (0.51–2.60)		
			≥ 30	6	3.12 (1.15–6.79)		
			Total	20	1.23 (0.75–1.90)		
		Lung	Cumulative exposure (mg/m^3-yr): predominantly SS welders				
			Cr(VI) < 0.5	3	1.91 (0.39–5.58)		
			Cr(VI) ≥ 0.5	9	1.67 (0.77–3.18)		
			Ni < 0.5	8	2.34 (1.01–4.61)		
			Ni ≥ 0.5	4	1.13 (0.31–2.90)		
		Lung	Cumulative exposure (mg/m^3-yr): SS ever welders				
			Cr(VI)< 0.5	7	1.23 (0.50–2.54)		
			Cr(VI) ≥ 0.5	14	1.70 (0.93–2.86)		
			Ni < 0.5	17	1.66 (0.97–2.66)		
			Ni ≥ 0.5	4	1.09 (0.30–2.79)		
		Urinary bladder	*Incidence*				
			Welders	22	1.21 (0.76–1.84)		
		Urinary bladder	Years since first exposure				
			0–9	2	2.19 (0.27–7.92)		
			10–19	3	1.36 (0.28–3.97)		
			20–29	4	1.66 (0.45–4.24)		
			≥ 30	6	2.59 (0.95–5.64)		
			Total	15	1.91 (1.07–3.15)		

Table 2.3 (continued)

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Simonato et al. (1991) (cont.)		Larynx: ICD-8 (code 161)	Welders	7	1.48 (0.59–3.04)		
		Larynx	Years since first exposure				
			0–9	0	0 (0–6.83)		
			10–19	3	2.09 (0.43–6.12)		
			20–29	4	2.41 (0.66–6.17)		
			≥ 30	0	0 (0–3.32)		
			Total	7	1.48 (0.59–3.04)		
		Oral/ pharyngeal combined	*Incidence*				
			Welders	18	1.60 (0.95–2.53)		
		Nasal cavity and sinuses	Welders	0	0 (0–4.44)		
		Prostate	*Incidence*				
			Welders	36	1.46 (1.02–2.02)		
		Prostate	Welders	10	0.77 (0.37–1.42)		
		Kidney	Welders	12	1.39 (0.72–2.43)		
		Kidney	Years since first exposure				
			0–9	1	0.97 (0.02–5.43)		
			10–19	1	0.43 (0.01–2.41)		
			20–29	7	2.44 (0.98–5.03)		
			≥ 30	3	1.24 (0.26–3.63)		
			Total	12	1.39 (0.72–2.43)		
		NHL: ICD-8 (code 200)	Welders	6	1.71 (0.63–3.71)		
			Years since first exposure				
			0–9	1	1.54 (0.04–8.56)		
			10–19	1	1.06 (0.03–5.91)		
			20–29	1	0.94 (0.02–5.24)		
			≥ 30	3	3.53 (0.73–10.33)		
			Total	6	1.71 (0.63–3.71)		
		HL: ICD-8 (code 201)	Welders	2	0.60 (0.07–2.18)		

Table 2.3 (continued)

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Simonato et al. (1991) (cont.)		Leukaemia: ICD-8 (code 204–207)	Welders	6	0.63 (0.23–1.38)		
		Leukaemia: ICD-7 (code 204)	*Incidence* Welders	11	1.26 (0.63–2.25)		
		Lymphatic neoplasms ICD-8 (code 202–203)	Welders	7	1.14 (0.46–2.36)		
		Other lymphatic ICD-7 (code 200–203 205)	Welders	15	1.12 (0.63–1.85)		

Table 2.3 (continued)

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Moulin et al. (1993) France Enrolment 1975–1976/follow-up 1975–1976 to 1987–1988 (depending on the factory) Cohort	2721 welders, 6683 controls; all male workers employed as welders at the beginning of the follow-up in 13 factories; internal comparison group: 6684 manual workers (excluding boilermakers, foundry workers, painters, or cutters) randomly selected among non-welders in the same factories; restricted to workers employed for at least 1 yr Exposure assessment method: records of welding processes, types of metal, and percentage of working time available at the individual level in eight factories and at the workshop level in five factories; smoking habits from medical records (recorded by the occupational physician once a year); information on asbestos available on factory level only so not relevant for the statistical analysis (it only accounted by separating shipyard from non-shipyard welders)	Lung	Welders vs controls (internal ref.)	NR	1.29	Age	Partial overlap with the IARC study, Simonato et al. (1991) No death from pleural cancer among welders; 3 deaths from pleural cancer among controls, 1.25 expected (SMR, 2.40; 95% CI, 0.49–7.01) Strengths: internal comparison group; smoking habits available for 87% of the cohort Limitations: no data on asbestos exposure
		Lung	Welders	19	1.24 (0.75–1.94)	Age, calendar time, sex	
		Lung	Welders: time since first employment (yr)				
			< 10	1	[0.75 (0.03–3.70)]		
			10–19	3	[0.90 (0.23–2.45)]		
			≥ 20	15	[1.41 (0.82–2.27)]		
		Lung	Welders: duration of employment (yr)				
			< 10	1	[1.19 (0.06–5.86)]		
			10–19	2	[0.63 (0.10–2.08)]		
			≥ 20	16	[1.41 (0.83–2.24)]		
		Lung	Duration of exposure (5-yr lag period)				
			Total welders	19	1.24 (0.75–1.94)		
			Shipyard welders	3	0.91 (0.19–2.67)		
			MS welders only	9	1.59 (0.73–3.02)		
			Ever SS welders	3	0.92 (0.19–2.69)		
			Predominantly Cr(VI)[a]	2	1.03 (0.12–3.71)		
		Larynx	Welders	3	0.67 (0.14–1.97)		
		Pleura	Welders	0	0 (0–8.82)		
		Brain	Welders	0	0 (0–2.75)		
		Leukaemia: ICD-8 (code 204–208)	Welders	2	1.13 (0.14–4.10)		
		HL: ICD-8 (code 200–203)	Welders	2	1.02 (0.12–3.68)		
		Urinary bladder	Welders	1	0.65 (0.02–3.64)		
		Prostate	Welders	0	0 (0–2.09)		

Table 2.3 (continued)

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Milatou-Smith et al. (1997) Sweden Enrolment 1950–1965/follow-up 1955–1992 Cohort	233 welders (high exposure cohort); 208 welders (low exposure cohort); two cohorts of welders, employed for at least 5 yr during 1950–1965: one of SS welders exposed to high levels of Cr(VI), and one of railway track welders exposed to low levels of Cr(VI) Exposure assessment method: records of information on average levels of exposure to Cr from Swedish measurements in 1975 (SS welders 110 µg/m^3, railway track welders 10 µg/m^3); no or minimal asbestos exposure (company statements)	Lung	Exposed to high levels of Cr: SS welders			Age, sex, cause, calendar year	Partial overlap with the IARC study, Simonato et al. (1991) Strengths: probably very low asbestos exposure; comparison between the two groups of welders unlikely to be affected by confounding due to smoking Limitations: small cohorts; no information on individual exposure levels; no actual measurements of asbestos exposure; no data on smoking
			Welders	6	1.64 (0.60–3.58)		
		Lung	Exposed to low levels of Cr: MS welders				
			Welders	2	0.41 (0.05–1.48)		
		Lung	Exposed to high vs low levels of Cr			Age	
			Welders	NR	3.98 (0.84–18.80)		

Table 2.3 (continued)

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Becker (1999) Germany Enrolment 1950–1970/follow-up 1950–1995 Cohort	1213 SS welders, 1688 turners (internal reference group); arc welders exposed to Cr and Ni and turners employed for at least 6 mo during 1950–1970 at 25 factories of the metal-processing industry Exposure assessment method: exposure duration from companies records; assessment of welding exposure characteristics (welding procedure, percentage of working time) and smoking habits at the individual level by interview of the foremen and superiors; average duration of exposure of the welders was 18.3 yr	Lung [includes bronchus and trachea]	*Mortality* Welders	28	1.21 (0.80–1.75)	Calendar period	Partial overlap with the IARC study, Simonato et al. (1991); strong excess of deaths from mesothelioma; confounding by asbestos likely to explain the lung cancer excess Strengths: internal comparison group; analyses by subgroups Limitations: no data on asbestos exposure
		Pleura	Welders	7	11.80 (4.73–24.30)		
		Urinary bladder	Welders	5	2.08 (0.67–4.84)		
		Other lymphatic and haematopoietic	Welders	0	–		
		MM	Welders	1	1.23 (0.03–6.86)		
		Leukaemia (lymphoid): ICD-9 (code 204)	Welders	1	1.52 (0.04–8.51)		
		Leukaemia (myeloid): ICD-9 (code 205)	Welders	0	–		
			Internal analysis				
		Lung	Welders	28	1.30 (0.80–2.12)	Age, calendar period	
		Lymphatic and haematopoietic	Welders	2	0.38 (0.08–1.75)		
		Lung	Duration of exposure (yr)			Calendar period	
			0 to < 10	6	0.99 (0.36–2.15)		
			10 to < 20	11	1.57 (0.78–2.81)		
			20 to < 30	8	1.18 (0.51–2.34)		
			≥ 30	3	1.10 (0.22–3.23)		
		Lung	Time since first exposure (yr)				
			0 to < 10	0	–		
			10 to < 20	2	0.56 (0.06–2.03)		
			20 to < 30	13	1.48 (0.78–2.53)		
			≥ 30	13	1.39 (0.74–2.38)		

Table 2.3 (continued)

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Becker (1999) (cont.)		Lung	Coated electrodes	11	1.21 (0.60–2.17)		
			Coated electrodes or MIG-MAG/WIG	14	1.40 (0.76–2.36)		
			Exclusively MIG-MAG/WIG, for malignant neoplasms	3	0.88 (0.18–2.58)		
		Urinary bladder	Coated electrodes	3	2.80 (0.57–8.19)		
			Coated electrodes or MIG-MAG/WIG	2	2.12 (0.25–7.66)		
			Exclusively MIG-MAG/WIG, for malignant neoplasms	0	–		
		Brain	Coated electrodes	4	6.18 (1.88–15.85)		
			Coated electrodes or MIG-MAG/WIG	0	–		
			Exclusively MIG-MAG/WIG, for malignant neoplasms	0	–		

Table 2.3 (continued)

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Becker (1999) (cont.)		Lymphatic and haematopoietic ICD-9 (code 200–208)	Coated electrodes	1	0.46 (0.01–2.60)		
			Coated electrodes or MIG-MAG/WIG	1	0.39 (0.01–2.19)		
			Exclusively MIG-MAG/WIG, for malignant neoplasms	0	–		
			Effective welding periods per day (%)				
		Lung	≤ 25	15	1.24 (0.69–2.04)		
			> 25	13	1.18 (0.63–2.02)		
		Urinary bladder	≤ 25	2	1.54 (0.18–5.56)		
			> 25	3	2.71 (0.55–7.92)		
		Lymphatic and haematopoietic	≤ 25	0	–		
			> 25	0	–		
		MM and immuno-proliferative neoplasm	≤ 25	0	–		
			> 25	1	2.59 (0.06–14.46)		
		Leukaemia (lymphoid): ICD-9 (code 204)	≤ 25	1	2.86 (0.07–15.94)		
			> 25	0	–		
		Leukaemia (myeloid): ICD-9 (code 205)	≤ 25	0	–		
			> 25	0	–		
			Mortality				
		Larynx	Welders	1	0.73 (0.02–4.09)		
		Kidney and other urinary organs	Welders	0	–		

Table 2.3 (continued)

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Becker (1999) (cont.)		Prostate	Welders	3	0.67 (0.14–1.95)		
		Lymphatic and haematopoietic	Welders	2	0.35 (0.04–1.26)		
		HL: ICD-9 (code 201)	Welders	0	–		
		Brain and parts of nervous system	Welders	4	2.02 (0.55–5.19)		
Sørensen et al. (2007) Denmark Enrolment 1964–1984/follow-up 1968–2003 Cohort	4539 welders; male production workers, employed for at least 1 yr at 74 SS or MS companies (shipyards, apprentices, and craftsman excluded), alive at 1 April 1968, born before 1965, who answered the questionnaire in 1986; study population restricted to ever welders who started in 1960 or later Exposure assessment method: welding exposure matrix (based on > 1000 measurements) for welding fume particulates combined with questionnaire data on welding characteristics; questionnaire for asbestos exposure and smoking; next-of-kin questionnaire for the subgroup of deceased	Lung	MS (never SS)	43	1	Age, smoking, asbestos	Partial overlap with the IARC study, Simonato et al. (1991), and Hansen et al. (1996) Strengths: long follow-up; semi-quantitative exposure assessment; adjustment for smoking and asbestos exposure Limitations: self-reported data on asbestos exposure
			SS	32	0.86 (0.52–1.42)		
		Lung	Ever welding	75	1.35 (1.06–1.70)	Age, calendar time, sex	
			Ever SS	34	1.15 (0.78–1.60)		
			Ever MMA-SS	25	1.46 (0.95–2.16)		
			Never MMA-SS	9	0.72 (0.35–1.36)		
			Ever MS, never SS	41	1.59 (1.14–2.16)		
		Lung	All welders: duration of welding (yr)			Age, smoking, asbestos	
			0–5	20	1		
			6–15	27	1.47 (0.73–2.92)		
			≥ 16	28	1.29 (0.65–2.57)		

Table 2.3 (continued)

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sørensen et al. (2007) (cont.)		Lung	MS (never SS) welder: duration of welding (yr)				
			0–5	16	1		
			6–15	19	1.19 (0.75–3.80)		
			≥ 16	8	0.83 (0.30–2.26)		
		Lung	SS welders: duration of welding (yr)				
			0–5	13	1		
			6–10	1	0.17 (0.02–1.28)		
			≥ 11	18	1.07 (0.50–2.28)		
		Lung	All welders: cumulative exposure estimate ($mg/m^3 \times yr$)				
			0–15	13	1		
			16–60	34	2.05 (1.02–4.09)		
			≥ 61	23	1.78 (0.84–3.66)		
		Lung	MS (never SS) welders: cumulative exposure estimate (mg/m^3-yr)				
			0–10	4	1		
			11–50	26	3.29 (0.97–11.10)		
			≥ 51	8	1.79 (0.46–6.99)		
		Lung	SS welders: cumulative exposure estimate (mg/m^3-yr)				
			0–5	11	1		
			6–10	6	1.18 (0.40–3.51)		
			≥ 11	15	2.34 (1.03–5.28)		

Table 2.3 (continued)

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Merlo et al. (1989) Genova, Italy Enrolment 1930–1980/follow-up 1960–1981 Cohort	527 welders: 274 oxyacetylene (MS); 253 electric arc welders (SS); all male shipyard workers employed for at least 6 mo as a welder; electric arc slowly replaced oxyacetylene welding over time (1940s: 66% oxyacetylene; 34% electric arc; 1986: 44% oxyacetylene; 56% electric arc). Exposure assessment method: records of job title (electric arc workers: open spaces, lower levels of gases and fumes; oxyacetylene workers: inside oil tankers, higher levels of gases and fumes); air samples during cutting in oil tankers: B[*a*]P (3–22 μg/m^3), NO_x (3–8.5 ppm), dust (9–27 mg/m^3); higher Ni and Cr(VI) found in SS and MIG welding; asbestos fibres not detected	Respiratory tract	Shipyard welders: external analysis			Age, calendar period	One death from asbestosis among electric arc workers; no information on mesothelioma Strengths: indirect adjustment for smoking based on survey data Limitations: small numbers of exposed cases in subcohorts; follow-up did not start until 30 yr after first date of enrolment (may have missed cases)
			All	16	1.67 (0.95–2.71)		
			Oxyacetylene	12	2.34 (1.21–4.09)		
			Electric Arc	4	0.88 (0.24–2.30)		
		Respiratory tract	Shipyard welders: internal analysis				
			Electric arc welders (ref.)	NR	0		
			Welding	16	2.45 (0.77–7.83)		
		Larynx	Shipyard welders: external analysis				
			All	0	0 (0–2.67)		
			Oxyacetylene	0	0 (0–4.92)		
			Electric arc	0	0 (0–5.83)		
		Bladder and kidney	Shipyard welders: external analysis				
			All	5	2.11 (0.68–4.92)		
			Oxyacetylene	5	3.70 (1.19–8.64)		
			Electric arc	0	0 (0–3.60)		
		Lymphatic and haematopoietic	Shipyard welders: external analysis				
			All	2	0.98 (0.11–3.54)		
			Oxyacetylene	1	0.93 (0.01–5.19)		
			Electric arc	1	1.03 (0.01–5.74)		

Table 2.3 (continued)

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Puntoni et al. (2001) Italy Enrolment 1960–1980/follow-up 1960–1995 Cohort	3984 male shipyard workers (267 electric arc welders and 228 gas welders); male shipyard workers (whole cohort) employed at the harbour of Genoa Exposure assessment method: records of individual data on job titles from the personnel department; coding the most prevalent job for individuals with different job titles	Lung Pleura Larynx Urinary bladder Kidney	Electric arc Gas Electric arc Gas Electric arc Gas Electric arc Gas All Electric arc Gas	19 14 3 1 1 2 5 1 5 3 2	[1.64 (1.07–2.51)] [1.57 (0.89–2.57)] [3.77 (0.96–10.26)] [1.69 (0.08–8.33)] [0.82 (0.04–4.04)] [2.00 (0.33–6.60)] [2.74 (1.00–6.07)] [0.70 (0.03–3.45)] 3.82 (1.24–8.91) 4.00 (0.82–11.69) 3.57 (0.43–12.90)		Three deaths from pleural cancer among arc welders (SMR, 3.8; NS); 1 death from pleural cancer in gas welders (SMR, 1.7; NS) Limitations: only job titles; confounding by asbestos
Newhouse et al. (1985) NE England Enrolment 1940–1968/follow-up 1940–1986 Cohort	3489 workers (welders, caulkers, electricians, and platters; identified from personnel records) at a shipyard; 1027 welders Exposure assessment method: 1960 measurements of iron oxide in mg/m^3 (total general air: 6.3; personal: 13.6); confined spaces without ventilation (general air: 23.6; personal: 31.9); caulkers also exposed to fumes similar in magnitude and composition to welding fumes; asbestos used throughout shipyard but no specific information	Lung All cancers combined	Welders Caulkers Welders Caulkers	26 12 49 18	1.13 (0.80–1.57) 2.32 (1.33–3.74) 1.03 (0.79–1.27) 1.68 (1.09–2.49)	Age, calendar year	15% of workforce had died; 1 mesothelioma among welders and 1 among caulkers Strengths: exposure monitoring data available Limitations: limited exposure information; no information on smoking; incomplete employment records did not allow for assessment of employment duration; workers moved between shipyards

Table 2.3 (continued)

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Melkild et al. (1989) Norway Enrolment: 1946–1977/follow-up: 1953–1986 Cohort	4778 male shipyard workers (783 MS workers); male workers first employed at shipyard on southwest coast of Norway for at least 3 mo during the enrolment period; MMA-MS welding predominant until 1970; SS welding did not become common until the mid-1970s; gas-shielded welding introduced in the 1960s Exposure assessment method: questionnaire and company records, classifying job titles within 10 categories; 1973 survey: total fumes 7.3 mg/m^3 (3.6–23.6); Ni: 0.34 mg/m^3 (0.11–1.97); Cr: 0.12 mg/m^3 (0.03–0.65); personal protection equipment and ventilation provided to shops in early 1970s; asbestos used until early 1970s	Lung	Welders	7	2.21 (0.88–4.54)	Age, calendar period	Workers may have contributed to a cancer site in more than one occupational category; may have missed cases occurring during 1947–1952; 2 mesotheliomas observed among non-welders Strengths: description of the type of welding over time and some exposure monitoring data Limitations: limited exposure assessment, which was based on personnel register; no information on smoking in the cohort; exposure to asbestos possible, small numbers of exposed cases
		Lung	Employment duration (yr)				
			< 1	0	–		
			1–5	5	[5.56 (2.04–12.31)]		
			> 5	1	[0.59 (0.03–2.90)]		
		Urinary bladder	Welders	2	[1.33 (0.22–4.41)]		

Table 2.3 (continued)

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Danielsen et al. (1993) Norway Enrolment 1940–1979/follow-up 1953–1990 Cohort	4571 male shipyard workers (623 MS welders); identified by personnel register with information regarding name, start, and end dates; mainly MMA welding performed on MS Exposure assessment method: records of interviews with retired workers; high-exposure welders were defined as welders employed ≥ 3 yr and identified as a welder by veteran workers; very high exposure was defined as a subgroup employed ≥ 5 yr as a welder and followed up from the 5th year of employment Environmental monitoring data: total dust 2.5 mg/m^3 (0.8–9.5 mg/m^3)	Lung	Welders	9	2.50 (1.14–4.75)		Smoking differences were estimated to explain a SIR of ~1.25; Cr and Ni levels were low and no mesotheliomas were observed among welders; may have missed cases occurring during 1940–1953 Strengths: high and very high exposure subgroups; internal reference group of shipyard production workers who were not welders or burners Limitations: no quantitative exposure (or semiquantitative exposure assessment); a small number of exposed lung cases among welders; limited information on smoking habits
		Lung	Duration of employment and lag time (yr)				
			≤ 5; no lag	NR	1.7 (0.5–5.5)		
			> 5; no lag	NR	3.0 (1.3–6.9)		
			≤ 5; 10 yr lag	NR	1.8 (0.5–5.7)		
			> 5; 10 yr lag	NR	3.2 (1.3–8.1)		
		Lung	15-yr lag: external analysis				
			All	8	3.08 (1.35–6.08)		
			High exposure	6	3.75 (1.38–8.19)		
			Very high exposure	4	4.00 (1.10–10.20)		
			Shipyard excluding welders and burners	38	1.35 (0.96–1.86)		
		Lung	Employment duration (yr): external analysis				
			≤ 4	3	[2.14 (0.55–5.83)]		
			5–9	0	–		
			≥ 10	6	[3.75 (1.52–7.80)]		
		Urinary bladder	Welders	1	0.59 (0–3.29)		

Table 2.3 (continued)

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Danielsen et al. (2000) Norway Enrolment 1945–1980/follow-up 1953–1995 Cohort	4480 male shipyard workers; 861 welders; 908 welded some time; 24 welders in machinery production (SS); workers identified by personnel register with information regarding name, start, and end dates; mainly MS welders Exposure assessment method: records of job title and work history. Welding fumes (mg/m^3): MS, 14.5 (1973) and 1.87 (1989); SS, 1.5 (1977) and 7.0–38 (1989); SS grinders, 25.5 (1977). Information on employment outside the shipyard (prior to or between jobs) available from the early 1950s; average length of employment 10.1 yr	Lung	Shipyard welders: employment duration (yr): internal analysis			Age, calendar year	Strengths: information on smoking habits and previous employment; internal comparison of shipyard workers excluding welders Limitations: no quantitative exposure (or semi-quantitative exposure assessment)
			Non-welding shipyard workers (ref.)	36	1		
			< 2	3	2.42 (0.73–8.01)		
			2–4	1	0.66 (0.09–4.85)		
			5–14	1	0.56 (0.08–4.17)		
			≥ 15	4	1.90 (0.67–5.38)		
		Lung	External analysis				
			Welders	9	1.27 (0.58–2.42)		

Table 2.3 (continued)

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Danielsen et al. (1998) Norway Enrolment 1975/ follow-up 1976–1992 Cohort	428 male welders (23 with siderosis) who had welded for > 10 yr, mostly MMA welding in confined spaces from 15 shipyards, and examined for siderosis in 1975 Exposure assessment method: records, assumed to have long-term exposure to high levels 10 yr or more before 1975; only limited information about smoking habits was available	Lung	Welders	10	1.55 (0.74–2.84)	Age, calendar period	No cases of mesothelioma or asbestosis; electric arc welding on MS was predominant until 1975; gas-shielded welding introduced in the 1970s and SS after 1975 Strengths: presumed high exposure cohort; analysis by time since first exposure Limitations: potential healthy worker effect; welders who died before 1975 or who quit welding due to adverse health effects were not included in the cohort; limited information on smoking habits or exposure to asbestos; small cohort with few exposed cases
		Kidney	Welders	2	1.13 (0.14–4.10)		
		Urinary bladder	Welders	1	0.30 (0.01–1.69)		
		Leukaemia: ICD-7 (code 204)	Welders	1	0.69 (0.02–3.85)		
		Lung	Years since first exposure				
			10–19	0	0 (0–10.91)		
			20–29	3	1.49 (0.31–4.34)		
			30–39	4	1.57 (0.43–4.01)		
			≥ 40	3	1.93 (0.40–5.64)		
		All cancers combined: ICD-7	Welders	32	0.77 (0.53–1.09)		

Table 2.3 (continued)

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Yiin et al. (2005) USA Enrolment 1952–1992/follow-up 1952–1996 Cohort	13 468 workers; men and women, all races, employed as civilian workers at Portsmouth Naval Shipyard for at least 1 d and monitored for radiation Exposure assessment method: expert judgement; exposure to welding fumes and asbestos (0, none; 1, possible; 2, probable) assigned to each job title/ shop combination by an expert panel; cumulative exposure score calculated as the sum of the duration of exposed jobs, weighted by exposure probability	Lung	Total exposure to shipyard welding fumes (based on intensity and duration) Never > 0–5[b] > 5	 174 125 112	 1 1.45 (1.10–1.92) 1.50 (1.09–2.06)	Radiation, age, calendar period, asbestos, SES	Strengths: large cohort; semi-quantitative exposure assessment; adjustment for radiation, asbestos, and SES as a proxy for smoking Limitations: the exposure of interest is radiation; welding fumes analysed as a potential confounder for lung cancer only (no information reported for leukaemia); possible misclassification of exposure; no actual data on smoking habits

Table 2.3 (continued)

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Yiin et al. (2007) USA Enrolment 1952–1992/follow-up 1952–1996 Nested case–control	Cases: 1097 deaths from lung cancer Controls: 3291 risk-set-matched controls (3 per case, randomly selected by incidence density sampling) Exposure assessment method: expert judgement; intensity and frequency of exposure to welding fumes (as Fe_2O_3 fumes) and asbestos assessed by an expert panel of 3 industrial hygienists for 3519 job/ shop/period combinations. Good concordance, weak inter-rater agreement. Cr and Ni content of welding fumes were also assessed (not used in the analysis). 53% of the study subjects were ever exposed to welding fumes; 64% to asbestos, 8% to Ni and 6% to Cr	Lung	Shipyard welding fumes: multivariate analysis (mg-d/m³)			Radiation, asbestos exposure, SES, birth cohort	Radiation exposure is the focus of the paper; welding fumes as a confounder was analysed as a continuous variable; unadjusted ORs associated with categorical exposure to welding fumes did not suggest a linear relationship Strengths: detailed exposure assessment; adjustment for asbestos, radiation, SES and birth cohort (surrogates for smoking) Limitations: no actual smoking data; no monitoring data to validate panel estimates
			1000	NR	1.01 (0.98–1.04)		
		Lung	Shipyard welding fumes: individual risk factor effects (mg-d/m³)			None	
			1000	NR	1.03 (1.0–1.05)		
		Lung	Shipyard welding fume TLV-1 categories: individual risk factor effects (mg-d/m³)				
			< 0.5	807	1		
			0.5–1	116	1.35 (1.07–1.70)		
			1–2	86	1.58 (1.20–2.07)		
			2–4	40	1.20 (0.82–1.72)		
			≥ 4	48	1.26 (0.88–1.76)		

Table 2.3 (continued)

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Rinsky et al. (1988) Kittery, Maine, USA 1952–1977 Nested case–control	Cases: 405 white male deaths from malignant neoplasm of bronchus, trachea. or lung; diagnosis based on death certificates Controls: 1215 selected from the same cohort, matched by date of birth, year of 1st employment, and duration of employment 3:1 Exposure assessment method: personnel records indicating the specific shops to which a person had been assigned; job classification and date of each change in employment were used to code work history	Lung	Shipyard: asbestos and welding				Nested case–control study of Portsmouth Naval Shipyard workers; primary research question was the assessment of lung cancer risk due to ionizing radiation emitted from nuclear reactor components Strengths: specific focus on asbestos and welding in addition to radiation exposure; classification of welding exposure by probability (potential, probable) and duration (ever, ≥ 5 yr, ≥ 10 yr) Limitations: limited confounder information; no adjustment for smoking
			Never exposed	138	1		
			Ever exposed	267	1.43 (1.12–1.81)		
			Min 5 yr	152	1.50 (1.11–2.04)		
			Min 10 yr	96	1.38 (0.97–1.98)		
		Lung	Shipyard: Welding shop)				
			Never exposed	364	1		
			Ever exposed	41	1.13 (0.76–1.68)		
			Min 5 yr	28	1.16 (0.73–1.86)		
			Min 10 yr	16	0.83 (0.46–1.53)		
		Lung	Shipyard: probable or potential exposure				
			Never exposed	169	1		
			Ever exposed	236	1.46 (1.17–1.83)		
			Min 5 yr	143	1.41 (1.06–1.87)		
			Min 10 yr	91	1.24 (0.89–1.74)		
		Lung	Shipyard: probable exposure				
			Never exposed	364	–		
			Ever exposed	41	1.13 (0.76–1.68)		
			Min 5 yr	28	1.20 (0.74–1.92)		
			Min 10 yr	16	0.93 (0.50–1.72)		

Table 2.3 (continued)

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Stern et al. (1986) USA Enrolment 1952–1977/follow-up 1952–1980 Nested case–control	Cases: 53 deaths from leukaemia (death certificates, checked with medical records) Controls: 212; 4 matched controls by case (exclusion: deaths from haematopoietic or lymphatic malignancies) Exposure assessment method: records of job titles and duration of employment of the different jobs; radiation dose	Leukaemia Leukaemia (myeloid)	Welder Welder	NR NR	3.19 (1.09–9.37) 6.23 (1.64–23.64)	Radiation, employment as electrician, employment in jobs exposed to solvents	Strengths: ORs associated with employment as a welder adjusted for radiation exposure, employment as electrician, and jobs exposed to solvents Limitations: crude assessment of exposure
Park et al. (1994) USA Enrolment 1966–1989/follow-up 1978–1988 Cohort	16 197 hourly workers (76% assembly plant, 24% stamping plant); 3887 stamp workers; all hourly employees who worked ≥ 2 yr at 2 automotive assembly plants and a metal stamping plant before 1989 Exposure assessment method: records of six process-related categories for stamping plant; ~25 of the decedents worked in more than one exposure category; welding was performed on sheet metal	Lung Lung Lung Lymphatic and haematopoietic	Stamping or assembly plant: Welding Stamping plant: welding lines and welder repair: long latency weighted duration, cumulative exposure (mo) 0 1–50 51–100 All Stamping plant: adjusted MOR: weighted duration/ latency cumulative exposure Long latency Long latency Short latency Welders	 7 8 5 2 15 NR NR NR 1	 2.73 (1.20–6.30) 1 [2.00 (0.61–6.61)] [5.81 (0.92–36.8)] [1.38 (0.56–3.40)] 1.90 (0.93–3.90) 2.73 (1.09–6.90) 3.95 (1.39–11.00) 0.99 (0.14–7.20)	Age, sex, race, chronological time	No information on mesothelioma Strengths: regression analysis and modelling to evaluate similar activities of previous employment, latency, and duration Limitations: no quantitative or semi-quantitative exposure assessment; only 5% of cohort had died due to young ages and short follow-up (11 yr); healthy worker effect in stamping plant; mortality odds ratio; no information on smoking and other potential confounders

Table 2.3 (continued)

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Steenland (2002) Illinois, USA Enrolment 1950s–1980s/follow-up mid-1950–1998 Cohort	4459 welders; 4286 never welders; hourly male (90% white) workers with ≥ 2 yr of experience as a production arc welder or welder helper at 3 heavy equipment manufacturing plants Exposure assessment method: records of person monitoring available from 1974 to 1987; smoking data available for subset of workers; TWA geometric mean across plants (particulate levels, 5.5–7.4 mg/m^3; Fe_2O_3, 3–4.1 mg/m^3); average duration of welder 8.5 yr	Lung	Welders vs US population: exposure (yr); 15-yr lag time			Age, race, calendar time	Update of Beaumont & Weiss (1980); 26% of the population had died; potential misclassification of exposure duration since 14% of the population still worked at the end of follow-up; smoking probably cannot explain all the excess of lung cancer in welders; no deaths from asbestosis or nonspecific pneumoconiosis Strengths: exposure monitoring data; non-welder cohort; some data on smoking; exposure to asbestos unlikely Limitations: no quantitative or semiquantitative exposure assessment
			Total mortality	97	1.47 (1.19–1.79)		
			2–5	34	1.39 (0.96–1.94)		
			5–10	23	1.30 (0.82–1.95)		
			10–15	23	1.94 (1.23–2.91)		
			15–20	12	1.65 (0.85–2.88)		
			> 20	15	1.02 (0.57–1.68)		
			Latency < 20	66	1.39 (1.07–1.77)		
			Latency ≥ 20	31	1.66 (1.23–2.36)		
		Lung	Welders vs non-welders: exposure (yr); 15 yr lag time				
			Total mortality	97	1.22 (0.93–1.59)		
			2–5	34	1.10 (0.67–1.81)		
			5–10	23	0.89 (0.49–1.59)		
			10–15	23	1.69 (0.92–3.11)		
			15–20	12	1.63 (0.75–3.51)		
			> 20	15	0.77 (0.29–2.05)		
			Latency < 20	66	1.20 (0.88–1.64)		
			Latency ≥ 20	31	1.10 (0.67–1.79)		
		Larynx	Welders	4	1.42 (0.39–3.62)		
		Kidney	Welders	10	1.84 (0.88–3.38)		
		Urinary bladder	Welders	7	1.71 (0.69–3.53)		

Table 2.3 (continued)

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Danielsen et al. (1996) Norway Enrolment 1942–1981/follow-up 1953–1992 Cohort	2957 male welders; 606 SS welders; members of the National Registry of Boiler Welders from 385 different businesses who registered before 1981 with information on DOB; foreigners without permanent addresses in Norway excluded; most registered welders welding on MS; MMA welding predominant method in early years Exposure assessment method: records of welder registration information contained the method of welding for certification and information on previous work experience	Lung	Boiler welders: lag time (yr)			Age, calendar period	SS welders: boiler welders ever welding on SS; excess risk of mesothelioma found among boiler welders (3 cases); use of gas shielded and TIG welding increased in 1970s Strengths: exposure misclassification with respect to welders unlikely Limitations: no information on exposure duration, exposure intensity, potential confounders (e.g. asbestos), or smoking; small numbers of exposed cases
			No lag	50	[1.33 (1.00–1.74)]		
			15-yr lag	46	[1.27 (0.94–1.69)]		
		Lung	SS welder: lag time (yr)				
			No lag	6	[1.03 (0.41–2.15)]		
			15-yr lag	2	[0.59 (0.10–1.90)]		
		Lung	Boiler welders: year of first registration				
			1940–1949	7	[1.05 (0.46–2.07)]		
			1950–1959	25	[1.70 (1.12–2.47)]		
			1960–1969	9	[0.75 (0.36–1.37)]		
			1970–1982	9	[2.20 (1.07–4.03)]		
		Lung	SS welder: year of first registration				
			1940–1949	2	[1.66 (0.27–5.50)]		
			1950–1959	1	[0.62 (0.03–3.08)]		
			1960–1969	0	–		
			1970–1982	3	[3.00 (0.76–8.16)]		
		All cancers combined	Boiler welders	269	1.02 (0.90–1.15)		
			SS welders	41	1.00 (0.71–1.35)		
		Nasal cavity and sinuses	Boiler welders	3	3.33 (0.66–9.78)		
		Larynx	Boiler welders	3	0.75 (0.15–2.20)		
			SS welders	0	–		
		Kidney	Boiler welders	19	1.78 (1.07–2.78)		
			SS welders	2	1.18 (0.12–4.24)		
		Urinary bladder	Boiler welders	20	1.05 (0.64–1.63)		
			SS welders	0	0 (0–1.28)		
		Brain	Boiler welders	10	1.02 (0.49–1.88)		

Table 2.3 (continued)

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Danielsen et al. (1996) cont.)		HL: ICD-7 (code 201)	Boiler welders	3	1.43 (0.29–4.19)		
		NHL: ICD-7 (code 200/2)	Boiler welders	9	0.83 (0.38–1.57)		
		Leukaemia: ICD-7 (code 204)	Boiler welders	11	1.77 (0.89–3.18)		
			SS welders	2	2.00 (0.20–7.20)		
Meguellati-Hakkas et al. (2006) France Enrolment 1978–1994/follow-up 1978–1996 Cohort	34 305 men ever employed as telephone linemen in 1978 and new hires from 1978 to 1994 Exposure assessment method: expert judgement; semiquantitative assessment based on expert assessment of job tasks for specific calendar/time periods; exposure duration was estimated for welding; highest category was 0.04 yr or more	Lung	Duration of arc welding exposure (yr)			Age, calendar period, engine exhaust, PAHs, asbestos	No information on smoking but use of internal analyses decreases concerns Strengths: semi-quantitative exposure assessment; adjustment for exposure to asbestos Limitations: focus of the paper was exposure to asbestos; welding was assessed as a potential confounder; exposure to welding does not seem to be substantial (80% of deaths exposed to less than 0.04 yr of welding)
			0	54	1		
			> 0 to 0.03	127	1.2 (0.8–1.6)		
			> 0.03 to 0.04	64	1.3 (0.8–2.2)		
			> 0.04	63	1.4 (0.7–2.8)		

Table 2.3 (continued)

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Dunn & Weir (1968) California, USA Enrolment 1954–1957/follow-up 1954–1962 Cohort	68 153 men in all occupations; 10 233 welders and burners; male workers aged 35–64 employed in 14 selected occupational groups were selected from union mailing lists and questionnaires Exposure assessment method: questionnaire; occupational title, employment duration, working conditions, type of welding, and specific exposures associated with particular occupations	Lung	Welders and burners	49	[1.05 (0.79–1.38)]	Age, smoking	Strengths: adjusted for smoking; prospective study Limitations: limited information on occupational co-exposures; short follow-up (7 yr average); referent group was the total population, some of which were exposed to asbestos

Table 2.3 (continued)

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Polednak (1981) Tennessee, USA Enrolment 1943–1974/follow-up 1974 Cohort	1059 white male welders employed at Oak Ridge nuclear facilities during the enrolment period; two subgroups of welders: (1) 536 welders at K-25 Ni alloy pipes (MS and Ni); and (2) 533 welders at Y-12 and X-10 plants conducting various types of welding (SMA, TIG, MIG) Exposure assessment method: records of personal air monitoring (Ni and Fe_2O_3) for different welding procedures: Fe_2O_3, 0.18–0.47 mg/m^3; Ni (mg/m^3) was highest for MIG/Ni (0.57), intermediate for SMA/Ni (0.13) and MIG carbon steel (0.25), and lowest for TIG welding with Ni (0.04) or carbon steel (0.08). Biomonitoring data (metals) among 33 Ni welders in K-25 facility (0.053 mg/L Ni). Information on smoking available for 33% of workers	Lung	Total cohort of welders	17	1.50 (0.87–2.40)	Age, calendar period	16.7% of workers had died; excess risk of emphysema in total cohort and two subcohorts observed; smoking higher in other plants than K-25; K-25 smoking habits similar to national rates; no information on radiation exposure Strengths: monitoring data, including exposure to Ni, from different types of welding available; long follow-up for 50% of workers; some data on tobacco smoking habits Limitations: small number of cases for employment duration analysis; healthy worker effect (SMR for all causes, 0.87; 95% CI, 0.75–1.01)
			Welders: 15-yr lag	16	[1.76 (1.04–2.80)]		
		Lung: ICD-8	K-25 plant: subgroups of welders				
			Welders	7	1.24 (0.50–2.55)		
			Welders: 15-yr lag	6	[1.26 (0.51–2.62)]		
			Other welders	10	1.75 (0.84–3.22)		
		Respiratory tract: cancer	Total cohort: length of employment as a welder (wk)				
			< 50	10	1.57 (0.75–2.89)		
			≥ 50	7	1.21 (0.49–2.49)		
		Respiratory tract	K-25 plant: length of employment as a welder (wk)				
			< 50	2	[0.62 (0.10–2.05)]		
			≥ 50	5	1.75 (0.57–4.08)		
		Larynx	Total cohort: welders	0	0		
		Brain	Total cohort: welders	3	[1.94 (0.49–5.27)]		
		Leukaemia: ICD-8	Total cohort: welders	1	[0.64 (0.03–3.17)]		

Table 2.3 (continued)

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Steenland et al. (1986) Western Washington, USA Enrolment 1950–1973/follow-up 1950–1976 Cohort	3247 welders, 5432 non-welders; male members of a metal trades union/local boilermakers, employed at least 1 d during the period 1950–1973, who had worked for at least for 3 yr Exposure assessment method: job categories from union records	Lung Lung	SMR: Welding Cox: Welding	NR NR	[1.32 (0.99–1.76)] [1.29 (0.90–1.85)]	None Age, employment	Reanalysis of the cohort reported by Beaumont & Weiss (1980, 1981) using internal reference group Strengths: internal comparison group Limitations: no exposure data
Sorahan et al. (1994) UK Enrolment 1946–1990/follow-up 1946–1978 Cohort	10 438 (total cohort); 401 welders in the fettling shop, 99 welders in pattern/ machine/maintenance/ inspection; men employed for at least 1 yr in 9 English and 1 Scottish steel foundries Exposure assessment method: records of work area and occupational category	Lung Lung	Fettling shop: burning and welding Pattern/ machine/ maintenance/ inspection: welding	19 2	[1.69 (1.04–2.58)] [0.95 (0.16–3.15)]	Age, sex, calendar year	Update of Fletcher & Ades (1984) Limitations: small number of welders; no exposure data

Table 2.3 (continued)

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Austin et al. (1997) Ohio, USA 1970–1987 Nested case–control	Cases: 231 deaths from lung cancer Controls: 408 selected from the same cohort matched by race, sex, and year of birth using density sampling Exposure assessment method: records of complete work history from plant personnel files; telephone interview for lifestyle characteristics	Lung Lung	Ever welding Longest welding job held	10 7	0.66 (0.29–1.50) 0.76 (0.28–2.10)	Smoking, job Smoking	Strengths: controlling for smoking Limitations: small number of welders; no exposure data; possibly inadequate control group; crude adjustment for smoking (never, former, current, unknown); no adjustment for concomitant occupational exposures in foundry
Howe et al. (1983) Canada Enrolment 1965–1977/follow-up 1965–1977 Cohort	43 826 pensioners; 4629 exposed to welding fumes; male pensioners of the Canadian National Railroad company who retired before 1965, were known to be alive in 1965, and who retired during 1965–1977 Exposure assessment method: expert classification of workers exposed to welding fumes, diesel fumes, coal dust, and other exposure based on occupation at retirement	Brain	Individuals exposed to welding fumes	10	3.18 (1.53–5.86)	Age, calendar period	Strengths: not informative Limitations: potential for exposure misclassification; exposure only based on last occupation; no information on type of welding, duration, levels, etc.; findings only reported for brain cancer; no information on smoking or other potential co-exposures

Table 2.3 (continued)

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bonde et al. (1992) Denmark Enrolment 1964–1984 fathers/follow-up of children (date of birth to date of death, emigration) or 1987 Cohort	27 071 fathers; 5020 children with cancer; Danish fathers who were employed at 74 MS and SS manufacturing companies (as identified by the Danish Pension Fund) for at least 1 year Exposure assessment method: metalworking cohort questionnaire sent through mail, included data on drinking and smoking habits and occupational exposures including the type of welding methods used during three calendar periods; response rate 85%	Childhood cancer	Parental exposure SS welding MS welding	 2 4	 0.77 (0.13–2.54) 0.93 (0.30–2.24)	Age, sex, calendar period	Based on the Danish welding cohort study (Hansen, 1982) Limitations: limited exposure information; small number of cancers occurring in children fathered by welders

Table 2.3 (continued)

Reference, location, enrolment period/ follow-up, study design	Population size, description, exposure assessment method	Organ site/ cancer type	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Håkansson et al. (2005) Sweden 1985–1994 Nested case–control	Cases: 140 incident cases of tumours of the endocrine glands: adrenal glands (n = 29), parathyroid gland (n = 67), pituitary gland (n = 36), and other subtypes (n = 8) Controls: 1306 matched by sex and year of birth (3-year intervals) Exposure assessment method: questionnaire; assessment at the individual level from questionnaire and telephone interview with a contact person at the workplace; blind as to case–control status	All cancers combined: endocrine glands	Any welding: exposure (h/wk)			Sex, year of birth, solvent exposure, year of inclusion	Focus of the paper is exposure to ELF-EMF Strengths: individual assessment of welding type and welding frequency Limitations: no assessment of exposure to welding fumes; small number of exposed cases in subgroups
			Ever	25	2.1 (1.3–3.5)		
			> 0–10	8	1.9 (0.8–4.4)		
			> 10–30	7	1.9 (0.8–4.6)		
			> 30–40	10	2.5 (1.2–5.5)		
			Trend test P value, 0.01				
		All cancers combined: endocrine glands	Resistance welding: exposure (h/wk)				
			Ever	7	1.1 (0.5–2.4)		
			> 0–10	3	1.2 (0.3–4.3)		
			> 10–30	4	1.4 (0.5–4.1)		
			> 30–40	0	0 (0–0)		
			Trend test P value, 0.63				
		All cancers combined: endocrine glands	Arc welding: exposure (h/wk)				
			Ever	20	2.9 (1.6–5.3)		
			> 0–10	6	2.2 (0.8–6.0)		
			> 10–30	5	2.8 (0.9–9.1)		
			> 30–40	9	3.8 (1.6–9.3)		
			Trend test P value, 0.00				

[a] Included in "ever stainless steel welders"

[b] Total exposures (based on intensity and duration) of welding fumes were arbitrarily classified into three categories (value of 0, .0–5 and .5)

B[*a*]P, benzo[*a*]pyrene; CI, confidence interval; Cr, chromium; Cr(VI), hexavalent chromium; d, day(s); DOB, date of birth; ELF-EMF, extremely low frequency electromagnetic field; Fe_2O_3, iron oxide; h, hour(s); HL, Hodgkin lymphoma; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; MAG, metal active gas; MIG, metal inert gas; MMA, manual metal arc; mo, month(s); MOR, mortality; odds ratio; MS, mild steel; NHL, non-Hodgkin lymphoma; Ni, nickel; NO_x, nitrogen oxides; NR, not reported; NS, not significant; PAH, polycyclic aromatic hydrocarbon; SES, socioeconomic status; SIR, standardized incidence ratio; SMA, shielded metal arc; SMR, standardized mortality ratio; SS, stainless steel; TIG, tungsten inert gas; TWA, time-weighted average; vs, versus; wk, week(s); WIG, Wolfram-Inert-Gas welding; yr, year(s)

Table 2.4 Cancer and welding or exposure to welding fumes: studies included in the IARC multicentre cohort (Simonato et al., 1991)

IARC subcohorts	IARC cohort (population)	Publications of the IARC subcohorts	Comments
Denmark	4642	Hansen et al. (1996) 6180 male welders (not shipyard); 105 lung cancer cases	Follow up until 1968–1986; larger cohort
		Lauritsen & Hansen (1996) 94 lung cancer cases from Hansen et al. (1996)	Case–control analysis; adjusted for smoking
		Sørensen et al. (2007) 4536 male welders (non-shipyard); incidence	Follow-up 1968–2003 (cohort restricted to those who started working by 1960); longer follow-up; more detailed analysis on welding types; adjusted for smoking and asbestos
England	393	No separate report published	–
Finland	1808	Tola et al. (1988) 1689 male welders (1308 shipyard, 381 machine shop); mortality	Smoking data; machine shop only SIR (minimal exposure to asbestos); complete overlap in study population with the Simonato et al. (1991) publication
France	1190	Moulin et al. (1993) 2721 male welders; mortality	Smoking data; internal referent group; expanded and longer follow-up
Germany	1199	Becker (1999) 1213 welders; mortality	Internal referent group; indirect assessment of asbestos; longer follow-up
Italy	447	Merlo et al. (1989) 527 welders; mortality Puntoni et al. (2001) 493 welders; mortality	Probable overlap between these studies and the Italian subcohort, and between these two studies; extent of overlapping unknown
Norway	737	No separate report published	–
Scotland	237	No separate report published	–
Sweden	439	Milatou-Smith et al. (1997) 233 male welders exposed to high levels of Cr; 208 railroad track male welders; incidence	Longer follow-up; separate analysis for the two different cohorts

Cr, chromium; IARC, International Agency for Research on Cancer; SIR, standardized incidence ratio

or setting (shipyards, MS, SS). A limitation was the lack of data on asbestos exposure, since confounding by asbestos may partly explain the excess of cancer of the lung, and that exposure–response analyses were not reported in the publication although they were conducted.]

(ii) IARC subcohorts

See Table 2.4

Studies of the IARC subcohorts overlapped with the multicentre cohort, had smaller sample sizes, and were overall considered to be less informative than the pooled analyses. However, they provided additional data on smoking habits and asbestos exposure, and/or an extended follow-up. (See Table 2.4 for information on the overlap between the IARC study and the separate reports of its subcohorts.)

The French subcohort included in the IARC study was further extended by adding new factories and by updating the follow-up from 1975 to 1988 (Moulin et al., 1993). In addition, a group of manual workers in the same factories was used as an internal reference group and smoking data were collected. The relative risk (RR) of cancer of the lung for welders compared with the reference group was 1.29 (non-significant, *P* value and CI not reported). [The Working Group noted that the inclusion of shipyard workers, potentially exposed to asbestos, in the reference group may have resulted in an underestimation of the relative risk.] An indirect adjustment suggested that the slight differences in smoking habits between welders and referents would result in a relative risk of 1.06. Analyses by type of welding showed a higher standardized mortality ratio in MS than in SS welders. An increase in mortality from cancer of the lung with duration and time since first employment was observed only in MS welders [the three deaths from cancer of the lung in the group of SS welders did not allow meaningful analysis]. No deaths from cancer of the pleura occurred among welders (0.41 expected), whereas three deaths from cancer of the pleura were identified in the reference group, all shipyard workers (expected, 0.26). [The Working Group noted that these data suggest that exposure to asbestos is not likely to explain the lung cancer excess observed in non-shipyard MS welders. No actual data on asbestos exposure were available.]

Mortality from cancer of the lung was further evaluated in the two Swedish subcohorts (Sjögren, 1980; Sjögren et al., 1987; Milatou-Smith et al., 1997): a cohort of 233 SS welders, who welded mainly with coated electrodes and were exposed to high concentrations of hexavalent chromium; and a cohort of 208 railway track welders, exposed to MS fumes with low concentrations of hexavalent chromium. Exposure to asbestos was assumed to be very low in the two cohorts [the occurrence of mesothelioma was not reported]. When compared with the national population, an elevated standardized mortality ratio was observed in SS welders, whereas mortality from cancer of the lung was decreased in MS welders. The relative risk of cancer of the lung in SS welders compared with the group of MS welders was 3.98 (95% CI, 0.84–18.80). [The small numbers of deaths from cancer of the lung limited the interpretation.]

The subcohort of German arc welders (Becker et al., 1985) was successively updated by Becker et al. (1991) and Becker (1999). A cohort of turners was also followed up as an internal comparison group. In the last follow-up (Becker, 1999), elevated standardized mortality ratios were found among welders for cancers of the lung (SMR, 1.21; 95% CI, 0.80–1.75), bladder (SMR, 2.08; 95% CI, 0.67–4.84), and brain (SMR, 2.02; 95% CI, 0.55–5.19). Mortality from cancer of the lung was also higher in welders than in the comparison group (RR, 1.30; 95% CI, 0.80–2.12). No clear trend with duration of employment or time since first employment was suggested. Analyses by welding technique or by average daily welding time did not reveal strong differences in mortality from cancer of the lung or from other cancer sites, with the exception

of an increased standardized mortality ratio of cancer of the brain among welders only welding with coated electrodes (SMR, 6.18; 95% CI, 1.88–15.85). Seven deaths from mesothelioma occurred among welders (0.6 expected; SMR, 11.67; 95% CI, 4.69–24.04), compared with one death in the comparison group (1.0 expected). An indirect assessment of asbestos-related cancers showed that the increased mortality from cancer of the lung among welders could be entirely explained by asbestos exposure. [The Working Group agreed that exposure to asbestos is likely to explain the excess of cancer of the lung observed in this German part of the IARC cohort.]

Cancer incidence among Danish welders employed in SS or MS industrial companies has been reported (Hansen, 1982; Hansen et al., 1996; Lauritsen & Hansen, 1996; Sørensen et al. 2007). Shipyard welders were specifically excluded. Data on occupational and smoking history were collected by questionnaire at baseline. The study by Sørensen et al. (2007) is considered to be the most informative report of this population due to the longer follow-up period, better exposure assessment, reduced left truncation by excluding workers hired before 1960, and adjustment for tobacco smoking and exposure to asbestos; the analyses of incidence of cancer of the lung by Hansen et al. (1996) and the nested case–control study of mortality from cancer of the lung by Lauritsen & Hansen (1996) are therefore not reviewed separately. Findings for other cancer sites are reported from Hansen et al. (1996) because Sørensen et al. (2007) did not report the data (see Table 2.4 for the overlap between these studies). In the first report (Hansen et al., 1996), standardized incidence ratios for other cancer sites of interest were 1.19 (95% CI, 0.78–1.74; 26 exposed cases) for the urinary tract and 0.92 (95% CI, 0.50–1.54; 14 exposed cases) for lymphatic tissues. The number of cancers of the pleura did not exceed the expected number [the numbers were not reported]. Sørensen et al. (2007) reported data mainly for incidence of cancer of the lung, and incorporated a specific assessment of exposure to welding fumes [different from that used in the IARC multicentre study] based on a JEM using all exposure measurements specific to the calendar year in Denmark. An internal analysis was also conducted, adjusted for age, smoking, asbestos exposure from welding, and jobs prior to enrolment.

The standardized incidence ratio for cancer of the lung was increased in the whole cohort (SIR, 1.35; 95% CI, 1.06–1.70) and was higher among the group of welders who only welded MS (SIR, 1.59; 95% CI, 1.14–2.16) than among the group of ever SS welders (SIR, 1.15; 95% CI, 0.78–1.60). However, an elevated ratio was observed in ever SS welders who had ever conducted manual metal arc (MMA) welding (SIR, 1.46; 95% CI, 0.95–2.16).

In the internal comparison, the hazard ratio of cancer of the lung was not increased in ever SS welders when compared with MS welders who never welded SS (HR, 0.86; 95% CI, 0.52–1.42). The risk did not increase with increasing duration for any type of welding. The risk increased with cumulative exposure to welding fume particulates among ever SS welders, while no clear positive trend was found among MS welders who never welded SS. In the highest cumulative exposure category of SS welders, the adjusted hazard ratio was 2.34 (95% CI, 1.03–5.28). [The strengths of this study were the long follow-up, individual data on asbestos exposure and smoking, and individual semi-quantitative exposure assessment to welding fumes.]

(b) Shipyard workers

Seven cohort studies of shipyard workers which assessed exposure by occupation as a welder, including one in England, four in Norway, and two in Italy, were identified. The two Italian shipyard studies may overlap with each other (Merlo et al., 1989; Puntoni et al., 2001) and with the Italian subcohort of the IARC study [this

is not explicitly reported in the publications]. In addition, a series of studies of workers at a naval shipyard who overhauled nuclear submarines was identified in which semi-quantitative or quantitative exposure to welding fumes was assessed. Shipyard welders in these cohorts were primarily MS welders and asbestos was widely used in the shipyards. The IARC study (see Section 2.4.1 (a)) also reported a risk estimate for cancer of the lung and shipyard welders.

Cancer mortality was evaluated in a cohort of four craftsmen groups (1027 welders, 235 caulker burners, 557 platers, and 1670 electricians) employed in a shipyard in north-east England (Newhouse et al., 1985). Standardized mortality ratios (using local rates) for cancer of the lung were 1.13 (95% CI, 0.80–1.57; 26 exposed cases) for welders and 2.32 (95% CI, 1.33–3.74) for caulker burners. Caulker burners performed burning and oxypropane cutting tasks and were exposed to fumes that were similar in magnitude and composition to welding fumes; however, these tasks were performed outside, most likely reducing exposure to the fumes. No excess risk of cancer of the lung was found for the two other groups of craftsmen. [Although there were indicators of potential confounding from asbestos (mesotheliomas) or smoking, these indicators may not explain the excess risk of cancer of the lung because they occurred in craftsmen subgroups with and without increased risk of cancer of the lung. The study was limited by incomplete records of employment, the mobility of workers in moving to other shipyards, and short follow-up time (during which only 15.7% of the workforce had died).]

(i) Shipyards in Norway

Using a somewhat similar study design, three cohort studies reported on cancer incidence of welders employed at three different Norwegian shipyards (Melkild et al., 1989; Danielsen et al., 1993, 2000). The cohorts included all male workers employed as welders, identified from the shipyard personnel records for the specific enrolment dates that covered several decades (from the 1940s to early 1980s). Follow-up began in 1953 with the establishment of the Norway Cancer Registry; cancer cases that occurred from the first enrolment date (1940s) to 1953 were not known. Most of the welders were MS welders, which was the predominant type of metal welding used in Norway until the mid-1970s. Asbestos was used in the shipyards until the 1970s. Little information on the smoking habits of cohort members was available. [The Working Group noted that exposure monitoring data was not used in the exposure assessment. The limitations of the studies included potential confounding from tobacco smoking and exposure to asbestos. No mesotheliomas occurred among welders in all three cohorts.]

The earliest cohort study included MS workers at a shipyard in south-west Norway (Melkild et al., 1989). Compared with non-welding Norwegian men, welders had an elevated risk of cancer of the lung (SIR, 2.21; 95% CI, 0.88–4.54; 7 exposed cases) which was concentrated among workers employed as welders for 1–5 years.

The second cohort study included MS welders at a shipyard on the west coast of Norway (Danielsen et al., 1993). In external 15-year lagged analysis, the standardized incidence ratio for cancer of the lung was 3.08 (95% CI, 1.35–6.08; 8 exposed cases) for all welders and somewhat higher among welders exposed to "high" (SIR, 3.75; 95% CI, 1.38–8.19; 6 exposed cases) or "very high" levels (SIR, 4.0; 95% CI, 1.10–10.20; 4 exposed cases). Similar results were found in an internal analysis that used other shipyard workers (who were not welders, burners, or administrative workers) as the referent group and a 10-year lagged time. There was some evidence of an exposure-duration–response in the internal analysis (unlagged and 10-year lagged); risks were higher among those that had worked as welders for 5 years compared with those that had worked for fewer years.

A 1984 survey of smoking habits found that daily smoking was 10–20% higher among Norwegian shipyard production workers and welders than the general public, and these smoking differences were estimated to explain a 25% increase risk (e.g. SIR, ~1.25). [The advantages of this study were lagged analysis by exposure to "high" and "very high" levels (although based on duration), internal analyses which helped to mitigate concerns for tobacco smoking and exposure to asbestos, and information, although limited, on smoking habits. Non-welding shipyard workers were presumed to have similar smoking habits as for welders.]

The third cohort was of MS welders at a shipyard on the island Stord (Danielsen et al., 2000). An excess risk of cancer of the lung occurred in both external (SIR, 1.27; 95% CI, 0.58–2.42) and internal analyses, using other shipyard workers as a referent, among welders employed for less than 2 years (RR, 2.42; 95% CI, 0.73–8.01; 3 exposed cases) and for more than 15 years (RR, 1.90; 95% CI, 0.67–5.38; 4 exposed cases). [The small numbers of cases limited the ability to look at employment-duration–response relationships.] The differences in risk of cancer of the lung among different types of shipyard workers were not explained by previous work history. In 1976 and 1984 surveys of the shipyard, the proportion of shipyard welders who were daily smokers was similar to shipyard non-welders, and approximately 10% higher than Norwegian men.

Another study in Norway investigated cancer incidence among shipyard welders employed for more than 10 years at 15 shipyard companies, and examined for siderosis in 1975 (Danielsen et al., 1998). Welders who had quit welding before 1975 because of health problems were not included in the study. The predominant welding technique was electric arc on MS; SS welding was introduced after 1975. Welders had an increased risk of cancer of the lung (SIR, 1.55; 95% CI, 0.74–2.84; 10 exposed cases) compared with non-welding Norwegian males. In analyses by time since first exposure, the highest risk was among those welders for whom 40 years had passed since their first exposure (SIR, 1.93; 95% CI, 0.40–5.64; 3 exposed cases); however, the number of exposed cases was small for each exposure period. No cases of cancer of the lung occurred among 23 welders who had siderosis. Asbestos was used in shipyards, although no cases of mesothelioma were reported among welders. [The Working Group noted the potential for a healthy worker effect, and potential confounding from exposure to asbestos and tobacco smoking.]

(ii) Shipyards in Genoa, Italy

Cancer mortality was evaluated in a cohort of active and retired 274 oxyacetylene (mainly MS) welders and 253 electric arc (mainly SS) welders employed at a shipyard in Genova, Italy, from 1930 to 1980 (Merlo et al., 1989). Welders were presumed to be potentially exposed to low concentrations of asbestos fibres according to company records. [The Working Group questioned the validity of this statement.] An increased risk of mortality due to cancer of the lung (reported as respiratory tract) was found among oxyacetylene welders in both external (SMR, 2.34; 95% CI, 1.21–4.09; 12 exposed cases) and internal analyses (RR, 2.45; 95% CI, 0.77–7.83) using electric arc welders (mainly SS) as the referent group, since they mainly worked outdoors and were therefore presumed to have lower exposures. Oxyacetylene welders worked inside oil tankers, and were assumed to be exposed to higher levels of gases and fumes than electric arc workers who worked in open spaces. No increased risk of cancer of the lung was found among electric arc workers compared with the general population. Excess mortality from cancer of the lung due to tobacco smoking was modelled to be equivalent to an excess relative risk of 21–30% (depending on the smoking habits of the referent population); information on smoking habits was ascertained from a 1986 survey. [The Working Group noted that the use of internal analyses

reduces concerns for potential confounding from lifestyle factors such as tobacco smoking and exposure to asbestos, which were thought to be similar between the two groups of welders. Follow-up did not start until 30 years after first date of enrolment, meaning that deaths resulting from cancer of the lung during 1930–1960 may have been missed.]

The mortality in a cohort of shipyard workers employed at the harbour of Genoa, Italy, from 1960 to 1980, including 267 arc welders and 228 gas welders, was studied and subsequently updated by Puntoni et al. (1979, 2001). Mortality from cancer of the lung was increased in both arc welders (SMR, 1.64; CI not reported) and gas welders (SMR, 1.57). Electric arc welders also showed increased mortality for cancers of the bladder (SMR, 2.74) and kidney (SMR, 4.0). Elevated standardized mortality ratios were observed among gas welders for cancers of the larynx (SMR, 2.0) and kidney (SMR, 3.57). Three deaths from cancer of the pleura (SMR, 3.77) and one death from asbestosis were observed among electric arc welders; one death from cancer of the pleura (SMR, 1.69) occurred among gas welders. [The Working Group inferred from the cancer of the pleura and asbestosis deaths that this cohort may have experienced substantial asbestos exposure, which limits the interpretation of excesses of cancer of the lung in welders. The Working Group also suspected some overlap with the study by Merlo et al. (1989) described in the paragraph above.]

(iii) Portsmouth Naval Shipyard

The risk of cancer of the lung and leukaemia was investigated in a cohort of workers monitored for radiation exposure at the Portsmouth Naval Shipyard in Maine, USA, initiated to study the effects of ionizing radiation exposure (Yiin et al., 2005). The main objective was to explore dose–response relationships between ionizing radiation and risk of cancer, while adjusting for previously unanalysed confounders. Semi-quantitative exposure scores were calculated for asbestos and welding fumes. After adjustment for socioeconomic status (as a proxy for smoking) and exposure to asbestos and radiation, the risk of cancer of the lung increased for workers exposed to welding fumes, although the relative risks were similar in the low (RR, 1.45; 95% CI, 1.1–1.92) and high (RR, 1.5; 95% CI, 1.09–2.06) categories of exposure.

A nested case–control study of cancer of the lung (Yiin et al., 2007) was also conducted in this cohort, extended to non-radiation workers, with an improved quantitative assessment of exposure to welding fumes, asbestos, and the chromium and nickel content of welding fumes (Seel et al., 2007). This study superseded a previous nested case–control study of cancer of the lung within the same cohort (Rinsky et al., 1988). Exposure estimates in the study population (Zaebst et al., 2009) showed that a large proportion of workers were exposed to welding fumes (53%) and to asbestos (64%). As most of the welding in this shipyard was on MS, exposure to chromium and nickel in welding fumes was much less frequent (6% and 8% of the workers, respectively), and these exposures were not considered in the epidemiological analysis. Socioeconomic status and birth cohort were used as a surrogate for smoking. When examining risk of cancer of the lung with exposure to welding fumes on a continuous scale (per 1000 mg-days/m^3), the multivariate odds ratio was 1.01 (95% CI, 0.98–1.04).

Although mortality from leukaemia was also examined in this cohort, neither the cohort analysis (Yiin et al., 2005) or the nested case–control study on leukaemia (Kubale et al., 2005) examined the association with exposure to welding fumes. However, in a previous case–control study of leukaemia within the Portsmouth Naval Shipyard cohort (Stern et al., 1986), an increased risk of leukaemia (OR, 3.19; 95% CI, 1.09–9.37), particularly myeloid leukaemia (OR, 6.23; 95% CI, 1.64–23.64), was found among welders after adjustment for radiation exposure,

employment as electrician, and exposure to solvents. [The Working Group noted that the focus of the Portsmouth Naval Shipyard study was ionizing radiation exposure; despite the comprehensive exposure assessment, the effects of exposure to welding fumes were not explored in detail.]

(c) Other welding industries

The other cohort studies evaluated cancer mortality or incidence in welders in a variety of industries including heavy equipment manufacturing plants, automobile assembly, stamp and engine plants, foundries, metal shops, telephone line workers, and nuclear plants. Some studies assembled workers from a large number of companies by using occupational registries or union records. Studies reporting on cancer of the lung are organized based on information regarding potential exposure to asbestos, and then by chronological date. Studies of welders with minimum exposure to asbestos include a cohort of automobile assembly and stamp workers (Park et al., 1994) and a cohort of heavy equipment manufacturing workers (Steenland, 2002). Exposure to asbestos may have been more substantial in the Norwegian study of boiler welders (Danielsen et al., 1996) and in a study of French telephone line workers (Meguellati-Hakkas et al., 2006). The remaining studies provided no or little information (such as use of asbestos or cases of mesothelioma) to evaluate potential confounding from exposure to asbestos (Dunn & Weir, 1968; Polednak, 1981; Steenland et al., 1986; Sorahan et al., 1994; Austin et al., 1997). With the exception of the French study of telephone line workers which assessed cumulative exposure to welding fumes, all of the other studies assessed exposure by occupation as a welder.

Park et al. (1994) conducted a cohort study of hourly employees who worked at an automotive metal stamping and assembly complex. Welding in the stamp plant was performed on sheet metal. Using controls who did not die from cancers of the lung, stomach, pancreas, and haematopoietic system, standardized mortality odds ratio (MOR) for cancer of the lung was significantly elevated for welding (MOR, 2.73; 95% CI, 1.20–6.30; 7 exposed deaths) and increased with increasing duration of employment in welding areas (although based on a small number of deaths). The highest mortality odds ratios were reported in logistic regression models that combined previous welding employment with employment in the stamping plant and models using short latency weighting. [The Working Group noted that potential exposure to asbestos was limited to a few workers in assembly operations and unlikely to be a concern for welders. No information was available on smoking habits; however, internal analyses helped to mitigate concerns from tobacco smoking. The limitations of the study included the healthy worker effect, a young cohort, and a short follow-up (5% of the cohort had died).]

Cancer mortality was evaluated in a cohort of male MS welders and non-welders employed at three heavy equipment manufacturing plants in Illinois, USA. Importantly, these workers were not exposed to asbestos, nickel, or chromium (Steenland, 2002). Workers who only worked as flame-cutters or burners, or on maintenance, were excluded. The 2002 study updated the findings of the original study (Steenland et al., 1991) with 10 years of additional follow-up. The average time since first exposure was 20 years, and 23% of the population had died. An excess risk of mortality from cancer of the lung was observed among welders compared with men in the general population (SMR, 1.47; 95% CI, 1.19–1.79; 97 deaths) or with male non-welder workers (standardized rate ratio (SRR), 1.22; 95% CI, 0.93–1.59). In internal analysis using a 10-year lagged time, standardized rate ratios increased with increasing employment duration with the exception of the longest employment duration, which showed no

increased risk. Trends for years of exposure (*P* for trend, 0.33) or log years of exposure (*P* for trend, 0.17) were not statistically significant. Based on a cross-sectional survey, welders and non-welders in the cohort smoked more than the general population. The authors estimated that smoking differences would result in a risk ratio of 1.08 between welders and non-welders within the cohort, and 1.23 between cohort welders and the US population. [The strengths of the study included an internal comparison group, information on smoking habits, little or no exposure to asbestos, a relatively large number of cases, and adequate follow-up. The major limitation was the lack of semiquantitative or quantitative exposure assessment to welding fumes.]

Danielsen et al. (1996) evaluated cancer incidence among welders listed in the Norway Registry of Boiler Welders from 385 different businesses throughout Norway. Standardized incidence ratios for cancer of the lung were 1.33 (95% CI, 1.00–1.74; 50 exposed cases) for all boiler welders and 1.03 (95% CI, 0.41–2.15; 6 exposed cases) for the subset of SS welders. In analysis by date of first registration, boiler welders who first registered during the periods 1950–1959 and 1970–1982 had an increased risk of cancer of the lung. Asbestos was used until the mid-1970s and an excess of pleural mesotheliomas was observed among welders (3 cases among boiler welders and 1 case among SS welders). The standardized incidence ratio for cancer of the kidney for boiler welders was 1.78 (95% CI, 1.07–2.78; 19 exposed cases).

A cohort study of cancer mortality was conducted among 34 305 French male telephone line workers exposed to low concentrations of asbestos during the installation of telephone cables (Meguellati-Hakkas et al., 2006). The cohort included both prevalent hires (as of 1978) as well as men newly hired during 1978–1994, and the workers were followed until 1996. In multivariable models adjusting for age, calendar period, and occupational co-exposures (asbestos, polycyclic aromatic hydrocarbons (PAHs), and engine exhausts), small, non-significant elevated risks of cancer of the lung were observed in all cumulative exposure categories of arc welding; the risk was somewhat higher in the longest exposure duration category (RR, 1.4; 95% CI, 0.7–2.8; 63 deaths). Exposure to asbestos but not engine exhaust or PAHs was associated with mortality from cancer of the lung in this study. [The advantages of this study were the use of a semiquantitative exposure assessment to arc welding and the large numbers of deaths from cancer of the lung for mortality analysis. The focus of the study was exposure to asbestos; exposure to welding fumes was included in the analyses as a potential confounder for the association with cancer of the lung. Exposure to welding fumes did not appear to be substantial in this cohort; 80% of deaths occurred in workers exposed to less than 0.04 cumulative exposure years of welding.]

Dunn & Weir (1968) conducted a prospective study of male workers employed in several different occupation groups in California, USA, chosen based on case–control studies which suggested a possible link with risk of cancer of the lung. The workers were selected from union mailing lists and questionnaires. No excess deaths from cancer of the lung occurred among the combined category of welders and burners compared with the expected deaths (adjusted for age and smoking) for the total study population (e.g. workers). [The Working Group noted that expected numbers included workers that were exposed to asbestos, and that the follow-up period was short (average 7 years).]

A cohort study was conducted of white male welders employed at three Oak Ridge nuclear plants in the USA (Polednak, 1981). The welders were divided into two groups: the first group worked at a facility (K-25 plant) that welded nickel-alloy pipes; and the second group ("other welders") worked with MS, SS, and other metals. Mortality from cancer of the lung was elevated in both type of welders, and was somewhat higher

among the "other welders" group (SMR, 1.75; 95% CI, 0.84–3.22; 10 exposed deaths) than the nickel-alloy workers ([SMR, 1.26; 95% CI, 0.51–2.62]; 7 exposed deaths); most of the risk in the latter group occurred in workers who had been employed for more than 50 weeks. [The available data on tobacco smoking suggested that a greater proportion of welders smoked compared with the general public, and tobacco smoking may be a potential confounder for cancer of the lung in this welder group. In contrast, nickel-alloy workers had smoking habits which were similar to that of the general public. The excess risk of cancer of the lung among K-25 plant workers may have been due to exposure to nickel; concentrations of nickel were above the National Institute for Occupational Safety and Health recommended standard of 0.015 mg/m^3. Other study limitations were the small numbers of exposed cases and the potential for a healthy worker effect (SMR, 0.87 for all causes). No information was provided about exposure to ionizing radiation.]

Sorahan et al. (1994) updated a cohort of foundry workers previously investigated by Fletcher & Ades (1984) and Sorahan & Cooke (1989). Workers were classified into 25 occupational categories, according to the first job held. An increased standardized mortality ratio for cancer of the lung was shown for "burning and welding" in the fettling shop, but higher standardized mortality ratios were found for other occupations in the fettling shop. Welding in "pattern/machine/maintenance/inspection" was not associated with elevated mortality from cancer of the lung. The numbers of deaths from cancer of the stomach were below expectations in both groups. Mortality from other cancers was not reported by occupational category. [The Working Group noted that the cohort included only a small number of welders, and no exposure data were available. However, at least some workers would have been exposed to foundry processes.]

A cohort of members of a metal trade union, including welders and non-welders, was investigated by Beaumont & Weiss (1980, 1981). Welders had an elevated mortality from cancer of the lung (SMR, 1.32), which increased with time since first employment (SMR, 1.74 for 20 years since first employment). A reanalysis of these data (Steenland et al., 1986) using Cox regression estimated the cancer of the lung rate ratio for welders versus non-welders as 1.29 (P = 0.17; CI not reported). [No exposure data were available.]

A nested case–control study of cancer of the lung (231 deaths, 408 controls) was conducted among workers at a foundry and two engine plants (Austin et al., 1997). Work histories were obtained from plant personnel files; smoking data were collected by telephone interview of next-of-kin for the cases, and of the subject (64%) or a next-of-kin for controls. After adjustment for smoking, no elevation of mortality from cancer of the lung was found in the welding group. This study did not identify any specific job or plant area with an increased risk of cancer of the lung.

(d) Less informative industrial cohort studies

The Working Group reviewed several additional studies of welders that were considered to be less informative because they were not specific to welding (McMillan & Pethybridge 1983; Silverstein et al., 1985; Verma et al., 1992; de Silva et al., 1999; Krstev et al., 2007; Wu et al., 2013) and/or had other limitations in the design or analysis (McMillan & Pethybridge, 1983; Verma et al., 1992; de Silva et al., 1999). Two studies were limited in their ability to detect an association between cancer of the lung and welding; one study included some welders in the reference group (McMillan & Pethybridge, 1983) and the other study was very small and had inadequate follow-up (de Silva et al., 1999). In the study by Verma et al. (1992), welders worked in a tank house in the vicinity of tar-laying operations and were exposed to high levels of PAHs (which were measured in the study).

(e) Cohort studies that did not report on cancer of the lung

See Table 2.3

Howe et al. (1983) reported on mortality from cancer of the brain of a cohort of male pensioners exposed to welding fumes during employment with the Canadian National Railway company over the period 1965–1977. The standardized mortality ratio for cancer of the brain was 3.18 (95% CI, 1.53–5.86; 10 exposed deaths). [The Working Group noted that there was potential for exposure misclassification due to a lack of detailed information or lifetime work history. No information was available on which occupations were considered to entail exposure to welding fumes, or on smoking and potential co-exposures.]

A study of paternal exposure to welding and childhood malignancies was conducted among a cohort of men employed at 74 Danish MS or SS manufacturing companies (Bonde et al., 1992). The study was based on the Danish welding cohort study (Hansen et al., 1996). Standardized incidence ratios were close to unity for childhood cancers for offspring of SS welders (2 cases of cancer) and those of MS welders (4 cases of cancer). [The study had limited power to detect childhood cancer risks.]

To examine cancer incidence in workers exposed to high levels of extremely low frequency electromagnetic fields (ELF-EMF), a cohort with an elevated prevalence of electric resistance welders was established (Håkansson et al., 2002). The cohort comprised all subjects ever employed during 1985–1994 in industries assumed to use electric resistance welding (537 692 men and 180 29 women). A case–control study on tumours of the endocrine glands was nested in this cohort, including 140 cases and 1306 controls frequency-matched by sex and age (Håkansson et al., 2005). An increased risk of tumours of the endocrine glands was found among welders (OR, 2.1; 95% CI, 1.3–3.5), which was limited to arc welding (OR, 2.9; 95% CI, 1.6–5.3). There was no evidence of an association with electric resistance welding (OR, 1.1; 95% CI, 0.5–2.4). Among arc welders, the risk increased with the average number of welding hours per week (*P* for trend, 0.63). Elevated odds ratios were observed for all subtypes (adrenal glands, parathyroid gland, pituitary gland). [Considering the elevated risks of arc welding and not electric resistance welding, ELF-EMF does not appear to explain these results.]

2.4.2 Population-based cohorts

See Table 2.1

Several studies evaluated the risk of exposure to welding fumes or occupation as a welder in population-based cohorts. In general, there was lower confidence in the exposure information than from industrial cohorts. The studies include: (1) three studies that used a JEM to assess exposure to welding fumes based on occupational questionnaire data; (2) two record-linkage studies; (3) a prospective cohort evaluating occupation and different types of cancer in Europe; and (4) a prospective cohort study evaluating the incidence of cancer of the lung among frequent smokers enrolled in a lung screening randomized trial.

A cohort of 869 men from the town of Zutphen, the Netherlands, born between 1900 and 1920, was used to compare the performance of different methods of exposure assessment in an analysis of incidence of cancer of the lung (Kromhout et al., 1992). Exposure to welding fumes and soldering fumes was assessed with a general JEM (Pannett et al., 1985) and a population-specific JEM, developed from self-reported exposures collected in a sample of the cohort. No clear associations were found between risk of cancer of the lung and exposure to fumes evaluated by the general JEM. When exposures were assessed by the population-specific JEM, elevated hazard ratios for cancer of the lung,

adjusted for smoking, were found for exposure to welding fumes (HR, 1.93; 95% CI, 1.05–3.55) and soldering fumes (HR, 2.24; 95% CI, 1.17–4.29).

A population-based cohort study was conducted in the Netherlands among 58 279 men, aged 55–69 years, who completed a self-administered questionnaire in 1986 and were followed up for incidence of cancer of the lung until 1990 (van Loon et al., 1997a). [The follow-up of this cohort was short and exposure was assessed retrospectively at baseline.] After adjustment for smoking, diet, and other occupational exposures, the relative risk for ever exposure to welding fumes was not increased (RR, 0.86; 95% CI, 0.46–1.58), and no clear trend was observed with the score of cumulative exposure. In the same cohort, the adjusted relative risk for incidence of cancer of the prostate (Zeegers et al., 2004) was 1.41 (95% CI, 0.51–3.88; 12 exposed cases) for those ever employed as a welder.

The cohort of 1.2 million economically active Finnish men who participated in the 1970 national census was followed for incidence of cancer of the lung during 1971–1995 (Siew et al., 2008). The Finnish job-exposure matrix (FINJEM) was linked to the occupation held for the longest time up to 1970 to assess cumulative exposure to welding fumes, iron fumes, asbestos, silica, chromium, nickel, lead, benzo[*a*]-pyrene, and smoking. Relative risks adjusted for age, smoking, socioeconomic status, and exposure to asbestos and silica were estimated using the Poisson regression. The standardized incidence ratio of cancer of the lung was 1.31 (95% CI, 0.84–1.95) among welders in the building industry, 1.05 (95% CI, 0.69–1.55) for welders in shipyards, 1.39 (95% CI, 1.14–1.69) among welders not otherwise specified, and 0.95 (95% CI, 0.78–1.15) among SS welders. The risk for cancer of the lung increased as the cumulative exposure to welding fumes increased, and the dose–response relationship was more evident for squamous cell carcinomas than for other histological types. An increase in risk of cancer of the lung with cumulative exposure to iron fumes was also found in this study. Exposures to iron fumes, chromium, nickel, lead, and benzo[*a*]-pyrene were so strongly correlated with exposure to welding fumes that they could not be included in the same statistical model. To assess any potential confounding effect, additional analyses excluding workers with exposures to moderate or high levels of iron fumes, chromium, nickel, lead, and benzo[*a*]pyrene were performed. These exclusions did not markedly change the estimated risks associated with exposure to welding fumes. [The main strengths of this study were the large number of workers, the semi-quantitative assessment of exposure to welding fumes, and the availability of data on major potential confounders.]

Pukkala et al. (2009) linked individual records of 14.9 million people aged 30–64 years in the 1960, 1970, 1980/1981, and/or 1990 censuses in Denmark, Finland, Iceland, Norway, and Sweden to the 2.8 million incident cancer cases recorded in cancer registries for these people in a follow-up study until around 2005. The original national occupation codes were converted to a common classification with 53 occupational categories. As Danish welders were included in the broader group of mechanics workers, they were excluded from the analysis of welders which concerned 74 857 men and 2606 women. Results were reported for 49 cancer sites, some of them further divided according to subsite and histological type. Among men, elevated standardized incidence ratios were found for cancer of the lung (SIR, 1.33; 95% CI, 1.27–1.40), mesothelioma (SIR, 1.79; 95% CI, 1.44–2.20), cancer of the kidney (SIR, 1.25; 95% CI, 1.14–1.36), particularly cancer of the renal pelvis (SIR, 1.39; 95% CI, 1.05–1.80), and acute myeloid leukaemia (SIR, 1.23; 95% CI, 0.99–1.52). Thirty-six cases of ocular melanoma were observed (SIR, 1.07; 95% CI, 0.75-1.48). Among women the number of cases was small for most cancer sites, but an increased risk of cancer of the lung was also reported (SIR, 1.70;

95% CI, 1.10–2.51). No case of mesothelioma was observed among female welders (vs 0.3 expected). In men, elevated standardized incidence ratios were observed for all histological types of cancer of the lung, whereas in women increased risk was limited to histological types other than adenocarcinoma. No data on smoking habits were available, but an earlier study based on a previous follow-up of the Norwegian component of this study (Haldorsen et al., 2004) showed that, in male welders, indirect adjustment for smoking increased the cancer of the lung standardized incidence ratio from 1.31 to 1.48.

The Swedish component of this study overlaps several other record-linkage studies conducted in Sweden (Englund et al., 1982; Sjögren & Carstensen, 1986; McLaughlin et al., 1987; Alguacil et al., 2003). These studies were considered to be subsumed by the Pukkala et al. (2009) study, and are not discussed further.

Cancer risks associated with welding were evaluated by linking records on current job from the 1991 Canadian census of 1.1 million male workers with the Canadian Cancer Registry, and followed up until 2010 (MacLeod et al., 2017). Welders and occasional welders were compared with non-welders. Among welders, elevated risks were found for cancer of the lung (HR, 1.16; 95% CI, 1.03–1.31), mesothelioma (HR, 1.78; 95% CI, 1.01–3.18), cancer of the bladder (HR, 1.40; 95% CI, 1.15–1.70), and cancer of the kidney (HR, 1.30; 95% CI, 1.01–1.67). Five cases of ocular melanoma were observed (HR, 1.55; 95% CI, 0.64–3.76). The risks of cancer of the lung and mesothelioma were increased among occasional welders, but no excess risks were found for other cancer sites. Analyses by industry showed higher hazard ratios for cancer of the lung among welders in vehicle repair, shipbuilding and repair, and construction. Welders in construction also had an elevated risk of mesothelioma. Less than 5 mesothelioma cases were observed in other industries, and risk estimates were not reported. The risk of cancers of the bladder and kidney was increased for welders in all industry groups. By histological type of cancer of the lung, the strongest associations were found for carcinomas of the small cell and squamous cell. In analyses restricted to blue-collar workers, risk estimates were slightly attenuated for cancer of the lung and mesothelioma, and slightly increased for cancers of the bladder and kidney, and ocular melanoma.

Associations between occupation and cancer incidence were investigated in several studies which were part of the European Prospective Investigation into Cancer and Nutrition (EPIC). These studies assessed the risk of cancer of the lung (Veglia et al., 2007), cancer of the bladder (Pesch et al., 2013), lymphoma (Neasham et al., 2011), and leukaemia (Saberi Hosnijeh et al., 2013). Data on 52 a priori hazardous job titles were collected through standardized questionnaires. After adjustment for smoking, increased risks of cancer of the lung were associated with having ever worked as a welder (RR, 1.67; 95% CI, 1.20–2.30) or in the welding shop (RR, 1.55; 95% CI, 1.20–2.10). Elevated risks of cancer of the bladder were also found for welders (RR, 1.39; 95% CI, 0.85–2.27) and for those who worked in a welding shop (RR, 1.54; 95% CI, 1.01–2.34). There was no indication of an increased risk of leukaemia or lymphoma in welding occupations.

Wong et al. (2017) analysed the association between the incidence of cancer of the lung and occupation as metalworker (foundry and welders) in a cohort of frequent smokers who were enrolled in 33 centres across the USA, included in the National Lung Screening Trial (NLST). (Workers from both arms of the randomized control trial were combined in the analysis after 5–7 years of follow-up.) The adjusted hazard ratio of incidence of cancer of the lung for ever employed as a welder (excluding foundry workers and those who previously worked in high-risk occupations, such as asbestos workers) was 1.12 (95% CI, 0.91–1.37; 101 exposed cases). In analyses by cancer subtypes, the strongest association

with welding was found for squamous cell carcinoma (adjusted HR, 1.91; 95% CI, 1.13–3.22; 11 cases) for those who had ever worked as a welder for 25 years or more, compared with workers without a history of metalwork (*P* for trend for employment duration, 0.003). [The strengths of this study included its prospective design, large number of cases, information on cancer of the lung subtypes, smoking habits, past exposure to asbestos and other carcinogens, and multivariate and sensitivity analyses. The study was limited by its short follow-up and lack of detailed exposure information for welding and occupational co-exposures.]

2.5 Case–control studies

2.5.1 Cancer of the lung

See Table 2.5 and Table 2.6

The Working Group identified more than 20 cancer of the lung case–control studies that reported on the association between welding-related occupations or exposure to welding fumes and cancer of the lung (Table 2.5). These include a pooled analysis of case–control studies (Kendzia et al., 2013) and a multicentre case–control study ('t Mannetje et al., 2012). The study by 't Mannetje et al. (2012) was included in the pooled analysis by Kendzia et al. (2013) for occupation as a welder; it is included in this review as it presents further analysis on exposure to welding fumes that was not presented in the analysis by Kendzia et al. (2013). We excluded studies that were superseded by subsequent publications using the same data (Jöckel et al., 1994; Richiardi et al. 2004; Brenner et al., 2010; Guida et al., 2011), but we retained studies (listed in Table 2.5) that were included in the pooling study if the original publication provided additional information. We also excluded studies whose job-exposure classification was so broad that it did not allow an assessment of the risk among welders specifically (Matos et al., 1998; Droste et al., 1999). Two studies conducted in different US coastal regions, with a reference category restricted to shipyard workers that consisted of non-welders likely exposed to asbestos (Blot et al., 1978, 1980), were also excluded. A case–control study that only included welders as cases and controls (Hull et al., 1989) and a case–case study (Paris et al., 2010) are not reported in Table 2.5 because they do not allow estimation of the risk of cancer of the lung among welders per se.

Most case–control studies reported elevated risks for workers employed as welders who reported welding as their job task, or workers who reported exposure to welding fumes (Breslow et al., 1954; Gerin et al., 1984; Buiatti et al., 1985; Kjuus et al., 1986; Lerchen et al., 1987; Schoenberg et al., 1987; Benhamou et al., 1988; Ronco et al., 1988; Zahm et al., 1989; Morabia et al., 1992; Jöckel et al., 1998; Pezzotto & Poletto, 1999; Gustavsson et al., 2000; Soskolne et al., 2007; Brenner et al., 2010; Corbin et al., 2011; Calvert et al., 2012; 't Mannetje et al., 2012; Tse et al., 2012; Vallières et al., 2012; Kendzia et al., 2013; Luqman et al., 2014; Matrat et al., 2016), but many of the observed associations were statistically non-significant [probably due to small sample sizes]. Two studies reported risk estimates close to unity (Pezzotto & Poletto, 1999; Vallières et al., 2012), but none reported odds ratios below unity for ever welding. Most studies were able to adjust for smoking, but adjustment for occupational co-exposures, in particular adjustment for asbestos exposure, was possible in fewer studies. Most studies report risk estimates only for men due to an insufficient number of women in this occupational group.

The SYNERGY pooling study with 15 483 male cases (568 of them being welders) and 18 388 male controls (427 of them being welders) is one of the most informative case–control studies on welding occupation and cancer of the lung (Kendzia et al., 2013). This analysis based on job title included adjustment for age, study centre, smoking, and occupations known to be

associated with cancer of the lung (so-called List A jobs, many of them entailing exposure to asbestos) resulted in an adjusted odds ratio of 1.50 (95% CI, 1.20–1.88) for the longest held job as a welder. [The Working Group noted that this study was adjusted for asbestos exposure, but not specifically for welding-related asbestos exposure.] Jobs entailing occasional welding were also associated with elevated risks, but the risk estimates were smaller compared with that of regular welders. Compared with never welders, the odds ratios increased with duration of occupation as a welder from 1 to less than 3 years (OR, 1.14; 95% CI, 0.80–1.61), 3 to less than 10 years (OR, 1.46; 95% CI, 1.26–1.91), 10 to 25 years or less (OR, 1.38; 95% CI, 1.06–1.79), to more than 25 years (OR, 1.77; 95% CI, 1.31–2.39) (*P* for trend, < 0.0001). When stratified by histological type, odds ratios appeared to be strongest for carcinomas of the squamous cell and small cell and somewhat lower for adenocarcinomas. For never-smoker welders, the odds ratio for cancer of the lung was 2.04 (95% CI, 1.16–3.61). The overlap between this biggest pooling study (SYNERGY) (Kendzia et al., 2013), which includes 22 case–control studies conducted between 1985 and 2010, and the overlap among these other studies, is summarized in Table 2.6. Results are reported by the individual studies included in the SYNERGY pooled analysis when not reported in the pooled analysis. The study by Schoenberg et al. (1987) was not included in the pooled analysis by Kendzia et al. (2013).

Confounding by asbestos is a major concern in the assessment of the association between welding and cancer of the lung. Workers may be exposed to asbestos as a bystander in shipyards, but also from heat-protective clothing or blankets used to cover the weld to prevent abrupt cooling. Studies that controlled for asbestos, and additionally for smoking, are described in the following.

A study in the USA (Schoenberg et al. 1987) not included in the analysis by Kendzia et al. (2013) reported an odds ratio of 3.5 (95% CI, 1.8–6.6) in welders overall and an odds ratio of 2.5 (95% CI, 1.1–5.5) in welders not exposed to asbestos, where exposure was classified by an industrial hygienist.

In a German study, Jöckel et al. (1998) reported a detailed assessment of exposure to welding fumes and exposure to asbestos through a set of job-specific questionnaires (around 20 questions) and a supplementary questionnaire on welding. After adjustment for smoking and asbestos exposure, the odds ratio for ever being employed as a welder was 1.93 (95% CI, 1.03–3.61). In this study, ever being exposed to welding fumes and gases was associated with a slightly elevated risk (OR, 1.25; 95% CI, 0.94–1.65), but no dose–effect relationship was seen with cumulative exposure expressed in lifetime hours of welding after adjustment for smoking and asbestos. Odds ratios were reported of 1.38 (95% CI, 0.91–2.09) for less than 1000 hours, 1.14 (95% CI, 0.73–1.79) for 1000–6000 hours, and 1.10 (95% CI, 0.73–1.66) for more than 6000 hours. [There is partial overlap with the study by Kendzia et al. (2013).]

A Swedish study reported that 62% of welding entailed asbestos exposure, according to a detailed exposure assessment by an industrial hygienist (Gustavsson et al., 2000). Based on a self-completed questionnaire that gathered information on the lifetime occupational history, including company name and location, occupation, and work tasks for each job held for at least 1 year, an industrial hygienist performed a case-by-case classification of the intensity and probability (0, 20, 50, or 80%) of exposure to 7 agents. Intensity units for welding were assigned as 1, 5, and 15, where 15 units corresponded to full-time employment as a MMA welder. Cumulative exposure was calculated as the product of intensity, probability, and duration of exposure over all job periods. In analysing the dose–effect relationship with cumulative welding exposure, Gustavsson et al. (2000) did not observe

Table 2.5 Case–control studies on cancer of the lung and welding or exposure to welding fumes

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Breslow et al. (1954) California, USA 1949–1952	Cases: 518 histopathologically verified cases of lung cancer, 25 of them women Controls: 518 patients admitted to the hospital around the same time of the same age (within 5 yr), sex, and race for a condition other than cancer or a chest disease, chosen at random as a matched control for each case Exposure assessment method: questionnaire; job title	Non-welder or flame cutter (ref.)	508	[1]	None	Strengths: careful in-person interviews; assessment of welding as a task; non-consideration of short-term occupations Limitations: no age-adjustment; crude adjustment for smoking in five categories; smoking status missing in 5% of subjects; small number of welders
		Welder or flame cutter of > 5 yr	10	[10.2 (1.3–79.8)]		
		Non-welder (ref.)	479	[1]	None	
		Welders and sheet metal workers doing welding > 5 yr	14	[7.2 (1.6–31.7)]		
		Welders and sheet metal workers doing welding > 5 yr	14	[7.66 (1.36–43.23)]	Smoking	
Gerin et al. (1984) Montreal, Canada 1979–1982	Cases: 246 male cancer cases aged 35–70 yr from entire Montreal population at major hospitals for 12 tumour sites identified through hospital pathology department (1343 patients of whom 246 were diagnosed with lung cancer) Controls: 1241, 144 general-population healthy subjects and all cases of the remaining 11 tumour sites Exposure assessment method: questionnaire; individual expert assessment of exposure (focusing on Ni and Cr) based on job histories and a semi-structured probing section	Welders			Age, smoking, SES, ethnicity	Overlaps with the study of Vallières et al. (2012) and therefore also with the SYNERGY pooling study (Kendzia et al., 2013) Strengths: individual expert assessment; specific and detailed assessment of exposure to Ni and Cr Limitations: no control for asbestos or other occupational carcinogens but stratification by Ni exposure
		Non-welders (ref.)	227	1		
		All	12	2.4 (1.0–5.4)		
		With Ni exposure	10	3.3 (1.2–9.2)		
		Without Ni exposure	2	1.2 (0.1–9.4)		

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Buiatti et al. (1985) Florence, Italy 1981–1983	Cases: 376 histologically confirmed primary lung cancer cases admitted to the hospital serving as the referral centre for all lung cancers in the province of Florence (340 men and 36 women); patients not resident in the metropolitan area of Florence excluded Controls: 892 controls from the medical service of the same hospital, frequency-matched by sex, age (± 5 yr), date of admission (± 3 mo), and smoking status (7 categories) with discharge diagnoses other than lung cancer Exposure assessment method: questionnaire; personal interview including all jobs held for > 1 yr and an exposure checklist of 16 known/ suspected carcinogens	Men Never welder (ref.) Welder	 NR 7	 1 2.8 (0.9–8.5)	Age, smoking, place of birth	Welding OR reported for men only Strengths: diligent consideration of possible selection biases possibly due to the hospital-based study design Limitations: small number; no adjustment for occupational co-exposure

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kjuus et al. (1986) SE Norway 1979–1983	Cases: 176 male incident lung cancer cases of age < 80 yr, admitted to the medical ward with the recent diagnosis of lung cancer Controls: 176 age-matched controls (± 5 yr) selected from the same ward; chronic obstructive lung diseases and conditions, implying physical or mental handicaps not eligible Exposure assessment method: questionnaire; subjects were interviewed at the bedside to obtain complete work history since 14 yr of age; job title and detailed information on relevant exposure factors were ascertained	Exposed for > 3 yr Not exposed to welding (ref.) Welding (all types) Welding (SS, acid proof)	 148 28 16	 1 1.9 (0.9–3.7) 3.3 (1.2–9.3)	Smoking	Results were similar for matched and unmatched analyses (accounting for age), but it is unclear whether this applies to welding Strengths: case–control status blinded in 90% of interviews; detailed work history included job descriptions; additional questionnaire on 17 agents and 5 specific work processes; diligent analysis including several sensitivity analyses to assess potential biases Limitations: small numbers; multiple comparisons and collinearity of exposures; age-adjustment not specifically mentioned for the analysis of welders

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Lerchen et al. (1987) New Mexico, USA 1980–1982	Cases: 506 Hispanic white and other white residents aged 25–84 yr with primary lung cancer identified by the New Mexico Tumor Registry; 333 men and 173 women Controls: 771; ~1.5 controls per case frequency-matched by sex, ethnicity, and 10 yr age category, randomly selected from residential telephone numbers and (for subjects aged > 65 yr) from Medicare roster; 499 men and 272 women; response proportion 83% (2% next-of-kin) Exposure assessment method: questionnaire; personal interview including lifetime occupational history and self-reported agent exposures for each job held for > 6 mo from age 12 yr; exclusion of subjects with < 20 yr of employment	Male welders Never employed as welders or in shipyard (ref.) All industries Shipyard industry Other industries	 NR 19 6 13	 1 3.2 (1.4–7.4) 2.2 (0.5–9.1) 3.8 (1.4–10.7)	Age, ethnicity, smoking	Welding risk estimates only reported for males Strengths: personal interview; jobs coded according to standard classifications and to an a priori list of high-risk occupations; stratification by industry (shipyard, other) Limitations: high proportion of next-of-kin in cases but not in controls

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Schoenberg et al. (1987) New Jersey, USA 1980–1981	Cases: 763 white male residents with incident histologically confirmed cancer of the lung trachea and bronchus, identified through reporting system based on pathology departments and cancer registry; response 70.4% Controls: 900; 1415 total general-population white male controls identified through death certificates and driver's license files (randomly), frequency matched by race, age, and area of residence; additionally matched for closest date of death for cases with next-of-kin respondent; deaths from lung cancer or respiratory disease excluded Exposure assessment method: questionnaire; personal interview including the history of all jobs held for > 3 mo since age 12 yr (job title, employer, type of business, tasks, materials handled, agent exposures); supplementary questions for shipbuilding workers; review of reported asbestos exposure by an industrial hygienist	Welders or burners Combined welders Combined welders with no asbestos exposure	NR 33 17	3.8 (1.8–7.8) 3.5 (1.8–6.6) 2.5 (1.1–5.5)	Age, respondent type, smoking, study area, education, vegetable intake	Enrolment from six geographic areas, two of which had heavy concentrations of shipyard workers; reported ORs refer to welders in shipbuilding Strengths: verification of self-reported asbestos exposure by industrial hygienist blinded for case–control status; in-depth analysis of job tasks in shipbuilding; stratification by asbestos exposure (yes/no) Limitations: limited adjustment for smoking (never, cigars, or < 10 cigarettes/d, 10–29 cigarettes/d, ≥ 30 cigarettes/d, unknown) that lacked information on smoking duration

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Benhamou et al. (1988) France 1976–1980	Cases: 1334 male cases with histologically confirmed lung cancer Controls: 2409; 1 or 2 hospital controls with nonsmoking related diseases were matched per case on sex, age at diagnosis (± 5 yr), hospital of admission, and interviewer Exposure assessment method: questionnaire; job history (jobs and duration of occupation); expert assessment of the data	Men only Never welders or flame cutters (ref.) Welders and flame cutters	 1316 18	 1 1.42 (0.79–2.88)	Age, sex, hospital admission, interviewer, smoking	Analysis restricted to male nonsmokers or male exclusive cigarette smokers Strengths: complete job history Limitations: crude adjustment for smoking (smoking status, age at starting (2 categories), frequency (2 categories), duration (2 categories); no adjustment for occupational carcinogens
Ronco et al. (1988) Turin, north Italy 1976–1980	Cases: 126 male residents who died from lung cancer from 1976–1980 Controls: 384, a random sample of men who died from other causes during 1976–1980, matched 3:1 by year of death and 10-yr age group (30–39 to 80–89); deaths from bladder and respiratory cancer excluded Exposure assessment method: questionnaire; next-of-kin interview at home (75–76%) or by telephone, including lifelong occupational history; job titles were coded blindly for case–control status according to ISCO and ICIT	Not welders (ref.) Welders	120 6	1 2.93 (0.87–9.82)	Age, smoking, other occupations	Strengths: detailed adjustment for smoking and List A/B jobs[a] Limitations: cause of death obtained from local death registers; next-of-kin interview; exposure classification only based on job title

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Zahm et al. (1989) Missouri, USA 1980–1985	Cases: 4431 histologically confirmed lung cancer cases identified through Missouri Cancer Registry; all white men Controls: 11 326 cancer controls identified through Missouri Cancer Registry from white male residents excluding cancer of the lip, oral cavity, oesophagus, lung, bladder, ill-defined/unknown sites Exposure assessment method: smoking status and occupation at the time of diagnosis obtained from medical records; codable information available from 52% of cases and 45% of controls; among subjects with known occupations, smoking status was unknown in 15% of cases and 37% of controls	Welders and solderers vs. all other occupations				
		All	29	1.2 (0.7–2.1)	Age, smoking	Strengths: large sample size; stratification by histological type Limitations: non-standardized assessment of occupation, only current job; crude adjustment for smoking (never, ex-, current, unknown smoker); a high proportion of missing smoking status; crude age adjustment (0–59, 60–69, >70 yr)
		Adenocarcinoma	8	1.7 (0.7–3.8)		
		SCC	15	1.7 (0.9–3.3)		
		Small cell/oat cell	2	0.4 (0.1–1.8)		
		Other	4	0.8 (0.2–2.2)		
Morabia et al. (1992) Chicago, Birmingham, Detroit, Long Island, New York, Philadelphia, Pittsburgh, San Francisco (USA) 1980–1989	Cases: 1793 hospital-based male cases confirmed by histology Controls: 3228; 1 or 2 controls hospitalized for conditions not related to smoking, matched for age (5 yr), race (black/white), hospital, date of admission, and smoking history (never, ex-, current 1–19, current >20 cigarettes) Exposure assessment method: questionnaire	All other occupations; never worked as welder (ref.)	1548	1	Age, race, smoking, region	Strengths: personal interview Limitations: contradictory statement regarding inclusion/ exclusion of smoking-related disorders in controls; only usual job title and the list of 44 exposures was asked; questionnaire version changed twice during the study; reference group not precisely defined
		Welders and flame cutters	18	1.5 (0.8–2.7)		

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Jöckel et al. (1998) West Germany 1988–1993	Cases: 1004; 839 men and 165 women from hospitals (females excluded from analysis) Controls: 1004 randomly drawn from a sample of mandatory residence registries, matched for region, sex, and age (±5 yr) Exposure assessment method: questionnaire; welding assessment for all workers reporting welding, regardless of job title, based on a welding-specific supplementary questionnaire; quantification of duration and frequency of each welding task; assessment of welding technique and type of metal; detailed quantitative assessment of asbestos exposure based on several job-specific questionnaires and a case-by-case expert assessment	Never exposed to welding fumes (ref.)	606	1	Smoking, asbestos	Included in the pooled SYNERGY analysis (Kendzia et al., 2013) Strengths: detailed supplementary questionnaire on welding independent of job title; quantitative assessment of welding hours; assessment of type of welding; assessment of type of metal; detailed adjustment for smoking and asbestos
		Welder or burner	47	1.93 (1.03–3.61)		
		Oxyacetylene welding	29	2.77 (1.20–6.38)		
		Welding fumes	233	1.25 (0.94–1.65)		
		Any type of welding: lifetime (h)				
		Never	608	1		
		< 1000	75	1.38 (0.91–2.09)		
		1000–6000	65	1.14 (0.73–1.79)		
		> 6000	91	1.10 (0.73–1.66)		
		Oxyacetylene welding: lifetime (h)				
		Never	668	1		
		< 1000	81	1.11 (0.75–1.63)		
		1000–6000	60	0.95 (0.60–1.51)		
		> 6000	30	1.46 (0.72–2.96)		
		> 10 000	NR	3.28		
		Gas-shielded welding	NR	3.6		
		Iron and steel welding	218	1.17 (0.87–1.56)		
		Welding in air/spacecraft industry				
		Never in industry/ never welding (ref.)	587	1		
		Ever in industry/ never welding	19	0.88 (0.42–1.84)		
		Never in industry/ ever welding	197	1.14 (0.85–1.53)		
		Ever in industry/ ever welding	36	2.29 (1.19–4.42)		

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pezzotto and Poletto (1999) Rosario, Argentina 1992–1998	Cases: 367 men with newly diagnosed lung cancer from three hospitals of Rosario city; no refusals Controls: 576 selected from same hospitals, admitted for non-smoking related diseases; age-matched (±3 yr); no refusals Exposure assessment method: questionnaire; personal interview including lifetime occupational history (job title, tasks, employer, type of industry) for each job held for > 1 yr	Administrative staff (ref.) Welders Welders (SCC) Welders (adenocarcinoma)	98 11 7 3	1 1.1 (0.4–3.1) 2.9 (1–10.1) 0.7 (0.1–3.6)	Age, smoking	Strengths: stratification by histologic type; personal interviews Limitations: subjects with more than two different jobs were excluded; small number; diagnostic validity of case status not reported; method for job classification not standard and insufficiently described

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Gustavsson et al. (2000) Stockholm, Sweden 1985–1990	Cases: 1042 men aged 40–75 yr with diagnosis of lung cancer Controls: 2364 randomly selected from the general-population registry, frequency-matched to the cases in 5-yr groups and year of inclusion (1985–1990); additional matching for vital status to balance cases and controls with regard to being alive at data collection Exposure assessment method: expert judgement; postal questionnaire on lifetime occupational history, residential history since 1950, and smoking habits, as well as on some other potential risk factors for lung cancer; completion by telephone interview; occupational history supplemented by detailed questionnaire on work tasks, frequency, and location(s) for occupations involving potential exposure to motor exhaust; next-of-kin questionnaires for deceased cases/controls	Welding fumes: intensity of exposure			Age, year, smoking, exposure to Rn, NO_x	Included in the pooled SYNERGY analysis (Kendzia et al., 2013) Strengths: individual exposure assessment by industrial hygienist for intensity and probability of exposure to 7 agents for each job period, blinded for case–control status; prevalence of co-exposure to 6 agents reported (62% of welding entailed asbestos exposure, 100% metal dust, and 67% other combustion products [not engine exhaust]); detailed adjustment for smoking; additional adjustment for asbestos, combustion products, and diesel exhaust; stratification by exposure intensity, cumulative exposure, and duration Limitations: no in-person interviews, only telephone in case of missing items; exposure metric difficult to interpret
		Unexposed to welding fumes (ref.)	923	1		
		Low	41	1.67 (1.06–2.64)		
		Intermediate	25	1.17 (0.66–2.06)		
		High	33	1.42 (0.88–2.30)		
		Welding fumes: quartile of cumulative exposure			Age, year, smoking, residential, exposure to Rn, NO_x, diesel, combustion products, asbestos	
		1	29	1.41 (0.83–2.40)		
		2	34	1.38 (0.82–2.33)		
		3	27	0.79 (0.45–1.36)		
		4	29	0.84 (0.46–1.52)		
		Duration of exposure to welding fumes (yr)			Age, year, smoking, exposure to Rn, NO_x	
		0 (ref.)	NR	1		
		> 0–9	NR	1.70 (0.97–2.96)		
		10–29	NR	1.45 (0.96–2.20)		
		≥ 30	NR	1.25 (0.82–1.90)		

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Soskolne et al. (2007) Campania region, Italy 1988–1990	Cases: 168 patients with respiratory tract cancers (lung $n = 111$, larynx $n = 35$, nasal/pharynx $n = 22$) Controls: 247 unmatched patients without any respiratory, bladder, or oral cavity cancers, including patients having any other reason for hospitalization; hospital-based case-control study Exposure assessment method: expert judgement; occupational history; exposure to 20 agents classified by the industrial hygienist	No exposure to welding fumes (ref.) Exposure to welding fumes	NR 13	1 3.91 (1.03–14.95)	Age, smoking	Strengths: exposure assessment by the industrial hygienist, blinded for case–control status Limitations: variables on which the assessment of welding fume exposure was based not described; exposure assessment method not standardized; small number; crude adjustment for smoking (based on the pack-year variable: very low, low, medium, high)
Brenner et al. (2010) Toronto, Canada 1997–2002	Cases: 445 incident cases of cancer of the trachea, bronchus, or lung diagnosed in men and women of age 20–84 yr from four major tertiary care hospitals in metropolitan Toronto Controls: 948 (425 population; 523 hospital); population-based controls were randomly sampled from property tax assessment files ($n = 425$), hospital-based controls were sampled from patients seen in the Mount Sinai Hospital Family Medicine Clinic ($n = 523$), frequency-matched with cases on sex and ethnicity Exposure assessment method: detailed questionnaire administered via interview either in person or over the telephone	Total study population Never worked/ exposed to welding equipment (ref.) Exposure to welding equipment Never smokers Never worked/ exposed to welding equipment (ref.) Exposure to welding equipment	 412 33 149 7	 1 1.7 (1–3) 1 3.4 (1.1–10.4)	Age, sex, smoking, ethnicity, education Age, sex, education, ethnicity	Included in the pooled SYNERGY analysis (Kendzia et al., 2013) Strengths: exposure category 'welding equipment' captures non-welding occupations with welding fume exposure; analysis of never smokers Limitations: frequency, intensity, duration of using 'welding equipment' is not stated

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Corbin et al. (2011) New Zealand 2007–2008	Cases: 457 incident cases of lung cancer aged 20–75 yr identified through the cancer registry; 53% of those eligible participated Controls: 792 controls selected from electoral rolls and recruited in two waves; frequency-matched for age distribution for lung cancer and three other cancer sites; 48% of those eligible participated Exposure assessment method: questionnaire; complete occupational history by telephone interview except for 432 controls who were interviewed face-to-face	Never employed as welder or flame cutter (ref.)	445	1	Age, sex, smoking, Maori ethnicity, SES	Included in the pooled SYNERGY analysis (Kendzia et al., 2013); no clear association with duration of employment (data not shown) Strengths: complete job history by interview; consideration of multiple comparisons by semi-Bayes adjustment Limitations: interviewing method not fully standardized; crude adjustment for smoking
		Welders and flame cutters (not SBA)	12	2.50 (0.86–7.25)		
		Welders and flame cutters (SBA)	12	1.92 (0.90–4.10)		
't Mannetje et al. (2012) UK, Romania, Hungary, Poland, Russian Federation, Slovakia, and Czech Republic 1998–2001	Cases: 2197 incident lung cancer (age, < 75 yr) Controls: 2295 frequency-matched on study area, sex, age (within 3 yr) and selected from hospital patients Exposure assessment method: expert judgement; face-to-face interview, and expert assessment of 70 agent exposures	Never exposed to welding fumes (ref.)	1615	1	Age, centre, education, asbestos, SiO_2, Ni, Cd, As, Cr, smoking	Included in the pooled SYNERGY analysis (Kendzia et al., 2013); *P* values for interaction between welding and co-exposures were 0.03 for asbestos and 0.54 for smoking Strengths: large multicentre study that used a common protocol; standardized exposure assessment methodology and high agreement in ratings between experts; results reported by welding activity; detailed questionnaire on welding activities Limitations: possible misclassification of assessed Cr exposure
		Ever worked as welder/flame cutter	NR	1.18 (0.84–1.66)		
		Ever worked as welder/flame cutter	NR	1.36 (1.00–1.86)	Age, centre, education, As, smoking	
		Weighted duration (h)			Age, centre, education, As, SiO_2, Cr, smoking	
		1–1680	173	1.03 (0.80–1.33)		
		1681–7000	180	1.05 (0.82–1.36)		
		> 7000	229	1.22 (0.94–1.58)		
		Trend test *P* value, 0.16				

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
't Mannetje et al. (2012) (cont.)		Cumulative exposure (h)				
		1–2520	156	0.94 (0.73–1.21)		
		2521–28 900	222	1.27 (0.99–1.43)		
		> 28 900	204	1.09 (0.84–1.43)		
		Trend test *P* value, 0.19				
		Duration of arc welding (yr)				
		Only arc welding fumes	200	1.00 (0.78–1.29)		
		1–8	70	0.92 (0.63–1.34)		
		9–25	66	1.01 (0.68–1.49)		
		> 25	63	1.09 (0.72–1.65)		
		Duration of gas welding (yr)				
		Only gas welding fumes	87	1.25 (0.88–1.78)		
		1–8	42	1.12 (0.69–1.82)		
		9–25	25	1.37 (0.70–2.70)		
		> 25	20	1.46 (0.72–2.94)		
		Duration of gas and arc welding (yr)			Age, centre, education, As, Cd, SiO_2, Cr, smoking	
		Gas and arc welding fumes	296	1.13 (0.90–1.43)		
		1–8	65	1.08 (0.72–1.61)		
		9–25	90	0.92 (0.65–1.30)		
		> 25	141	1.38 (1.00–1.90)		
		Trend test *P* value, 0.01				
		Duration of exposure to welding fumes without chromium (yr)				
		Ever exposure	393	1.14 (0.95–1.36)		
		1–8	123	0.98 (0.74–1.30)		
		9–25	117	1.00 (0.75–1.34)		
		> 25	153	1.48 (1.11–1.97)		

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
't Mannetje et al. (2012) (cont.)		Duration of exposure to welding fumes with chromium (yr)				
		Ever exposed	190	1.34 (1.04–1.71)		
		1–8	54	1.47 (0.94–2.30)		
		9–25	64	1.28 (0.85–1.92)		
		> 25	71	1.27 (0.87–1.85)		
		Duration of welding (yr)			Age, centre, education, As, SiO_2, Cr, smoking	
		1–8	177	1.02 (0.79–1.31)		
		9–25	181	1.00 (0.77–1.30)		
		> 25	224	1.29 (1.00–1.67)		
		Trend test *P* value, 0.11				
Calvert et al. (2012) California, USA 1988–2007	Cases: 110 937 male lung cancer cases identified from cancer registries, aged 18–97 yr; year of diagnosis during 1988–2007 Controls: 322 699; up to 5 cancer controls from CCR database (prostate, colon, brain, kidney, testis, bone, joint, thyroid) were matched to each case on age (±5 yr), year of diagnosis (±5 yr), race, and ethnicity; occupational cancers excluded Exposure assessment method: demographic information as recorded in the CCR includes 'usual (i.e. longest-held) industry and occupation'; information was available in 48% of all registered cases; for job title coding the narrative was searched for 90 keywords related to construction work	Welders vs Construction workers other than welders			None	Morbidity ORs calculated by logistic regression Strengths: large sample size; stratification by histologic subtype Limitations: no lifestyle factors assessed; smoking status unknown; no standardized assessment of occupation or industry; women excluded
		All	216	2.16 (1.81–2.58)		
		NSCLC	132	2.10 (1.68–2.63)		
		Small cell/oat cell	29	2.72 (1.64–4.51)		
		Other, including mesothelioma	43	1.97 (1.33–2.93)		
		Adenocarcinoma	62	1.84 (1.33–2.53)		
		SCC	45	2.48 (1.66–3.72)		
		Large cell cancer	6	1.25 (0.47–3.36)		
		Unspecified NSCLC	19	2.95 (1.60–5.43)		

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Tse et al. (2012) China, Hong Kong SAR 2004–2006	Cases: 1208 male histologically confirmed lung cancer cases aged 35–79 yr Controls: 1069 male randomly selected referents living in the same districts as the cases, identified from telephone directories, frequency-matched to cases (5-yr age groups); excluding subjects with a history of physician-diagnosed cancer at any site (48% participation) Exposure assessment method: questionnaire; cases were interviewed within 3 mo of the diagnosis of lung cancer; occupational history of jobs held at least 1 yr (industry, job title, specific tasks performed, beginning/end dates of each job period); job titles/ industries coded according to ISCO/ISIC	Self-reported exposure welding fumes			Age, smoking, education, birth place, alcohol, Rn, lung disease history, cancer in family, consumption of meat	Included in the pooled SYNERGY analysis (Kendzia et al., 2013); after adjustment for asbestos the result did not change significantly [data not shown] Strengths: ISCO-/ ISIC-coding blinded for case–control status; self-reported exposures at least 1×/wk for at least 6 mo; adjustment for suspected occupational carcinogens; stratification by histologic type Limitations: self-reported agent exposure (checklist of suspected carcinogens: asbestos, Ar, Ni, Cr, tars, asphalts, SiO_2, painting, pesticides, diesel engine exhaust, cooking fumes, welding fumes, man-made mineral fibres); no elevated risk for asbestos observed (OR, 0.8)
		All combined	112	1.69 (1.11–2.58)		
		Adenocarcinoma	39	1.68 (1.00–2.81)		
		Self-reported welding fumes				
		Lung (squamous cell and small cell carcinoma)	39	2.29 (1.26–4.16)		
		Duration of exposure to welding fumes (yr)				
		All combined				
		1 to < 19	33	3.03 (1.30–7.07)		
		≥ 20	79	1.38 (0.86–2.24)		
		Adenocarcinoma				
		1 to < 19	16	3.82 (1.49–9.80)		
		≥ 20	23	1.18 (0.63–2.20)		
		Self-reported duration of exposure to welding fumes (yr)				
		Squamous cell and small cell carcinoma				
		1 to < 19	11	4.57 (1.34–15.54)		
		≥ 20	28	1.84 (0.93–3.64)		

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Vallières et al. (2012) Montreal, Canada Study I: 1979–1986; Study II: 1996–2001	Cases: 857 (Study I), 736 (Study II) men, incident, histologically confirmed lung tumours, aged 35–75 yr Controls: 1066 (Study I), 894 (Study II); population controls randomly selected from electoral rolls, matched by age and area of residence Exposure assessment method: expert judgement; supplementary questionnaire for welding, including questions on the type of gases used, metal welded, and h/wk and wk/yr of exposure	Arc welding fumes: exposure duration (yr)			Age, ethno-linguistic group, education, asbestos, respondent, study indicator, smoking	Included in the pooled SYNERGY analysis (Kendzia et al., 2013); pooled analysis of two case–control studies; women excluded because exposure prevalence was only 1%; indication of elevated risk only in never or low-frequency smokers Strengths: sophisticated exposure assessment methodology with welding exposure assessed in individuals by experts, beyond using job title only; population-based study; comprehensive confounder adjustment including asbestos; high response proportion (79–86% among cases and 69–72% among population controls) Limitations: possible exposure misclassification due to proxy interviews in 10–20% of controls and 30–40% of cases
		Not exposed (ref.)	1373	1		
		Any level	220	1.0 (0.8–1.2)		
		≤ 20	136	1.1 (0.8–1.4)		
		> 20	84	0.9 (0.6–1.3)		
		Gas welding fumes: exposure duration (yr)				
		Not exposed (ref.)	1369	1		
		Any level	224	1.1 (0.9–1.4)		
		≤ 20	136	1.3 (1.0–1.7)		
		> 20	88	0.9 (0.7–1.3)		
		Gas welding fumes exposure				
		SCC				
		Not exposed (ref.)	528	1		
		Any level	92	1.1 (0.8–1.5)		
		Substantial level	31	1 (0.6–1.6)		
		Lung (small cell/oat cell)				
		Not exposed (ref.)	237	1		
		Any level	47	1.3 (0.9–1.9)		
		Substantial level	19	1.3 (0.7–2.3)		
		Adenocarcinoma				
		Not exposed (ref.)	356	1		
		Any level	52	1 (0.7–1.4)		
		Substantial level	19	1 (0.6–1.8)		
		SCC				
		Not exposed (ref.)	523	1		
		Any level	97	1.1 (0.8–1.5)		
		Substantial level	33	1.3 (0.8–2.1)		

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Vallières et al. (2012) (cont.)		Small cell/oat cell				
		Not exposed (ref.)	245	1		
		Any level	39	0.9 (0.6–1.4)		
		Substantial level	13	0.9 (0.5–1.6)		
		Adenocarcinoma				
		Not exposed (ref.)	353	1		
		Any level	55	1 (0.7–1.4)		
		Substantial level	22	1.2 (0.7–2.1)		
		Never smokers/low-frequency smokers				
		Gas welding fumes not exposed (ref.)	91	1		
		Gas welding fumes, any level of exposure	33	2.8 (1.7–4.8)		
		Gas welding fumes, substantial level	15	4.3 (1.9–9.7)		
		Arc welding fumes, not exposed (ref.)	93	1		
		Arc welding fumes, any level of exposure	31	2.2 (1.3–3.7)		
		Arc welding fumes, substantial level	13	3.5 (1.6–7.8)		

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kendzia et al. (2013) Europe, Canada, China, and New Zealand 1985–2010	Cases: 15 483; 568 cases had worked as welders Controls: 18 388; 427 controls had ever worked as welders Exposure assessment method: questionnaire; occupational and smoking histories were assessed in face-to-face interviews (81%); subjects considered exposed if job title was (1) 'welder' for ≥ 1 yr or (2) considered as potentially and occasionally involving welding activities	*All occupations*			Age, centre, smoking, List A job[a]	SYNERGY: pooled analysis of 16 studies; overlapping studies: Jöckel et al. (1998), Gustavsson et al. (2000), Richiardi et al. (2004), Brenner et al. (2010), Corbin et al. (2011), Guida et al. (2011), 't Mannetje et al. (2012), Vallières et al. (2012), Tse et al. (2012) Strengths: large pooled analysis that allowed stratification by duration of employment as a welder, histological type, smoking status (never smokers, pack-year), type of control, and blue-collar jobs; detailed adjustment for smoking (duration, intensity, duration of quitting, type of tobacco); adjustment for List A jobs[a]; restriction to blue-collar workers to indirectly and more tightly control for potential confounders Limitations: analysis based on job title with no information on welding process; no specific adjustment for asbestos exposure
		Never welding-related job (ref.)	12 921	1		
		Welder	568	1.44 (1.25–1.67)		
		Longest-held occupation	246	1.50 (1.20–1.88)		
		Ever blue-collar employee				
		Never welding-related job (ref.)	9796	1		
		Ever welder	568	1.33 (1.15–1.54)		
		Longest-held occupation	246	1.39 (1.11–1.73)		
		Ever welder				
		Never welding-related job (ref.)	12 921	1		
		Shipbuilding and repair	93	1.53 (1.06–2.21)		
		Construction and related building services	336	1.47 (1.22–1.78)		
		Manufacture of machines, equipment, appliances	352	1.40 (1.17–1.68)		
		Manufacture of motor vehicles and motor bikes	102	1.30 (0.94–1.80)		
		Repair of transport equipment	136	1.51 (1.12–2.03)		

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kendzia et al. (2013) (cont.)		*Longest-held job*				
		Never welding-related job (ref.)	12 921	1		
		Shipbuilding and repair	33	1.53 (0.89–3.41)		
		Construction and related building services	46	1.33 (0.81–2.20)		
		Manufacture of machines, equipment, appliances	104	2.11 (1.45–3.08)		
		Manufacture of motor vehicles and motor bikes	12	0.62 (0.28–1.36)		
		Repair of transport equipment	16	1.10 (0.49–2.46)		
		All cases				
		Duration as welder (yr)				
		Never welding-related job (ref.)	12 921	1		
		1 to < 3	82	1.14 (0.80–1.61)		
		3 to < 10	171	1.46 (1.26–1.91)		
		10 to ≤ 25	167	1.38 (1.06–1.79)		
		> 25	148	1.77 (1.31–2.39)		
		Trend test *P* value, < 0.0001				

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kendzia et al. (2013) (cont.)		*Adenocarcinoma*				
		Duration as welder (yr)				
		Never welding-related job (ref.)	3313	1		
		Ever welder	132	1.23 (0.99–1.53)		
		1 to < 3	18	0.84 (0.49–1.45)		
		3 to < 10	39	1.14 (0.77–1.68)		
		10 to ≤ 25	41	1.26 (0.85–1.87)		
		> 25	34	1.31 (0.85–2.02)		
		Trend test *P* value, 0.1041				
		SCC				
		Duration as welder (yr)				
		Never welding-related job (ref.)	5226	1		
		Ever welder	264	1.58 (1.32–1.89)		
		1 to < 3	41	1.38 (0.90–2.11)		
		3 to < 10	77	1.62 (1.16–2.25)		
		10 to ≤ 25	76	1.34 (0.97–1.85)		
		> 25	70	1.71 (1.19–2.46)		
		Trend test *P* value, 0.0002				
		Small cell/oat cell				
		Duration as welder (yr)				
		Never welding-related job (ref.)	1979	1		
		Ever welder	92	1.41 (1.09–1.82)		
		1 to < 3	14	1.25 (0.67–2.35)		
		3 to < 10	32	1.49 (0.96–2.32)		
		10 to ≤ 25	28	1.30 (0.82–2.07)		
		> 25	18	1.20 (0.69–2.11)		
		Trend test *P* value, 0.1311				

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kendzia et al. (2013) (cont.)		*All cases*				
		Never welding-related job (ref.)	12 921	1		
		Never-smoker welders	15	2.34 (1.31–4.17)		
		Adenocarcinoma				
		Never welding-related job (ref.)	3313	1		
		Never-smoker welders	6	1.89 (0.79–4.52)		
		SCC				
		Never welding-related job (ref.)	5226	1		
		Never-smoker welders	4	3.01 (1.07–8.49)		
		Small cell/oat cell				
		Never welding-related job (ref.)	1979	1		
		Never-smoker welders	2	4.45 (1.03–19.20)		
		Welding–smoking interaction				
		Never-smoker–never welding-related job (ref.)	439	1		
		Never-smoker welders	15	2.04 (1.16–3.61)		
		Trend test *P* value, 0.222				

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Luqman et al. (2014) Pakistan 2010–2013	Cases: 400 histologically confirmed cases of lung cancer from different hospitals Controls: 800 hospital controls with no cancer or chronic respiratory disease Exposure assessment method: questionnaire	Not exposed to welding fumes (ref.) Welding fumes	8 10	1 2.5 (1–6.5)	None	Strengths: the first epidemiological study on welding and lung cancer from Pakistan Limitations: a risk estimate for 'welding fumes' is presented even though there was no quantitative exposure assessment; it is unclear if there was multivariable adjustment (e.g. smoking, asbestos) in the statistical models
Matrat et al. (2016) France 2001–2007	Cases: 2276 population-based histologically confirmed, incident primary lung cancer cases in men aged 18–75 yr, identified through 10 of 11 cancer registries Controls: 2780 population controls from the same administrative department using random digit dialling, frequency-matched with cases for sex (only men) and age; additional statistical analysis on SES also performed Exposure assessment method: questionnaire; face-to-face interviews using standardized questionnaire, recording details of each occupation lasting ≥ 1 mo, with 20 job-specific questionnaires; asbestos exposure assessed by both a task-exposure matrix and a job-exposure matrix	No welding (ref.) Regular welders *Frequency of welding (%)* Regular welders, ≤ 5 > 5 Trend test *P* value, 0.19 *Duration (yr)* Regular welders, ≤ 10 > 10 Trend test *P* value, 0.02	1629 100 8 92 34 58	1 1.66 (1.11–2.49) 1.17 (0.31–4.51) 1.67 (1.10–2.54) 1.53 (0.91–2.55) 1.96 (0.98–3.92)	Age, department, smoking, asbestos, number of jobs	ICARE study. Complements study by Guida et al. (2011) and presents additional analyses beyond Kendzia et al. (2013). Data on soldering and brazing also available in the study Strengths: detailed questionnaire on welding; quantification of welding exposure and assessment of the type of welding; consideration of co-exposures; adjustment for asbestos exposure Limitations: each welder had worked with each type of metal, preventing isolation of groups that had welded a unique type of metal

Table 2.5 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Matrat et al. (2016) (cont.)		Regular ever welders: type of welding				
		No welding (ref.)	1629	1		
		Gas	64	1.98 (1.20–3.29)		
		Arc	65	1.99 (1.21–3.26)		
		Spot	38	1.35 (0.72–2.53)		
		Other	17	1.80 (0.72–4.51)		
		Regular welders, by covering and preparation of surfaces to be welded				
		No welding (ref.)	1629	1		
		Presence of grease or paint on the pieces	53	1.98 (1.15–3.43)		
		Cleaning with mechanical preparation only	25	0.97 (0.48–1.97)		
		Cleaning with chemical or mechanical preparation	26	2.79 (1.35–5.77)		
		Regular and occasional welders, chemicals used to clean the surface to be welded				
		Never used any chemical (ref.)	180	1		
		Paint stripper	33	1.46 (0.76–2.83)		
		Trichloroethylene	59	1.30 (0.77–2.20)		
		Gasoline	41	1.92 (1.01–3.65)		
		White spirit	34	1.69 (0.86–3.31)		
		Acid	26	2.54 (1.05–6.13)		

[a] List A/B jobs are defined as high-risk occupations known to be associated with lung cancer, many of which entail asbestos exposure

As, arsenic; CCR, Californian Cancer Registry; Cd, cadmium; CI, confidence interval; Cr, chromium; d, day(s); h, hour(s); ICIT, Index de la Classification Type; ISCO, International Standard Classification of Occupations; ISIC, International Standard Industrial Classification; mo, month(s); NO_x, nitrogen oxides; Ni, nickel; NR, not reported; NSCLC, non small cell lung carcinoma; OR, odds ratio; Rn, radon; SAR, Special Administrative Region; SBA, steel beam assembly; SCC, squamous cell carcinoma; SES, socioeconomic status; SiO_2, silicon dioxide; SS, stainless steel; wk, week(s); yr, year(s)

Table 2.6 Studies included in the SYNERGY pooling study

Study name	Country	Period	Overlapping studies
AUT	Germany	1990–1995	
HdA	Germany	1988–1993	Jöckel et al. (1998)
EAGLE	Italy	2002–2005	
TURIN/VENETO	Italy	1990–1994	Richiardi et al. (2004)
ROME	Italy	1993–1996	
LUCA	France	1989–1992	
PARIS	France	1988–1992	
ICARE	France	2001–2007	Guida et al. (2011); Matrat et al. (2016)
CAPUA	Spain	2000–2010	
MORGEN	Netherlands	1993–1997	
INCO	Czech Republic	1999–2002	't Mannetje et al. (2012)
INCO	Hungary	1998–2001	't Mannetje et al. (2012)
INCO	Poland	1998–2002	't Mannetje et al. (2012)
INCO	Slovakia	1998–2002	't Mannetje et al. (2012)
INCO	Romania	1998–2002	't Mannetje et al. (2012)
INCO	Russian Federation	1998–2001	't Mannetje et al. (2012)
INCO (LLP)	United Kingdom	1998–2005	't Mannetje et al. (2012)
LUCAS	Sweden	1985–1990	Gustavsson et al. (2000)
OCANZ	New Zealand	2003–2009	Corbin et al. (2011)
MONTREAL	Canada	1996–2002	Vallières et al. (2012) only study II included; Gerin et al. (1984) (recruitment 1979–82) not included; Vallières et al. (2012) includes Gerin et al. (1984)
TORONTO	Canada	1997–2002	Brenner et al. (2010)
HONG KONG	China	2003–2007	Tse et al. 2012

Compiled by the Working Group using information from Kendzia et al. (2013)

an elevated risk in the upper two quartiles of welding exposure after adjustment for asbestos and other potential confounders. Odds ratios of 1.41 (95% CI, 0.83–2.40), 1.38 (95% CI, 0.82–2.33), 0.79 (95% CI, 0.45–1.36), and 0.84 (95% CI, 0.46–1.52) were reported for quartiles 1, 2, 3, and 4, respectively. [The quality of exposure information in this study was limited due to the fact that it included mainly next-of-kin information (93% in cases, 19% in population controls, and 89% in mortality-matched controls) and was based on a mailed self-completed questionnaire. There is partial overlap with the study of Kendzia et al. (2013).]

Asbestos exposure was also assessed in detail in the multicentre study by 't Mannetje et al. (2012) conducted in eastern Europe and the UK, in which occupational histories were collected by face-to-face interviews. A total of 70 agent exposures were assessed by experts for each job regarding the expert's confidence in the presence of the exposure (possible, probable, certain), the percentage of working time exposed (1–5%, > 5–30%, > 30%), and the intensity (low, medium, high) according to a common protocol; high agreement was observed ($\kappa = 0.9$) between experts in the assessment of exposure to welding fumes. Analyses were reported adjusted for asbestos, smoking, and other occupational exposures such as chromium and nickel. In this study, the odds ratio for ever working as a welder or flame–cutter, adjusted for asbestos, silica, and metal exposure (e.g. Cr), not assessed from welding and smoking, was 1.36 (95% CI, 1.00–1.86). The similarly adjusted odds ratio for ever exposure to welding fumes was 1.18

(95% CI, 0.84–1.66). The odds ratios with lifetime exposure expressed in cumulative welding hours for 1–2520 hours, 2521–28 900 hours, and more than 28 900 hours were 0.94 (95% CI, 0.73–1.21), 1.27 (95% CI, 0.99–1.43), and 1.09 (95% CI, 0.84–1.43), respectively (*P* for trend, 0.19). This metric was calculated as the product of total hours exposed and intensity level (weights 1, 6, and 20). The study authors also calculated a weighted duration by multiplying the number of years (each year equivalent to 2000 hours) by the frequency (0.03, 0.175, and 0.65 for low, medium, and high, respectively) of exposure. This metric resulted in adjusted odds ratios for 1–1680 hours, 1681–7000 hours, and more than 7000 hours of 1.03 (95% CI, 0.80–1.33), 1.05 (95% CI, 0.82–1.36), and 1.22 (95% CI, 0.94–1.58), respectively (*P* for trend, 0.16). Categorized by years of exposure to both gas and arc welding fumes, adjusted odds ratios for 1–8 years, 9–25 years, and more than 25 years of 1.08 (95% CI, 0.72–1.61), 0.92 (95% CI, 0.65–1.30), and 1.38 (95% CI, 1.00–1.90), respectively, were observed (*P* for trend, 0.01). [The Working Group noted the partial overlap with the study by Kendzia et al. (2013).]

Vallières et al. (2012) conducted a study in Montreal, Canada, using a protocol similar to that of 't Mannetje et al. (2012). Exposure to asbestos and welding fumes was assessed in great detail by industrial hygienists. No elevated risks and no duration–effect relationship were observed for arc welding (OR, 1.0; 95% CI, 0.8–1.2) or gas welding (OR, 1.1; 95% CI, 0.9–1.4) for any level of exposure after adjustment for asbestos, smoking, and other confounders. In an analysis restricted to never and low-frequency smokers, statistically significant elevated risks were observed for any level of exposure to both gas and arc welding fumes, assessed separately. No association was observed among smokers of medium and high frequency. [The Working Group noted the partial overlap with the study by Kendzia et al. (2013).]

Matrat et al. (2016) adjusted for asbestos exposure in a recent case–control study conducted in France. Exposure was based on information gathered by face-to-face interviews that included a lifelong occupational history, including job periods, and 20 job-specific questionnaires. A detailed 4-page supplementary questionnaire was used if a respondent declared that more than 5% of his working time was devoted to welding, brazing, or gas cutting. Regular welders were defined as participants who reported being employed as a welder for at least one job period. From detailed information on asbestos exposure, a cumulative exposure index was calculated as the product of the duration of the corresponding job task, the probability of exposure, and the intensity of exposure. This index was categorized into four classes and then used for adjustment. The smoking- and asbestos-adjusted odds ratio for regular welders (which corresponds to ever being employed as a welder) compared with non-welders was 1.66 (95% CI, 1.11–2.49). The adjusted odds ratios for being a regular welder for less than 10 years was 1.53 (95% CI, 0.91–2.55) and for 10 years or more was 1.96 (95% CI, 0.98–3.92) (*P* for trend, 0.02). [The Working Group noted the partial overlap with the study by Kendzia et al. (2013).]

Several studies assessed the risks of cancer of the lung in relation to different welding processes (gas [oxyacetylene] welding, electric arc welding, gas-shielded welding [a type of arc welding preferably used on SS]) as well as type of metal (MS vs SS [chromium–nickel alloy]). See Section 1 for further details on welding types and processes.

Gerin et al. (1984) observed a higher odds ratio in welders with exposure to nickel (OR, 3.3; 95% CI, 1.2–9.2) than in welders without nickel exposure (OR, 1.2; 95% CI, 0.1–9.4). Kjuus et al. (1986) observed a difference in risk by material welded with an odds ratio of 3.3 (96% CI, 1.2–9.3) for 3 years or more of welding of SS and an odds ratio of 1.9 (95% CI, 0.9–3.7) for welding of any type of steel. In a case–control study

restricted to welders, Hull et al. (1989) did not consistently show higher risks due to welding of high-alloy steel/SS as compared with MS. [This study, conducted among welders only, was difficult to interpret due to a contaminated reference group.] The multicentre study by 't Mannetje et al. (2012) reported odds ratios for more than 25 years duration of exposure to welding fumes without chromium (OR, 1.48; 95% CI, 1.11–1.97) and containing chromium (OR, 1.27; 95% CI, 0.87–1.85). Although both Jöckel et al. (1998) and Matrat et al. (2016) collected information on the welding of SS in a welder-specific questionnaire, neither studies reported a corresponding risk estimate because most participants reported using different welding processes and on different metals. [These results indicate that any observed risks are not fully explained by exposure to high concentrations of nickel or chromium in the welded steel.]

Investigating the varying exposures to welding fumes between different types of welding, Jöckel et al. (1998) observed the higher odds ratio for gas welding in the highest category of cumulative exposure (6000 hours) (OR, 1.46; 95% CI, 0.72–2.96) in comparison with electric arc welding . Regular oxyacetylene welding for at least 2 hours per day, for 2 days per week for a minimum of 3 years, was associated with an odds ratio of 2.77 (95% CI, 1.20–6.38) in this study. 't Mannetje et al. (2012) also observed higher odds ratios for only gas welding for more than 25 years duration (OR, 1.46; 95% CI, 0.72–2.94) than for only arc welding for more than 25 years duration (OR, 1.09; 95% CI, 0.72–1.65). Matrat et al. (2016) also reported that gas welding exclusively was associated with a higher risk of cancer of the lung than arc welding. The study by Vallières et al. (2012) observed an association between welding and cancer of the lung mainly in nonsmokers and low-frequency smokers; odds ratios for gas as compared to arc welding (OR for substantial level of exposure to welding fumes in non-/low smokers were 4.3 (95% CI, 1.9–9.7) for gas welding and 3.5 (95% CI, 1.6–7.8), for arc welding) respectively.

Welding often takes place under particular circumstances, especially in maintenance and repair work when materials are coated or need to be cleaned before welding. When exploring the role of substances covering the metal surface to be welded and that of the cleaning procedure, Matrat et al. (2016) observed an increased risk among regular welders for the presence of grease or paint on the welded pieces (OR, 1.98; 95% CI, 1.15–3.43). They also reported an increased risk for cleaning with chemical or mechanical preparation (OR, 2.79; 95% CI, 1.35–5.77), but not for cleaning with mechanical preparation only (OR, 0.97; 95% CI, 0.48–1.97).

2.5.2 Cancer of the kidney

See Table 2.7

Eight case–control studies that reported on the association between cancer of the kidney and welding-related occupations or exposure to welding fumes were identified (Magnani et al., 1987; Siemiatycki, 1991; Keller & Howe, 1993; McCredie & Stewart, 1993; Mandel et al., 1995; Pesch et al., 2000; Mattioli et al., 2002; Brüning et al., 2003). [An additional report was identified (Parent et al., 2000) but not included in this review, as it covered the same study population as reported on in Siemiatycki (1991).]

Five of these studies reported odds ratios of 1.10–1.76 for welding occupations (Siemiatycki, 1991; Keller & Howe, 1993; McCredie & Stewart, 1993; Mandel et al., 1995; Brüning et al., 2003), none of which reached statistical significance.

Five of the eight case–control studies assessed exposure to welding fumes using a JEM or by expert assessment. A study from Canada (Siemiatycki, 1991), which included patients diagnosed with cancers other than kidney as controls, reported an odds ratio of 0.8 (95% CI, 0.5–1.3) for both exposure to arc welding fumes and exposure to gas welding fumes as assessed

by experts, based on 17 and 16 exposed cases, respectively. [The Working Group noted that the exposed cases and controls were likely the same for arc and gas welding fumes.] Odds ratios did not increase when analyses were restricted to "substantial" exposure to the two types of welding fumes. A study from northern Italy (Mattioli et al., 2002) reported an odds ratio of 5.67 (95% CI, 0.78–41.31) for expert-assessed exposure to welding fumes based on 8 exposed cases. Two studies used a JEM to assess exposure to welding fumes. A study from Germany (Pesch et al., 2000) reported an odds ratio of 1.3 (95% CI, 1.0–1.8) for exposure to medium levels of welding fumes based on 56 exposed cases, while exposure to high levels was associated with an odds ratio of 1.1 (95% CI, 0.8–1.6). A later study from Germany (Brüning et al., 2003) using a JEM to assess exposure to welding fumes reported an odds ratio of 2.73 (95% CI, 1.06–7.06) for low levels based on 9 exposed cases and 3.10 (95% CI, 1.37–7.02) for high levels based on 13 exposed cases. [The Working Group noted that the focus of this report was TCE as a risk factor for cancer of the renal pelvis; there was no adjustment for exposure to TCE however, so it is unclear how much of the elevated odds ratio for welding fumes is due to uncontrolled confounding by exposure to TCE.]

2.5.3 Cancer of the haematopoietic system

See Table 2.8 (web only; available at: http://publications.iarc.fr/569)

(a) Leukaemia

The Working Group identified nine case–control studies of leukaemia in adults that reported estimates of increased risk for welding-related jobs (Stern et al., 1986; Preston-Martin & Peters, 1988; Keller & Howe, 1993; Bethwaite et al., 2001; Costantini et al., 2001; Oppenheimer & Preston-Martin, 2002; Adegoke et al., 2003; Wong et al., 2010; Luckhaupt et al., 2012). Several studies reported risk estimates for a combined group of leukaemias (Keller & Howe, 1993; Costantini et al., 2001; Adegoke et al., 2003; Luckhaupt et al., 2012), reporting odds ratios ranging from 0.90 to 2.25; these were based on relatively small numbers of exposed cases however, and none reached statistical significance. [The Working Group noted that chronic lymphocytic leukaemia (CLL) was included in the definition of leukaemia by Adegoke et al. (2003) and Luckhaupt et al. (2012), not included in the definition by Costantini et al. (2001), and it was not clear whether it was included in the definition by Keller & Howe (1993).]

(i) Leukaemia subtypes

Several studies reported risk estimates for myeloid leukaemia or subtypes of myeloid leukaemia. An exceptionally high odds ratio was reported in 1988 for a chronic myeloid leukaemia case–control study based in Los Angeles County (Preston-Martin & Peters, 1988). A total of 22 of the 130 cases in the study had been employed as welders (compared with 4 of the 130 controls), yielding an adjusted odds ratio of 25.4 (95% CI, 2.78–232.54). A later study from California reported an odds ratio of 0.86 (95% CI, 0.29–2.53) for chronic myeloid leukaemia (Luckhaupt et al., 2012) related to welding in the construction industry. Three studies reported on acute myeloid leukaemia (AML), all with odds ratios above unity but none reaching statistical significance (Oppenheimer & Preston-Martin, 2002; Wong et al., 2010; Luckhaupt et al., 2012). A study from New Zealand on AML and acute lymphoblastic leukaemia (ALL) combined reported an odds ratio of 2.79 (95% CI, 1.2–6.8) for welders/flame-cutters; separate odds ratios for AML and ALL were not presented, however. [The Working Group assumed that the majority of the study population would be AML, but numbers were not provided.]

None of the leukaemia case–control studies reported associations with exposure to welding fumes, and none reported duration–response associations.

Table 2.7 Case–control studies on cancer of the kidney and welding or exposure to welding fumes

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Magnani et al. (1987) UK (three English counties) 1959–1963/ 1965–1979	Cases: 147 deaths at age 18–54 yr, identified from death certificates Controls: 556 deaths in the same year from other causes matched for sex, county of residence, age; identified from death certificates Exposure assessment method: expert judgement; Pannett JEM, based on job title on death certificate	Welding fumes	NR	1.8 (0.7–2.2)	Sex, county, age at death	Strengths: JEM assessed exposure Limitations: small size; occupational data obtained from death certificates; occupational histories available more often for cases than for controls; no adjustment for smoking
Siemiatycki (1991) Canada, Montreal 1979–1985	Cases: 177 male residents of the Montreal metropolitan area with histologically confirmed incident kidney cancer, age 35–70 yr Controls: 2481 study subjects with other cancers Exposure assessment method: expert judgement	Arc welding fumes (any)	17	0.8 (0.5–1.3)	Age, family income, cigarette index, ethnic origin	Strengths: expert assessment based on full occupational history and detailed task descriptions, and job-specific questionnaires Limitations: small size; use of cancer controls
		Arc welding fumes (substantial)	6	1.0 (0.5–1.9)		
		Gas welding fumes (any)	16	0.8 (0.5–1.3)		
		Gas welding fumes (substantial)	5	0.7 (0.3–1.5)		
		Welding fumes	6	1.5 (0.7–3.1)		
Keller & Howe (1993) USA, Illinois 1986–1989	Cases: 1372 newly diagnosed male kidney cancer cases reported in Illinois hospitals (hospital based) Controls: 4326 random sample of approximately 10% of all other cancers Exposure assessment method: questionnaire; job title recorded at cancer registration	Male welder	NR	1.75 (0.96–3.18)	Age, history of tobacco use	This study reports on multiple cancer sites Strengths: large size Limitations: only job at cancer registration is recorded; only welders within the construction industry are selected in the exposed group; unclear how many welders (outside of the construction industry) are categorized as unexposed; cancer controls

Table 2.7 (continued)

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
McCredie & Stewart (1993) Australia, NSW 1989–1990	Cases: 636 age 20–79 yr at diagnosis (population based); 489 RCC and 147 renal pelvic cancer cases Controls: 523 electoral rolls, randomly selected (population based) Exposure assessment method: questionnaire, face-to-face interviews; employment in certain industries and occupations, exposure to chemicals with suspected associations with kidney cancer; question on employment as welder (among other)	Welder Welder Welder (RCC and urinary pelvis)	40 8 48	1.37 (0.80–2.34) 1.66 (0.68–4.03) 1.50 (0.27–8.16)	Age, sex, method of interview	Strengths: large size, population controls, specific questions on welding Limitations: no specific assessment of exposure to welding fumes
Mandel et al. (1995) Australia, Denmark, Germany, Sweden, USA 1989–1991	Cases: 1732 cases of incident renal cell adenocarcinomas, age 20–79 yr, confirmed by histopathology or cytology Controls: 2309 population controls Exposure assessment method: questionnaire; Germany collected full occupational histories, other centres asked specific occupations and welding industry	Welder	77	1.1 (0.8–1.6)	Age, tobacco, BMI, education, study centre	Strengths: large size Limitations: no results by duration
Pesch et al. (2000) Germany 1991–1995	Cases: 935; 570 men and 365 women with no age limit (population based) Controls: 4298 population; 2650 men and 1648 women (population based) Exposure assessment method: expert judgement; British JEM	Level of exposure to welding fumes for men only Medium High Substantial	 56 46 16	 1.3 (1–1.8) 1.1 (0.8–1.6) 1.2 (0.7–2.1)	Age, study centre, smoking, region	ORs for 'welding, soldering, milling' were also reported, but this occupational group was considered too broad Strengths: large size, welding fumes assessed through JEM Limitations: exposure assessment beyond that provided by use of a JEM not provided

Table 2.7 (continued)

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mattioli et al. (2002) North Italy 1986–1994	Cases: 249 histologically confirmed RCC cases (hospital based) Controls: 238 hospital controls with non-RCC diagnosis (hospital-based) Exposure assessment method: questionnaire; occupational history, plus expert assessment for selected exposures including welding fumes	Men only: welding fumes	8	5.67 (0.78–41.31)	Age, birthplace, residence, smoking	Strengths: expert assessment Limitations: small size, small number of exposed cases
Brüning et al. (2003) Arnsberg, Germany 1999–2000	Cases: 134 incident histologically confirmed RCC cases with nephrectomy 1992–2000 Controls: 401 hospital controls (no dementia, no cancer), 3:1 frequency-matched by sex and age (5 yr) Exposure assessment method: questionnaire; job title, plus Pannett JEM; next of kin interviews included	Welding job Level of exposure to welding Low High	10 9 13	1.76 (0.75–4.11) 2.73 (1.06–7.06) 3.10 (1.37–7.02)	Age, sex, smoking	TCE was a risk factor in this study, but ORs for welding were not adjusted for TCE Strengths: although the study is small, the prevalence of welding is substantial Limitations: small size

BMI, body mass index; CI, confidence interval; JEM, job-exposure matrix; NR, not reported; OR, odds ratio; RCC, renal cell carcinoma; TCE, trichloroethylene; UUT, upper urinary tract; yr, year(s)

(b) Non-Hodgkin lymphoma

The Working Group identified 13 NHL case–control studies (Persson et al., 1989; Siemiatycki, 1991; Persson et al., 1993; Figgs et al., 1995; Costantini et al., 1998; Mao et al., 2000; Costantini et al., 2001; Fabbro-Peray et al., 2001; Zheng et al., 2002; Band et al., 2004; Dryver et al., 2004; Karunanayake et al., 2008; 't Mannetje et al., 2008) that reported on the association between NHL and welding-related occupations or exposure to welding fumes, and one large pooled case–control study ('t Mannetje et al., 2016).

Reported risk estimates for occupation as a welder were close to unity for 4 out of the 13 studies and above unity for 9 individual studies, 4 of which reported statistically significant increased risk estimates for all NHL (Persson et al., 1993; Zheng et al., 2002; Dryver et al., 2004) or specific NHL subtypes (Band et al., 2004). With the exception of the study by Dryver et al. (2004), these odds ratios were based on relatively small numbers of exposed cases. The largest NHL case–control study reporting on welding occupation was a pooled analysis of 10 case–control studies from Australia, Canada, Europe, and the USA ('t Mannetje et al., 2016). Ever employment in a welding-related occupation was associated with an odds ratio of 1.03 (95% CI, 0.83–1.27) based on 174 exposed cases. An odds ratio of 1.01 (95% CI, 0.69–1.48) was observed for those who had held a welding-related job for more than 10 years (53 exposed cases). Analyses were conducted for the main NHL subtypes (diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, and small lymphocytic lymphoma (SLL/CLL), showing an elevated odds ratio only for DLBCL (OR, 1.31; 95% CI, 0.99–1.74). Compared with never welders, those who had worked for more than 10 years in a welding-related job had an increased risk of DLBCL (OR, 1.20; 95% CI, 0.70–2.05) and of follicular lymphoma (OR, 1.25; 95% CI, 0.63–2.49).

Three NHL case–control studies assessed exposure to welding fumes or frequency of welding tasks. A study from Canada (Siemiatycki, 1991), using patients diagnosed with cancers other than NHL as controls and expert assessment for exposure to welding fumes, reported an odds ratio of 0.8 (95% CI, 0.6–1.2) for arc welding fumes and 0.8 (95% CI, 0.5–1.2) for gas welding fumes. [The Working Group noted that the odds ratios on the same numbers of exposed cases were very similar, suggesting that most exposed cases and controls were assessed by the experts as exposed to both gas welding and arc welding fumes.] A study from Sweden (Dryver et al., 2004) reported odds ratios for both welding occupation and exposure to welding fumes (self-reported). The risk for welding was elevated (OR, 1.41; 95% CI, 1.01–1.99), while the risk for exposure to welding fumes was not (OR, 0.98; 95% CI, 0.73–1.30). [The Working Group noted that more people reported exposure to welding fumes than occupation as a welder. The group exposed to welding fumes was therefore likely to include many that only performed occasional welding or worked in areas where welding was conducted.] A study from France (Fabbro-Peray et al., 2001) assessed the frequency of welding-related tasks (self-reported), reporting an odds ratio of 1.7 (95% CI, 0.8–3.4) for those who welded often and one of 2.6 (95% CI, 1.4–5.1) for those who welded daily. Associations remained after adjusting for benzene exposure, which was found to be a risk factor in this study.

(c) Multiple myeloma

The Working Group identified five case–control studies of multiple myeloma in adults that reported risk estimates for welding-related jobs (Eriksson & Karlsson, 1992; Heineman et al., 1992; Demers et al., 1993; Costantini et al., 2001; Baris et al., 2004). Most were based on 10 or less exposed cases, with the exception of a study from Canada (Demers et al., 1993) which reported an odds ratio of 1.2 (95% CI, 0.7–2.0) for

welders and cutters based on 22 exposed cases. One of the five studies (Costantini et al., 2001) reported a statistically significant increased odds ratio for welders (OR, 3.3; 95% CI, 1.3–8.5) based on 7 exposed cases.

(d) Other haematopoietic cancers: Hodgkin lymphoma

The Working Group identified three case–control studies of Hodgkin lymphoma in adults that reported risk estimates for welding-related jobs (Persson et al., 1989; Persson et al., 1993; Costantini et al., 2001), all based on a small number of exposed cases. The oldest of these reported a statistically significant increased odds ratio (Persson et al., 1989). [The Working Group noted that information on the number of cases exposed was not available for this study but, given the size of the study and the wide confidence interval, it is expected to be small.]

2.5.4 Cancer of the urinary bladder

See Table 2.9 (web only; available at: http://publications.iarc.fr/569)

The Working Group identified 18 case–control studies on cancer of the urinary bladder (Howe et al., 1980; Silverman et al., 1983, 1989a, b, 1990; Schifflers et al., 1987; Claude et al., 1988; Risch et al., 1988; Burns & Swanson, 1991; Siemiatycki, 1991; Kunze et al., 1992; Zaridze et al., 1992; Cordier et al., 1993; Teschke et al., 1997; Colt et al., 2004; Gaertner et al., 2004; Samanic et al., 2008; Colt et al., 2011) and one pooled case–control study (Kogevinas et al., 2003) that reported on the association between cancer of the bladder and welding-related occupations or exposure to welding fumes. [The Working Group excluded two studies from Islamic Republic of Iran because the occupational group was too broad (Aminian et al., 2014; Ghadimi et al., 2015). To avoid duplicate inclusion, one study from Italy (Porru et al., 1996) was not included because it was included in the pooled analysis also listed in the table (Kogevinas et al., 2003).]

Most of the individual studies were conducted in Canada, Europe, or the USA and ranged in size from 74 to 2160 cases, most including incident cases of cancer of the bladder. Most presented risk estimates were adjusted for smoking. [The Working Group noted that the odds ratios presented in Silverman et al. (1983) were not adjusted for smoking, although the study authors reported that smoking adjustment did not change the results.] Most of the reported risk estimates for welding-related occupations from cancer of the bladder case–control studies were close to unity and did not reach statistical significance; the exception was the earliest study from Canada (Howe et al., 1980), which reported an odds ratio of 2.8 (95% CI, 1.1–8.8) based on 16 exposed cases. Several studies reported risk estimates close to unity based on a relatively large number of exposed cases (> 20) (e.g. Silverman et al., 1989b; Burns & Swanson, 1991; Cordier et al., 1993).

Three studies reported on the duration of employment as a welder. A large study from Canada reported an odds ratio of 0.93 (95% CI, 0.78–1.10) for a 10-year increment of duration of employment as a welder (Risch et al., 1988). A later study from Canada (Gaertner et al., 2004) reported an odds ratio of 1.66 (95% CI, 0.78–3.48) for the group with the longest duration of employment as a welder (> 15 years) compared with those never employed as a welder. A study from Spain (Samanic et al., 2008) reported an odds ratio of 1.32 (95% CI, 0.74–2.36) for the group with the longest duration of employment as a welder (≥ 10 years) compared with those never employed as a welder.

The largest cancer of the bladder case–control study reporting on employment as a welder, a pooled analysis of 11 cancer of the bladder case–control studies from six European countries (Kogevinas et al., 2003), reported a pooled odds ratio of 1.22 (95% CI, 0.91–1.63) after adjusting for age, smoking, and study centre,

based on 88 exposed cases (men only). [The Working Group noted there was no overlap between this pooled study and the other studies listed in Table 2.9 (web only; available at: http://publications.iarc.fr/569). The Cordier et al. (1993) estimate for ever worked as a welder was included in the pooled estimate, but not the estimates for exposure to specific welding fumes reported on in the following paragraph and in the table.] Risk estimates by duration of employment as a welder were not reported.

Two studies used expert assessment, based on detailed work histories completed by the cases and the controls, to identify exposure to welding fumes generally and gas welding fumes versus arc welding fumes specifically. A study from Canada (Siemiatycki, 1991), using patients diagnosed with cancers other than bladder as controls, reported an odds ratio of 1.2 (95% CI, 0.9–1.5) for both arc welding fumes and gas welding fumes, based on 63 exposed cases. [The Working Group noted that the odds ratios were the same and based on the same numbers of exposed cases for both types of welding fume, suggesting that all cases were assessed by the experts as exposed to both gas welding and arc welding fumes.] Risk estimates did not increase when restricting the exposed group to those with "substantial" exposure. A study from France (Cordier et al., 1993) reported that exposure to any type of welding fumes was associated with an odds ratio of 1.40 (95% CI, 0.98–2.01) based on 86 exposed cases. An odds ratio of 1.61 (95% CI, 0.95–2.72) was reported for gas welding fumes and of 1.34 (95% CI, 0.79–2.27) for arc welding fumes, based on 40 and 37 exposed cases, respectively. [The Working Group noted that the numbers exposed to gas welding fumes and arc welding fumes would suggest that these groups were not fully, but largely, mutually exclusive.] Only 4 cases were exposed to SS welding fumes (OR, 1.10; 95% CI, 0.24–5.05). Risk estimates by level or duration of exposure to welding fumes were not reported.

(a) Subtypes of cancer of the bladder

With transitional cell carcinoma (TCC) being the dominant histological type of malignant tumours of the urinary bladder in industrialized countries (Fortuny et al., 1999), studies generally lacked statistical power to report on occupational risk factors for non-TCC of the bladder, including squamous cell carcinomas and adenocarcinomas. The above-mentioned pooled analysis of 11 case–control studies on cancer of the bladder from six European countries (Kogevinas et al., 2003) also reported on occupational risk factors for the 146 cases with non-TCC of the bladder (Fortuny et al., 1999), but an odds ratio specific to welding was not presented. The Working Group identified one study that reported a relative risk for welders, specifically for squamous cell carcinoma (RR, 5.9), based on 5 exposed cases; it was reported as being statistically significant, but the 95% confidence interval and *P* value were not provided (Kantor et al., 1988). Relative risks for all types of cancer of the bladder or adenocarcinoma of the bladder for welders were not significantly increased. [The Working Group noted that no further details were provided and that the study population overlaps that of Silverman et al. (1983); this study is therefore not included in the table.]

(b) Meta-analysis of cancer of the bladder

A meta-analysis of cohort and case–control studies that reported on the association between occupation and cancer of the bladder (all adjusted for smoking) was published in 2008 (Reulen et al., 2008), including 14 of the reports listed in Table 2.9 (web only; available at: http://publications.iarc.fr/569)

The meta-estimate for case–control studies was 1.04 (95% CI, 0.88–1.23). [The Working Group noted a major limitation in that the pooled analysis of 11 case–control studies on cancer of the bladder from six European countries (Kogevinas et al., 2003), which had already published by the time of the meta-analysis, was not included.]

2.5.5 Cancers of the head, neck, and upper aerodigestive tract

See Table 2.10 (web only; available at: http://publications.iarc.fr/569)

Studies on specific cancers of the head and neck are reviewed in the following. Two other studies reported results for all cancers of the head and neck combined. A case–control study which was part of the ICARE (Investigation of Occupational and Environmental Causes of Respiratory Cancers) study in France reported risk estimates for occupations and duration of occupation, adjusted for tobacco and alcohol consumption, separately for women (296 cases and 775 controls) (Carton et al., 2014) and men (1833 cases and 2747 controls) (Paget-Bailly et al., 2013). Odds ratios of 2.18 (95% CI, 0.33–14.4) and 21.7 (95% CI, 1.54–304) were reported for women who had ever worked as welders and flame-cutters (4 cases) and for women who had been employed for 10 years or more in this occupational group, respectively (*P* for trend, 0.05) (Carton et al., 2014). For men who had ever worked as welders and flame-cutters (109 cases) or who had been employed for 10 years or more in this occupational group, odds ratios of 1.9 (95% CI, 1.3–2.8) and 2.0 (95% CI, 1.0–3.9) were reported, respectively (*P* for trend, 0.01) (Paget-Bailly et al., 2013). Odds ratios for type of welding were also reported for men: 3.2 (95% CI, 1.6–6.3) for gas and electric welders (44 cases) and 1.9 (95% CI, 1.0–3.6) for electric arc welders (36 cases). Paget-Bailly et al. (2013) also reported odds ratios for specific head and neck cancer sites, particularly elevated for cancers of the hypopharynx (OR, 2.1; 95% CI, 1.2–3.6), oral cavity (see Section 2.5.5(c) below), and larynx (see Section 2.5.5(d) below).

(a) Cancer of the nasal cavity and sinuses

See Table 2.10 (web only; available at: http://publications.iarc.fr/569)

The Working Group identified four case–control studies that reported on welding or exposure to welding fumes (Hernberg et al., 1983; Luce et al., 1993; Teschke et al., 1997; d'Errico et al., 2009). These studies were all relatively small (48–207 cases), but a pooled analysis (Leclerc et al., 1997) included 930 cases. [The Working Group noted that the Luce et al. (1993) study population was included in this pooled analysis.]

Two of these four studies (Hernberg et al., 1983; Teschke et al., 1997) and the pooled analysis (Leclerc et al., 1997) reported odds ratios for welding-related occupations. A study from Denmark, Finland, and Sweden (Hernberg et al., 1983) reported an odds ratio of 2.8 (95% CI, 1.2–6.9) based on 17 exposed cases, noting that 13 were also exposed to chromium and/or nickel (as assessed by experts). A small study from Canada (Teschke et al., 1997) reported an odds ratio of 3.5 (95% CI, 0.2–53.7) based on 2 exposed cases. The pooled analysis (Leclerc et al., 1997) reported an odds ratio of 0.92 (95% CI, 0.38–2.22) based on 6 exposed cases.

Two studies assessed exposure to welding fumes through expert assessment. A study from France (Luce et al., 1993) reported odds ratios for exposure to welding fumes of 0.5 (95% CI, 0.2–1.4) for squamous cell carcinoma and 0.8 (95% CI, 0.4–1.6) for adenocarcinoma. A study from Italy (d'Errico et al., 2009) reported an odds ratio of 2.0 (95% CI, 1.00–3.82) for ever exposure to welding fumes based on 17 exposed cases, noting that additional adjustment for exposure to wood dust further strengthened the association (OR, 2.70; 95% CI, 1.31–5.45). Odds ratios by duration of exposure to welding fumes were also presented, with one of 2.40 (95% CI, 0.92–6.38) for 1–10 years of exposure to welding fumes and 3.0 (95% CI, 1.13–8.0) for more than 10 years. Odds ratios by level of welding fumes (low/high) were also reported, with 3.30 (95% CI, 1.47–7.26) and 1.60 (95% CI, 0.34–7.75) for low and high exposure levels, respectively. The odds ratio for

exposure to welding fumes was reported as 4.30 (95% CI, 1.01–18.10) for squamous cell carcinoma and 1.30 (95% CI, 0.52–3.52) for adenocarcinoma (d'Errico et al., 2009).

[The Working Group noted that results stratified by the material being welded, which could evaluate the potential effect of exposure to chromium and nickel, were not presented in the identified studies. Results adjusted for wood dust suggest that wood dust is not a strong confounder in associations between welding and cancers of the nasal cavity and sinuses.]

(b) Cancer of the nasopharynx

One case–control study conducted in Hong Kong Special Administrative Region, China, on carcinomas of the nasopharynx was identified (Xie et al., 2017), reporting an odds ratio of 9.18 (95% CI, 1.05–80.35) for self-reported expose to welding fumes at any time in the job history, based on 7 exposed cases and 1 exposed control. [The Working Group noted that carcinomas of the nasopharynx differ from other cancers of the head and neck in terms of occurrence and identified risk factors. They are more common in certain geographical areas, including east Asia where this study is set, and found to be strongly linked to infection with the Epstein–Barr virus.]

(c) Cancer of the oral cavity and oropharynx

The Working Group identified five case–control studies on cancer of the oral cavity and/or oropharynx (Vaughan, 1989; Merletti et al., 1991; Huebner et al., 1992; Gustavsson et al., 1998; Paget-Bailly et al., 2013). With the exception of the study from France (Paget-Bailly et al., 2013), all reported odds ratios close to unity for welding-related occupations. Paget-Bailly et al. (2013) reported an odds ratio for cancer of the oral cavity of 1.9 (95% CI, 1.1–3.3) based on 21 cases that had ever worked as a welder or flame-cutter.

(d) Cancer of the larynx

The Working Group identified 10 case–control studies on cancer of the larynx that reported on welding or exposure to welding fumes (Olsen et al., 1984; Brown et al., 1988; Ahrens et al., 1991; Wortley et al., 1992; Goldberg et al., 1997; De Stefani et al., 1998; Gustavsson et al., 1998; Elci et al., 2001; Shangina et al., 2006; Paget-Bailly et al., 2013).

Seven of these studies reported on welding occupations (Brown et al., 1988; Ahrens et al., 1991; Wortley et al., 1992; Goldberg et al., 1997; De Stefani et al., 1998; Elci et al., 2001; Paget-Bailly et al., 2013). Four of the studies reported odds ratios at or below unity, while three reported an odds ratio above unity (Brown et al., 1988; Goldberg et al., 1997; Paget-Bailly et al., 2013); one of these (Paget-Bailly et al., 2013) [already discussed above (at the beginning of Section 2.5.5) in relation to all cancers of the head and neck combined] reported an odds ratio for cancer of the larynx of 2.4 (95% CI, 1.5–4.0) for men who had ever worked as a welder and flame-cutter (33 exposed cases). An additional international case–control study on cancer of the larynx (Boffetta et al., 2003) reported that an increased risk for welders was not observed, but an odds ratio was not reported (this study was therefore not included in the table). [The Working Group identified one study that reported results by duration of welding employment (Wortley et al., 1992), but the number of exposed cases was small and a trend was not observed.]

Three studies reported on the association between cancer of the larynx and exposure to welding fumes (Olsen et al., 1984; Gustavsson et al., 1998; Shangina et al., 2006). The earliest published study (Olsen et al., 1984), based in Denmark, reported an odds ratio for all cancers of the larynx combined of 1.3 (95% CI, 0.9–2.0) based on 42 cases that reported exposure to welding fumes. Results by type of cancer of the larynx were also presented, with an odds ratio

of 1.1 (95% CI, 0.7–1.8) for glottic (23 exposed cases), 1.5 (95% CI, 0.8–2.9) for supraglottic (13 exposed cases), and 6.3 (95% CI, 1.8–21.6) for subglottic (5 exposed cases). A relatively large study from Sweden (Gustavsson et al., 1998) reported an odds ratio of 1.56 (95% CI, 0.92–2.53) for cancer of the larynx associated with ever exposure to welding fumes (based on 32 exposed cases), and a positive duration–response association was reported (*P* for trend, 0.04). A study from central and eastern Europe (Shangina et al., 2006), including 316 cases of cancer of the larynx and 34 cases of cancer of the hypopharynx, reported an odds ratio of 0.78 (95% CI, 0.54–1.14) for exposure to arc welding fumes (56 exposed cases) and 0.89 (95% CI, 0.58–1.37) for exposure to gas welding fumes (42 exposed cases).

(e) Cancer of the oesophagus

The Working Group identified four case–control studies on cancer of the oesophagus that reported on welding or exposure to welding fumes (Magnani et al., 1987; Siemiatycki, 1991; Gustavsson et al., 1998; Engel et al., 2002), all reporting odds ratios close to unity. Siemiatycki (1991) reported odds ratios for arc welding and gas welding separately, and for any as well as substantial exposure to welding fumes, but none were above unity.

2.5.6 Cancer of the brain

See Table 2.11 (web only; available at: http://publications.iarc.fr/569)

Six case–control studies investigating the risk of either malignant cancer of the brain or meningioma (a commonly diagnosed benign brain tumour) were identified by the Working Group.

Four studies were cancer of the brain case–control studies conducted in Canada, the UK, and the USA using either JEMs, job title, or exposure questionnaires, reporting on the association between malignant cancer of the brain and welding-related occupations or exposure to welding fumes (Magnani et al., 1987; Carozza et al., 2000; Pan et al., 2005; Ruder et al., 2012). Three of these studies reported odds ratios below or close to unity (Magnani et al., 1987; Carozza et al., 2000; Ruder et al., 2012), all based on a small number of exposed cases. The fourth, a large study of 1009 cases and 5039 matched controls (Pan et al., 2005), collected information on 18 employment-related chemical exposures including "welding", and reported an elevated odds ratio of 1.26 (95% CI, 0.98–1.45) based on 183 exposed cases. The same study found a 40% increase in risk of cancer of the brain in relation to duration of welding, with an odds ratio of 1.41 (95% CI, 0.98–1.84) in those exposed to welding fumes for 20 years or more (48 cases) compared with the reference group of non-exposed.

Two studies included exclusively meningiomas (Hu et al., 1999; Sadetzki et al., 2016). The first, a study from China using self-reported occupational exposures and hospital-recruited cases and controls (Hu et al., 1999), reported an odds ratio for exposure to welding rod fumes of 1.99 (95% CI, 0.40–9.89) for men based on 4 exposed cases and 3.05 (95% CI, 0.52–18.03) for women based on 5 exposed cases. The second, a large and recent international case–control study on meningioma (Sadetzki et al., 2016), reported that ever exposure to welding fumes, assessed using an updated version of FINJEM, was associated with risk of meningioma; an odds ratio of 1.19 (95% CI, 0.91–1.56) was reported, based on 94 exposed cases. Odds ratios were also reported separately for women (OR, 1.79; 95% CI, 0.78–4.10; 12 exposed cases) and men (OR, 1.15; 95% CI, 0.86–1.54; 82 exposed cases).

2.5.7 Parental exposure and cancer in offspring

See Table 2.12 (web only; available at: http://publications.iarc.fr/569)

Several case–control studies on childhood cancers have reported on the association between

occupation of a parent (mostly father) as a welder and the risk of cancer in their offspring; no studies on childhood leukaemia were identified.

(a) All childhood cancers

One study conducted in Moscow reported on the association between the father's welding history before conception (Smulevich et al., 1999) and all childhood cancers combined. The number of fathers working as welders was significantly higher among cases than among controls, yielding an odds ratio of 1.8. [The Working Group noted that a breakdown of the specific childhood cancer sites was not provided, and no confidence interval was reported.]

(b) Childhood cancer of the central nervous system

A neuroblastoma case–control study evaluating parental occupation from age 18 onwards as a potential risk factor (Olshan et al., 1999) reported an odds ratio for father's occupation as a welder/cutter of 0.5 (95% CI, 0.1–1.6). A childhood central nervous system tumour case–control study focusing on paternal occupations with exposure to electric and magnetic fields (Wilkins & Wellage, 1996) reported an odds ratio for preconception paternal occupation as welder of 1.75 (95% CI, 0.23–13.21) based on 3 exposed case fathers and an odds ratio of paternal occupation as welder during pregnancy of 1.00 (95% CI, 0.09–11.03) based on 2 exposed case fathers. A broader definition of welding, also including those jobs with welding tasks (welding-related jobs), yielded an odds ratio for preconception paternal welding-related job of 3.83 (95% CI, 0.95–15.55) based on 6 exposed case fathers. [The Working Group noted that the higher odds ratio obtained when using a broader definition of welding-related jobs may suggest that exposures other than welding may have to be considered.] A large international case–control study on childhood brain tumours and parental occupations (Cordier et al., 2001) reported an odds ratio of 0.97 (95% CI, 0.50–1.70) for paternal occupation as a welder. [The Working Group noted that the number of exposed cases on which this odds ratio was based was not reported, but estimated that it was based on 19–20 exposed cases according to the reported percentage exposed controls.]

(c) Wilms' tumour

The Working Group identified four case–control studies on Wilms' tumour (a childhood neoplasm of the kidney) that evaluated the association with parental welding, three of which were too small to be able to report risk estimates (Kantor et al., 1979; Wilkins & Sinks, 1984; Bunin et al., 1989). The largest study (Olshan et al., 1990) included 200 cases and 233 controls. Among different exposure periods explored (i.e. preconception, pregnancy, and postnatal), 6 of the case fathers and 1 of the control fathers worked as a welder during pregnancy, yielding the highest odds ratio of 8.22 (95% CI, 0.95–71.27).

(d) Other childhood cancers

A case–control study on hepatoblastoma (Buckley et al., 1989) reported an odds ratio of 1.0 related to self-reported father's exposure to welding, based on 12 exposed case fathers. A case–control study of childhood sporadic bilateral retinoblastoma (Abdolahi et al., 2013) reported an odds ratio of 1.22 (95% CI, 0.68–2.19) associated with paternal ever exposure to welding fumes, as assessed by experts using the detailed job history, based on 29 exposed case fathers. The same study reported no risk in relation to intensity of exposure to welding fumes (comparing none to low with moderate and high levels), either during the 10 years before conception or during the year before conception only, and no trends in risk were observed. A recent data linkage study from Finland, Norway, and Sweden (Togawa et al., 2016) included 8112 cases of testicular germ cell tumour (age, 14–49 years) and 26 264 controls;

the occupation of participants' parents were obtained from the census, and exposure was assessed by applying a JEM. Paternal low exposure to welding fumes based on 953 exposed cases and 2904 exposed controls lead to an odds ratio of 1.09 (95% CI, 1.01–1.18), which decreased at high exposure levels to 0.97 (95% CI, 0.79–1.19), based on 124 exposed cases. The odds ratios for maternal exposure were 1.02 (95% CI, 0.65–1.59) and 1.23 (95% CI, 0.64–2.36) for exposure to low and high levels of welding fumes, respectively.

2.5.8 Cancer of the pancreas

See Table 2.13 (web only; available at: http://publications.iarc.fr/569)

A total of five case–control studies on cancer of the pancreas that reported on the association with welding or exposure to welding fumes were identified (Norell et al., 1986; Magnani et al., 1987; Siemiatycki, 1991; Ji et al., 1999; Luckett et al., 2012). [The Working Group did not include several other studies for evaluation (Ji et al., 1999; Alguacil et al., 2000; Luckett et al., 2012) as the occupational category was too broad.]

Three studies assessed exposure to welding fumes or "welding materials". A small case–control study from Sweden (Norell et al., 1986) reported an odds ratio of 2.0 (90% CI, 0.9–4.3) associated with exposure to "welding materials" based on 13 exposed cases. [The Working Group noted that the exact definition of "welding materials" was not reported.] A mortality study that used a JEM to assess exposure to welding fumes (Magnani et al., 1987) reported an odds ratio of 1 [the Working Group noted that the number of exposed cases was not reported]. A study using other cancer cases as controls (Siemiatycki, 1991), and expert assessment of exposure to arc welding fumes and gas welding fumes, reported odds ratios close to unity for any exposure to either type of fumes and substantial exposure to arc welding fumes; an odds ratio for substantial exposure to gas welding fumes of 1.4 (95% CI, 0.7–2.8) was reported, based on 6 exposed cases.

None of the studies reported relative risks by duration of exposure.

2.5.9 Other cancers

See Table 2.14 (web only; available at: http://publications.iarc.fr/569)

(a) Cancer of the stomach

The Working Group identified three case–control studies on cancer of the stomach that reported on associations with welding or exposure to welding fumes (Siemiatycki, 1991; Keller & Howe, 1993; Engel et al., 2002). Two studies from the USA reported risk estimates for welding occupation; one reported an odds ratio of 2.11 (95% CI, 1.09–4.09) for cancer of the stomach (Keller & Howe, 1993); and another reported an odds ratio of 2.0 (95% CI, 0.8–5.2) for adenocarcinoma of the gastric cardia and 0.8 (95% CI, 0.3–2.3) for adenocarcinoma of the gastric noncardia (Engel et al., 2002). A Canadian case–control study on cancer of the stomach that used expert assessment and cancer controls reported an odds ratio of 0.9 (95% CI, 0.6–1.3) for exposure to arc welding fumes and 0.9 (95% CI, 0.6–1.3) for exposure to gas welding fumes (Siemiatycki, 1991). [The Working Group noted that the estimates were likely to have been based on the same cases and controls, assessed as being exposed to both gas and arc welding fumes.]

(b) Cancer of the small bowel

The Working Group identified one case–control study on adenocarcinoma of the small bowel that included 79 cases from five countries (Kaerlev et al., 2000). An odds ratio of 2.6 (95% CI, 1.0–6.4; 6 exposed cases) was reported for welders and flame-cutters, with a positive duration–response relationship (*P* for trend, 0.01).

(c) Cancer of the colon and rectum

Three case–control studies on cancer of the colon were identified that examined the association with a welding-related occupation or exposure to welding fumes (Siemiatycki, 1991; Keller & Howe, 1993; Fang et al., 2011), reporting odds ratios ranging from 0.49 to 1.10, none reaching statistical significance. One of these studies also investigated the increased risk of cancer of the rectum in relation to exposure to welding fumes, reporting odds ratios close to unity (Siemiatycki, 1991).

(d) Cancer of the liver

One case–control study on cancer of the liver was identified that reported on the association between cancer of the liver and exposure to welding fumes, as assessed by expert (Kauppinen et al., 1992). Odds ratios adjusted for alcohol consumption of 1.38 (95% CI, 0.52–3.64), based on 6 exposed cases, and 13.40 (95% CI, 2.02–88.1) for exposure to high levels of welding fumes, based on 5 exposed cases, were reported.

(e) Cancer of the prostate

The Working Group identified four case–control studies on cancer of the prostate that reported on the association with welding or exposure to welding fumes. A Canadian study using expert assessment and cancer controls reported odds ratios of 1.7 (95% CI, 1.0–2.6) and 1.4 (95% CI, 0.9–2.1) for exposure to substantial levels of arc welding fumes and gas welding fumes, respectively (Siemiatycki, 1991). [The Working Group noted that the estimates are likely to have been based on largely the same cases and controls, assessed as being exposed to both gas and arc welding fumes.] A case–control study from the Netherlands (van der Gulden et al., 1995) reported an odds ratio of 1.51 (95% CI, 0.48–4.78; 4 cases) for longest-held occupation as welder and an odds ratio of 1.19 (95% CI, 0.73–1.95; 22 cases) for workers "frequently exposed to welding fumes". A study from the US reported an odds ratio of 1.0 (95% CI, 0.61–1.64) for welders (Keller & Howe, 1993). A recent cancer of the prostate case–control study from Canada (Sauvé et al., 2016) reported an odds ratio of 0.97 (95% CI, 0.62–1.50; 50 cases) for ever having worked in welding and flame-cutting occupations. Odds ratios by duration of employment in the occupational group, and separately for arc welders and gas welders, were also presented, but did not reveal a positive duration–response association or differences in risk estimates between welding types.

(f) Cancer of the testis

The Working Group identified one case–control study on cancer of the testis that reported a risk estimate for a welding-related occupation (Walschaerts et al., 2007), with an odds ratio of 1.49 (95% CI, 0.53–4.15) after adjusting for risk factors, based on 20 exposed cases. [The Working Group identified an additional case–control study on testicular germ cell tumours, addressing parental occupation (Togawa et al., 2016); see also Section 2.5.7.]

(g) Melanoma of the skin

The Working Group identified two case–control studies on skin melanoma that reported on the association with exposure to welding fumes, both reporting odds ratios close to and below unity (Magnani et al., 1987; Siemiatycki, 1991).

2.6 Occupational studies of cancer mortality and incidence based on routinely collected data

See Table 2.15

Several studies conducted in Canada, New Zealand, the UK, and the USA evaluated the relationship between occupation and cancer using occupation reported on death certificates.

Table 2.15 Occupational studies on cancer mortality and incidence based on routinely collected data

Reference	Location	Exposure group	Cancer outcome and outcome measure	Risk estimate (95% CI)
Menck & Henderson (1976)	CA, USA	Welders	Lung; mortality and incidence: SMR	1.37 (1.01–1.81), 21 deaths, 27 cases
Decouflé et al. (1977)	NY, USA	Welders and flame cutters	Lung; incidence: RR (smoking adjusted)	0.67 (NR), 11 cases
Logan (1982)	UK	Welders	Lung; mortality: SMR	1951: 1.18 (NR) 1971: 1.51 (NR)
Gallagher & Threlfall (1983)	BC, Canada	Welders	Lung; mortality: PMR	1.45 (1.15–1.83), 74 deaths
Firth et al. (1993)	New Zealand	Welders	Lung; mortality: SMR	1.40 (1.20–1.61)
Coggon et al. (2009)	UK	Welders (men)	Mortality: PMR	
			Lung	1.11 (1.05–1.17), 1263 deaths
			Pleura	1.40 (1.04–1.86), 49 deaths
			Sinonasal	0.61 (0.13–1.78), 3 deaths
NIOSH (2015) National Occupational Mortality Surveillance (NOMS)	USA	Welders and cutters All races/sexes combined (1999, 2003–2004, 2007–2010)	Mortality: PMR	
			Lung	1.22 (1.21–1.30) 1975 deaths
			Oral cavity and pharynx	1.35 (1.11–1.63), 109 deaths
			Oesophagus	1.31 (1.13–1.52), 180 deaths
			Sinonasal	1.72 (0.79–3.27), 9 deaths
			Larynx	1.78 (1.38–2.25), 69 deaths
			Mesothelioma	2.88 (2.24–3.66), 68 deaths
			Liver and gall bladder	1.17 (1.03–1.33), 241 deaths
			Urinary bladder	1.25 (1.05–1.47), 141 deaths
			Kidney	0.99 (0.82–1.17), 130 deaths
			Prostate	1.79 (1.62–1.78), 395 deaths
			Brain	0.60 (0.48–0.75), 85 deaths
			Eye	–, < 5 deaths
			Chronic myeloid leukaemia	0.86 (0.39–1.63), 9 deaths
			Acute myeloid leukaemia	0.89 (0.69–1.12), 67 deaths
			Lymphatic leukaemia	1.02 (0.77–1.34), 53 deaths
			Multiple myeloma	0.77 (0.61–0.97), 76 deaths
			Non-Hodgkin lymphoma	0.82 ((0.70–0.96), 159 deaths
Dolin & Cook-Mozaffari (1992)	UK	Welders	Urinary bladder; mortality: SMR	0.74 (0.38–1.29)
Firth et al. (1993)	New Zealand	Welders	Stomach; mortality: SMR	1.45 (significant)

CI, confidence interval; PMR, proportional mortality ratio; RR, relative risk; SMR, standardized mortality ratio

Less frequently, cancer incidence data from various sources (e.g. not a newly assembled cohort) have also been used. Other countries have also conducted such studies on an ad hoc basis. Most studies were described by the Working Group in 1990 (IARC, 1990), but some have been updated or extended since then. [These studies are not described in detail (see Table 2.15 for a summary) due to several limitations, including: (1) lack of detailed exposure information or the use of occupation reported on death certificates; (2) limited information on potential confounders; (3) use of different data sources for observed (death certificates) and expected (census) deaths; and (4) chance findings due to multiple comparisons in evaluating the associations between many different occupations and causes of deaths in the USA (NIOSH, 2015) and the UK (Coggon et al., 2009).] These studies have been used repeatedly for occupational mortality surveillance purposes, and only the most recent update is reported.

Among all the studies that reported on cancer of the lung in welders, an excess of cancer of the lung was found in all but one study. The two studies that reported on cancer of the pleura and/or mesothelioma also found an excess among welders (Coggon et al., 2009; NIOSH, 2015). Excesses of several other types of cancer were also reported, including cancers of the stomach (Firth et al., 1993), oral cavity and pharynx, oesophagus, larynx, liver and gall bladder, and urinary bladder (NIOSH, 2015). In contrast, no excess risk of cancer of the urinary bladder was found in a study in the UK (Dolin & Cook-Mozaffari, 1992). No clear excess of mortality from cancer of the nasal cavity and sinuses was apparent (Coggon et al., 2009; NIOSH, 2015), and no excesses of deaths from cancer of the kidney, cancer of the brain, leukaemia, multiple myeloma, or NHL were found in the only study that reported on these cancer sites (NIOSH, 2015).

References

Abdolahi A, van Wijngaarden E, McClean MD, Herrick RF, Allen JG, Ganguly A, et al. (2013). A case-control study of paternal occupational exposures and the risk of childhood sporadic bilateral retinoblastoma. *Occup Environ Med*, 70(6):372–9. doi:10.1136/oemed-2012-101062 PMID:23503471

Adegoke OJ, Blair A, Shu XO, Sanderson M, Jin F, Dosemeci M, et al. (2003). Occupational history and exposure and the risk of adult leukemia in Shanghai. *Ann Epidemiol*, 13(7):485–94. doi:10.1016/S1047-2797(03)00037-1 PMID:12932623

Ahrens W, Jöckel KH, Patzak W, Elsner G (1991). Alcohol, smoking, and occupational factors in cancer of the larynx: a case-control study. *Am J Ind Med*, 20(4):477–93. doi:10.1002/ajim.4700200404 PMID:1785612

Ajani UA, Seddon JM, Hsieh CC, Egan KM, Albert DM, Gragoudas ES (1992). Occupation and risk of uveal melanoma. An exploratory study. *Cancer*, 70(12):2891–900. doi:10.1002/1097-0142(19921215)70:12<2891::AID-CNCR2820701228>3.0.CO;2-1 PMID:1451071

Alguacil J, Pollán M, Gustavsson P (2003). Occupations with increased risk of pancreatic cancer in the Swedish population. *Occup Environ Med*, 60(8):570–6. doi:10.1136/oem.60.8.570 PMID:12883017

Alguacil J, Porta M, Benavides FG, Malats N, Kogevinas M, Fernández E, et al.; PANKRAS II Study Group (2000). Occupation and pancreatic cancer in Spain: a case-control study based on job titles. *Int J Epidemiol*, 29(6):1004–13. doi:10.1093/ije/29.6.1004 PMID:11101541

Aminian O, Saburi A, Mohseni H, Akbari H, Chavoshi F, Akbari H (2014). Occupational risk of bladder cancer among Iranian male workers. *Urol Ann*, 6(2):135–8. doi:10.4103/0974-7796.130643 PMID:24833825

Austin H, Delzell E, Lally C, Rotimi C, Oestenstad K (1997). A case-control study of lung cancer at a foundry and two engine plants. *Am J Ind Med*, 31(4):414–21. doi:10.1002/(SICI)1097-0274(199704)31:4<414::AID-AJIM6>3.0.CO;2-V PMID:9093655

AWS (1997). Standard welding terms and definitions. ANSI/AWS A3.0–94. Miami (FL), USA: American Welding Society.

Band PR, Le ND, Fang R, Gallagher R (2004). Identification of occupational cancer risks in British Columbia: a population-based case-control study of 769 cases of non-Hodgkin's lymphoma analyzed by histopathology subtypes. *J Occup Environ Med*, 46(5):479–89. doi:10.1097/01.jom.0000126028.99599.36 PMID:15167397

Baris D, Silverman DT, Brown LM, Swanson GM, Hayes RB, Schwartz AG, et al. (2004). Occupation, pesticide exposure and risk of multiple myeloma. *Scand J Work Environ Health*, 30(3):215–22. doi:10.5271/sjweh.782 PMID:15250650

Beaumont JJ, Weiss NS (1980). Mortality of welders, shipfitters, and other metal trades workers in boilermakers Local No. 104, AFL-CIO. *Am J Epidemiol*, 112(6):775–86. PMID:7457470

Beaumont JJ, Weiss NS (1981). Lung cancer among welders. *J Occup Med*, 23:839–44.

Becker N (1999). Cancer mortality among arc welders exposed to fumes containing chromium and nickel. Results of a third follow-up: 1989-1995. *J Occup Environ Med*, 41(4):294–303. doi:10.1097/00043764-199904000-00012 PMID:10224596

Becker N, Chang-Claude J, Frentzel-Beyme R (1991). Risk of cancer for arc welders in the Federal Republic of Germany: results of a second follow up (1983-8). *Br J Ind Med*, 48(10):675–83. PMID:1931726

Becker N, Claude J, Frentzel-Beyme R (1985). Cancer risk of arc welders exposed to fumes containing chromium and nickel. *Scand J Work Environ Health*, 11(2):75–82. doi:10.5271/sjweh.2242 PMID:4001902

Benhamou S, Benhamou E, Flamant R (1988). Occupational risk factors of lung cancer in a French case-control study. *Br J Ind Med*, 45(4):231–3. PMID:3377999

Bethwaite P, Cook A, Kennedy J, Pearce N (2001). Acute leukemia in electrical workers: a New Zealand case-control study. *Cancer Causes Control*, 12(8):683–9. doi:10.1023/A:1011297803849 PMID:11562108

Blot WJ, Harrington JM, Toledo A, Hoover R, Heath CW Jr, Fraumeni JF Jr (1978). Lung cancer after employment in shipyards during World War II. *N Engl J Med*, 299(12):620–4. doi:10.1056/NEJM197809212991202 PMID:683235

Blot WJ, Morris LE, Stroube R, Tagnon I, Fraumeni JF Jr (1980). Lung and laryngeal cancers in relation to shipyard employment in coastal Virginia. *J Natl Cancer Inst*, 65(3):571–5. PMID:6931936

Boffetta P, Richiardi L, Berrino F, Estève J, Pisani P, Crosignani P, et al. (2003). Occupation and larynx and hypopharynx cancer: an international case-control study in France, Italy, Spain, and Switzerland. *Cancer Causes Control*, 14(3):203–12. doi:10.1023/A:1023699717598 PMID:12814199

Bonde JP, Olsen JH, Hansen KS (1992). Adverse pregnancy outcome and childhood malignancy with reference to paternal welding exposure. *Scand J Work Environ Health*, 18(3):169–77. doi:10.5271/sjweh.1591 PMID:1615291

Brenner DR, Hung RJ, Tsao MS, Shepherd FA, Johnston MR, Narod S, et al. (2010). Lung cancer risk in never-smokers: a population-based case-control study of epidemiologic risk factors. *BMC Cancer*, 10(1):285 doi:10.1186/1471-2407-10-285 PMID:20546590

Breslow L, Hoaglin L, Rasmussen G, Abrams HK (1954). Occupations and cigarette smoking as factors in lung cancer. *Am J Public Health Nations Health*, 44(2):171–81. doi:10.2105/AJPH.44.2.171 PMID:13114492

Brown LM, Mason TJ, Pickle LW, Stewart PA, Buffler PA, Burau K, et al. (1988). Occupational risk factors for laryngeal cancer on the Texas Gulf Coast. *Cancer Res*, 48(7):1960–4. PMID:3349470

Brüning T, Pesch B, Wiesenhütter B, Rabstein S, Lammert M, Baumüller A, et al. (2003). Renal cell cancer risk and occupational exposure to trichloroethylene: results of a consecutive case-control study in Arnsberg, Germany. *Am J Ind Med*, 43(3):274–85. doi:10.1002/ajim.10185 PMID:12594774

Buckley JD, Sather H, Ruccione K, Rogers PC, Haas JE, Henderson BE, et al. (1989). A case-control study of risk factors for hepatoblastoma. A report from the Childrens Cancer Study Group. *Cancer*, 64(5):1169–76. doi:10.1002/1097-0142(19890901)64:5<1169::AID-CNCR2820640534>3.0.CO;2-I PMID:2547509

Buiatti E, Kriebel D, Geddes M, Santucci M, Pucci N (1985). A case control study of lung cancer in Florence, Italy. I. Occupational risk factors. *J Epidemiol Community Health*, 39(3):244–50. doi:10.1136/jech.39.3.244 PMID:4045367

Bunin GR, Nass CC, Kramer S, Meadows AT (1989). Parental occupation and Wilms' tumor: results of a case-control study. *Cancer Res*, 49(3):725–9. PMID:2535965

Burns PB, Swanson GM (1991). Risk of urinary bladder cancer among blacks and whites: the role of cigarette use and occupation. *Cancer Causes Control*, 2(6):371–9. doi:10.1007/BF00054297 PMID:1764561

Calvert GM, Luckhaupt S, Lee SJ, Cress R, Schumacher P, Shen R, et al. (2012). Lung cancer risk among construction workers in California, 1988-2007. *Am J Ind Med*, 55(5):412–22. doi:10.1002/ajim.22010 PMID:22237930

Carozza SE, Wrensch M, Miike R, Newman B, Olshan AF, Savitz DA, et al. (2000). Occupation and adult gliomas. *Am J Epidemiol*, 152(9):838–46. doi:10.1093/aje/152.9.838 PMID:11085395

Carton M, Guida F, Paget-Bailly S, Cyr D, Radoi L, Sanchez M, et al. (2014). Occupation and head and neck cancer in women-Results of the ICARE study. *Am J Ind Med*, 57(12):1386–97. doi:10.1002/ajim.22394 PMID:25351857

Claude JC, Frentzel-Beyme RR, Kunze E (1988). Occupation and risk of cancer of the lower urinary tract among men. A case-control study. *Int J Cancer*, 41(3):371–9. doi:10.1002/ijc.2910410309 PMID:3346100

Coggon D, Harris EC, Brown T, Rice S, Palmer KT (2009). Occupational mortality in England and Wales, 1991–2000. Newport, UK: Office for National Statistics, Health and Safety Executive. Available from: https://www.ons.gov.uk.

Colt JS, Baris D, Stewart P, Schned AR, Heaney JA, Mott LA, et al. (2004). Occupation and bladder cancer risk in a population-based case-control study in New Hampshire. *Cancer Causes Control*, 15(8):759–69. doi:10.1023/B:CACO.0000043426.28741.a2 PMID:15456989

Colt JS, Karagas MR, Schwenn M, Baris D, Johnson A, Stewart P, et al. (2011). Occupation and bladder cancer in a population-based case-control study in Northern New England. *Occup Environ Med*, 68(4):239–49. doi:10.1136/oem.2009.052571 PMID:20864470

Corbin M, McLean D, Mannetje A, Dryson E, Walls C, McKenzie F, et al. (2011). Lung cancer and occupation: A New Zealand cancer registry-based case-control study. *Am J Ind Med*, 54(2):89–101. doi:10.1002/ajim.20906 PMID:20957667

Cordier S, Clavel J, Limasset JC, Boccon-Gibod L, Le Moual N, Mandereau L, et al. (1993). Occupational risks of bladder cancer in France: a multicentre case-control study. *Int J Epidemiol*, 22(3):403–11. doi:10.1093/ije/22.3.403 PMID:8359955

Cordier S, Mandereau L, Preston-Martin S, Little J, Lubin F, Mueller B, et al. (2001). Parental occupations and childhood brain tumors: results of an international case-control study. *Cancer Causes Control*, 12(9):865–74. doi:10.1023/A:1012277703631 PMID:11714115

Costantini AS, Miligi L, Kriebel D, Ramazzotti V, Rodella S, Scarpi E, et al. (2001). A multicenter case-control study in Italy on hematolymphopoietic neoplasms and occupation. *Epidemiology*, 12(1):78–87. doi:10.1097/00001648-200101000-00014 PMID:11138825

Costantini AS, Miligi L, Vineis P; WILL (Working Group on Hematolymphopoietic Malignancies in Italy) (1998). [An Italian multicenter case-control study on malignant neoplasms of the hematolymphopoietic system. Hypothesis and preliminary results on work-related risks] *Med Lav*, 89(2):164–76. PMID:9673106

d'Errico A, Pasian S, Baratti A, Zanelli R, Alfonzo S, Gilardi L, et al. (2009). A case-control study on occupational risk factors for sino-nasal cancer. *Occup Environ Med*, 66(7):448–55. doi:10.1136/oem.2008.041277 PMID:19153109

Danielsen TE, Langård S, Andersen A (1998). Incidence of lung cancer among shipyard welders investigated for siderosis. *Int J Occup Environ Health*, 4(2):85–8. doi:10.1179/oeh.1998.4.2.85 PMID:10026469

Danielsen TE, Langård S, Andersen A (1996). Incidence of cancer among Norwegian boiler welders. *Occup Environ Med*, 53(4):231–4. doi:10.1136/oem.53.4.231 PMID:8664959

Danielsen TE, Langård S, Andersen A (2000). Incidence of cancer among welders and other shipyard workers with information on previous work history. *J Occup Environ Med*, 42(1):101–9. doi:10.1097/00043764-200001000-00023 PMID:10652696

Danielsen TE, Langård S, Andersen A, Knudsen O (1993). Incidence of cancer among welders of mild steel and other shipyard workers. *Br J Ind Med*, 50(12):1097–103. PMID:8280640

de Silva SR, Bundy ED, Smith PD, Gaydos JC (1999). A geographical information system technique for record-matching in a study of cancer deaths in welders. *J Occup Environ Med*, 41(6):464–8. doi:10.1097/00043764-199906000-00012 PMID:10390697

De Stefani E, Boffetta P, Oreggia F, Ronco A, Kogevinas M, Mendilaharsu M (1998). Occupation and the risk of laryngeal cancer in Uruguay. *Am J Ind Med*, 33(6):537–42. doi:10.1002/(SICI)1097-0274(199806)33:6<537::AID-AJIM3>3.0.CO;2-N PMID:9582944

Decouflé P, Stanislawczyk K, Houten L, Bross J, Viadana E (1977). Retrospective survey of cancer in relation to occupation. DHEW (NIOSH) Publication No. 77–178. Cincinnati (OH), USA: National Institute for Occupational Safety and Health.

Demers PA, Vaughan TL, Koepsell TD, Lyon JL, Swanson GM, Greenberg RS, et al. (1993). A case-control study of multiple myeloma and occupation. *Am J Ind Med*, 23(4):629–39. doi:10.1002/ajim.4700230410 PMID:8338527

Dolin PJ, Cook-Mozaffari P (1992). Occupation and bladder cancer: a death-certificate study. *Br J Cancer*, 66(3):568–78. doi:10.1038/bjc.1992.316 PMID:1520596

Droste JH, Weyler JJ, Van Meerbeeck JP, Vermeire PA, van Sprundel MP (1999). Occupational risk factors of lung cancer: a hospital based case-control study. *Occup Environ Med*, 56(5):322–7. doi:10.1136/oem.56.5.322 PMID:10472306

Dryver E, Brandt L, Kauppinen T, Olsson H (2004). Occupational exposures and non-Hodgkin's lymphoma in Southern Sweden. *Int J Occup Environ Health*, 10(1):13–21. doi:10.1179/oeh.2004.10.1.13 PMID:15070021

Dunn JE Jr, Linden G, Breslow L (1960). Lung cancer mortality experience of men in certain occupations in California. *Am J Public Health Nations Health*, 50(10):1475–87. doi:10.2105/AJPH.50.10.1475 PMID:13725049

Dunn JE Jr, Weir JM (1968). A prospective study of mortality of several occupational groups. Special emphasis on lung cancer. *Arch Environ Health*, 17(1):71–6. doi:10.1080/00039896.1968.10665192 PMID:5671094

Elci OC, Dosemeci M, Blair A (2001). Occupation and the risk of laryngeal cancer in Turkey. *Scand J Work Environ Health*, 27(4):233–9. doi:10.5271/sjweh.610 PMID:11560337

Engel LS, Vaughan TL, Gammon MD, Chow WH, Risch HA, Dubrow R, et al. (2002). Occupation and risk of esophageal and gastric cardia adenocarcinoma. *Am J Ind Med*, 42(1):11–22. doi:10.1002/ajim.10077 PMID:12111686

Englund A, Ekman G, Zabrielski L (1982). Occupational categories among brain tumor cases recorded in the cancer registry in Sweden. *Ann N Y Acad Sci*, 381(1):188–96. doi:10.1111/j.1749-6632.1982.tb50384.x PMID:6953789

Eriksson M, Karlsson M (1992). Occupational and other environmental factors and multiple myeloma: a population based case-control study. *Br J Ind Med*, 49(2):95–103. PMID:1536825

Fabbro-Peray P, Daures JP, Rossi JF (2001). Environmental risk factors for non-Hodgkin's lymphoma: a population-based case-control study in Languedoc-Roussillon, France. *Cancer Causes Control*, 12(3):201–12. doi:10.1023/A:1011274922701 PMID:11405325

Fang R, Le N, Band P (2011). Identification of occupational cancer risks in British Columbia, Canada: a population-based case-control study of 1,155 cases of colon cancer. *Int J Environ Res Public Health*, 8(10):3821–43. doi:10.3390/ijerph8103821 PMID:22073015

Figgs LW, Dosemeci M, Blair A (1995). United States non-Hodgkin's lymphoma surveillance by occupation 1984-1989: a twenty-four state death certificate study. *Am J Ind Med*, 27(6):817–35. doi:10.1002/ajim.4700270606 PMID:7645576

Firth HM, Herbison GP, Cooke KR, Fraser J (1993). Male cancer mortality by occupation: 1973-86. *N Z Med J*, 106(961):328–30. PMID:8341471

Fletcher AC, Ades A (1984). Lung cancer mortality in a cohort of English foundry workers. *Scand J Work Environ Health*, 10(1):7–16. doi:10.5271/sjweh.2361 PMID:6740279

Fortuny J, Kogevinas M, Chang-Claude J, González CA, Hours M, Jöckel KH, et al. (1999). Tobacco, occupation and non-transitional-cell carcinoma of the bladder: an international case-control study. *Int J Cancer*, 80(1):44–6. doi:10.1002/(SICI)1097-0215(19990105)80:1<44::AID-IJC9>3.0.CO;2-8 PMID:9935228

Gaertner RR, Trpeski L, Johnson KC; Canadian Cancer Registries Epidemiology Research Group (2004). A case-control study of occupational risk factors for bladder cancer in Canada. *Cancer Causes Control*, 15(10):1007–19. doi:10.1007/s10552-004-1448-7 PMID:15801485

Gallagher RP, Threlfall WJ (1983). Cancer mortality in metal workers. *Can Med Assoc J*, 129(11):1191–4. PMID:6640455

Gérin M, Fletcher AC, Gray C, Winkelmann R, Boffetta P, Simonato L (1993). Development and use of a welding process exposure matrix in a historical prospective study of lung cancer risk in European welders. *Int J Epidemiol*, 22:Suppl 2: S22–8. doi:10.1093/ije/22.Supplement_2.S22 PMID:8132388

Gerin M, Siemiatycki J, Richardson L, Pellerin J, Lakhani R, Dewar R (1984). Nickel and cancer associations from a multicancer occupation exposure case-referent study: preliminary findings. In: Sunderman FW, editor. Nickel in the human environment. Lyon, France: International Agency for Research on Cancer. IARC Scientific Publication No. 53, pp. 105–115.

Ghadimi T, Gheitasi B, Nili S, Karimi M, Ghaderi E (2015). Occupation, smoking, opium, and bladder cancer: A case-control study. *South Asian J Cancer*, 4(3):111–4. doi:10.4103/2278-330X.173174 PMID:26942139

Goldberg P, Leclerc A, Luce D, Morcet JF, Brugère J (1997). Laryngeal and hypopharyngeal cancer and occupation: results of a case control-study. *Occup Environ Med*, 54(7):477–82. doi:10.1136/oem.54.7.477 PMID:9282123

Guénel P, Laforest L, Cyr D, Févotte J, Sabroe S, Dufour C, et al. (2001). Occupational risk factors, ultraviolet radiation, and ocular melanoma: a case-control study in France. *Cancer Causes Control*, 12(5):451–9. doi:10.1023/A:1011271420974 PMID:11545460

Guida F, Papadopoulos A, Menvielle G, Matrat M, Févotte J, Cénée S, et al. (2011). Risk of lung cancer and occupational history: results of a French population-based case-control study, the ICARE study. *J Occup Environ Med*, 53(9):1068–77. doi:10.1097/JOM.0b013e318229ab2e PMID:21866050

Gustavsson P, Jakobsson R, Johansson H, Lewin F, Norell S, Rutkvist LE (1998). Occupational exposures and squamous cell carcinoma of the oral cavity, pharynx, larynx, and oesophagus: a case-control study in Sweden. *Occup Environ Med*, 55(6):393–400. doi:10.1136/oem.55.6.393 PMID:9764099

Gustavsson P, Jakobsson R, Nyberg F, Pershagen G, Järup L, Schéele P (2000). Occupational exposure and lung cancer risk: a population-based case-referent study in Sweden. *Am J Epidemiol*, 152(1):32–40. doi:10.1093/aje/152.1.32 PMID:10901327

Håkansson N, Floderus B, Gustavsson P, Johansen C, Olsen JH (2002). Cancer incidence and magnetic field exposure in industries using resistance welding in Sweden. *Occup Environ Med*, 59(7):481–6. doi:10.1136/oem.59.7.481 PMID:12107298

Håkansson N, Stenlund C, Gustavsson P, Johansen C, Floderus B (2005). Arc and resistance welding and tumours of the endocrine glands: a Swedish case-control study with focus on extremely low frequency magnetic fields. *Occup Environ Med*, 62(5):304–8. doi:10.1136/oem.2004.015479 PMID:15837851

Haldorsen T, Andersen A, Boffetta P (2004). Smoking-adjusted incidence of lung cancer by occupation among Norwegian men. *Cancer Causes Control*, 15(2):139–47. doi:10.1023/B:CACO.0000019485.74818.d6 PMID:15017126

Hansen EB (1982). A survey on welding and cutting in stainless steel in the Danish Industry. Copenhagen, Denmark: Copenhagen Svejsecentralen [Danish].

Hansen KS, Lauritsen JM, Skytthe A (1996). Cancer incidence among mild steel and stainless steel welders and other metal workers. *Am J Ind Med*, 30(4):373–82.

doi:10.1002/(SICI)1097-0274(199610)30:4<373::AID-AJIM1>3.0.CO;2-X PMID:8892541

Heineman EF, Olsen JH, Pottern LM, Gomez M, Raffn E, Blair A (1992). Occupational risk factors for multiple myeloma among Danish men. *Cancer Causes Control*, 3(6):555–68. doi:10.1007/BF00052753 PMID:1420859

Hernberg S, Westerholm P, Schultz-Larsen K, Degerth R, Kuosma E, Englund A, et al. (1983). Nasal and sinonasal cancer. Connection with occupational exposures in Denmark, Finland and Sweden. *Scand J Work Environ Health*, 9(4):315–26. doi:10.5271/sjweh.2405 PMID:6635610

Holly EA, Aston DA, Ahn DK, Smith AH (1996). Intraocular melanoma linked to occupations and chemical exposures. *Epidemiology*, 7(1):55–61. doi:10.1097/00001648-199601000-00010 PMID:8664402

Howe GR, Burch JD, Miller AB, Cook GM, Esteve J, Morrison B, et al. (1980). Tobacco use, occupation, coffee, various nutrients, and bladder cancer. *J Natl Cancer Inst*, 64(4):701–13. PMID:6928984

Howe GR, Fraser D, Lindsay J, Presnal B, Yu SZ (1983). Cancer mortality (1965-77) in relation to diesel fume and coal exposure in a cohort of retired railway workers. *J Natl Cancer Inst*, 70(6):1015–9. PMID:6574269

Hu J, Little J, Xu T, Zhao X, Guo L, Jia X, et al. (1999). Risk factors for meningioma in adults: a case-control study in northeast China. *Int J Cancer*, 83(3):299–304. doi:10.1002/(SICI)1097-0215(19991029)83:3<299::AID-IJC2>3.0.CO;2-Z PMID:10495419

Huebner WW, Schoenberg JB, Kelsey JL, Wilcox HB, McLaughlin JK, Greenberg RS, et al. (1992). Oral and pharyngeal cancer and occupation: a case-control study. *Epidemiology*, 3(4):300–9. doi:10.1097/00001648-199207000-00005 PMID:1637894

Hull CJ, Doyle E, Peters JM, Garabrant DH, Bernstein L, Preston-Martin S (1989). Case-control study of lung cancer in Los Angeles county welders. *Am J Ind Med*, 16(1):103–12. doi:10.1002/ajim.4700160111 PMID:2750746

IARC (1990). Chromium, nickel and welding. *IARC Monogr Eval Carcinog Risks Hum*, 49:1–648. Available from: http://publications.iarc.fr/67 PMID:2232124

IARC (2012a). Arsenic, metals, fibres, and dusts. *IARC Monogr Eval Carcinog Risks Hum*, 100(Pt C):11–465. Available from: http://publications.iarc.fr/120 PMID:23189751

IARC (2012b). Radiation. *IARC Monogr Eval Carcinog Risks Hum*, 100(Pt D):7–303. Available from http://publications.iarc.fr/121 PMID:23189752

Ji BT, Silverman DT, Dosemeci M, Dai Q, Gao YT, Blair A (1999). Occupation and pancreatic cancer risk in Shanghai, China. *Am J Ind Med*, 35(1):76–81. doi:10.1002/(SICI)1097-0274(199901)35:1<76::AID-AJIM10>3.0.CO;2-6 PMID:9884748

Jöckel K-H, Ahrens W, Bolm-Audorff U (1994). Lung cancer risk and welding–preliminary results from an ongoing case-control study. *Am J Ind Med*, 25(6):805–12. doi:10.1002/ajim.4700250605 PMID:8067358

Jöckel KH, Ahrens W, Pohlabeln H, Bolm-Audorff U, Müller KM (1998). Lung cancer risk and welding: results from a case-control study in Germany. *Am J Ind Med*, 33(4):313–20. doi:10.1002/(SICI)1097-0274(199804)33:4<313::AID-AJIM1>3.0.CO;2-V PMID:9513638

Kaerlev L, Teglbjaerg PS, Sabroe S, Kolstad HA, Ahrens W, Eriksson M, et al. (2000). Occupation and small bowel adenocarcinoma: a European case-control study. *Occup Environ Med*, 57(11):760–6. doi:10.1136/oem.57.11.760 PMID:11024200

Kantor AF, Curnen MG, Meigs JW, Flannery JT (1979). Occupations of fathers of patients with Wilms's tumour. *J Epidemiol Community Health*, 33(4):253–6. doi:10.1136/jech.33.4.253 PMID:231629

Kantor AF, Hartge P, Hoover RN, Fraumeni JF Jr (1988). Epidemiological characteristics of squamous cell carcinoma and adenocarcinoma of the bladder. *Cancer Res*, 48(13):3853–5. PMID:3378221

Karunanayake CP, McDuffie HH, Dosman JA, Spinelli JJ, Pahwa P (2008). Occupational exposures and non-Hodgkin's lymphoma: Canadian case-control study. *Environ Health*, 7(1):44 doi:10.1186/1476-069X-7-44 PMID:18687133

Kauppinen T, Riala R, Seitsamo J, Hernberg S (1992). Primary liver cancer and occupational exposure. *Scand J Work Environ Health*, 18(1):18–25. doi:10.5271/sjweh.1616 PMID:1313183

Keller JE, Howe HL (1993). Cancer in Illinois construction workers: a study. *Am J Ind Med*, 24(2):223–30. doi:10.1002/ajim.4700240208 PMID:8213848

Kendzia B, Behrens T, Jöckel KH, Siemiatycki J, Kromhout H, Vermeulen R, et al. (2013). Welding and lung cancer in a pooled analysis of case-control studies. *Am J Epidemiol*, 178(10):1513–25. doi:10.1093/aje/kwt201 PMID:24052544

Kjuus H, Skjaerven R, Langård S, Lien JT, Aamodt T (1986). A case-referent study of lung cancer, occupational exposures and smoking. I. Comparison of title-based and exposure-based occupational information. *Scand J Work Environ Health*, 12(3):193–202. doi:10.5271/sjweh.2158 PMID:3749833

Kogevinas M, 't Mannetje A, Cordier S, Ranft U, González CA, Vineis P, et al. (2003). Occupation and bladder cancer among men in Western Europe. *Cancer Causes Control*, 14(10):907–14. doi:10.1023/B:CACO.0000007962.19066.9c PMID:14750529

Kromhout H, Heederik D, Dalderup LM, Kromhout D (1992). Performance of two general job-exposure matrices in a study of lung cancer morbidity in the Zutphen cohort. *Am J Epidemiol*, 136(6):698–711. doi:10.1093/oxfordjournals.aje.a116549 PMID:1442736

Krstev S, Stewart P, Rusiecki J, Blair A (2007). Mortality among shipyard Coast Guard workers: a retrospective cohort study. *Occup Environ Med*, 64(10):651–8. doi:10.1136/oem.2006.029652 PMID:17881470

Kubale TL, Daniels RD, Yiin JH, Couch J, Schubauer-Berigan MK, Kinnes GM, et al. (2005). A nested case-control study of leukemia mortality and ionizing radiation at the Portsmouth Naval Shipyard. *Radiat Res*, 164(6):810–9. doi:10.1667/RR3473.1 PMID:16296888

Kunze E, Chang-Claude J, Frentzel-Beyme R (1992). Life style and occupational risk factors for bladder cancer in Germany. A case-control study. *Cancer*, 69(7):1776–90. doi:10.1002/1097-0142(19920401)69:7<1776::AID-CNCR2820690721>3.0.CO;2-P PMID:1551063

Lauritsen JM, Hansen KS (1996). Lung cancer mortality in stainless steel and mild steel welders: a nested case-referent study. *Am J Ind Med*, 30(4):383–91. doi:10.1002/(SICI)1097-0274(199610)30:4<383::AID-AJIM2>3.0.CO;2-X PMID:8892542

Leclerc A, Luce D, Demers PA, Boffetta P, Kogevinas M, Belli S, et al. (1997). Sinonasal cancer and occupation. Results from the reanalysis of twelve case-control studies. *Am J Ind Med*, 31(2):153–65. doi:10.1002/(SICI)1097-0274(199702)31:2<153::AID-AJIM4>3.0.CO;2-0 PMID:9028431

Lerchen ML, Wiggins CL, Samet JM (1987). Lung cancer and occupation in New Mexico. *J Natl Cancer Inst*, 79(4):639–45. PMID:3477658

Logan WPD (1982). Cancer mortality by occupation and social class 1851–1971. Lyon: International Agency for Research on Cancer. IARC Scientific Publication No. 36.

Luce D, Gérin M, Leclerc A, Morcet JF, Brugère J, Goldberg M (1993). Sinonasal cancer and occupational exposure to formaldehyde and other substances. *Int J Cancer*, 53(2):224–31. doi:10.1002/ijc.2910530209 PMID:8425759

Luckett BG, Su LJ, Rood JC, Fontham ET (2012). Cadmium exposure and pancreatic cancer in south Louisiana. *J Environ Public Health*, 2012:180186 doi:10.1155/2012/180186 PMID:23319964

Luckhaupt SE, Deapen D, Cress R, Schumacher P, Shen R, Calvert GM (2012). Leukemia among male construction workers in California, 1988-2007. *Leuk Lymphoma*, 53(11):2228–36. doi:10.3109/10428194.2012.690873 PMID:22563817

Luqman M, Javed MM, Daud S, Raheem N, Ahmad J, Khan AU (2014). Risk factors for lung cancer in the Pakistani population. *Asian Pac J Cancer Prev*, 15(7):3035–9. doi:10.7314/APJCP.2014.15.7.3035 PMID:24815443

Lutz JM, Cree I, Sabroe S, Kvist TK, Clausen LB, Afonso N, et al. (2005). Occupational risks for uveal melanoma results from a case-control study in nine European countries. *Cancer Causes Control*, 16(4):437–47. doi:10.1007/s10552-004-5029-6 PMID:15953986

MacLeod JS, Harris MA, Tjepkema M, Peters PA, Demers PA (2017). Cancer risks among welders and occasional welders in a national population-based cohort study: Canadian Census Health and Environmental Cohort. *Saf Health Work*, 8(3):258–66. doi:10.1016/j.shaw.2016.12.001 PMID:28951802

Magnani C, Coggon D, Osmond C, Acheson ED (1987). Occupation and five cancers: a case-control study using death certificates. *Br J Ind Med*, 44(11):769–76. PMID:3689708

Mandel JS, McLaughlin JK, Schlehofer B, Mellemgaard A, Helmert U, Lindblad P, et al. (1995). International renal-cell cancer study. IV. Occupation. *Int J Cancer*, 61(5):601–5. doi:10.1002/ijc.2910610503 PMID:7768630

Mao Y, Hu J, Ugnat AM, White K; Canadian Cancer Registries Epidemiology Research Group (2000). Non-Hodgkin's lymphoma and occupational exposure to chemicals in Canada. *Ann Oncol*, 11:Suppl 1: 69–73. doi:10.1093/annonc/11.suppl_1.S69 PMID:10707783

Matos E, Vilensky MV, Boffetta PB (1998). Environmental and occupational cancer in Argentina: a case-control lung cancer study. *Cad Saude Publica*, 14:Suppl 3: 77–86. doi:10.1590/S0102-311X1998000700008 PMID:9819466

Matrat M, Guida F, Mattei F, Cénée S, Cyr D, Févotte J, et al.; Icare Study Group (2016). Welding, a risk factor of lung cancer: the ICARE study. *Occup Environ Med*, 73(4):254–61. doi:10.1136/oemed-2015-102964 PMID:26865654

Mattioli S, Truffelli D, Baldasseroni A, Risi A, Marchesini B, Giacomini C, et al. (2002). Occupational risk factors for renal cell cancer: a case–control study in northern Italy. *J Occup Environ Med*, 44(11):1028–36. doi:10.1097/00043764-200211000-00009 PMID:12448354

McCredie M, Stewart JH (1993). Risk factors for kidney cancer in New South Wales. IV. Occupation. *Br J Ind Med*, 50(4):349–54. PMID:8494775

McLaughlin JK, Malker HSR, Blot WJ, Malker BK, Stone BJ, Weiner JA, et al. (1987). Occupational risks for intracranial gliomas in Sweden. *J Natl Cancer Inst*, 78(2):253–7. PMID:3468289

McMillan GHG, Pethybridge RJ (1983). The health of welders in naval dockyards: proportional mortality study of welders and two control groups. *J Soc Occup Med*, 33(2):75–84. doi:10.1093/occmed/33.2.75 PMID:6865346

Meguellati-Hakkas D, Cyr D, Stücker I, Févotte J, Pilorget C, Luce D, et al. (2006). Lung cancer mortality and occupational exposure to asbestos among telephone linemen: a historical cohort study in France. *J Occup Environ Med*, 48(11):1166–72. doi:10.1097/01.jom.0000243357.70143.47 PMID:17099453

Melkild A, Langård S, Andersen A, Tønnessen JN (1989). Incidence of cancer among welders and other workers

in a Norwegian shipyard. *Scand J Work Environ Health*, 15(6):387–94. doi:10.5271/sjweh.1834 PMID:2617255

Menck HR, Henderson BE (1976). Occupational differences in rates of lung cancer. *J Occup Med*, 18(12):797–801. doi:10.1097/00043764-197612000-00005 PMID:993873

Merletti F, Boffetta P, Ferro G, Pisani P, Terracini B (1991). Occupation and cancer of the oral cavity or oropharynx in Turin, Italy. *Scand J Work Environ Health*, 17(4):248–54. doi:10.5271/sjweh.1706 PMID:1925436

Merlo F, Costantini M, Doria M (1989). Cause specific mortality among workers exposed to welding fumes and gases: a historical prospective study. *J UOEH*, 11:Suppl: 302–15. PMID:2749060

Milatou-Smith R, Gustavsson A, Sjögren B (1997). Mortality among Welders Exposed to High and to Low Levels of Hexavalent Chromium and Followed for More Than 20 Years. *Int J Occup Environ Health*, 3(2):128–31. doi:10.1179/107735297800407749 PMID:9891110

Monárrez-Espino J, Stang A, Bromen K, Merzenich H, Anastassiou G, Jöckel KH (2002). Occupation as a risk factor for uveal melanoma in Germany. *Scand J Work Environ Health*, 28(4):270–7. doi:10.5271/sjweh.675 PMID:12199429

Morabia A, Markowitz S, Garibaldi K, Wynder EL (1992). Lung cancer and occupation: results of a multicentre case-control study. *Br J Ind Med*, 49(10):721–7. PMID:1419861

Moulin JJ, Wild P, Haguenoer JM, Faucon D, De Gaudemaris R, Mur JM, et al. (1993). A mortality study among mild steel and stainless steel welders. *Br J Ind Med*, 50(3):234–43. PMID:8457490

Neasham D, Sifi A, Nielsen KR, Overvad K, Raaschou-Nielsen O, Tjønneland A, et al. (2011). Occupation and risk of lymphoma: a multicentre prospective cohort study (EPIC). *Occup Environ Med*, 68(1):77–81. doi:10.1136/oem.2009.048173 PMID:20884795

Newhouse ML, Oakes D, Woolley AJ (1985). Mortality of welders and other craftsmen at a shipyard in NE England. *Br J Ind Med*, 42(6):406–10. PMID:4005194

NIOSH (2015). National Occupational Mortality Surveillance (NOMS). Available from: https://www.cdc.gov/niosh/topics/NOMS/chart2.html

Norell S, Ahlbom A, Olin R, Erwald R, Jacobson G, Lindberg-Navier I, et al. (1986). Occupational factors and pancreatic cancer. *Br J Ind Med*, 43(11):775–8. PMID:3790458

Office of Population Censuses and Surveys (1978). Occupational mortality. The Registrar General's decennial supplement for England and Wales, 1970–72. London, UK: Her Majesty's Stationery Office; p. 140.

Olsen J, Sabroe S, Lajer M (1984). Welding and cancer of the larynx: a case-control study. *Eur J Cancer Clin Oncol*, 20(5):639–43. doi:10.1016/0277-5379(84)90010-5 PMID:6539700

Olshan AF, Breslow NE, Daling JR, Falletta JM, Grufferman S, Robison LL, et al. (1990). Wilms' tumor and paternal occupation. *Cancer Res*, 50(11):3212–7. PMID:2159375

Olshan AF, De Roos AJ, Teschke K, Neglia JP, Stram DO, Pollock BH, et al. (1999). Neuroblastoma and parental occupation. *Cancer Causes Control*, 10(6):539–49. doi:10.1023/A:1008998925889 PMID:10616823

Oppenheimer M, Preston-Martin S (2002). Adult onset acute myelogenous leukemia and electromagnetic fields in Los Angeles County: bed-heating and occupational exposures. *Bioelectromagnetics*, 23(6):411–5. doi:10.1002/bem.10031 PMID:12210558

Paget-Bailly S, Guida F, Carton M, Menvielle G, Radoï L, Cyr D, et al. (2013). Occupation and head and neck cancer risk in men: results from the ICARE study, a French population-based case-control study. *J Occup Environ Med*, 55(9):1065–73. doi:10.1097/JOM.0b013e318298fae4 PMID:23969505

Pan SY, Ugnat AM, Mao Y; Canadian Cancer Registries Epidemiology Research Group (2005). Occupational risk factors for brain cancer in Canada. *J Occup Environ Med*, 47(7):704–17. doi:10.1097/01.jom.0000165747.95801.c5 PMID:16010197

Pannett B, Coggon D, Acheson ED (1985). A job-exposure matrix for use in population based studies in England and Wales. *Br J Ind Med*, 42(11):777–83. PMID:4063222

Parent ME, Hua Y, Siemiatycki J (2000). Occupational risk factors for renal cell carcinoma in Montreal. *Am J Ind Med*, 38(6):609–18. doi:10.1002/1097-0274(200012)38:6<609::AID-AJIM1>3.0.CO;2-4 PMID:11071683

Paris C, Clement-Duchene C, Vignaud JM, Gislard A, Stoufflet A, Bertrand O, et al. (2010). Relationships between lung adenocarcinoma and gender, age, smoking and occupational risk factors: A case-case study. *Lung Cancer*, 68(2):146–53. doi:10.1016/j.lungcan.2009.06.007 PMID:19586681

Park R, Krebs J, Mirer F (1994). Mortality at an automotive stamping and assembly complex. *Am J Ind Med*, 26(4):449–63. doi:10.1002/ajim.4700260403 PMID:7810544

Persson B, Dahlander AM, Fredriksson M, Brage HN, Ohlson CG, Axelson O (1989). Malignant lymphomas and occupational exposures. *Br J Ind Med*, 46(8):516–20. PMID:2775671

Persson B, Fredriksson M, Olsen K, Boeryd B, Axelson O (1993). Some occupational exposures as risk factors for malignant lymphomas. *Cancer*, 72(5):1773–8. doi:10.1002/1097-0142(19930901)72:5<1773::AID-CNCR2820720542>3.0.CO;2-6 PMID:8348507

Pesch B, Gawrych K, Rabstein S, Weiss T, Casjens S, Rihs HP, et al. (2013). N-acetyltransferase 2 phenotype, occupation, and bladder cancer risk: results from the EPIC cohort. *Cancer Epidemiol Biomarkers Prev*, 22(11):2055–65. doi:10.1158/1055-9965.EPI-13-0119-T PMID:24092628

Pesch B, Haerting J, Ranft U, Klimpel A, Oelschlägel B, Schill W (2000). Occupational risk factors for renal cell carcinoma: agent-specific results from a case-control study in Germany. MURC Study Group. Multicenter urothelial and renal cancer study. *Int J Epidemiol*, 29(6):1014–24. doi:10.1093/ije/29.6.1014 PMID:11101542

Pezzotto SM, Poletto L (1999). Occupation and histopathology of lung cancer: A case-control study in Rosario, Argentina. *Am J Ind Med*, 36(4):437–43. doi:10.1002/(SICI)1097-0274(199910)36:4<437::AID-AJIM4>3.0.CO;2-C PMID:10470008

Polednak AP (1981). Mortality among welders, including a group exposed to nickel oxides. *Arch Environ Health*, 36(5):235–42. doi:10.1080/00039896.1981.10667630 PMID:7294887

Porru S, Aulenti V, Donato F, Boffetta P, Fazioli R, Cosciani Cunico S, et al. (1996). Bladder cancer and occupation: a case-control study in northern Italy. *Occup Environ Med*, 53(1):6–10. doi:10.1136/oem.53.1.6 PMID:8563860

Preston-Martin S, Peters JM (1988). Prior employment as a welder associated with the development of chronic myeloid leukaemia. *Br J Cancer*, 58(1):105–8. doi:10.1038/bjc.1988.173 PMID:3166887

Pukkala E, Martinsen JI, Lynge E, Gunnarsdottir HK, Sparén P, Tryggvadottir L, et al. (2009). Occupation and cancer - follow-up of 15 million people in five Nordic countries. *Acta Oncol*, 48(5):646–790. doi:10.1080/02841860902913546 PMID:19925375

Puntoni R, Merlo F, Borsa L, Reggiardo G, Garrone E, Ceppi M (2001). A historical cohort mortality study among shipyard workers in Genoa, Italy. *Am J Ind Med*, 40(4):363–70. doi:10.1002/ajim.1110 PMID:11598985

Puntoni R, Vercelli M, Merlo F, Valerio F, Santi L (1979). Mortality among shipyard workers in Genoa, Italy. *Ann N Y Acad Sci*, 330(1):353–77. doi:10.1111/j.1749-6632.1979.tb18738.x PMID:230774

Reulen RC, Kellen E, Buntinx F, Brinkman M, Zeegers MP (2008). A meta-analysis on the association between bladder cancer and occupation. *Scand J Urol Nephrol Suppl*, 42(218):64–78. doi:10.1080/03008880802325192 PMID:18815919

Richiardi L, Boffetta P, Simonato L, Forastiere F, Zambon P, Fortes C, et al. (2004). Occupational risk factors for lung cancer in men and women: a population-based case-control study in Italy. *Cancer Causes Control*, 15(3):285–94. doi:10.1023/B:CACO.0000024223.91059.ed PMID:15090723

Rinsky RA, Melius JM, Hornung RW, Zumwalde RD, Waxweiler RJ, Landrigan PJ, et al. (1988). Case-control study of lung cancer in civilian employees at the Portsmouth Naval Shipyard, Kittery, Maine. *Am J Epidemiol*, 127(1):55–64. doi:10.1093/oxfordjournals.aje.a114791 PMID:3337077

Risch HA, Burch JD, Miller AB, Hill GB, Steele R, Howe GR (1988). Occupational factors and the incidence of cancer of the bladder in Canada. *Br J Ind Med*, 45(6):361–7. PMID:3395572

Rolland P, Gramond C, Lacourt A, Astoul P, Chamming's S, Ducamp S, et al.; PNSM Study Group (2010). Occupations and industries in France at high risk for pleural mesothelioma: A population-based case-control study (1998-2002). *Am J Ind Med*, 53(12):1207–19. doi:10.1002/ajim.20895 PMID:20886529

Ronco G, Ciccone G, Mirabelli D, Troia B, Vineis P (1988). Occupation and lung cancer in two industrialized areas of northern Italy. *Int J Cancer*, 41(3):354–8. doi:10.1002/ijc.2910410306 PMID:3346099

Ruder AM, Waters MA, Carreón T, Butler MA, Calvert GM, Davis-King KE, et al.; Brain Cancer Collaborative Study Group(2012). The Upper Midwest Health Study: industry and occupation of glioma cases and controls. *Am J Ind Med*, 55(9):747–55. doi:10.1002/ajim.22085 PMID:22715102

Saberi Hosnijeh F, Christopher Y, Peeters P, Romieu I, Xun W, Riboli E, et al. (2013). Occupation and risk of lymphoid and myeloid leukaemia in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Occup Environ Med*, 70(7):464–70. doi:10.1136/oemed-2012-101135 PMID:23576671

Sadetzki S, Chetrit A, Turner MC, van Tongeren M, Benke G, Figuerola J, et al. (2016). Occupational exposure to metals and risk of meningioma: a multinational case-control study. *J Neurooncol*, 130(3):505–15. doi:10.1007/s11060-016-2244-4 PMID:27664150

Samanic CM, Kogevinas M, Silverman DT, Tardón A, Serra C, Malats N, et al. (2008). Occupation and bladder cancer in a hospital-based case-control study in Spain. *Occup Environ Med*, 65(5):347–53. doi:10.1136/oem.2007.035816 PMID:17951336

Sauvé JF, Lavoué J, Parent ME (2016). Occupation, industry, and the risk of prostate cancer: a case-control study in Montréal, Canada. *Environ Health*, 15(1):100 doi:10.1186/s12940-016-0185-1 PMID:27769264

Schifflers E, Jamart J, Renard V (1987). Tobacco and occupation as risk factors in bladder cancer: a case-control study in southern Belgium. *Int J Cancer*, 39(3):287–92. doi:10.1002/ijc.2910390304 PMID:3818120

Schoenberg JB, Stemhagen A, Mason TJ, Patterson J, Bill J, Altman R (1987). Occupation and lung cancer risk among New Jersey white males. *J Natl Cancer Inst*, 79(1):13–21. PMID:3474440

Seddon JM, Gragoudas ES, Glynn RJ, Egan KM, Albert DM, Blitzer PH (1990). Host factors, UV radiation, and risk of uveal melanoma. A case-control study. *Arch Ophthalmol*, 108(9):1274–80. doi:10.1001/archopht.1990.01070110090031 PMID:2400347

Seel EA, Zaebst DD, Hein MJ, Liu J, Nowlin SJ, Chen P (2007). Inter-rater agreement for a retrospective exposure assessment of asbestos, chromium, nickel and welding fumes in a study of lung cancer and ionizing radiation. *Ann Occup Hyg*, 51(7):601–10. PMID:17846032

Shah CP, Weis E, Lajous M, Shields JA, Shields CL (2005). Intermittent and chronic ultraviolet light exposure and uveal melanoma: a meta-analysis. *Ophthalmology*, 112(9):1599–607. doi:10.1016/j.ophtha.2005.04.020 PMID:16051363

Shangina O, Brennan P, Szeszenia-Dabrowska N, Mates D, Fabiánová E, Fletcher T, et al. (2006). Occupational exposure and laryngeal and hypopharyngeal cancer risk in central and eastern Europe. *Am J Epidemiol*, 164(4):367–75. doi:10.1093/aje/kwj208 PMID:16801374

Siemiatycki J (1991). Risk factors for cancer in the workplace. Boca Raton (FL), USA: CRC Press.

Siew SS, Kauppinen T, Kyyrönen P, Heikkilä P, Pukkala E (2008). Exposure to iron and welding fumes and the risk of lung cancer. *Scand J Work Environ Health*, 34(6):444–50. doi:10.5271/sjweh.1296 PMID:19137206

Silverman DT, Hoover RN, Albert S, Graff KM (1983). Occupation and cancer of the lower urinary tract in Detroit. *J Natl Cancer Inst*, 70(2):237–45. PMID:6571931

Silverman DT, Levin LI, Hoover RN (1989a). Occupational risks of bladder cancer in the United States: II Nonwhite men. *J Natl Cancer Inst*, 81(19):1480–3. doi:10.1093/jnci/81.19.1480 PMID:2778835

Silverman DT, Levin LI, Hoover RN (1990). Occupational risks of bladder cancer among white women in the United States. *Am J Epidemiol*, 132(3):453–61. doi:10.1093/oxfordjournals.aje.a115680 PMID:2389750

Silverman DT, Levin LI, Hoover RN, Hartge P (1989b). Occupational risks of bladder cancer in the United States: I. White men. *J Natl Cancer Inst*, 81(19):1472–80. doi:10.1093/jnci/81.19.1472 PMID:2778834

Silverstein M, Maizlish N, Park R, Mirer F (1985). Mortality among workers exposed to coal tar pitch volatiles and welding emissions: an exercise in epidemiologic triage. *Am J Public Health*, 75(11):1283–7. doi:10.2105/AJPH.75.11.1283 PMID:4051064

Simonato L, Fletcher AC, Andersen A, Anderson K, Becker N, Chang-Claude J, et al. (1991). A historical prospective study of European stainless steel, mild steel, and shipyard welders. *Br J Ind Med*, 48(3):145–54. PMID:2015204

Sjögren B (1980). A retrospective cohort study of mortality among stainless steel welders. *Scand J Work Environ Health*, 6(3):197–200. doi:10.5271/sjweh.2616 PMID:6937824

Sjögren B, Carstensen J (1986). Cancer morbidity among Swedish welders and gas-cutters. In: Stern RM, Berlin A, Fletcher AC, Järvisalo J editors. Health hazards and biological effects of welding fumes and gases. Amsterdam: Excerpta Medica; pp. 461–3.

Sjögren B, Gustavsson A, Hedström L (1987). Mortality in two cohorts of welders exposed to high- and low-levels of hexavalent chromium. *Scand J Work Environ Health*, 13(3):247–51. doi:10.5271/sjweh.2056 PMID:3616554

Smulevich VB, Solionova LG, Belyakova SV (1999). Parental occupation and other factors and cancer risk in children: II. Occupational factors. *Int J Cancer*, 83(6):718–22. doi:10.1002/(SICI)1097-0215(19991210)83:6<718::AID-IJC3>3.0.CO;2-T PMID:10597184

Sorahan T, Cooke MA (1989). Cancer mortality in a cohort of United Kingdom steel foundry workers: 1946-85. *Br J Ind Med*, 46(2):74–81. PMID:2923828

Sorahan T, Faux AM, Cooke MA (1994). Mortality among a cohort of United Kingdom steel foundry workers with special reference to cancers of the stomach and lung, 1946-90. *Occup Environ Med*, 51(5):316–22. doi:10.1136/oem.51.5.316 PMID:8199681

Sørensen AR, Thulstrup AM, Hansen J, Ramlau-Hansen CH, Meersohn A, Skytthe A, et al. (2007). Risk of lung cancer according to mild steel and stainless steel welding. *Scand J Work Environ Health*, 33(5):379–86. doi:10.5271/sjweh.1157 PMID:17973064

Soskolne CL, Jhangri GS, Pagano G, Botte G, Di Cintio P, Claudio L, et al. (2007). Using established occupational respiratory cancer risk factors for assessing the internal validity in an unmatched case-control study in the Campania Region of Italy, 1988–1990. *Eur J Oncol*, 12:23–9.

Steenland K (2002). Ten-year update on mortality among mild-steel welders. *Scand J Work Environ Health*, 28(3):163–7. doi:10.5271/sjweh.660 PMID:12109555

Steenland K, Beaumont J, Elliot L (1991). Lung cancer in mild steel welders. *Am J Epidemiol*, 133(3):220–9. doi:10.1093/oxfordjournals.aje.a115866 PMID:2000839

Steenland K, Beaumont J, Hornung R (1986). The use of regression analyses in a cohort mortality study of welders. *J Chronic Dis*, 39(4):287–94. doi:10.1016/0021-9681(86)90050-0 PMID:3958115

Stern FB, Waxweiler RA, Beaumont JJ, Lee ST, Rinsky RA, Zumwalde RD, et al. (1986). A case-control study of leukemia at a naval nuclear shipyard. *Am J Epidemiol*, 123(6):980–92. doi:10.1093/oxfordjournals.aje.a114350 PMID:3458360

't Mannetje A, Brennan P, Zaridze D, Szeszenia-Dabrowska N, Rudnai P, Lissowska J, et al. (2012). Welding and lung cancer in Central and Eastern Europe and the United Kingdom. *Am J Epidemiol*, 175(7):706–14. doi:10.1093/aje/kwr358 PMID:22343633

't Mannetje A, De Roos AJ, Boffetta P, Vermeulen R, Benke G, Fritschi L, et al. (2016). Occupation and risk of non-Hodgkin lymphoma and its subtypes: a pooled analysis from the InterLymph Consortium. *Environ Health Perspect*, 124(4):396–405. PMID:26340796

't Mannetje A, Dryson E, Walls C, McLean D, McKenzie F, Maule M, et al. (2008). High risk occupations for non-Hodgkin's lymphoma in New Zealand: case-control study. *Occup Environ Med*, 65(5):354–63. doi:10.1136/oem.2007.035014 PMID:18032530

Teschke K, Morgan MS, Checkoway H, Franklin G, Spinelli JJ, van Belle G, et al. (1997). Surveillance of nasal and bladder cancer to locate sources of exposure to occupational carcinogens. *Occup Environ Med*, 54(6):443–51. doi:10.1136/oem.54.6.443 PMID:9245952

Togawa K, Le Cornet C, Feychting M, Tynes T, Pukkala E, Hansen J, et al. (2016). Parental occupational exposure to heavy metals and welding fumes and risk of testicular germ cell tumors in offspring: a registry-based case-control study. *Cancer Epidemiol Biomarkers Prev*, 25(10):1426–34. doi:10.1158/1055-9965.EPI-16-0328 PMID:27439405

Tola S, Kalliomäki PL, Pukkala E, Asp S, Korkala ML (1988). Incidence of cancer among welders, platers, machinists, and pipe fitters in shipyards and machine shops. *Br J Ind Med*, 45(4):209–18. PMID:3377996

Tse LA, Yu IT, Qiu H, Au JS, Wang XR (2012). Occupational risks and lung cancer burden for Chinese men: a population-based case-referent study. *Cancer Causes Control*, 23(1):121–31. doi:10.1007/s10552-011-9861-1 PMID:22037909

Tucker MA, Hartge P, Shields JA (1986). Epidemiology of intraocular melanoma. *Recent Results Cancer Res*, 102:159–65. doi:10.1007/978-3-642-82641-2_14 PMID:3738184

Tucker MA, Shields JA, Hartge P, Augsburger J, Hoover RN, Fraumeni JF Jr (1985). Sunlight exposure as risk factor for intraocular malignant melanoma. *N Engl J Med*, 313(13):789–92. doi:10.1056/NEJM198509263131305 PMID:4033707

Vajdic CM, Kricker A, Giblin M, McKenzie J, Aitken JF, Giles GG, et al. (2004). Artificial ultraviolet radiation and ocular melanoma in Australia. *Int J Cancer*, 112(5):896–900. doi:10.1002/ijc.20476 PMID:15386378

Vallières E, Pintos J, Lavoué J, Parent ME, Rachet B, Siemiatycki J (2012). Exposure to welding fumes increases lung cancer risk among light smokers but not among heavy smokers: evidence from two case-control studies in Montreal. *Cancer Med*, 1(1):47–58. doi:10.1002/cam4.6 PMID:23342253

van der Gulden JW, Kolk JJ, Verbeek AL (1995). Work environment and prostate cancer risk. *Prostate*, 27(5):250–7. doi:10.1002/pros.2990270504 PMID:7479392

van Loon AJ, Goldbohm RA, Kant IJ, Swaen GM, Kremer AM, van den Brandt PA (1997a). Socioeconomic status and lung cancer incidence in men in The Netherlands: is there a role for occupational exposure? *J Epidemiol Community Health*, 51(1):24–9. doi:10.1136/jech.51.1.24 PMID:9135784

van Loon AJ, Kant IJ, Swaen GM, Goldbohm RA, Kremer AM, van den Brandt PA (1997b). Occupational exposure to carcinogens and risk of lung cancer: results from The Netherlands cohort study. *Occup Environ Med*, 54(11):817–24. doi:10.1136/oem.54.11.817 PMID:9538355

Vaughan TL (1989). Occupation and squamous cell cancers of the pharynx and sinonasal cavity. *Am J Ind Med*, 16(5):493–510. doi:10.1002/ajim.4700160503 PMID:2589327

Veglia F, Vineis P, Overvad K, Boeing H, Bergmann M, Trichopoulou A, et al. (2007). Occupational exposures, environmental tobacco smoke, and lung cancer. *Epidemiology*, 18(6):769–75. doi:10.1097/EDE.0b013e318142c8a1 PMID:18062064

Verma DK, Julian JA, Roberts RS, Muir DC, Jadon N, Shaw DS (1992). Polycyclic aromatic hydrocarbons (PAHs): a possible cause of lung cancer mortality among nickel/copper smelter and refinery workers. *Am Ind Hyg Assoc J*, 53(5):317–24. doi:10.1080/15298669291359717 PMID:1609742

Walschaerts M, Muller A, Auger J, Bujan L, Guérin JF, Le Lannou D, et al. (2007). Environmental, occupational and familial risks for testicular cancer: a hospital-based case-control study. *Int J Androl*, 30(4):222–9. doi:10.1111/j.1365-2605.2007.00805.x PMID:17708752

Wilkins JR 3rd, Sinks TH Jr (1984). Paternal occupation and Wilms' tumour in offspring. *J Epidemiol Community Health*, 38(1):7–11. doi:10.1136/jech.38.1.7 PMID:6323612

Wilkins JR 3rd, Wellage LC (1996). Brain tumor risk in offspring of men occupationally exposed to electric and magnetic fields. *Scand J Work Environ Health*, 22(5):339–45. doi:10.5271/sjweh.151 PMID:8923606

Wong JYY, Bassig BA, Seow WJ, Hu W, Ji BT, Blair A, et al. (2017). Lung cancer risk in welders and foundry workers with a history of heavy smoking in the USA: The National Lung Screening Trial. *Occup Environ Med*, 74(6):440–8. doi:10.1136/oemed-2016-104168 PMID:28069970

Wong O, Harris F, Armstrong TW, Hua F (2010). A hospital-based case-control study of acute myeloid leukemia in Shanghai: analysis of environmental and occupational risk factors by subtypes of the WHO classification. *Chem Biol Interact*, 184(1-2):112–28. doi:10.1016/j.cbi.2009.10.017 PMID:19900423

Wortley P, Vaughan TL, Davis S, Morgan MS, Thomas DB (1992). A case-control study of occupational risk factors for laryngeal cancer. *Br J Ind Med*, 49(12):837–44. PMID:1472441

Wu WT, Lu YH, Lin YJ, Yang YH, Shiue HS, Hsu JH, et al. (2013). Mortality among shipbreaking workers in Taiwan–a retrospective cohort study from 1985 to 2008. *Am J Ind Med*, 56(6):701–8. doi:10.1002/ajim.22135 PMID:23532723

Xie S-H, Yu IT, Tse LA, Au JSK, Lau JSM (2017). Occupational risk factors for nasopharyngeal carcinoma in Hong Kong Chinese: a case-referent study. *Int*

Arch Occup Environ Health, 90(5):443–9. doi:10.1007/s00420-017-1212-4 PMID:28255757

Yiin JH, Schubauer-Berigan MK, Silver SR, Daniels RD, Kinnes GM, Zaebst DD, et al. (2005). Risk of lung cancer and leukemia from exposure to ionizing radiation and potential confounders among workers at the Portsmouth Naval Shipyard. *Radiat Res*, 163(6):603–13. doi:10.1667/RR3373 PMID:15913392

Yiin JH, Silver SR, Daniels RD, Zaebst DD, Seel EA, Kubale TL (2007). A nested case-control study of lung cancer risk and ionizing radiation exposure at the portsmouth naval shipyard. *Radiat Res*, 168(3):341–8. doi:10.1667/RR0843.1 PMID:17705634

Zaebst DD, Seel EA, Yiin JH, Nowlin SJ, Chen P (2009). Summary of retrospective asbestos and welding fume exposure estimates for a nuclear naval shipyard and their correlation with radiation exposure estimates. *J Occup Environ Hyg*, 6(7):404–14. doi:10.1080/15459620902922573 PMID:19378213

Zahm SH, Brownson RC, Chang JC, Davis JR (1989). Study of lung cancer histologic types, occupation, and smoking in Missouri. *Am J Ind Med*, 15(5):565–78. doi:10.1002/ajim.4700150509 PMID:2741962

Zaridze DG, Nekrasova LI, Basieva TKh (1992). [Increased risk factors for the occurrence of bladder cancer] *Vopr Onkol*, 38(9):1066–73. [Russian] PMID:1300819

Zeegers MP, Friesema IH, Goldbohm RA, van den Brandt PA (2004). A prospective study of occupation and prostate cancer risk. *J Occup Environ Med*, 46(3):271–9. doi:10.1097/01.jom.0000116961.48464.6b PMID:15091290

Zheng T, Blair A, Zhang Y, Weisenburger DD, Zahm SH (2002). Occupation and risk of non-Hodgkin's lymphoma and chronic lymphocytic leukemia. *J Occup Environ Med*, 44(5):469–74. doi:10.1097/00043764-200205000-00015 PMID:12024692

3. CANCER IN EXPERIMENTAL ANIMALS

A previous *IARC Monographs* Working Group concluded in 1989 that there was *inadequate evidence* for the carcinogenicity of welding fumes in experimental animals (IARC, 1990).

3.1 Mouse

See Table 3.1

3.1.1 Inhalation

Groups of age- and weight-matched male A/J mice (age, 5 weeks) were exposed by whole-body inhalation to gas metal arc stainless steel (GMA-SS) welding fumes at 40 mg/m^3 of filtered air for 3 hours per day for 6 (n = 45 per group) or 10 (n = 55 per group) days (Zeidler-Erdely et al., 2011a). The automated system for the generation of welding fumes consisted of a welding power source, an automated, programmable six-axis robotic arm, a water-cooled arc welding torch, a wire feeder, and an automatic welding torch cleaner. For the initial studies on characterization of fumes, GMA welding was performed using a SS electrode. Welding was performed on A36 carbon steel plates. A shielding gas combination of 95% argon (Ar) and 5% carbon dioxide (CO_2) was used during welding. The resulting aerosol was carried into a whole-body animal exposure chamber through a flexible tube. Particle concentrations within the exposure chamber were continuously monitored. Mice inhaled welding fumes composed of iron (57 percentage by weight or wt%), chromium (20.2 wt%), manganese (13.8 wt%), nickel (8.8 wt%), and copper (0.2 wt%), with trace amounts of silicon, aluminium, and vanadium. The particle diameters ranged from ultrafine (0.01–0.10 μm) to coarse (1.0–10 μm), with most particles in the fine size range (0.10–1.0 μm). Gas generation, including carbon monoxide (CO) and ozone (O_3), was continuously monitored. In the exposure chamber, carbon monoxide and ozone concentrations were not significantly higher than background levels (Antonini et al., 2006; Erdely et al., 2011). The 6- and 10-day inhalation regimes were estimated to be equivalent to 30 and 50 days of exposure, respectively, in a 75 kg person working an 8-hour shift using the previous threshold limit value time-weighted average of 5 mg/m^3 for welding fumes (Zeidler-Erdely et al., 2011a). The deposited human dose was calculated as: fume concentration (5 mg/m^3) multiplied by minimum volume (20 L/min × 10^{-3} m^3/L), exposure duration (8 hours per day × 60 minutes per hour), and alveolar deposition efficiency (0.16). The deposited human dose at these conditions is 7.7 mg/day. The proportional equivalent deposition in mice, assuming a mouse body weight of 20 g, is 7.7 mg/day multiplied by 20 g divided by 75 kg, which equals 2.05 μg/day. To simulate an exposure period of approximately 50 days, measured deposition in the study was 11 μg/day for 10 days of inhalation exposure (Erdely et al., 2011). The effect of welding fumes on grossly observed lung tumour multiplicity (average number of tumours per lung) and incidence

Table 3.1 Studies of carcinogenicity in experimental animals exposed to welding fumes

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Results	Significance	Comments
Full carcinogenicity Mouse, A/J (M) 5 wk 78 wk Zeidler-Erdely et al. (2011a)	Inhalation (whole-body) GMA-SS welding fumes (see Comments) Air Air for 6 d, GMA-SS for 6 d (40 mg/m^3 for 3 h/d), air for 10 d, GMA-SS for 10 d (40 mg/m^3 for 3 h/d) 45, 45, 55, 55 33, 37, 43, 42	Lung: tumours (gross lesions) Tumour incidence 6 d: air, 24/33; GMA-SS, 19/37 10 d: air, 33/43; GMA-SS, 26/42 Tumour multiplicity: 6 d: air, 1.36 ± 0.21; GMA-SS, 0.84 ± 0.16 10 d: air, 0.93 ± 0.11; GMA-SS, 0.86 ± 0.14 Total tumours: 6 d: air, 45; GMA-SS, 31 10 d: air, 40; GMA-SS, 36	 NS NS NS	Principal limitations: short duration of exposure; histopathological examination of the lung only; use of a low dose; lung histopathology only on selected animals Metals (wt%): Fe (57), Cr (20.2), Mn (13.8), Ni (8.8), Cu (0.2); trace amounts of Si, Al, and V Mass median aerodynamic diameter: 0.255 µm with SD of 1.352
Full carcinogenicity Mouse, A/J (M) 5 wk 48 wk, 78 wk Zeidler-Erdely et al. (2008)	Oropharyngeal aspiration GMA-MS and GMA-SS welding fumes; MMA-SS welding fumes (see Comments) PBS 85 µg 4 × (once every 3 d) in 25 µL PBS Sham control (25 µL/aspiration), GMA-MS (340 µg), GMA-SS 340 µg), MMA-SS (340 µg) evaluated after 48 wk and 78 wk 25, 25, 25, 25, 25, 25, 25, 25 21, 24, 20, 24, 19, 20, 16, 20	Lung, alveolar/bronchiolar: tumours (gross lesions) Tumour incidence: 48 wk: sham control, 7/21; GMA-MS, 8/24; GMA-SS, 8/20; MMA-SS, 5/24 78 wk: sham control, 10/19; GMA-MS, 13/20; GMA-SS, 13/16; MMA-SS, 16/20 Tumour multiplicity: 48 wk: sham control, 0.38 ± 0.13; GMA-MS, 0.42 ± 0.14; GMA-SS, 0.45 ± 0.14; MMA-SS, 0.25 ± 0.11 78 wk: sham control, 1.00 ± 0.35; GMA-MS, 1.00 ± 0.22; GMA-SS, 1.75 ± 0.32; MMA-SS, 1.55 ± 0.34 Total tumours: 48 wk: sham control, 8; GMA-MS, 10; GMA-SS, 9; MMA-SS, 6 78 wk: sham control, 19; GMA-MS, 20; GMA-SS, 28; MMA-SS, 31	 NS NS NS	Principal strengths: well-described and -conducted study Principal limitations: only one dose; histopathological examination of the lung only; small numbers of animals; non-physiological route of exposure Metals (wt%): GMA-MS, Fe (85), Mn (14); GMA-SS, Fe (53), Mn (23), Cr (19), Ni (5) MMA-SS: Fe (41), Cr (29), Mn (17), Ni (3) Soluble/insoluble ratio: GMA-MS, 0.020; GMA-SS, 0.006; MMA-SS, 0.345 (soluble metals: Cr, 87%; Mn, 11%) Count mean diameters: GMA-MS, 1.22 µm; GMA-SS 1.38 µm; MMA-SS 0.92 µm

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Results	Significance	Comments
Full carcinogenicity Mouse, A/J (M) 8–10 wk 78 wk Zeidler-Erdely et al. (2011b)	Oropharyngeal aspiration MMA-SS welding fumes (see Comments) PBS 60 µL (sham control), 20 mg/kg bw 1 ×/mo for 4 mo NR 8, 11	Lung, alveolar/bronchiolar: preneoplastic epithelial proliferations, adenoma, carcinomas, or microcarcinomas (combined)		Principal strengths: well-described and -conducted study Principal limitations: only one dose; small number of animals; lung histopathology only; non-physiological route of exposure Metals (wt%): Fe (41), Cr (29), Mn (17), and Ni (3); trace amounts of Cu and Ti Soluble fraction (%): Cr (87), Fe (0.39), Mn (11.7), Ni (0.65) Insoluble fraction (%): Cr (9.97), Fe (53.7), Mn (18.4), Ni (3.35)
		Tumour incidence: sham control(grossly observed), 7/8; sham control (histopathology), 6/8; MMA-SS (grossly observed), 11/11; MMA-SS (histopathology), 11/11	NS	
		Tumour multiplicity: sham control (grossly observed), 2.38 ± 0.42; sham control (histopathology), 1.25 ± 0.31; MMA-SS (grossly observed), 3.00 ± 0.57; MMA-SS (histopathology), 2.36 ± 0.39*	*$P < 0.05$	

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Results	Significance	Comments
Initiation–promotion (tested as promoter) Mouse, A/J (M) 6–7 wk 30 wk Zeidler-Erdely et al. (2013)	Oropharyngeal aspiration GMA-SS welding fumes (see Comments) PBS CO/sham, 3-MC/sham, CO/GMA-SS 340 µg, 3-MC/GMA-SS 340 µg, CO/GMA-SS 680 µg, 3-MC/GMA-SS 680 µg 3-MC: 1× intraperitoneal injection; GMA-SS (at 1 wk after initiation with 3-MC) 1×/wk for 5 wk 30, 30, 28, 28, 30, 30 28, 26, 26, 26, 28, 29	Lung: "tumours" (gross lesions)		Principal strengths: multiple-dose study; adequate number of tumours produced; well-described and -conducted study Principal limitations: lung histopathology only Metals (wt%): GMA-SS, Fe (57), Cr (20.2), Mn (13.8), Ni (8.8), and Cu (0.2); trace amounts of Si, Al, and V Chromium (VI) levels were 2929 pm (µg/g) Sham exposure with PBS Tumour incidence reported as average percentage for CO groups combined and 3-MC groups combined Histopathology: 3-MC/GMA-SS low, 4 adenocarcinomas were observed (2 were in 1 mouse); 3-MC/GMA-SS high, 6 adenocarcinomas and 1 carcinoma were observed ($P < 0.01$ vs 1 carcinoma in 3-MC/sham group)
		Tumour incidence: CO/sham, 25.8 ± 6.4%; 3-MC/sham and 3-MC/GMA-SS, > 93%; 3-MC/sham, > 93%; CO/GMA-SS, 25.8 ± 6.4%; 3-MC/GMA-SS, > 93%; CO/GMA-SS, 25.8 ± 6.4%; 3-MC/GMA-SS, > 93%	NS	
		Tumour multiplicity: CO/sham, 0.21 ± 0.09; 3-MC/sham, 4.77 ± 0.7; CO/GMA-SS low, 0.42 ± 0.11; 3-MC/GMA-SS low, 12.1 ± 1.5*; CO/GMA-SS high, 0.21 ± 0.08; 3-MC/GMA-SS high, 14.0 ± 1.8*	*$P < 0.0001$ vs 3-MC/sham	
		Total tumours: CO/sham, 6; 3-MC/sham, 124; CO/GMA-SS low, 11; 3-MC/GMA-SS low, 314*; CO/GMA-SS high, 6; 3-MC/GMA-SS high, 405*	*$P < 0.004$ vs 3-MC/sham	
		Lung, alveolar/bronchiolar: preneoplastic epithelial proliferation, adenoma, adenocarcinoma or carcinoma (combined)		
		Tumour multiplicity (histopathology): CO/sham, NR; 3-MC/sham, 2.15 ± 0.32; CO/GMA-SS low, NR; 3-MC /GMA-SS low, 5.85 ± 0.76*; CO/GMA-SS high, NR; 3-MC/GMA-SS high, 6.00 ± 0.87*	*$P < 0.0001$	

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Results	Significance	Comments
Initiation–promotion (tested as promoter) Mouse, A/J (M) 5–6 wk 30 wk Falcone et al. (2017)	Inhalation (whole-body) GMA-SS welding fumes (see Comments) Filtered air CO/air, 3-MC/air, CO/GMA-SS 360 µg, 3-MC/GMA-SS 360 µg 40 mg/m³ for 4 h/d, 4 d/wk, for 9 wk 30, 30, 30, 30 28, 29, 29, 28	Lung, alveolar/bronchiolar: bronchiolo-alveolar hyperplasia and adenoma		Principal strengths: complete histopathology; well-described and -conducted study Principal limitations: only one dose group; lung histopathology only Metals (wt%): Fe (57), Cr (20.2), Mn (13.8), Ni (8.8), and Cu (0.2); trace amounts of Si, Al, and V Chromium (VI) levels: 2929 ppm (µg/g) Mass median aerodynamic diameter: 0.350 µm Lung metals analysis showed an increase of ~10.1 µg of total GMA-SS welding fume deposited in the lungs from a single 4-h exposure day Initiation with 3-MC: single intraperitoneal injection of 10 µg/g bw 1 wk before inhalation exposure
		Tumour incidence (grossly observed): CO/air, 29%; 3-MC/air, > 96%; CO/GMA-SS, 38%; 3-MC/GMA-SS, > 96%	NS	
		Tumour multiplicity (grossly observed): CO/air, 0.32 ± 0.10; 3-MC/air, 7.93 ± 0.82; CO/GMA-SS, 0.45 ± 0.13; 3-MC/GMA-SS, 16.11 ± 1.18*	*$P < 0.0001$ vs 3-MC/air	
		Total tumours: Grossly observed: CO/air, 9; 3-MC/air, 230; CO/GMA-SS, 13; 3-MC/GMA-SS, 451* Histopathology: CO/air, 5; 3-MC/air, 90; CO/GMA-SS, 2; 3-MC/GMA-SS, 153**	*$P < 0.009$ and **$P < 0.05$ vs 3-MC/air	
Full carcinogenicity Hamster, Syrian golden (M) 6 wk 100 wk Reuzel et al. (1986)	Intratracheal instillation MIG-SS welding fumes; MMA-SS welding fumes (see Comments) Saline MMA-SS 0.5 mg, MMA-SS 2.0 mg, MIG-SS 2.0 mg, saline 0.2 mL 1×/wk for 56 wk, reduced to 1×/wk every 4 wk (after wk 26) in MMA-SS high-dose group due to increased morbidity/mortality 35, 35, 35, 35 NR	Lung: malignant tumours		Principal strengths: multiple-dose study Principal limitations: lack of detailed histopathology; no survival data; limited methodology; no statistics reported; historical controls were undocumented Metals (wt%): MIG-SS, Cr (0.4), Ni (2.4); MMA-SS, Cr (5), and Ni (0.4) Historical control incidence for lung tumours: 0/429 males
		Tumour incidence: 1/35, 1/35, 0/35, 0/35		
		Total tumours: 1, 1, 0, 0	NS	

3-MC, 3-methylcholanthrene; Al, aluminium; bw, body weight; CO, corn oil; Cr, chromium; Cu, copper; d, day(s); Fe, iron; GMA, gas metal arc; h, hour(s); M, male; MIG, metal inert gas; Mn, manganese; MMA, manual metal arc; Mo, month(s); MS, mild steel; Ni, nickel; NR, not reported; NS, not significant; PBS, phosphate buffered saline; ppm, parts per million; SD, standard deviation; Si, silicon; SS, stainless steel; Ti, titanium; V, vanadium; vs, versus; wk, week(s); wt%, percentage by weight

(percentage of tumour-bearing mice out of the total number of mice) was evaluated 78 weeks after exposure; survival was greater than 73% for all groups. Lung tumour multiplicity or incidence was not significantly different between the groups exposed to air (6 days, 1.36 ± 0.21, 73%; 10 days, 0.93 ± 0.11, 77%) and to GMA-SS welding fumes (6 days, 0.84 ± 0.16, 51%; 10 days, 0.86 ± 0.14, 62%). Average tumour size was approximately 3 mm and no significant differences between the groups were found. Histopathological analysis of selected lungs (air, n = 10; GMA-SS, n = 28) showed no significant changes related to the 6-day or 10-day exposures, except for the presence of a minimal amount of welding fumes in the latter only (Zeidler-Erdely et al., 2011a). [This was a subchronic exposure study with an extended observation period. The Working Group noted the short-term duration of exposure of this inhalation study and also the low dose used.]

3.1.2 Oropharyngeal aspiration

Groups of 25 age- and weight-matched male A/J mice (age, 5 weeks) were exposed to 85 µg of gas metal arc mild steel (GMA-MS), GMA-SS, or manual metal arc stainless steel (MMA-SS) welding fumes, or 25 µL of Ca^{+2}- and Mg^{+2}-free phosphate-buffered saline vehicle (sham control) by oropharyngeal aspiration, once every 3 days for 4 exposures. The welding fumes were generated in a cubical open-front fume chamber by a skilled welder using a manual or automatic technique appropriate for the electrode, and then collected on a sterile 0.2 µm filter. The samples were generated by three welding processes: GMA (with Ar and CO_2 shielding gases) using a MS electrode; GMA using a SS electrode; and MMA using a flux-cored SS electrode. The cumulative dose of welding fumes, 340 µg, was reported to be equivalent to approximately 196 days of exposure in a 75-kg human working an 8-hour shift using a calculation similar to that described in Section 3.1.1. The effects of the different welding fumes on grossly observed lung tumour multiplicity (average number of tumours per lung) and incidence (percentage of tumour-bearing mice out of the total number of mice) were evaluated 48 and 78 weeks after exposure. Survival was greater than 91% 48 weeks after exposure for all groups. Survival was 80% for the sham control, GMA-MS, and MMA-SS groups and 73% for the GMA-SS group 78 weeks after exposure. No significant increases in grossly observed lung tumour multiplicity or incidence were found for the groups exposed to welding fumes compared with the sham control groups (sham control, 0.38 ± 0.13, 33%; GMA-MS, 0.42 ± 0.14, 33%; GMA-SS, 0.45 ± 0.14, 40%; MMA-SS, 0.25 ± 0.11, 21%) 48 weeks after exposure. A similar result was reported (sham control, 1.00 ± 0.35, 53%; GMA-MS, 1.00 ± 0.22, 65%; GMA-SS, 1.75 ± 0.32, 81%; MMA-SS, 1.55 ± 0.34, 80%) 78 weeks after exposure. Histopathological analysis of the lungs at 48 weeks showed that the group exposed to GMA-SS welding fumes had a significant ($P < 0.05$) increase in the incidence of preneoplastic or neoplastic lesions (combined) of the lung (65%) compared with the group exposed to GMA-MS welding fumes (33%), but not compared with sham controls (50%). The difference in lesion incidence between the groups exposed to MMA-SS (33%) and GMA-SS (65%) welding fumes was not significant. Lung lesion types were preneoplastic epithelial proliferations and adenomas. No significant differences were found among the groups 78 weeks after exposure, but the group exposed to GMA-SS welding fumes had the highest multiplicity and incidence (sham control, 1.47 ± 0.33, 68%; GMA-MS, 1.40 ± 0.32, 75%; GMA-SS, 1.94 ± 0.38, 88%; MMA-SS, 1.85 ± 0.46, 75%). Lesion types 78 weeks after exposure were similar to those at 48 weeks, with carcinomas arising in adenomas, carcinomas, and microcarcinomas also present, but less common. A significant increase ($P < 0.05$) in lymphoid infiltrates

was also found in the group exposed to GMA-SS welding fumes (sham control, 1.53 ± 0.29; GMA-MS, 0.78 ± 0.24; GMA-SS, 2.53 ± 0.36; MMA-SS, 1.70 ± 0.27) (Zeidler-Erdely et al., 2008). [The Working Group noted the non-physiological route of exposure.]

Male A/J and C57BL/6J mice (age, 8–10 weeks) were exposed to MMA-SS welding fumes at a dose of 20 mg/kg body weight (bw) or 60 µL of Ca^{+2}- and Mg^{+2}-free phosphate-buffered saline vehicle (sham control) by oropharyngeal aspiration (Zeidler-Erdely et al., 2011b) once per month for 4 months. The MMA-SS welding fumes were generated by a skilled welder and collected onto sterile filters as described in the paragraph above (Zeidler-Erdely et al., 2008). The cumulative dose of welding fumes, 1.6 mg, was estimated to be equivalent to approximately 4 years of exposure in a 75-kg human working an 8-hour shift using a calculation similar to that described in Section 3.1.1. The lung-tumour-resistant strain C57BL/6J served as a negative control. The effect of MMA-SS welding fumes on grossly observed lung tumour multiplicity (average tumour number per lung) and incidence (percentage of tumour-bearing mice of total number of mice) was evaluated 78 weeks after the first exposure. No significant difference in grossly observed tumour multiplicity or incidence was found between the groups of A/J mice: sham control (n = 8), 2.38 ± 0.42, 88%; and MMA-SS (n = 11), 3.00 ± 0.57, 100%. The C57BL/6J groups (sham control, n = 6; MMA-SS, n = 5) had no grossly observed tumours 78 weeks after exposure. Histopathological analysis of the A/J mice lungs showed that exposure to MMA-SS welding fumes significantly ($P < 0.05$) increased the multiplicity of preneoplastic or neoplastic lesions (combined) compared with sham controls (2.36 ± 0.39 vs 1.25 ± 0.31). Incidence was 75% and 100% for the sham control and group exposed to MMA-SS welding fumes, respectively, and the difference was not statistically different. Exclusion of the preneoplastic lesions from the histopathology data resulted in no significant difference in multiplicity between the A/J sham control group and the group exposed to MMA-SS welding fumes. Lung lesion types (total number in parentheses) were preneoplastic epithelial proliferations (sham control, 3; MMA-SS, 10), adenomas arising within a proliferation (sham control, 2; MMA-SS, 0), adenomas (sham control, 4; MMA-SS, 6), microcarcinomas (sham control, 1; MMA-SS, 2), and carcinomas arising within an adenoma (sham control, 0; MMA-SS, 8) (Zeidler-Erdely et al., 2011b). [The Working Group noted the high number of carcinomas found in the group exposed to MMA-SS welding fumes; however, the authors did not report the incidence of individual tumour type in each group so no additional conclusions could be made by the Working Group in this regard. Group sizes at the start of the study were not provided by the authors. The non-physiological route of exposure was also noted by the Working Group.]

3.1.3 Initiation–promotion studies

The effect of GMA-SS welding fumes as a lung tumour promoter was evaluated in a two-stage initiation–promotion model of lung tumorigenesis. Groups of 28 or 30 age- and weight-matched male A/J mice (age, 6–7 weeks) were given the chemical initiator 3-methylcholanthrene (3-MC; 10 µg/g bw) dissolved in corn oil or corn oil alone (vehicle) by intraperitoneal injection (Zeidler-Erdely et al., 2013). One week after initiation, mice were exposed to GMA-SS welding fumes (340 or 680 µg per exposure) or 50 µL of Ca^{+2}- and Mg^{+2}-free phosphate-buffered saline vehicle (sham control) by oropharyngeal aspiration once per week for 5 weeks. The welding aerosols were generated by the automated system described in Section 3.1.1. For the oropharyngeal exposure, the GMA-SS welding fumes from the weld area were collected onto sterile filters for use in the experimental protocol. The cumulative doses of welding fumes, 1700 and 3400 µg, were estimated

to be equivalent to approximately 450 days (1.84 working years) and 900 days (3.68 working years) of exposure, respectively, in a 75-kg human working an 8-hour shift using a calculation similar to that described in Section 3.1.1. Grossly observed lung tumour multiplicity (average number of tumours per lung) and incidence (percentage of tumour-bearing mice out of total number of mice) were determined 30 weeks after initiation. Survival was approximately 93% for all groups. Both groups exposed to GMA-SS welding fumes (low, 1700 μg; high, 3400 μg) initiated with 3-MC had significantly increased lung tumour multiplicity based on gross observations (low, 12.1 ± 1.5; high, 14.0 ± 1.8) compared with 3-MC/sham (4.77 ± 0.7; $P < 0.0001$). Similar results for total tumour number were also found across all five individual lung lobes (left:apical:cardiac:diaphragmatic:azygos): corn oil/sham, 1:1:2:2:0; corn oil/GMA-SS low, 4:3:2:1:1; corn oil/GMA-SS high, 4:1:0:1:0; 3-MC/sham, 52:12:13:39:8; 3-MC/GMA-SS low, 119:46:40:81:28 ($P < 0.004$, increase for all five lobes compared with 3-MC/sham); 3-MC/GMA-SS high, 132:64:66:106:37 ($P < 0.004$, increase for all five lobes compared with 3-MC/sham). Tumour multiplicity across the groups given corn oil was similar (sham, 0.21 ± 0.09; low, 0.42 ± 0.11; high, 0.21 ± 0.08). There were no significant differences in tumour incidence between the different groups given corn oil and between the different groups given the chemical initiator 3-MC. The grossly observed lung tumour multiplicity was confirmed by histopathological analysis: 3-MC/GMA-SS low, 5.85 ± 0.76 ($P < 0.0001$) and 3-MC/GMA-SS high, 6.00 ± 0.87 ($P < 0.0001$), compared with 3-MC/sham, 2.15 ± 0.32. Based on histopathology, lung tumour incidence (preneoplastic or neoplastic lesions, combined) was 21.9 ± 3.4% and 85.0 ± 4.1% for the groups given corn oil or the chemical initiator 3-MC, respectively, and no differences were found among the different groups given corn oil or among the different groups given the initiator 3-MC. The number of microscopically observed lung lesion types (primarily preneoplastic epithelial proliferations and adenomas, pre-neoplasia: adenomas within pre-neoplasia:adenoma: adeno-carcinoma:carcinoma) were reported as: corn oil/sham, 5:2:2:0:0; corn oil/GMA-SS low, 1:0:3:1:0; corn oil/GMA-SS high, 0:1:4:0:0; 3-MC/sham, 16:5:34:0:1; 3-MC/GMA-SS low, 61:17:70:4:0; 3-MC/GMA-SS high, 65:9:93:6:1. The group given initiator 3-MC and the high dose of GMA-SS welding fumes had a significantly increased ($P < 0.01$) incidence of malignant tumours (7 out of 29 mice had adenocarcinomas or carcinomas) compared with the 3-MC/sham group (1 carcinoma-bearing mouse out of 26 mice). The group given initiator 3-MC and the low dose of GMA-SS welding fumes had 4 adenocarcinomas, but 2 were present in a single mouse [the Working Group noted that the significance was not relevant in this case] (Zeidler-Erdely et al., 2013). [The Working Group concluded that GMA-SS welding fumes act as a lung tumour promoter in male A/J mice initiated with the chemical carcinogen 3-MC. The Working Group noted the non-physiological route of exposure.]

The effect of GMA-SS welding fumes as a lung tumour promoter was evaluated in a two-stage initiation–promotion model of lung tumorigenesis. Groups of 30 age- and weight-matched male A/J mice (age, 5–6 weeks) were given the chemical initiator 3-MC (10 μg/g bw) dissolved in corn oil or corn oil alone (vehicle) by intraperitoneal injection (Falcone et al., 2017). One week after initiation, mice were exposed to GMA-SS welding fumes (4 hours per day, 4 days per week, for 9 weeks) at a target concentration of 40 mg/m^3 (estimated total, 360 μg) or filtered air by whole-body inhalation, as described in Section 3.1.1. The exposure was estimated to be equivalent to approximately 14 weeks in a 75-kg human working an 8-hour shift using a calculation similar to that described in Section 3.1.1. Grossly observed lung tumour multiplicity and incidence were determined 30 weeks after

initiation. Survival was approximately 95% at 30 weeks for all groups. Tumour incidence was greater than 96% for both groups given initiator 3-MC. Mice initiated with 3-MC and exposed to GMA-SS welding fumes (3-MC/GMA-SS) had significantly increased lung tumour multiplicity (16.11 ± 1.18) compared with 3-MC/air groups (7.93 ± 0.82; $P < 0.0001$); no significant difference was found between the corn oil groups (corn oil/air, 0.32 ± 0.10; corn oil/GMA-SS, 0.45 ± 0.13). Tumour incidences were 29% and 38% in the corn oil/air and corn oil/GMA-SS groups, respectively, and were not significantly different. Similar results for total tumour number were also found across all five individual lung lobes (left:apical:cardiac:diaphragmatic:azygos): corn oil/air, 3:3:0:3:0; corn oil/GMA-SS, 5:1:0:5:2; 3-MC/air, 78:30:25:67:30; 3-MC/GMA-SS, 150:68:63:110:60 ($P < 0.009$, increase for all five lobes compared with 3-MC/air). The increase in grossly observed lung tumour multiplicity was confirmed by histopathological analysis: 3-MC/air mice had 90 total lesions (20 bronchioloalveolar adenomas and 70 bronchioloalveolar hyperplasia) versus 153 (34 bronchioloalveolar adenomas and 119 bronchioloalveolar hyperplasia) in the 3-MC/GMA-SS group ($P < 0.05$, increase). Abnormal morphological changes in the lung included significantly increased severity scores for lymphoid infiltrates in the corn oil/GMA-SS and 3-MC /GMA-SS groups compared with the respective controls. The authors noted that, compared with their oropharyngeal aspiration initiation–promotion study (Zeidler-Erdely et al., 2013), the tumour promoter effect was similar in the two studies despite a significantly lower total lung burden and dose rate via inhalation (Falcone et al., 2017). [The Working Group concluded that GMA-SS welding fumes act as a lung tumour promoter in male A/J mice initiated with the chemical carcinogen 3-MC. The Working Group noted the use of a single dose.]

3.2 Rat

Intrabronchial implantation

[The Working Group reviewed a 34-month intrabronchial implantation study of pellets loaded with the particulate fraction of MMA-SS welding fumes in male and female Sprague-Dawley rats (Berg et al., 1987). The study was judged to be inadequate for the evaluation because of the limited methodology, the rapid decline of the health of the rats, and the poor survival rate of the rats including controls.]

3.3 Hamster

Intratracheal instillation

Four groups of 35 male Syrian golden hamsters (age, ~6 weeks) were exposed to metal inert gas stainless steel (MIG-SS; 2.0 mg) or MMA-SS (2.0 or 0.5 mg) welding fumes, or saline vehicle (0.2 mL), by intratracheal instillation once per week for 56 weeks. A fifth group similarly treated with calcium chromate ($CaCrO_4$; 1.0 mg) was used as a positive control. The hamsters showed signs of respiratory distress after each intratracheal instillation. The exposures were reduced to once every 4 weeks after week 26 in the group given the high dose of MMA-SS welding fumes due to increased morbidity and mortality. Carcinogenic effects were evaluated after an additional 44 weeks after the last exposure (the experiment was terminated at week 100) and histopathology was performed on the respiratory tract, liver, and kidneys. At termination of the experiment, one lung tumour, a well-differentiated combined epidermoid and adenocarcinoma, was found in the group given the high dose of MMA-SS welding fumes. A single anaplastic tumour (that was likely to be a carcinoma, as noted by the study authors) was found in the lung of a hamster given the low dose of MMA-SS welding fumes, which died after 1 year of treatment. No lung tumours were found in

the three other groups (Reuzel et al., 1986). [No histopathological scoring or survival data were reported and the methodology was limited. The study authors concluded that these two tumours suggest a carcinogenic action of MMA-SS welding fumes because no lung tumours were observed in a group of 429 male and 363 female historical control hamsters. The origin of the historical controls was not specified by the study authors. The Working Group suggested caution in drawing such a conclusion based on a single potentially malignant tumour in each dose group of the hamsters exposed to MMA-SS welding fumes. Overall, the Working Group judged the study to be inconclusive.]

References

Antonini JM, Santamaria AB, Jenkins NT, Albini E, Lucchini R (2006). Fate of manganese associated with the inhalation of welding fumes: potential neurological effects. *Neurotoxicology*, 27(3):304–10. doi:10.1016/j.neuro.2005.09.001 PMID:16219356

Berg NO, Berlin M, Bohgard M, Rudell B, Schütz A, Warvinge K (1987). Bronchocarcinogenic properties of welding and thermal spraying fumes containing chromium in the rat. *Am J Ind Med*, 11(1):39–54. doi:10.1002/ajim.4700110105 PMID:3812497

Erdely A, Hulderman T, Salmen-Muniz R, Liston A, Zeidler-Erdely PC, Chen BT, et al. (2011). Inhalation exposure of gas-metal arc stainless steel welding fume increased atherosclerotic lesions in apolipoprotein E knockout mice. *Toxicol Lett*, 204(1):12–6. doi:10.1016/j.toxlet.2011.03.030 PMID:21513782

Falcone LM, Erdely A, Meighan TG, Battelli LA, Salmen R, McKinney W, et al. (2017). Inhalation of gas metal arc-stainless steel welding fume promotes lung tumorigenesis in A/J mice. *Arch Toxicol*, 91(8):2953–62. doi:10.1007/s00204-016-1909-2 PMID:28054104

IARC (1990). Chromium, nickel and welding. *IARC Monogr Eval Carcinog Risks Hum*, 49:1–648. Available from: http://publications.iarc.fr/67 PMID:2232124

Reuzel PGJ, Beems RB, de Raat WK, Lohman PHM (1986). Carcinogenicity and in vitro genotoxicity of the particulate fraction of two stainles steel welding fumes. In: Stern RM, Berlin A, Fletcher AC, Järvisalo J, editors. Health hazards and biological effects of welding fumes and gases. Amsterdam, The Netherlands: Excerpta Medica; pp. 329–332.

Zeidler-Erdely PC, Battelli LA, Salmen-Muniz R, Li Z, Erdely A, Kashon ML, et al. (2011a). Lung tumor production and tissue metal distribution after exposure to manual metal ARC-stainless steel welding fume in A/J and C57BL/6J mice. *J Toxicol Environ Health A*, 74(11):728–36. doi:10.1080/15287394.2011.556063 PMID:21480047

Zeidler-Erdely PC, Battelli LA, Stone S, Chen BT, Frazer DG, Young SH, et al. (2011b). Short-term inhalation of stainless steel welding fume causes sustained lung toxicity but no tumorigenesis in lung tumor susceptible A/J mice. *Inhal Toxicol*, 23(2):112–20. doi:10.3109/08958378.2010.548838 PMID:21309664

Zeidler-Erdely PC, Kashon ML, Battelli LA, Young SH, Erdely A, Roberts JR, et al. (2008). Pulmonary inflammation and tumor induction in lung tumor susceptible A/J and resistant C57BL/6J mice exposed to welding fume. *Part Fibre Toxicol*, 5(1):12. doi:10.1186/1743-8977-5-12 PMID:18778475

Zeidler-Erdely PC, Meighan TG, Erdely A, Battelli LA, Kashon ML, Keane M, et al. (2013). Lung tumor promotion by chromium-containing welding particulate matter in a mouse model. *Part Fibre Toxicol*, 10(1):45. doi:10.1186/1743-8977-10-45 PMID:24107379

4. MECHANISTIC AND OTHER RELEVANT DATA

4.1 Absorption, distribution, and excretion

4.1.1 Humans

All types of welding are associated with siderosis, pulmonary accumulation of iron (Doherty et al., 2004).

(a) Mild steel

In shipyard manual metal arc mild steel (MMA-MS), tungsten inert gas stainless steel (TIG-SS) and manual metal arc stainless steel (MMA-SS) welders, particulates mainly accumulated in the lower parts of the respiratory organs (Kalliomäki et al., 1982). Shipyard arc welders with 2 or 18 years of exposure showed an average of 7 mg and 200–700 mg, respectively, of welding dust in their lungs, compared with less than 4 mg in lungs of unexposed controls (Kalliomäki et al., 1978). [These data suggest time-dependent accumulation of welding dust in lungs of arc welders. The Working Group noted the lack of information on the technique, type of steel used, or on metals in fumes.]

Biological chromium (Cr) was assessed in MS welders (MMA and TIG) compared with SS welders (MMA, metal inert gas (MIG), and TIG) (Edmé et al., 1997). SS welders (MMA, MIG, and TIG techniques) had higher chromium levels in urine, blood, and plasma than MS welders. MMA-SS fumes contained the highest chromium concentrations (mostly hexavalent chromium, Cr(VI), followed by MIG-SS, TIG-SS, MIG-MS, and MMA-MS. Analysis of variance for urinary chromium concentration showed a metal effect, a process effect, and a metal–process interaction. [The Working Group noted that urine levels were not corrected for creatinine levels or osmolarity.]

Using nanoparticle respiratory deposition samplers (worn in the breathing zone, on the lapel), Cena et al. (2015) demonstrated that MS and SS welders using gas metal arc (GMA-SS or GMA-MS) or flux-cored arc (FCA-MS) welding methods are exposed to manganese (Mn), chromium, and nickel (Ni), which can deposit in the respiratory system. Based on the measured size, the estimated percentage of the nanofraction of manganese deposited in an MS welder's respiratory system ranged from 10% to 56%.

Total chromium was elevated in urine, blood plasma, and erythrocytes in MS, high-alloy steel, and SS welders compared with controls (Scheepers et al., 2008). Total chromium in plasma was twofold higher in SS and high-alloy steel welders than in MS welders. Median total content of chromium in erythrocytes was 10 µg/L in all three welder groups. Uptake of total chromium during the shift was confirmed for welders of SS by a median increase of urinary total chromium from before to after the shift of 0.30 µg/g creatinine. Total chromium was not increased for welders of MS and high-alloy steel as a group (Scheepers et al., 2008).

Dufresne et al., (1997) detected quartz was detected in the lungs of four welders. Compared with other subjects working in other occupations, the welders had the highest concentrations of metallic particles (rich in aluminium (Al), Ni, Mn, cadmium (Cd) and Cr). [The Working Group noted the small number of subjects and that the welding technique used was not indicated.]

(b) Stainless steel

A cross-sectional study of 241 welders that included 228 SS welders (GMA, n = 95; FCA, n = 47; TIG, n = 66; and shielded metal arc (SMA) with stick electrodes, n = 20) reported overall urinary levels of chromium and nickel of 1.2 and 2.9 µg/L, respectively (Weiss et al., 2013).

Two cross-sectional studies (Ellingsen et al., 2006, 2014) investigated the levels of manganese, iron (Fe), and other metals in controls, welders (MS or SS base metals; SMA, GMA, or FCA techniques), and former welders (average cessation of welding 5.8 years before, all diagnosed with manganism). Blood manganese levels and urinary chromium and nickel levels were higher in all welders compared with the controls, while cobalt (Co) levels were lower in welders. Blood manganese levels were higher in former welders (8.7 µg/L) than in controls (7.0 µg/L), while urinary concentrations of manganese, cobalt, and iron were lower in the group of former welders. Serum iron levels did not differ significantly between the groups. [The Working Group noted that the welders came from two different facilities: one that produces heavy machinery and the other a shipyard. The results were not reported separately according to material welded or welding technique.]

A 5-year longitudinal study biologically monitored aluminium welders (n = 62) and controls (n = 60 assembly workers) to compare aluminium plasma levels between the two groups (Rossbach et al., 2006). Having a nearly constant dust exposure, welders showed a decrease in median concentrations of aluminium in urine from 40.1 to 19.8 µg/g creatinine, and in plasma aluminium from 8.7 to 4.6 µg/L. Corresponding concentrations in controls ranged from 4.8 to 5.2 µg/g creatinine in urine and from 2.4 to 4.3 µg/L plasma aluminium. No correlation between dust exposure and concentrations of aluminium in either plasma or urine was seen.

In a study of six welders who used three different welding techniques (MMA with alloyed or unalloyed material, or GMA with alloyed material), welding caused an increase in chromium in blood and urine at all time points, an increase in nickel in the blood after 6 and 24 hours, and a decrease in iron after 3 and 6 hours (Brand et al., 2010). [The Working Group noted the small sample size, and that each welder used multiple arc welding methods.] In contrast, no significant elevation of chromium was seen in blood or urine in welders using either TIG-SS or TIG-MS techniques in another study (Bonde & Ernst, 1992).

In MMA-SS shipyard welders (38 men, 2 women) monitored for 1–5 workdays, total chromium and hexavalent chromium in air correlated with total chromium in blood and urine (Stridsklev et al., 1993). Smokers had higher chromium levels than nonsmokers. [The Working Group noted that it was unclear whether analyses were adjusted for differences in the workplace setting, in monitoring (i.e. across or within workweeks), in conditions at the same site, or in materials welded.]

Urinary excretion of aluminium was examined in 23 welders performing mainly MIG, but less frequently TIG welding (Sjögren et al., 1988) after an exposure-free interval of 16–37 days. Air concentrations of aluminium (8-hour time-weighted averages) varied from 0.2 to 5.3 mg/m^3. Urine aluminium concentration depended on the level of current exposure and duration of exposure. The aluminium levels of urine collected before the exposure-free interval varied over the range 6–322 µg/g (creatinine adjusted). After an exposure-free interval, the

urinary aluminium concentrations decreased to 4–285 µg/g (creatinine adjusted). The half-time of urinary aluminium was 9 days for those exposed for less than 1 year, but was 6 months or more for those exposed for longer than 10 years. [The Working Group noted that that the type of steel (SS or MS) was not specified.]

In a study of six welders exposed to aluminium-containing welding fumes from MIG welding, urinary aluminium decreased after cessation (over the weekend) in welders exposed for 2 years or less, but not in welders with more than 15 years of exposure (Sjögren et al., 1985). Urinary aluminium rose rapidly in volunteers exposed to welding fumes containing aluminium for 1 hour, and returned to baseline with an estimated half-life of 8 hours. [The Working Group noted the small number of subjects and that the type of steel (MS or SS) was not specified.]

SS arc welders had elevated chromium concentrations in lungs and urine, and correlated with duration of exposure to welding. Urinary chromium levels were highest in the steel and ferrochromium smelting shops (Huvinen et al., 1997).

An arc welder using galvanized steel showed the highest zinc (Zn) levels reported in the literature, coupled with previously unreported pleural friction rub. The subject was diagnosed with "metal fume fever", which is usually caused by inhalation of zinc oxide, and the subject's elevated urinary zinc excretion markedly decreased after 2 weeks of no welding (Fuortes & Schenck, 2000).

4.1.2 Experimental systems

(a) Mild steel

In male Wistar rats exposed by inhalation to MMA-MS welding fumes (43 mg/m^3; particle size, 0.12 µm average diameter) for 1 hour/workday for up to 4 weeks, a saturation level of 550 µg/g dry lung of the welding fumes was observed. Most of the accumulated particles were excreted from lungs with a half-time of 6 days, and the remainder with a half-time of 35 days. Iron and manganese demonstrated similar patterns of lung retention, but manganese was initially cleared much faster. Some inhaled manganese was quickly absorbed from the lung, whereas the absorption of exogenous iron was slower and was obscured by a simultaneous occurrence of endogenous iron in lung tissue. Following the same protocol but with SS welding fumes, alveolar retention of the MS fumes was much lower and its clearance much faster than the corresponding parameters for SS fumes (Kalliomäki et al., 1983a, b).

Significantly more iron accumulated in the lungs after exposure of male Sprague-Dawley rats to GMA-MS compared with MMA-HS (hard-surfacing) welding fumes by intratracheal instillation (0.5 mg per rat, once per week for 7 weeks), at 1 day and 35, but not 105, days after treatment (Antonini et al., 2010). Manganese increased in lungs at all time points with MMA-HS, and after 1 and 35 days with GMA-MS. Chromium and nickel were similarly elevated in the lungs of the MMA-HS group at all time points compared with other groups. Copper (Cu) levels significantly increased in the lungs of the GMA-MS group at 1 and 35 days compared with the MMA-HS group. At 105 days after treatment, copper and manganese levels in the lungs of the GMA-MS group decreased to levels similar to the control group, while all other metals remained significantly elevated compared with controls. Manganese cleared from the lungs fastest and to the greatest extent, followed by iron, and then chromium and nickel which cleared at similar rates. [The Working Group noted that no data on copper clearance were given.] Manganese and chromium increased in the blood (MMA-HS fumes only) 1 day after the last treatment, but not at 35 and 105 days. Importantly, manganese was elevated in the striatum (1 day) and midbrain (1 and 4 days with MMA-HS fumes). Manganese levels were also elevated 1 day after treatment in the olfactory bulb, frontal cortex, hippocampus, thalamus,

and cerebellum for MMA-HS welding fumes. At 1 day after exposure to MMA-HS welding fumes, manganese was elevated in lung-associated lymph nodes, heart, kidney, and spleen; concentrations were back to that of controls 35 days after treatment in all tissues except lymph nodes. Iron was elevated in lung-associated lymph nodes (both groups) at 1 and 35 days after treatment, but similar to that of controls at 105 days. Chromium was elevated in lymph nodes, liver, kidney, and spleen 1 day after treatment (MMA-HS welding fumes only), and remained elevated in the lymph nodes at 35 days and in the spleen at 105 days after treatment. Copper was elevated in the lungs (GMA-MS welding fumes only) at 35 days after treatment (Antonini et al., 2010).

Significant deposition of manganese in the striatum and midbrain was seen in male Sprague-Dawley rats given dissolved or suspended fumes from GMA-MS or MMA-HS welding by intratracheal instillations at doses related to workplace exposures of welders on 8-hour shifts (5 mg/m^3) (Sriram et al., 2012). The accumulation of manganese, as well as high concentrations of chromium and iron, was also measured in the lung. The group exposed to MMA-HS welding fumes had significant increases in chromium in the liver, manganese and chromium in the heart, and manganese in the kidney. Both welding methods increased manganese in nail clippings, which strongly correlated with concentrations of manganese in the brain and liver.

(b) Stainless steel

A marked dose-dependent increase in lung manganese concentration (change over baseline of 432-fold for the low dose, and 567-fold for the high dose) was reported in a study of six male cynomolgus monkeys (*Macaca fascicularis*) (Park et al., 2007a). Exposure was to MMA-SS welding fumes (low dose, 31 mg/m^3 total suspended particulate, 0.9 mg/m^3 of Mn; high dose, 62 mg/m^3 total suspended particulate, 1.95 mg/m^3 of Mn) for 2 hours per day in an inhalation chamber system equipped with an automatic fume generator for 240 days. Fumes mainly consisted of iron, manganese, chromium, and nickel. Noticeable manganese increases were reported in the liver (twofold), kidneys (twofold), and testes (four- to fivefold). A dose-dependent increase in manganese concentration was seen in the globus pallidus. [The Working Group noted the small sample size (n = 2) for each test group.]

Mice of the A/J strain, but not of the C57BL/6j strain, had elevated hepatic concentrations of chromium, copper, manganese, and zinc in kidney, and chromium after exposure to MMA-SS welding fumes (Zeidler-Erdely et al., 2011a). The mice were exposed monthly for 4 months to MMA-SS fumes (20 mg/kg body weight) by pharyngeal aspiration and assessed 78 weeks after the beginning of the study.

Lung concentrations of chromium, manganese, nickel, and iron increased with duration of exposure in 42 rats exposed via inhalation to MIG-SS welding fumes for 1 hour per day for 1–4 weeks, followed by observation for up to 106 days (Kalliomäki et al., 1983a). Clearance did not occur for iron, was slow for chromium, and was initially rapid for manganese and nickel (2-day and 3-day half-lives, respectively) but then slowed (125-day and 85-day half-lives, respectively). Under comparable exposure conditions, similar results were seen for MMA-SS with half-lives for iron, chromium, manganese, and nickel of 50, 40, 40, and 30 days, respectively (Kalliomäki et al., 1983b).

Male Sprague-Dawley rats showed dose- and time-dependent increases in manganese concentrations in the lungs and liver, and slight but significant increases in the blood (after 60 days), after exposure to MMA-SS welding fumes for 60 days (63.6 and 107.1 mg/m^3, containing 1.6 and 3.5 mg/m^3 Mn, respectively). Marked, significant increases in manganese were seen in the cerebellum (after 60 days), while slight increases were found in the substantia nigra, basal ganglia,

temporal cortex, and frontal cortex (Yu et al., 2003).

The maximum amount of MIG welding fumes retained in the lungs (1100 µg) was somewhat, but not significantly, higher than that for MMA welding fumes (800 µg) in Wistar rats exposed by inhalation to both following the same protocol as in Kalliomäki et al. (1983a, b, 1984). Chromium and nickel were both retained in the lungs. Chromium from exposure to MMA welding fumes was partly cleared, but there was no clearance of chromium from exposure to MIG welding fumes. The half-life of chromium was 40 days from MMA fumes and 240 days from MIG fumes, and the half-life of nickel was 30–85 days from MMA fumes. Chromium found in blood from MMA fumes had a half-life of approximately 6 days. Chromium and nickel were both found in blood from MIG fumes. The amounts of nickel cleared from the lungs during exposure to the MMA and MIG fumes were 0.9 and 8 µg, respectively, and corresponding amounts of chromium were 9.6 and 2 µg. Practically all the lost metals were found in the urine, for which the excretion rates were 0.07 (MMA) and 6.39 µg per day (MIG) for nickel, and 0.23 (MMA) and 0.11 µg per day (MIG) for chromium. [The Working Group noted that metal content in urine was determined by atomic absorption spectroscopy and not corrected for creatinine.]

Tissue distribution of manganese was similar in iron-deficient compared with iron-sufficient male Sprague-Dawley rats exposed to MMA-SS welding fumes (63.5 mg/m^3) for 2 hours per day for up to 30 days (Park et al., 2007b). Fumes consisted mainly of iron (6 mg/m^3), chromium (2.9 mg/m^3), and manganese (2.7 mg/m^3). In both groups of rats, manganese concentrations increased significantly during fume exposure in lungs and livers (on days 15 and 30), in the olfactory bulb (on day 30), and in the cerebellum and frontal and temporal lobe of the cerebrum (on day 15).

4.2 Mechanisms of carcinogenesis

The sections that follow summarize the evidence for key characteristics of carcinogens (Smith et al., 2016). The sections address, in the following order, if welding fumes: induce chronic inflammation; are immunosuppressive; are genotoxic; induce oxidative stress; alter cell proliferation, cell death, and nutrient supply; and modulate receptor-mediated effects. There were insufficient data for the evaluation of the other key characteristics of human carcinogens.

4.2.1 Chronic inflammation and immune suppression

(a) Humans

Numerous studies have reported that the metal content of particles in welding fumes is associated with measures of pulmonary inflammation, oxidative stress, and/or systemic inflammation (e.g. Kim et al., 2005). Several of these studies investigated boilermakers, who perform two major types of activities: the use of oxyacetylene gas torch sets to cut or gouge steel plate and tubes, followed by gas tungsten arc (GTA), SMA, or GMA welding to attach and mend the cut sections of MS tubes and plates. Acute (cross-shift) welding exposure is associated with a blunting of systemic inflammation in acutely exposed boilermakers at the end of work shifts, as measured by biomarkers such as 8-isoprostane (e.g. Nuernberg et al., 2008) whereby chronically exposed workers had a higher value consistent with chronic inflammation at the start of the shift. In contrast, longer-term exposure is related to an increase in markers of tissue damage.

There are also systemic inflammatory effects caused by epithelial damage induced by metal particulate or macrophage activation via cytokine signalling (e.g. Zeidler-Erdely et al., 2012). In a study of 27 welders with regular, long-term exposure to metal fumes (type of welding not specified) and 31 unexposed matched controls,

an increase in blood eosinophil and basophils in welders versus non-welders, with some correlation to exposure level, was observed (Palmer et al., 2006). This study also reported trends for increased blood C-reactive protein (CRP), neutrophil oxidative burst, sputum immunoglobulin-A (IgA), and decreased sputum eosinophils (Palmer et al., 2006). In another study of chronic exposure to manganese fumes (work experience, 6–36 years), significant decreases in blood CD8+ T and CD19+ B lymphocytes were found in welders with high concentrations of manganese in blood compared with workers with lower manganese concentrations (Nakata et al., 2006). In a longitudinal study of mostly healthy, middle-aged, white American men, increased inflammatory markers such as plasma CRP and serum amyloid A (SAA) concentrations were associated with decreased leukocyte telomere length (Wong et al., 2014a). [The Working Group noted that this study provides a window into the relationship between systemic inflammation, immune response, and genomic degeneration.]

Studies using a repeated measures panel design investigated the short-term effects of exposure to welding fumes among boilermakers (Kim et al., 2005; Wang et al., 2005, 2008; Fang et al., 2008, 2009, 2010a; Nuernberg et al., 2008). These studies included assessment of exposure to welding fumes within the personal breathing zone and a self-controlled design to assess biological variability among individuals. Blood samples were collected from welders and non-welding controls before and after their work shift. In nonsmokers, exposure to welding fumes was associated with a significant increase in leukocyte and neutrophil counts immediately after exposure. A significant decrease in fibrinogen levels was observed in nonsmoking welders. No significant changes in leukocyte, neutrophil, and fibrinogen levels were found with exposure to welding fumes in smokers. Sixteen hours after exposure to welding fumes, CRP levels were significantly increased in both nonsmokers and smokers. Concentrations of particulate matter of diameter less than 2.5 μm ($PM_{2.5}$) were significantly associated with absolute neutrophil counts in nonsmokers, and CRP levels in both nonsmokers and smokers (Kim et al., 2005; Fang et al., 2009). [The Working Group noted that exposure to high levels of welding fumes induced acute systemic inflammation in a relatively young and healthy working population, and that smoking may modify the effect of exposure to welding fumes on specific inflammatory markers.]

Reported susceptibility to pneumococcal pneumonia in welders provides evidence of immune suppression as a result of exposure to welding fumes (Coggon et al., 1994; Wergeland & Iversen, 2001; Palmer et al., 2003; Palmer et al., 2009; Wong et al., 2010; Torén et al., 2011; Patterson et al., 2015; Marongiu et al., 2016). A likely mechanism involving platelet-activating factor receptor (PAFR) has been investigated for the observed increase of pneumococcal pneumonia among active welders (Suri et al., 2016; Grigg et al., 2017). Pneumococci co-opt PAFR to infect respiratory epithelial cells, and exposure of respiratory cells to welding fumes upregulates PAFR-dependent pneumococcal infection. Nasal PAFR expression was increased in welders compared with controls. Exposure to welding fumes also significantly increased PAFR expression, and enhanced pneumococcal infection of respiratory cells harvested in vivo.

A toxicogenomic study using whole-blood RNA of welders revealed that welding fumes induced alteration in the expression of genes involved in various aspects of the inflammatory response, including proinflammatory mediators, cytokine receptors, downstream signal transduction genes, and cytotoxic granulysin (Wang et al., 2005). A follow-up study using a similar population extended these observations into a period after exposure. Some acute effects on gene expression profiling induced by welding fumes were transient in nonsmoking welders,

with most diminishing within 19 hours after exposure (Wang et al., 2008).

Wei et al. (2013) performed a two-stage, self-controlled exploratory study including 11 boilermakers from a 2011 discovery panel and 8 boilermaker welders from a 2012 validation panel. Eicosapentaenoic or docosapentaenoic acid metabolic changes after welding were significantly associated with $PM_{2.5}$ exposure ($P < 0.05$). The combined analysis by linear mixed-effects model showed that exposure was associated with a statistically significant decline in eicosapentaenoic acid, docosapentaenoic acid n_3, and docosapentaenoic acid n_6. Pathway analysis identified an association between the unsaturated fatty acid pathway and exposure, indicating that exposure to high concentrations of metal welding fumes decreases unsaturated fatty acids with an exposure–response relationship.

(b) Experimental systems

Numerous studies were available, nearly all of which evaluated males, and examined end-points related to inflammation and immune suppression.

(i) Inflammation in vivo

Despite particle accumulation in the lungs of male cynomolgus monkeys exposed to MMA-SS fumes via inhalation (31.4 or 62.5 mg/m^3, 2 hours per day, 5 days per week, for 229 exposure days), there was no effect on blood leukocyte populations and no significant lung damage ($n = 1$ per group per time point) compared with an unstressed, unexposed control group [control primates were not described as being handled or removed from their housing cages] (Heo et al., 2010).

Exposure to SS welding fumes led to an accumulation of inflammatory cytokines in the bronchoalveolar lavage fluid (BALF) of male rats, along with a cellular influx consisting primarily of alveolar macrophages, neutrophils (polymorphonuclear leukocytes, PMNs), and lymphocytes, effects which were not typically observed after exposure to MS welding fumes (reviewed by Zeidler-Erdely et al., 2012). Exposure to MMA-SS fumes via inhalation (44.1–65.6 or 80.1–116.8 mg/m^3, 2 hours per day, for up to 60 exposure days) did not change BALF tumour necrosis factor alpha (TNFα) or IL-1β levels in Sprague-Dawley rats (Yu et al., 2004). However, after similar exposures, increases in BALF cellularity corresponded to increased reactive pulmonary hyperplasia incidence and severity; this persisted for more than 60 days, and was exacerbated after two cycles of alternating 30-day periods of exposure to high concentration and recovery (Sung et al., 2004; Yang et al., 2009). [The Working Group noted that this indicated incomplete pulmonary recovery and a predisposition to more significant injury upon re-exposure.] Other investigators reported similar changes in Sprague-Dawley rats after exposure to GMA-SS welding fumes via inhalation (40 mg/m^3, 3 hours per day, for 3 days), with increased BALF levels of the PMN chemokine Cxcl2 (Chemokine (C-X-C motif) ligand 2) preceding a transient peak in PMN accumulation, while numbers of alveolar macrophages remained elevated throughout 30 days of recovery (Antonini et al., 2007). A similar influx of BALF leukocytes was also reported in Wistar rats exposed to unspecified welding fumes via inhalation (60 mg/m^3, 6 hours per day, for 5 or 10 days) (Halatek et al., 2017). [The fumes are described as only 10% soluble, consisting primarily iron >> chromium > nickel > aluminium > manganese.] In contrast to SS, short-term exposure to GMA-MS fumes (40 mg/m^3, 3 hours per day, for 3 or 10 days) or resistance spot MS welding fumes (25 mg/m^3, 4 hours per day, for 3, 8, or 13 days) via inhalation in Sprague-Dawley rats had a minimal effect on the cellular composition of the BALF or local lung-associated lymph nodes (LALN) (Antonini et al., 2009a; Zeidler-Erdely et al., 2014).

Immune effector cells in BALF from Sprague-Dawley rats were affected in a route-specific

manner following GMA-SS fume administration; after intratracheal instillation (ITI), there was an immediate PMN influx that was delayed after the inhalation exposure described above [possibly due to inhibition of alveolar macrophages] (Taylor et al., 2003; Antonini et al., 2007, 2009a). Exposure to GMA-SS and MMA-SS fumes by intratracheal instillation increased BALF TNFα and/or IL-6 levels along with increases in pulmonary leukocyte populations and persistently elevated numbers of alveolar macrophages, with MMA-SS welding fumes characterized as the most potent (Antonini et al., 1996, 1997, 2004a, 2013; Taylor et al., 2003). The soluble fraction of SS fumes appeared to elicit the weakest inflammatory response compared with the total fume or insoluble fractions (Taylor et al., 2003); these differed from other reports of relative potency after administration of higher (White et al., 1982) or lower doses (McNeilly et al., 2005).

Similar to rats, exposure to MMA-SS and GMA-SS welding fumes induced persistent pulmonary inflammation in male mice of strains both sensitive (A/J) and resistant C57Bl/6 (B6) to chemically induced lung tumorigenesis (reviewed by Zeidler-Erdely et al., 2012). While lung inflammation was not persistently elevated 78 weeks after short-term exposure of A/J mice to GMA-SS fumes by inhalation (40 mg/m^3, 3 hours per day, for 6 or 10 days; respective cumulative lung burden, approximately 0.071 or 0.120 mg) (Zeidler-Erdely et al., 2011a), subchronic inhalation (40 mg/m^3, 4 hours per day, 4 days per week, for 9 weeks; cumulative lung burden, approximately 0.255 mg), and pharyngeal aspiration (approximately 1.7 or 3.4 mg), the increased severity of pulmonary inflammation was observed after 30 weeks, characterized by infiltrating peribronchial/perivascular-associated lymphocytes, macrophages, and plasma cells (Zeidler-Erdely et al., 2013; Falcone et al., 2017; see Section 3). Similarly, exposure to a high concentration of MMA-SS welding fumes via pharyngeal aspiration (cumulative lung burden, approximately 1.6 mg) increased alveolar macrophage accumulation as well as pulmonary inflammation after 78 weeks in A/J but not B6 mice (Zeidler-Erdely et al., 2011a); this was not observed after exposure to a lower dose (cumulative burden, approximately 0.340 mg; Zeidler-Erdely et al., 2008). After a shorter 28-day recovery period, exposure to GMA-SS fumes via inhalation induced a sustained inflammatory response in A/J and B6 mice (Zeidler-Erdely et al., 2011b); this was consistent with the remaining histiocytic inflammation reported after exposure to MMA-SS fumes via pharyngeal aspiration in A/J mice (cumulative lung burden, approximately 1.0 mg) (Solano-Lopez et al., 2006).

Also similar to rats, BALF cellular content in mice was potently and persistently increased by exposure to SS welding fumes via inhalation (40 mg/m^3 for 3 hours per day, 5 days per week for 2 weeks) or pharyngeal aspiration, whereas exposure to MS fumes (via pharyngeal aspiration) only induced a mild and transient increase in PMNs (Zeidler-Erdely et al., 2008; Erdely et al., 2012). Qualitative differences were also evident between both exposure routes and mouse strains, although the magnitude of the cellular response was not remarkably different between A/J and B6 mice. After exposure to SS fumes by inhalation (as described above), BALF levels of several cytokines increased (IL-6, interferon-gamma or IFNγ) or greatly increased (Cxcl2, Ccl2, and TNFα) in B6 versus A/J mice (Zeidler-Erdely et al., 2011b), while exposures via aspiration elicited responses in similar BALF cytokines that tended to be greater in A/J compared with B6 mice (Zeidler-Erdely et al., 2008).

(ii) Inflammation in vitro

Evidence supporting induction of an inflammatory response in vitro is less consistent [the Working Group noted that studies in vitro may be less informative for chronic inflammation]. Release of β-*N*-acetyl-glucosaminidase (β-NAG)

from primary Sprague-Dawley rat alveolar macrophages was induced by treatment with both MS and SS fumes and, to a greater extent, with the soluble versus insoluble fractions with MMA-SS fumes eliciting the most potent effect (Antonini et al., 1999). Conversely, no effects were reported on β-NAG release from primary bovine AMs [sex not reported] (White et al., 1983) or cytokine production in mouse peritoneal macrophages (RAW 264.7) (Badding et al., 2014) after exposure to MS or SS welding fumes.

(iii) Immunosuppression in vivo

Several studies in male Sprague-Dawley rats have consistently demonstrated a reduced ability to clear bacteria from the lung after exposure to both SS and MS welding fumes by inhalation (reviewed by Zeidler-Erdely et al., 2012). Exposure to GMA-MS and GMA-SS welding fumes via inhalation (40 mg/m^3, 3 hours per day, for 3 days) inhibited pulmonary bacterial clearance of subsequently inoculated *Listeria monocytogenes* in rats (Antonini et al., 2007, 2009a). While prior exposure to GMA-SS and GMA-MS fumes by intratracheal instillation had no effect, prior exposure to MMA-SS welding fumes increased PMN influx and BALF oxidant levels but impaired resolution of infection (Antonini et al., 2004a). Among other effects on BALF cytokines, exposure to MMA-SS fumes via intratracheal instillation decreased IL-2 levels and prevented the *L. monocytogenes* challenge-induced increase in IL-2 and IL-10 content; similarly, soluble chromium also decreased IL-2 levels and inhibited bacterial clearance when given separately (Antonini et al., 2004b; Antonini & Roberts, 2007). [The Working Group noted that this suggests suppression of T-lymphocyte activity, mediated by the soluble chromium component.] GMA-SS fumes had qualitatively similar effects as MMA-SS fumes on rat pulmonary bacterial clearance and cytokine levels, while GMA-MS fumes elicited a weaker response (Antonini et al., 2007, 2009a). Although iron-rich GMA-MS fumes inhibited bacterial clearance in rats, exposure to iron oxide (Fe_2O_3) did not (Antonini and Roberts, 2007). [The Working Group noted that the specific mediator(s) responsible for GMA-MS immunosuppression remains unclear.] Additionally, in uninfected rats, MMA-SS fumes administered via intratracheal instillation increased total peripheral blood mononuclear cell (PBMC) numbers, specifically monocyte and PMN subpopulations, and attenuated leukocyte release of chemokines (e.g. Cxcl10, Ccl4, and Cxcl2) at the post-transcriptional level in response to lipopolysaccharide (LPS) challenge ex vivo (Erdely et al., 2014).

In female mice, two studies reported pulmonary or systemic immunosuppression after exposure to MMA-SS or MMA-MS fumes. MMA-SS fumes increased *Pafr* mRNA expression in the lungs of B6 mice exposed via inhalation (40 mg/m^3, 3 hours per day, for 10 days) (Suri et al., 2016). This induction was associated with increased bacterial colony-forming units (CFUs) in the BALF and lung tissue of female CD-1 mice inoculated with *S. pneumoniae* after exposure to MMA-MS fumes via intranasal instillation. A selective PAFR blocker significantly attenuated BALF CFU concentrations in mice exposed to fumes (Suri et al., 2016). After exposure to total MMA-SS fumes or soluble fractions via pharyngeal aspiration, splenocytes from female B6C3F$_1$ mice exhibited reduced immunoglobulin-M (IgM) activity in response to sheep erythrocyte stimulation in vitro, and a similar reduction in immune function was observed in LALN B-lymphocytes (Anderson et al., 2007). Exposure to the insoluble fraction did not result in this effect.

(iv) Immunosuppression in vitro

Evidence for decreased immune function in rats and mice in vivo is supported by two complementary in vitro studies in rodent cells. GMA welding fumes generated from a consumable of high nickel and copper concentration

(very low levels of Fe, Cr, and Mn) reduced phagocytic activity in RAW 264.7 cells, while no effects were observed after exposure to either MS or SS fumes (Badding et al., 2014). In female $B6C3F_1$ mouse splenocytes, the total and soluble fractions of MMA-SS welding fumes decreased the number of plaque-forming cells in response to sheep erythrocyte challenge, while the insoluble fraction had no significant effect (Anderson et al., 2007).

4.2.2 Genetic and related effects

(a) Humans

The results of the investigations are listed in Table 4.1. Except where noted, the studies generally matched exposed and unexposed subjects on age and sex, and most studies adjusted for smoking.

(i) Cytogenetic end-points

Exposure to welding fumes was without effect on chromosomal aberrations or sister-chromatid exchange in two of the three studies describing cytogenetic effects described in *IARC Monographs* Volume 49 (Husgafvel-Pursiainen et al., 1982; Littorin et al., 1983; IARC, 1990). The third study reported a significant increase in both cytogenetic parameters (Koshi et al., 1984).

Results were also mixed in the additional studies on chromosomal aberrations in welders available to the Working Group. Three studies that controlled for smoking (Elias et al., 1989; Knudsen et al., 1992; Jelmert et al., 1994) and a fourth that did not (Borská et al., 2003) described a positive association between lymphocyte chromosomal aberrations and exposure, while two studies reported negative results (Jelmert et al., 1995; Halasova et al., 2012). The positive results were reported in TIG welders exposed to chromium (Borská et al., 2003), in MMA-SS welders (Jelmert et al., 1994), and in pooled groups of welders involved in different types of welding (TIG, MMA+TIG, and MIG; Knudsen et al., 1992; metal active gas (MAG) with cored wire containing Ni, TIG, and MMA; Elias et al., 1989). It is noteworthy that a significant increase in lymphocyte chromosomal aberrations was only observed in MMA+TIG welders who, unlike other welders, also had increased concentrations of chromium and nickel in blood (Knudsen et al., 1992). Elias et al. reported positive results for MAG with cored wire containing nickel welders group, but not for TIG and MMA groups (Elias et al., 1989).

Negative results for an increase in lymphocyte chromosomal aberrations in welders (type of welding was not specified) were reported by Halasova et al. (2012), and in TIG welders by Jelmert et al. (1995). [The Working Group noted that Jelmert et al. reported a statistically significant decrease of rates of chromosomal breaks and cells with chromosomal aberrations in welders compared with the control subjects.]

Positive findings for micronuclei (MN) in lymphocytes of welders were reported in most available studies, but several had notable deficiencies. In Italian electric arc welders, who were also exposed to extremely low-frequency electromagnetic fields, a significantly higher frequency of MN was found (Dominici et al., 2011). Positive results were obtained in lymphocytes of MMA, TIG, and metal inert/active gas welders in two studies carried out in France (Iarmarcovai et al., 2005, 2006), in one in Turkey (Sener & Eroglu, 2013), and in one in India (Sellappa et al., 2010). A study of 5 MMA-SS welders that did not control for smoking reported negative results compared with 27 control subjects (Medeiros et al., 2003). [The Working Group noted that most of these studies assessed MN in 500 or 1000 binucleated lymphocytes, whereas the recommended number is 2000 OECD (2016).]

Results from studies in exfoliated epithelial cells of welders were mixed. One study (Wultsch et al., 2014) reported increased MN frequencies in nasal cells, but not buccal cells, in TIG welders. In both cell types, significant increases were seen

Table 4.1 Genetic and related effects of welding fumes in exposed humans[a]

End-point	Cell type	Description of exposure and controls	Response	Comments	Reference
Chromosomal aberrations	Lymphocytes	55 welders (group 1, MMA, $n = 22$; group 2, MAG, $n = 18$; group 3, TIG, $n = 15$); 55 control subjects	+	No correlation with Cr, Ni, and Mn in serum, urine; higher CA in smokers; effect of exposure duration	Elias et al. (1989)
Chromosomal aberrations	Lymphocytes	47 TIG, 56 MMA+TIG, and 11 MIG welders; 68 control subjects	+	Higher CA in smoking welders vs smoking controls; higher Cr in serum and urine of welders; urinary Ni increased only in MMA+TIG welders	Knudsen et al. (1992)
Chromosomal aberrations	Lymphocytes	31 MMA welders tested after shift, 20 welders before the start of work and retested 1–4 months after; 40 control subjects	+	No effect of smoking; increased Cr but not Ni in blood and urine of welders	Jelmert et al. (1994)
Chromosomal aberrations	Lymphocytes	23 TIG and 21 MAG or MIG welders on SS; 38 control subjects and 94 reference subjects	–	Decreased CA in welders; no effect of smoking; increased Cr and Ni in urine and blood	Jelmert et al. (1995)
Chromosomal aberrations	Lymphocytes	73 welders (type of welding not specified); 71 control subjects	–	Correlation with blood Cr; no effect of smoking	Halasova et al. (2012)
Chromosomal aberrations	Lymphocytes	20 TIG welders; 20 control subjects	(+)	Did not control for smoking	Borská et al. (2003)
Micronucleus formation	Lymphocytes	21 electric arc welders; 21 control subjects	+	No effect of smoking	Dominici et al. (2011)
Micronucleus formation	Lymphocytes	27 MMA, TIG, and MIG welders working without any protection device; 30 control subjects	(+)	Inadequate number of scored cells (1000, whereas 2000 are recommended)	Iarmarcovai et al. (2005)
Micronucleus formation and FISH with a pancentromeric DNA probe	Lymphocytes	27 MMA, MIG, and TIG welders working in areas without any collective protection device; 30 control subjects	(+)	Inadequate number of scored cells (1000, whereas 2000 are recommended)	Iarmarcovai et al. (2006)
Micronucleus formation	Lymphocytes	23 MAG welders; 25 control subjects	(+)	Inadequate number of scored cells (500, whereas 2000 are recommended)	Sener & Eroglu (2013)
Micronucleus formation	Lymphocytes	93 MMA welders; 60 control subjects	(+)	Effect of smoking, exposure duration, and alcohol consumption; inadequate number of scored cells (500, whereas 2000 are recommended)	Sellappa et al. (2010)
Micronucleus formation	Lymphocytes	5 MMA-SS welders; 27 control subjects	(–)	Did not control for smoking; low number of welders	Medeiros et al. (2003)
Micronucleus formation	Nasal and buccal cells	22 TIG welders; 22 control subjects	+ (nasal cells) – (buccal cells)	Increased Mo, Cr, Mn, Ni, and Cu in blood plasma of welders; no effect of smoking and alcohol consumption	Wultsch et al. (2014)

Table 4.1 (continued)

End-point	Cell type	Description of exposure and controls	Response	Comments	Reference
Micronucleus formation	Buccal cells	58 MMA welders; 52 controls	+		Danadevi et al. (2004)
Micronucleus formation	Buccal cells	66 MMA welders; 60 control subjects	+		Sudha et al. (2011)
Micronucleus formation	Buccal cells	33 MIG welders; 33 control subjects	–	No effect of smoking	Jara-Ettinger et al. (2015)
Micronucleus formation	Buccal cells	11 welders (type of welding not specified); 20 control subjects	(–)	Did not control for smoking; cells were stained with Giemsa (DNA-non-specific stain)	Domínguez Odio et al. (2005)
Sister-chromatid exchange	Lymphocytes	39 MAG and MMA welders; 18 control subjects	–	Increased Cr and Ni in urine of welders; no effect of smoking	Popp et al. (1991)
Sister-chromatid exchange	Lymphocytes	24 MMA-SS welders; 2 matched control groups (24 + 46 subjects) One subgroup of 10 welders tested before the start of work and again 1–4 months after; 10 matched controls	– –	No effect of smoking; increased Cr and Ni in urine and blood	Jelmert et al. (1994)
Sister-chromatid exchange	Lymphocytes	6 TIG and 11 MIG/MAG welders; 7 and 10 controls for each group, respectively	–		Jelmert et al. (1995)
Sister-chromatid exchange	Lymphocytes	39 SS welders; 22 controls	+	Association with blood Cr (increased in welders); no effect of smoking or exposure duration	Myślak & Kośmider (1997)
Sister-chromatid exchange	Lymphocytes	49 TIG, 60 MMA+TIG, and 12 MIG welders; 75 control subjects	–	SCE rates lower in total welders group and in smokers group, but not in nonsmokers	Knudsen et al. (1992)
Sister-chromatid exchange	Lymphocytes	21 electric arc welders; 21 control subjects	–	No effect of smoking; 1.3 times decrease in exposed compared with control subjects	Dominici et al. (2011)
Sister-chromatid exchange	Lymphocytes	39 MMA welders; 39 control subjects	+	Increased Cr in erythrocytes and Ni in whole blood in welders; no effect of smoking	Werfel et al. (1998)
DNA strand breaks (comet assay)	Lymphocytes	26 welders (type of welding not specified); 26 control subjects	+	No effect of smoking or exposure duration	Sardas et al. (2010)
DNA strand breaks (comet assay)	Lymphocytes	30 MMA, TIG, and MIG/MAG welders, 22 control subjects	+	Positive correlation with blood Al, Co, Ni, and Pb; no effect of smoking or alcohol consumption	Botta et al. (2006)
DNA strand breaks (comet assay)	Lymphocytes	102 MMA welders; 102 controls	+	Effect of exposure duration but not smoking, alcohol consumption, or age; positive correlation with Cr and Ni	Danadevi et al. (2004)

Table 4.1 (continued)

End-point	Cell type	Description of exposure and controls	Response	Comments	Reference
DNA strand breaks (comet assay)	Leukocytes	93 MMA welders; 60 control subjects	+	Effect of smoking, alcohol consumption, and exposure duration	Sellappa et al. (2010)
DNA strand breaks (comet assay)	Leukocytes	35 welders (type of welding not specified); 35 control subjects	+	No effect of smoking, exposure duration, or alcohol consumption	Singh & Chadha (2016)
DNA strand breaks (comet assay)	Lymphocytes	26 welders working in areas without any collective protection device, 4 welders working in places equipped with smoke extraction systems; 22 control subjects	+	No effect of smoking or alcohol consumption; association with *XRCC1* gene variant	Iarmarcovai et al. (2005)
DNA strand breaks (comet assay)	Lymphocytes	120 welders (type of welding not specified); 40 controls (managerial workers)	–	No effect of smoking or exposure duration	Zhu et al. (2001)
DNA strand breaks (alkaline elution assay)	Lymphocytes	39 MAG and MMA welders; 18 control subjects	–	Reduced frequency of DNA-strand breaks compared with controls; no effect of smoking	Popp et al. (1991)
DNA strand breaks (alkaline elution assay)	Lymphocytes	39 MMA and other welders; 39 controls	+ with (but not without) proteinase K	Increased Cr in erythrocytes and Ni in blood of welders; no effect of smoking	Werfel et al. (1998)
DNA strand breaks (comet assay)	Buccal cells	66 MMA welders; 60 control subjects	+	Effect of smoking, alcohol consumption, and exposure duration	Sudha et al. (2011)
DNA–protein cross-links	Leukocytes	21 MMA welders; 26 control subjects	+	No effect of smoking	Costa et al. (1993), Toniolo et al. (1993)
DNA–protein cross-links	Lymphocytes	5 male SS welders; 22 control subjects	(+)	Did not control for smoking; small number of exposed subjects	Quievryn et al. (2001)
DNA–protein cross-links	Leukocytes	5 MMA-SS welders; 30 control subjects	(+)	Did not control for smoking; small number of exposed subjects	Medeiros et al. (2003)

[a] Most studies accounted for age, sex and smoking, except where indicated

+, positive; –, negative; (+) or (–), positive or negative in a study with of limited quality; Al, aluminium; CA, chromosomal aberration; Co, cobalt; Cr, chromium; Cu, copper; FISH, fluorescent in situ hybridization; MAG, metal active gas; MIG, metal inert gas; MMA-SS, manual metal arc stainless steel; Mn, manganese; Mo, molybdenum; Ni, nickel; Pb, lead; SCE, sister-chromatid exchange; SS, stainless steel; TIG, tungsten inert gas; vs, versus

in other nuclear anomalies (reflecting genotoxic as well as cytotoxic effects). Of the four studies that used a DNA-non-specific stain, Giemsa [which the Working Group noted can lead to false-positive results (Nersesyan et al., 2006)], two were positive and two were negative. Studies of MMA welders in India reported significantly increased levels of MN in oral mucosa cells (Danadevi et al., 2004; Sudha et al., 2011). MN rates were significantly correlated with the age and smoking status of welders, as well as the duration of exposure. A study of MIG welders in Mexico (Jara-Ettinger et al., 2015), and a study of welders (not otherwise specified) in Cuba that did not control for smoking (Domínguez Odio et al., 2005), gave negative results.

In several studies available on sister-chromatid exchange in lymphocytes of welders, mixed results were obtained. Popp et al. (1991) and Jelmert et al. (1994, 1995) observed no effect in stainless steel (MMA, TIG, MIG, and MAG) welders. Interestingly, a statistically significant negative association was observed between the total chromium in inhaled air and frequency of sister-chromatid exchange (Jelmert et al., 1995). A slight but significant increase in sister-chromatid exchange rates was observed in MMA, MIG, and MMA+MIG welders in the Czech Republic (Myślak & Kośmider, 1997). In TIG, MMA+TIG, MIG, and electric arc welders, the rate of sister-chromatid exchange in lymphocytes was significantly lower in total welders and in nonsmoking welders than in reference groups (Knudsen et al., 1992; Dominici et al., 2011).

Significantly elevated rates of sister-chromatid exchange were observed in MMA welders in Germany. However, no significant difference was found in comparisons between exposed and control smokers, or between exposed and control nonsmokers (Werfel et al., 1998).

(ii) DNA damage

Most studies of DNA damage were positive, but many used an imprecise measure of DNA damage (i.e. Olive tail moment or tail length instead of percentage DNA in tail (%DNA) for the comet assay) (Collins et al., 2008).

A significant increase in the mean %DNA was observed in lymphocytes of welders (type of welding not specified) (Sardas et al., 2010).

Significantly increased levels of DNA damage were seen in lymphocytes of MMA and TIG welders at the end of the working week, but not at the beginning (Botta et al., 2006). Spearman rank correlation analysis indicated positive correlations between blood concentrations of aluminium, cobalt, nickel, and lead and the levels of DNA damage. A significant increase in DNA strand breaks in lymphocytes (Danadevi et al., 2004; Sellappa et al., 2010) or in buccal cells (Sudha et al., 2011) was also found in MMA welders in three studies in India. In another study in India (Singh & Chadha, 2016), significant increases were seen in both damaged cell frequency and mean tail length in welders (type of welding not specified) who were heavily exposed to welding fumes due to poor ventilation and no mask. MMA, TIG, and GMA welders had a significant increase in Olive tail moment distribution at the end of the week when compared with the beginning, and also with controls (Iarmarcovai et al., 2005).

No significant elevation of DNA tail moment was found in the lymphocytes of welders in Guangzhou, China (welding type not specified) compared with controls (Zhu et al., 2001). One study using the alkaline filter elution method reported reduced DNA strand breaks in MAG and MMA welders compared with controls (Popp et al., 1991), whereas another study using the same method and by the same team reported a significantly higher rate of DNA single-strand breaks in the lymphocytes of MMA and other welders (Werfel et al., 1998).

(iii) DNA–protein cross-links

Positive results were reported for DNA–protein cross-links in welders, but most available studies were small and did not control for smoking. In two publications on the same study, higher levels of DNA–protein cross-links were seen in 21 MMA welders (Costa et al., 1993; Toniolo et al., 1993). Two studies evaluated five welders; one reported significantly higher levels of DNA–protein cross-links in peripheral leukocytes of MMA-SS welders (Medeiros et al., 2003), and a study of SS welders in Portugal reported a higher number of DNA–protein cross-links in lymphocytes compared with controls (Quievryn et al., 2001).

(iv) Point mutations and unscheduled DNA synthesis

Exposure to welding fumes was associated with an odds ratio (OR) of 5.65 (95% CI, 1.39–22.93; 6 exposed cases with von Hippel–Lindau (*VHL*) gene mutations) for multiple *VHL* mutations in multivariate analysis restricted to renal cell carcinoma (RCC) patients in Sweden who were smokers (Hemminki et al., 2002). [The Working Group noted that there were only 21 RCC cases exposed to welding fumes; 8 had G-to-A *VHL* mutations, and 6 of the 8 were smokers.]

Knudsen et al. (1992) did not find an increase in unscheduled DNA synthesis and DNA repair capacity in peripheral lymphocytes of TIG, MMA+TIG, and MIG welders.

(v) Oxidative damage to DNA

In a controlled crossover inhalation study of healthy welding apprentices (n = 20), 60 minutes of exposure to TIG welding fumes (Ar shielding gas) on aluminium cubes significantly increased the concentrations of 8-hydroxydeoxyguanosine (8-OHdG) in plasma and urine. The increase in plasma 8-OHdG was related to the exposure level to smaller particles of welding fumes (geometric mean diameter, 44 nm), while no associations were observed with gravimetric mass (Graczyk et al., 2016a, b). Further, in a short-term observational study, 8-OHdG concentrations in urine increased over a full shift in 41 MS stick-welding boilermakers, with a decline back to baseline in samples taken the next morning (Nuernberg et al., 2008). In another study involving 20 boilermakers, all mean concentrations of 8-OHdG in the urine after a work shift were significantly higher than values before the shift; exposure–response was observed with $PM_{2.5}$ (Kim et al., 2004). However, nonsmokers had higher levels of 8-OHdG before the start of the working week, and an interaction between smoking and exposure to welding fumes (varying by metal) was indicated (Mukherjee et al., 2004). In a comparison of 8-OHdG in urine, concentrations at the end of 5 working days were higher than at the start of the first day in both 118 shipyard TIG welders and 45 office worker controls, but the concentrations at the end of the 5 working days were significantly higher in the welders than in controls. Exposure–response was observed with $PM_{2.5}$, and with iron and zinc in urine (Lai et al., 2016).

The effects were less clear in three cross-sectional observational studies. No difference in urinary 8-OHdG was observed in a study of 57 male and female welders and 42 office worker controls (welding technique and material not reported) (Liu et al., 2013), while in another study of MAG welders no significant increase was seen after adjustment for relevant confounders (Li et al., 2015a). Finally, in a study of MIG and TIG welders, and also welders wearing a powered air-purifying respirator (PAPR) in Germany, urinary 8-oxo-guanosine (8-oxoGuo) concentrations did not differ significantly (Pesch et al., 2015). The number of 8-oxo-deoxyguanosine (8-oxodGuo) per 10^6 deoxyguanosine (dGuo) in leukocytes of MIG welders exposed to high concentrations of fumes was significantly higher than in TIG welders and welders wearing a PAPR. For urinary 8-oxoGuo, nonlinear associations were observed with serum Fe.

Table 4.2 Genetic and related effects of welding fumes in non-human mammals in vivo

Species, strain, sex	Tissue	End-point	Test system	Result	Concentration (LEC or HIC)	Route, duration, dosing regimen	Reference
Rat, Sprague-Dawley, M	Lung cells	DNA damage	DNA strand breaks, comet assay; 8-OHdG	+	65.6 mg/m³ of MMA-SS fumes	Inhalation, 2 h/d for 1, 15, 30 d	Yu et al. (2004)
Rat, Sprague-Dawley, M	Blood (leukocytes), kidney, liver	DNA strand breaks	Comet assay	+ (leukocytes, 1–15 d only; liver and kidney, 40 d only)	12.32 mg/kg of MMA fumes	Inhalation for 10 min/d, up to 40 d	Chuang et al. (2010)
Rat, Wistar, M+F	Peripheral blood lymphocytes, bone marrow	Chromosomal damage	Chromosomal aberrations	–	217 mg/m³ of MMA-MS or 144 mg/m³ of MIG-MS	Inhalation for 6 h/day, 5 d/wk, 2 wk	Etienne et al. (1986)
Rats, Wistar, M+F,	Peripheral blood lymphocytes	Chromosomal rearrangement	Sister-chromatid exchanges	–	217 mg/m³ of MMA-MS or 144 mg/m³ of MIG-MS	Inhalation for 6 h/d, 5 d/wk, 2 wk	Etienne et al. (1986)
Mouse, C57BL/6J/BOM9, F	Fur	Gene mutation	Fur spot test	+	100 mg/kg particles of MMA-SS welding fumes	i.p. at 8, 9, 10 d of gestation	Knudsen (1980)

+, positive; –, negative; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; d, day(s); F, female; h, hour(s); HIC, highest ineffective concentration; i.p., intraperitoneally; LEC, lowest effective concentration; M, male; MIG, metal inert gas; min, minute(s); MMA, manual metal arc; MS, mild steel; SS, stainless steel; wk, week(s)

(b) Experimental systems

See Table 4.2, Table 4.3

DNA damage (comet assay) and 8-OHdG increased with exposure duration in a dose-dependent manner in the lung tissue of Sprague-Dawley rats exposed to MMA-SS welding fumes for up to 30 days (Yu et al., 2004). In a study in which Sprague-Dawley rats were exposed to MMA-SS welding fumes for up to 40 days, DNA damage (comet assay, tail moment) increased significantly in leukocytes (1–15 days only) and in liver and kidney cells (40 days only) (Chuang et al., 2010). No increase in chromosomal aberrations in bone marrow cells and in peripheral blood lymphocytes, or in lymphocyte sister-chromatid exchange, was seen in Wistar rats after exposure to welding fumes (MMA-MS, MIG-MS) by inhalation for 60 hours (Etienne et al., 1986).

One study reported positive results in the fur spot test in mice after receiving 100 mg/kg body weight of MMA-SS welding fumes on days 8, 9, and 10 of gestation by intraperitoneal injection (Knudsen, 1980).

SS and MS welding fumes increased DNA damage in a study in vitro in RAW 264.7 mouse peritoneal monocytes, with significantly higher damage from the SS welding fumes (Leonard et al., 2010). [The Working Group noted that DNA damage was assessed by the comet tail length instead of %DNA in comet tail.]

Only a few studies in bacteria were available. MMA-SS and MIG-SS fumes were positive in *S. typhimurium* strain TA100 without metabolic activation (starting from 2.5 µg water-soluble Cr in fume sample) (Pedersen et al., 1983). In the SOS *umu*-test in *S. typhimurium* strain TA1535/pSK1002, exposure to MMA-SS welding fumes

Table 4.3 Genetic and related effects of welding fumes in experimental systems in vitro

Species, strain	End-point	Test system	Results		Concentration (LEC or HIC)	Reference
			Without metabolic activation	With metabolic activation		
Mouse peritoneal monocytes RAW 264.7	DNA damage	DNA strand breaks, comet assay	+	NT	250 µg/mL; SS and MS fumes	Leonard et al. (2010)
Salmonella typhimurium TA 100	Gene mutation	Reverse mutation	+	NT	2.5 µg; MMA-SS and MIG-SS fumes per plate	Pedersen et al. (1983)
Salmonella typhimurium TA1535/pSK1002	DNA damage	SOS *umu* assay	+	NT	NS; MMA–SS welding fumes	Ong et al. (1987)

+, positive; HIC, highest ineffective concentration; LEC, lowest effective concentration; MIG, metal inert gas; MMA, manual metal arc; MS, mild steel; NS, not specified; NT, not tested; SS, stainless steel.

for 4 and 6 hours generated a marked response (Ong et al., 1987).

In a study in an acellular system, DNA damage associated with hydroxyl radical (·OH) formation was demonstrated for MMA welding fumes in plasmid λ *Hind* III (Antonini et al., 2005).

4.2.3 Oxidative stress

(a) Humans

Effects on 8-OHdG are described in Section 4.2.2 (a)(v).

Significant increases in hydrogen peroxide (H_2O_2) were observed in plasma and urine in a controlled crossover experimental inhalation study of TIG aluminium welding (1 hour; particulate matter of diameter < 4 µm or PM_4, 0.72 mg/m³) (Graczyk et al., 2016a). Similarly, an increase of the hydrogen peroxide to tyrosine ratio in exhaled breath condensate was observed during the work shift in a field study of 45 welders using mixed welding techniques (respirable dust, 0.7 mg/m³), but in smokers only (Gube et al., 2010).

No change in urinary 8-isoprostane measured before and after the work shift was observed among 41 boilermaker apprentices and current and retired welders (metal arc welding, MS; $PM_{2.5}$, 0.82 mg/m³) in a controlled experiment of crossover design (Nuernberg et al. 2008). However, the concentrations decreased significantly from the end of the shift to bedtime, and to the next day. Urinary 8-isoprostane increased significantly from the start of day 1 to the end of day 5 in a 5-day observational study of 118 TIG shipyard welders ($PM_{2.5}$, 0.76 mg/m³). Exposure–response relationships were observed with $PM_{2.5}$ in air, and with iron and zinc in urine (Lai et al., 2016). Two cross-sectional studies (concentrations only measured at the end of the work shift) observed higher concentrations of 8-isoprostane in serum and exhaled breath condensate among welders than among unexposed controls; Han et al. (2005) evaluated 197 shipyard (GMA) welders and 150 office controls, while Hoffmeyer et al. (2012a) studied 58 healthy MAG-MS welders. Two other cross-sectional studies found higher 8-isoprostane concentrations in welders at the end of shifts, with high and low concentrations of chromium in exhaled breath condensate and nasal lavage fluid, respectively (Hoffmeyer et al., 2012b; Raulf et al., 2016).

In another cross-sectional study, glutathione (GSH) in blood was lower in welders (44 spot welders and 80 arc welders; material not stated) and in those with bystander (59 assemblers) exposure to welding fumes compared with controls (29 office workers), with no gradient in effect between full-time welders, part-time welders and bystanders, and no effect on plasma malondialdehyde (MDA) (Luo et al., 2009).

Gube et al. (2010) found no overall cross-sectional group difference between 45 welders and 24 controls in the MDA to tyrosine ratio (an indicator of lipid peroxidation), but the ratio was significantly increased in workers without respiratory protection, compared to those with respiratory protection.

Levels of antioxidants in plasma (vitamins C and E) and erythrocytes (superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPX) activity) were all lower in nonsmoking male and female construction welders (n = 70; electric arc welding) as compared with unexposed controls (n = 70), while erythrocyte lipoperoxide concentrations were higher. Antioxidant levels (except catalase) decreased with years working as a welder (adjusted for age), while lipoperoxide concentrations increased. A significant negative association between ozone exposure levels among the welders and each antioxidant was observed, while lipoperoxide concentrations were positively associated with the ozone exposure (Zhu et al., 2004).

No significant differences in plasma MDA and total antioxidant concentrations, or erythrocyte GPX and glutathione *S*-transferase activity, were observed between male and female welders (welding technique and material not stated; n = 57) and office worker controls (n = 42). However, welders had lower erythrocyte GSH concentrations and erythrocyte SOD activities (Liu et al., 2013). [The Working Group noted that these specific comparisons were not adjusted for other factors; sex, smoking, and alcohol intake differed significantly between the exposed group and the control group.] Welders (n = 40) performing MMA welding (material not stated) had significantly lower whole-blood GSH concentrations and higher MDA concentrations when compared with controls (n = 10, Harisa et al., 2014). In another small cross-sectional study including 34 welders (technique and material not reported) and 20 controls, serum thiobarbituric acid reactive substances and protein carbonyl concentrations were higher in welding workers than in controls, while total protein sulfhydryl groups and GSH levels were significantly lower in welders than in controls (Fidan et al., 2005).

No significant difference was observed in total serum antioxidant status, but erythrocyte SOD and GPX activity was lower in male nonsmoking car factory spot welders (n = 46) compared with controls (n = 45) (Sharifian et al., 2009). A negative correlation was observed between the magnetic field intensity from welding, and SOD and GPX activity. No such associations were observed with metal concentrations in air (Pb, Fe, Cu, and Zn). Increasing zinc concentrations in blood were associated with significantly lower total antioxidant concentrations in a cross-sectional study of 94 smoking welders (manual electric arc or gas welding, material not stated) (Kolarzyk et al., 2006), while copper levels in blood were positively associated with total antioxidant status.

Male and female vehicle manufacturer electric arc welders with high exposure to manganese (geometric mean, 1.45 mg/m^3; n = 37) had cross-sectionally higher serum MDA levels and lower erythrocytic SOD activity when compared with controls (n = 50) (Li et al., 2004). In the highly-exposed shipyard welders studied by Han et al. (2005), the total antioxidant status in serum was significantly higher than in 150 controls, as were levels of aconitase and GPX, while no significant difference was observed for manganese SOD (MnSOD). Dose–response associations were observed between the concentrations of manganese or lead in the blood of welders and various

measures of antioxidant status, including GPX and MnSOD (Han et al., 2005).

Haem oxygenase-1 was significantly higher, and associated with particulate matter of diameter < 2 μm, in induced sputum samples from short-term (mean 10 years) aluminium-iron welders (n = 30) compared with non-exposed subjects (n = 27) (Stark et al., 2009). Intermediate levels were seen in long-term (mean, 21 years; n = 16) MS welders.

In a study of 75 male SS and MS shipyard welders using electrodes containing up to 22% chromium, blood levels of Cr(VI) were associated with increased serum apolipoprotein J/Clusterin (ApoJ/CLU) in SS welders (Alexopoulos et al., 2008). The ApoJ/CLU levels decreased in the workers exposed to the highest concentrations after participating in a worker educational programme aimed at reducing exposure levels.

Mitochondrial DNA methylation levels in blood were lower at the end of a work shift compared with before the shift among 48 men, including 35 welding boilermakers (MMA-MS and MIG-MS welding; mean $PM_{2.5}$ concentration, 0.38 mg/m^3), and an exposure–response association indicated that mitochondrial DNA methylation was negatively associated with $PM_{2.5}$ concentrations (Byun et al., 2016). In a cross-sectional approach, Xu et al. (2017) also found less methylation of the mitochondrial regulatory region and higher mitochondrial DNA in 101 welders (mainly GMA-MS; mean respirable dust concentration, 1.2 mg/m^3) compared with 127 controls.

(b) *Experimental systems*

(i) *In vivo*

Several studies reported increases in markers of lung oxidative stress in male Sprague-Dawley rats after exposure to SS fumes via intratracheal instillation. After exposure to MMA-SS welding fumes, increases were observed in lipid peroxidation products in lung tissue homogenate (Taylor et al., 2003), nitric oxide species in the BALF, inducible nitric oxide synthase (iNOS) protein expression in inflammatory infiltrates, and AM or PBMC reactive oxygen species (ROS) production ex vivo (Antonini et al., 2004a; Erdely et al., 2014). Although all fractions of MMA-SS fumes induced lipid peroxidation, the total fraction of fumes was the most potent and the soluble fraction the least potent (Taylor et al., 2003). GMA-SS fumes induced lower levels of lipid peroxidation in rat lungs compared with MMA-SS fumes, and GMA-MS fumes had only a marginal effect (Taylor et al., 2003). Neither GMA-SS nor GMA-MS fumes increased levels of nitric oxide species in the lung BALF, or induced greater alveolar macrophage ROS production ex vivo (Antonini et al., 2004b). No change in serum concentrations of lipid peroxidation products was reported in male Wistar rats exposed to unspecified welding fumes [containing chromium] via inhalation (60 mg/m^3, 6 hours per day, for 5 or 10 days), and lung concentrations were not determined (Halatek et al., 2017).

In male A/J and C57BL/6J mice exposed to SS or MS welding fumes by pharyngeal aspiration, no changes were observed in the lung tissue mRNA expression levels of enzymes involved in oxidative stress (*iNOS*, prostaglandin-endoperoxide synthase 2 (*Ptgs2*) and glutathione *S*-transferase pi-1 (*Gstp1*)) (cumulative lung burden, approximately 0.340 mg) (Zeidler-Erdely et al., 2008). [The Working Group noted that the welding fumes used were not freshly generated, and loss of pro-oxidant activity soon after the generation of SS fumes was hypothesized by Antonini et al. (1998) and Badding et al. (2014) to result from the degradation of a short-lived, reactive chromium species.]

(ii) *In vitro*

Welding fumes have been reported to oxidize biological components in both biochemical assays and cell culture models. MIG-MS welding fumes increased the oxidation of dopamine in a

manner directly related to the generating current and inversely related to the iron:manganese ratio of the fumes (Hudson et al., 2001), while MMA-MS fumes increased the oxidation of both ascorbate and GSH in artificial BALF (Suri et al., 2016). Welding fumes generated ROS as determined by electron spin resonance, with the total fractions eliciting the strongest signals and the soluble fraction the weakest, although CrV was similarly produced (from Cr(VI)) by both fractions (Taylor et al., 2003; Antonini et al., 2005). Initially, neither GMA-SS nor GMA-MS welding fumes produced ROS (Taylor et al., 2003); however, later studies reported ROS generation induced by GMA welding of SS, MS, and a consumable of high nickel and copper content (Leonard et al., 2010; Badding et al., 2014).

MMA-SS, GMA-SS, and GMA-MS fumes increased ROS production in rat BALF lung macrophages (Antonini et al., 1997, 1999; Chang et al., 2013) and in mouse RAW 264.7 macrophages (Leonard et al., 2010).

Iron-chelation did not inhibit the activity of soluble fractions [which suggests that non-ferrous metals were responsible], while total MMA-SS fractions elicited the greatest ROS production in rat lung macrophages (Antonini et al., 1999); ultrafine particle size fractions elicited a greater effect than coarse fractions for both SS and MS fumes (Leonard et al., 2010; Chang et al., 2013).

4.2.4 Altered cell proliferation or death

(a) Humans

As noted previously (see Section 4.2.2 (a) (i)), one study reported nuclear anomalies (reflecting genotoxic as well as cytotoxic effects) in buccal and nasal cells of TIG welders (Wultsch et al., 2014). An in vitro study reported cytotoxicity in human lung A549 cells exposed to SS welding fumes (McNeilly et al., 2004).

(b) Experimental systems

(i) In vivo

Studies in male rats and mice suggest that SS welding fumes induce more lung toxicity when compared with MS fumes, via both inhalation and intratracheal instillation exposure routes (reviewed in Zeidler-Erdely et al., 2012). In Sprague-Dawley rats, BALF albumin concentrations and lactate dehydrogenase (LDH) activity increased within 1 day after inhalation exposure to GMA-SS (40 mg/m^3, 3 hours per day, for 3 days) or MMA-SS (44.1–65.6 or 80.1–116.8 mg/m^3, 2 hours per day, for up to 60 exposure days) welding fumes; levels remained elevated for at least 14 days after exposure cessation, and resolved to baseline after 30 days (Yu et al., 2004; Antonini et al., 2007; Yang et al., 2009). Decreased viability in BALF leukocytes, coupled with increased serum LDH activity, was also induced in Wistar rats exposed to unspecified welding fumes [containing chromium] via inhalation (60 mg/m^3, 6 hours per day, for 5 or 10 days; Halatek et al., 2017). While high metal (HM) fumes (25 mg/m^3, 4 hours per day, for 3, 8, or 13 days) via inhalation induced an initial, transient, increase in albumin levels, there was no corresponding cytotoxicity to the pulmonary epithelium (Zeidler-Erdely et al., 2014). No effects were observed in rats after similar exposures to low metal (LM) MS resistance spot welding fumes (Zeidler-Erdely et al., 2014) or GMA-MS fumes (40 mg/m^3, 3 hours per day, for 3 or 10 days) (Antonini et al., 2009a).

A single intratracheal instillation of MMA-SS welding fumes in Sprague-Dawley rats induced apoptosis in clusters of pulmonary epithelial cells 6–10 days after treatment (Antonini et al., 2005). BALF albumin and LDH activity levels increased after 1 day, remained elevated for up to 6 days (Taylor et al., 2003; Antonini et al., 2004a), and resolved to background levels after 10–35 days (Antonini et al., 1996, 1997, 2004b). MMA-SS fumes were more

potent than GMA-SS and GMA-MS fumes; the total fraction of MMA-SS welding fumes was the most potent compared with the soluble fraction, which induced a lesser lung injury (Taylor et al., 2003).

Several studies from the same group reported increases in proliferative lesions and persistent lung cytotoxicity in male mice after exposure to welding fumes. Short-term exposure to GMA-SS fumes by inhalation (40 mg/m^3, 4 hours per day, 4 days per week, for 9 weeks; cumulative lung burden, approximately 0.255 mg) induced the appearance of hyperplastic foci in 2 A/J mice (vs 0 in control) 30 weeks after exposure initiation (Falcone et al., 2017), consistent with the increased incidence of preneoplastic lesions (hyperplasias and/or adenomas) after a similar duration after pharyngeal exposure (cumulative lung burden, approximately 1.7 or 3.4 mg) (Zeidler-Erdely et al., 2013) (see Section 3). [The Working Group noted that hyperplasia, atypical adenomatous hyperplasia, and early adenoma are difficult to distinguish from each other, so combining the lesions reduces the potential for misclassification.] After a shorter duration of exposure to GMA-SS fumes by inhalation (40 mg/m^3, 3 hours per day, for 6 or 10 days; respective cumulative lung burden, approximately 0.071 or 0.120 mg), BALF LDH activity and albumin levels increased to a similar extent in both A/J and B6 mice and remained elevated during 28 days of recovery (Zeidler-Erdely et al., 2011b; Erdely et al., 2012). Exposure to GMA-MS fumes by pharyngeal aspiration (cumulative lung burden, approximately 0.340 mg) transiently increased BALF LDH activity to a greater extent in A/J compared with B6 mice, with no change in albumin levels. Exposure to MMA-SS and GMA-SS fumes increased both LDH activity and albumin levels, resolving in B6 mice and diminishing in A/J mice after 28 days or more of recovery (Solano-Lopez et al., 2006; Zeidler-Erdely et al., 2008, 2011a; Erdely et al., 2011a). Administration of a mass-equivalent Cr(VI) solution elicited a similar toxicity profile to MMA-SS fumes in B6 mice, but was not as effective in A/J mice (Zeidler-Erdely et al., 2008). [The Working Group noted that this suggests that other mediators contribute to MMA-SS toxicity in the lungs of A/J mice.]

(ii) In vitro

Both SS and MS welding fumes have been consistently reported to induce cytotoxicity and/or alter mitochondrial function in mammalian cells. SS or MS fumes generated from MMA, GMA, and MIG welding induced cytotoxicity in primary rat alveolar macrophages from male rats (Pasanen et al., 1986; Antonini et al., 1997, 1999, 2005), primary bovine alveolar macrophages [sex not reported] (White et al., 1983), and hamster kidney or embryo cells (Hansen & Stern, 1985; Stern et al., 1988). MMA-SS fumes were the most potent, and induced cytotoxicity qualitatively similar to a molar-equivalent Cr(VI) solution (White et al., 1983; Hansen & Stern, 1985; Pasanen et al., 1986). Welding fumes from a consumable of high nickel and copper content were more cytotoxic than GMA-SS or GMA-MS fumes in mouse RAW 264.7 cells (Badding et al., 2014), and preincubation with the antioxidant *N*-acetyl-L-cysteine afforded no protection. All three types of welding fumes attenuated mitochondrial adenosine triphosphate production, maximal respiratory rate, and bioenergenic reserve capacity (Leonard et al., 2010; Badding et al., 2014). SS fumes were the most potently cytotoxic, as were the total or soluble fractions of fumes (Pasanen et al., 1986; Antonini et al., 1999) and the ultrafine particle fractions (Leonard et al., 2010).

4.2.5 Receptor-mediated effects

(a) Humans

Studies available to the Working Group examined the effects of welding and welding fumes on sex hormones such as testosterone, luteinizing

hormone (LH), and follicle-stimulating hormone (FSH). Decreased serum testosterone concentrations were seen in a cross-sectional study of TIG-SS welders (n = 35) compared with non-welding metalworkers (n = 54) (Bonde, 1990), and in male welders exposed to manganese [type of welding not specified] (Tutkun et al., 2014). In contrast, two other studies (Bonde & Ernst, 1992; Hjollund et al., 1998) observed no association between welding (TIG-SS, MMA-SS, MAG-SS) and serum testosterone levels (Bonde & Ernst, 1992). [The Working Group noted that part of the referent group was non-welding metalworkers in the Bonde & Ernst study; a period of only 3 months without welding was considered in the referent group of metal workers in the Hjollund et al. study; and no differences in urine concentrations of chromium, manganese, or nickel were detected between welders and non-welders, or between measurements made at the beginning and end of the work shift.] Serum testosterone levels were higher in welders [type of welding not specified] exposed to manganese [the only metal analysed] for less than 5 years compared with controls and workers exposed for 5 years or more (Wang et al., 2011).

No association was seen between exposure to welding fumes (TIG-SS, MMA-SS, MAG-SS) and levels of FSH and LH (Bonde & Ernst, 1992; Hjollund et al., 1998), or in levels of LH or thyroid-stimulating hormone (TSH) in male welders exposed to manganese [type of welding not specified] (Tutkun et al., 2014). Welders exposed to manganese had significantly higher concentrations of manganese in blood and urine. Long-term exposure to manganese in this group of welders resulted in significantly lower serum levels of LH and FSH (Wang et al., 2011). However, male MMA shipyard welders (CO_2 gas) had significantly higher manganese concentrations in blood and urine, and higher levels of LH, FSH, and TSH-releasing hormone (TRH) compared with control subjects (Kim et al., 2007). [The Working Group noted that hormone levels were not normally distributed, which was not accounted for in the analyses; manganese was the only metal measured.]

Increased serum prolactin levels were observed in a cross-sectional study of male shipyard welders (Ellingsen et al., 2007) and in male welders exposed to manganese (Niu et al., 2004), and a strong positive correlation was seen between whole-blood manganese concentrations and serum prolactin in welders (Tutkun et al., 2014). In contrast, serum prolactin levels decreased in a group of welders exposed to manganese (Wang et al., 2011).

Compared with age-matched controls (turners/fitters from the same shipyard), welders [type of welding not specified] showed increased levels of inhibin B [no differences in geometric mean values], which can downregulate the synthesis and inhibit the secretion of FSH (Ellingsen et al., 2007).

(b) Experimental systems

No data were available to the Working Group.

4.2.6 Other mechanisms

Several studies of exposure to welding fumes in humans reported effects related to epigenetics and telomere length. Using a repeated measure study design, $PM_{2.5}$ was significantly associated with long interspersed nuclear elements-1 (LINE-1) hypermethylation in 66 welders (MMA-MS welding) (Fan et al., 2014). Additionally, $PM_{2.5}$ exposure was associated with increased methylation in the promoter region of the inducible nitric oxide synthase *iNOS* (MMA welding, MS and SS) (Kile et al., 2013). Wong et al. (2014b) found a statistically significant decrease in relative telomere length, and genomic trauma to leukocyte telomeres was more consistent with recent occupational $PM_{2.5}$ exposure, among 48 welders with an 8-year follow-up (MMA welding, mainly MS) (Wong et al., 2014b). Li et al. (2015a) found that telomere

length was significantly shorter in welders, associated with number of years as a welder after controlling for age. Further, a repeated-measures longitudinal study in a panel of 87 MMA (mainly MS) welders with a 29-month follow-up period showed a positive association between both LINE-1 and Alu methylation levels, and telomere length. The interaction between LINE-1 methylation and follow-up time was statistically significant, suggesting that the rate of telomeric change was modified by the degree of LINE-1 methylation (Wong et al., 2014c). Using the same study population as in Li et al. (2015a), Hossain et al. (2015) found that measured exposure to respirable dust as a welder, as well as years worked as a welder, was associated with increased coagulation factor II (thrombin) receptor-like 3 (*F2RL3*) gene hypomethylation.

4.2.7 Gene expression arrays in vivo

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

Lung gene expression studies in rats and mice exposed to welding fumes indicate a dysregulation of cellular signalling and proliferation pathways, and a strong immune response (reviewed in Zeidler-Erdely et al., 2012), also supported by the results of gene expression profiling in non-human primates. Adverse lung pathology was not observed in male cynomolgus monkeys subchronically exposed to MMA-SS fumes via inhalation (31.4 or 62.5 mg/m^3, 2 hours per day, 5 days per week, for 229 days), but gene induction was observed in cancer, immunological disease, inflammatory disease, cellular growth, and proliferation pathways, including activation of pregnane X receptor/retinoid X receptor (*Pxr*/*Rxr*), peroxisome proliferator-activated receptor (*Ppar*), *p53*, nuclear respiratory factor-2 (*Nrf2*), and retinoic acid receptor (*Rar*) (Heo et al., 2010). When compared with the results previously reported in male Sprague-Dawley rats also exposed to MMA-SS fumes via inhalation (51.4 or 84.6 mg/m^3, 2 hours per day, for 30 days), associated with severe lung inflammation and injury (Oh et al., 2009), 7% of the differentially expressed genes were similarly affected between species (Heo et al., 2010). [The Working Group noted that the control and exposed primates were not handled in a similar manner, and statistical analyses in both studies may have inadequately controlled for multiple comparisons.]

In the most comprehensive study from this group, Oh et al. (2012) evaluated the impact of exposure to MMA-SS welding fumes (44.1–51.4 or 80.1–84.6 mg/m^3, 2 hours per day, for 30 days) by inhalation with recovery periods in male Sprague-Dawley rats, including the re-evaluation of tissues from their earlier report (Oh et al., 2009), and compared genetic changes with tissue histopathology and BALF cytology from Yang et al. (2009). Lung immune cell infiltration and inflammation was detectable at both the genetic and cellular level, and pathways related to leukocyte extravasation and activation, antigen presentation, immunosuppression, angiogenesis, and cell cycle, growth, and proliferation were perturbed after repeated exposure and recovery periods (Oh et al., 2012). In PBMCs, approximately three times as many genes were downregulated compared with those induced, including an attenuation of stress response, cell growth, and differentiation pathways, while inflammatory responses were both induced (angiotensinogen, *Agt*, and major histocompatibility complex, *Mhc*) and attenuated (cathepsin E, *Ctse*, and dipeptidase, *Dpep*) (Rim et al., 2004).

Similar changes were reported after exposure to GMA-SS welding fumes in mice as described above after MMA-SS exposure in rats, i.e. responses were largely consistent across rodent species as well as SS welding fume sources (discussed in Zeidler-Erdely et al., 2012). GMA-SS exposure via pharyngeal aspiration

also altered genes involved in inflammatory and immunological disease pathways in both mouse strains, with strain-specificity in the network components and direction of induction affected. Cancer networks were induced primarily in the A/J strain, while haematological disease emerged in the B6 mice (Zeidler-Erdely et al., 2010). Follow-up studies revealed disruption of gene networks related to type I interferon signalling, specifically involving induction of interferon regulatory factor-7 (*Irf7*), and several type I interferon-related genes were upregulated in the blood and lung tissue of B6 mice exposed to GMA-SS but not GMA-MS welding fumes (Erdely et al., 2011a, 2012). [The Working Group noted that this response may be similar to that induced by lung infection.] After exposure to GMA-MS welding fumes via pharyngeal aspiration, Zeidler-Erdely et al. (2010) unexpectedly found differential expression of behavioural genes associated with circadian rhythm signalling, such as increased expression of *Nr1d1* in both A/J and B6 mice. Top networks induced in A/J lungs involved circadian rhythm signalling, stress response, and cell survival involving the *Tp53* and *Myc* pathways. Genes commonly associated with inflammatory lung response and apoptosis were altered in both A/J and B6 mice. The gene induction could not be attributed to a generalized inflammatory response, however, because pulmonary toxicity and lung inflammation were induced by exposure to both SS and MS fumes (Erdely et al., 2012).

While GMA-SS welding fumes were the most potent inducers of inflammation and stress-response pathway activation in the lungs (compared with GMA-MS or MMA-SS fumes), MMA-SS fumes induced stress-response pathway activation in cardiovascular tissues, associated with greater pulmonary cytotoxicity (Erdely et al., 2011a). MMA-SS fumes also transiently activated the inflammation and immune regulation pathways in rat PMBCs (Erdely et al., 2014), although no changes in serum CRP or IL-6 levels were reported after weekly exposure to MMA-HS welding fumes (Popstojanov et al., 2014).

4.3 Cancer susceptibility

No data were available to the Working Group.

4.4 Other adverse effects

4.4.1 Humans

Epidemiological studies show that long-term exposure to welding fumes is associated with respiratory health effects including asthma, bronchitis, lung function changes, neurological disorders and, if cadmium is present, renal tubular dysfunction (Wang et al., 1994; Antonini, 2003; El-Zein et al., 2003; Antonini et al., 2004a; Ding et. al., 2011; Racette et. al., 2012; Szram et al., 2013). Cardiac arrhythmias, myocardial ischaemia, and atherosclerosis have also been reported and epidemiological studies of male welders showed increased risk of cardiovascular disease, including hypertension (Fang et al., 2010b; Ibfelt et al., 2010; Li et. al., 2015b; Mocevic et al., 2015).

The exposure of boilermaker construction workers to $PM_{2.5}$ from metal fumes was associated with alterations in the heart rate variability (HRV) (Cavallari et al., 2007), an effect associated with impaired cardiac health (Kleiger et al., 1987). Long-term metal particulate exposure was shown to decrease cardiac acceleration and deceleration capacities in welding workers (Umukoro et al., 2016). Crossover panel studies of welders showed that HRV was inversely associated with work $PM_{2.5}$ exposures in each of the 14 hours post-work, with a multiphasic cardiovascular autonomic response with immediate (2 hours) and delayed (9–13 hours) responses (Cavallari et al., 2008a), especially at night (Cavallari et al., 2007). Moreover, after analysing workday $PM_{2.5}$ samples, a statistically significant association between HRV and manganese exposure was

observed, but this alone did not account for the observed declines in night-time (non-work) HRV (Cavallari et al., 2008b).

Other well-documented effects are ocular disorders related to welding (both in welders and in nearby workers), including disorders associated with exposure to ultraviolet radiation (cataracts, keratoconjunctivitis) as well as foreign bodies (Lombardi et al., 2005; Zamanian et al., 2015; Slagor et al., 2016).

4.4.2 Experimental systems

Lung function decrements and fibrosis were reported in male Sprague-Dawley rats after exposure to welding fumes by inhalation (reviewed in Zeidler-Erdely et al., 2012). Early perivascular and peribronchiolar fibrosis was induced after treatment for 30 days (44.1–65.6 or 80.1–116.8 mg/m^3, 2 hours per day) (Yu et al., 2004) and was associated with decreased tidal volume, which persisted in the group exposed to the higher concentration after 60 days of recovery (Sung et al., 2004). Fibrosis was not observed in the alveolar spaces after repeated exposure and recovery periods (Yang et al., 2009).

Other pulmonary effects, including pneumonia, pneumonitis, metaplasia, and emphysema were observed in male Syrian Golden hamsters and Sprague-Dawley rats after exposure to SS welding fumes. Hamsters exposed to MMA-SS and MIG-SS fumes via intratracheal instillation for 56 weeks developed moderate interstitial or nonspecific pneumonia, metaplasia, and mild emphysema when evaluated after nearly 2 years (Reuzel et al., 1986). Exposure to MMA-SS welding fumes via intratracheal instillation once per week for 28 weeks induced granulomatous areas associated with inflammatory cell influx and significant pulmonary injury throughout the lungs; the nature and extent of pulmonary injury, as well as the deposition and composition of welding particle agglomerates, were qualitatively similar to that observed in the lung of a human welder (Antonini et al., 2013). Pneumonitis, characterized by a peribronchiolar accumulation of neutrophils and macrophages, was observed in rats exposed once to GMA-SS fumes via intratracheal instillation (Antonini et al., 1996), and in rats infected with *L. monocytogenes* after a single exposure to MMA-SS fumes via intratracheal instillation (Antonini et al., 2004b). Pneumonitis was not reported after exposure to GMA-MS welding fumes.

Decrements in cardiac function and blood flow have been reported in several studies in male rats and mice after exposure to welding fumes. Cardiomyocte contraction was reduced in male Sprague-Dawley rats after exposure to MMA welding fumes by intratracheal instillation once per week for 7 weeks (Popstojanov et al., 2014), while tail artery endothelium relaxation was attenuated in male Sprague-Dawley rats after 3 days of exposure to welding fumes by inhalation (25 mg/m^3, 4 hours per day) (Zeidler-Erdely et al., 2014). Exposure to GMA-SS fumes (40 mg/m^3, 3 hours per day, for 10 days) by inhalation increased markers of systemic inflammation and increased atherosclerotic plaque lesion area development in B6 *ApoE*$^{-/-}$ mice (Erdely et al., 2011a), and a single pharyngeal aspiration of MMA-SS fumes induced stress-response genes in cardiovascular tissues of B6 mice (Erdely et al., 2011b).

Dopaminergic neurotoxicity has been observed in several studies in male Sprague-Dawley rats after exposure to SS and MS welding fumes, with reported effects on *Th* expression (Antonini et al., 2009b; Sriram et al., 2010) and the levels of dopamine, serotonin, and norepinephrine in the olfactory bulb (Sriram et al., 2014).

References

Alexopoulos EC, Cominos X, Trougakos IP, Lourda M, Gonos ES, Makropoulos V (2008). Biological monitoring of hexavalent chromium and serum levels of the senescence biomarker apolipoprotein J/Clusterin in welders. *Bioinorg Chem Appl*, 2008:420578. doi:10.1155/2008/420578 PMID:18464919

Anderson SE, Meade BJ, Butterworth LF, Munson AE (2007). The humoral immune response of mice exposed to manual metal arc stainless steel-welding fumes. *J Immunotoxicol*, 4(1):15–23. doi:10.1080/15476910601115119 PMID:18958709

Antonini JM (2003). Health effects of welding. *Crit Rev Toxicol*, 33(1):61–103. doi:10.1080/713611032 PMID:12585507

Antonini JM, Clarke RW, Krishna Murthy GG, Sreekanthan P, Jenkins N, Eagar TW, et al. (1998). Freshly generated stainless steel welding fume induces greater lung inflammation in rats as compared to aged fume. *Toxicol Lett*, 98(1-2):77–86. doi:10.1016/S0378-4274(98)00103-9 PMID:9776564

Antonini JM, Krishna Murthy GG, Brain JD (1997). Responses to welding fumes: lung injury, inflammation, and the release of tumor necrosis factor-alpha and interleukin-1 beta. *Exp Lung Res*, 23(3):205–27. doi:10.3109/01902149709087368 PMID:9184789

Antonini JM, Krishna Murthy GG, Rogers RA, Albert R, Ulrich GD, Brain JD (1996). Pneumotoxicity and pulmonary clearance of different welding fumes after intratracheal instillation in the rat. *Toxicol Appl Pharmacol*, 140(1):188–99. doi:10.1006/taap.1996.0212 PMID:8806885

Antonini JM, Lawryk NJ, Murthy GG, Brain JD (1999). Effect of welding fume solubility on lung macrophage viability and function in vitro. *J Toxicol Environ Health A*, 58(6):343–63. doi:10.1080/009841099157205 PMID:10580758

Antonini JM, Leonard SS, Roberts JR, Solano-Lopez C, Young SH, Shi X, et al. (2005). Effect of stainless steel manual metal arc welding fume on free radical production, DNA damage, and apoptosis induction. *Mol Cell Biochem*, 279(1-2):17–23. doi:10.1007/s11010-005-8211-6 PMID:16283511

Antonini JM, Roberts JR (2007). Chromium in stainless steel welding fume suppresses lung defense responses against bacterial infection in rats. *J Immunotoxicol*, 4(2):117–27. doi:10.1080/15476910701336953 PMID:18958720

Antonini JM, Roberts JR, Chapman RS, Soukup JM, Ghio AJ, Sriram K (2010). Pulmonary toxicity and extrapulmonary tissue distribution of metals after repeated exposure to different welding fumes. *Inhal Toxicol*, 22(10):805–16. doi:10.3109/08958371003621641 PMID:20560776

Antonini JM, Roberts JR, Schwegler-Berry D, Mercer RR (2013). Comparative microscopic study of human and rat lungs after overexposure to welding fume. *Ann Occup Hyg*, 57(9):1167–79. doi:10.1093/annhyg/met032 PMID:23798603

Antonini JM, Roberts JR, Stone S, Chen BT, Schwegler-Berry D, Frazer DG (2009a). Short-term inhalation exposure to mild steel welding fume had no effect on lung inflammation and injury but did alter defense responses to bacteria in rats. *Inhal Toxicol*, 21(3):182–92. doi:10.1080/08958370802360661 PMID:18925477

Antonini JM, Sriram K, Benkovic SA, Roberts JR, Stone S, Chen BT et al. (2009b). Mild steel welding fume causes manganese accumulation and subtle neuroinflammatory changes but not overt neuronal damage in discrete brain regions of rats after short-term inhalation exposure. *Neurotoxicology*, 30(6):915–25. doi:10.1016/j.neuro.2009.09.006 PMID:19782702

Antonini JM, Stone S, Roberts JR, Chen B, Schwegler-Berry D, Afshari AA, et al. (2007). Effect of short-term stainless steel welding fume inhalation exposure on lung inflammation, injury, and defense responses in rats. *Toxicol Appl Pharmacol*, 223(3):234–45. doi:10.1016/j.taap.2007.06.020 PMID:17706736

Antonini JM, Taylor MD, Millecchia L, Bebout AR, Roberts JR (2004a). Suppression in lung defense responses after bacterial infection in rats pretreated with different welding fumes. *Toxicol Appl Pharmacol*, 200(3):206–18. doi:10.1016/j.taap.2004.04.022 PMID:15504457

Antonini JM, Taylor MD, Zimmer AT, Roberts JR (2004b). Pulmonary responses to welding fumes: role of metal constituents. *J Toxicol Environ Health A*, 67(3):233–49. doi:10.1080/15287390490266909 PMID:14681078

Badding MA, Fix NR, Antonini JM, Leonard SS (2014). A comparison of cytotoxicity and oxidative stress from welding fumes generated with a new nickel-, copper-based consumable versus mild and stainless steel-based welding in RAW 264.7 mouse macrophages. *PLoS One*, 9(6):e101310. doi:10.1371/journal.pone.0101310 PMID:24977413

Bonde JP (1990). Semen quality and sex hormones among mild steel and stainless steel welders: a cross sectional study. *Br J Ind Med*, 47(8):508–14. PMID:2118383

Bonde JP, Ernst E (1992). Sex hormones and semen quality in welders exposed to hexavalent chromium. *Hum Exp Toxicol*, 11(4):259–63. doi:10.1177/096032719201100404 PMID:1354973

Borská L, Fiala Z, Smejkalová J, Tejral J (2003). Health risk of occupational exposure in welding processes I. Genotoxic risk. *Acta Medica (Hradec Kralove)*, 46(1):25–9. PMID:12747536

Botta C, Iarmarcovai G, Chaspoul F, Sari-Minodier I, Pompili J, Orsière T, et al. (2006). Assessment of occupational exposure to welding fumes by inductively coupled plasma-mass spectroscopy and by the alkaline

Comet assay. *Environ Mol Mutagen*, 47(4):284–95. doi:10.1002/em.20205 PMID:16489626

Brand P, Gube M, Gerards K, Bertram J, Kaminski H, John AC, et al. (2010). Internal exposure, effect monitoring, and lung function in welders after acute short-term exposure to welding fumes from different welding processes. *J Occup Environ Med*, 52(9):887–92. doi:10.1097/JOM.0b013e3181f09077 PMID:20798644

Byun HM, Colicino E, Trevisi L, Fan T, Christiani DC, Baccarelli AA (2016). Effects of air pollution and blood mitochondrial DNA methylation on markers of heart rate variability. *J Am Heart Assoc*, 5(4):e003218. doi:10.1161/JAHA.116.003218 PMID:27107129

Cavallari JM, Eisen EA, Chen JC, Fang SC, Dobson CB, Schwartz J, et al. (2007). Night heart rate variability and particulate exposures among boilermaker construction workers. *Environ Health Perspect*, 115(7):1046–51. doi:10.1289/ehp.10019 PMID:17637921

Cavallari JM, Eisen EA, Fang SC, Schwartz J, Hauser R, Herrick RF, et al. (2008b). PM2.5 metal exposures and nocturnal heart rate variability: a panel study of boilermaker construction workers. *Environ Health*, 7(1):36. doi:10.1186/1476-069X-7-36 PMID:18613971

Cavallari JM, Fang SC, Eisen EA, Schwartz J, Hauser R, Herrick RF, et al. (2008a). Time course of heart rate variability decline following particulate matter exposures in an occupational cohort. *Inhal Toxicol*, 20(4):415–22. doi:10.1080/08958370801903800 PMID:18302049

Cena LG, Chisholm WP, Keane MJ, Chen BT (2015). A field study on the respiratory deposition of the nano-sized fraction of mild and stainless steel welding fume metals. *J Occup Environ Hyg*, 12(10):721–8. doi:10.1080/15459624.2015.1043055 PMID:25985454

Chang C, Demokritou P, Shafer M, Christiani D (2013). Physicochemical and toxicological characteristics of welding fume derived particles generated from real time welding processes. *Environ Sci Process Impacts*, 15(1):214–24. doi:10.1039/C2EM30505D PMID:24592438

Chuang CH, Huang CE, Chen HL (2010). DNA strand breakage and lipid peroxidation after exposure to welding fumes in vivo. *Mutagenesis*, 25(1):71–6. doi:10.1093/mutage/gep047 PMID:19884118

Coggon D, Inskip H, Winter P, Pannett B (1994). Lobar pneumonia: an occupational disease in welders. *Lancet*, 344(8914):41–3. doi:10.1016/S0140-6736(94)91056-1 PMID:7912307

Collins AR, Oscoz AA, Brunborg G, Gaivão I, Giovannelli L, Kruszewski M, et al. (2008). The comet assay: topical issues. *Mutagenesis*, 23(3):143–51. doi:10.1093/mutage/gem051 PMID:18283046

Costa M, Zhitkovich A, Toniolo P (1993). DNA-protein cross-links in welders: molecular implications. *Cancer Res*, 53(3):460–3. PMID:8425177

Danadevi K, Rozati R, Banu BS, Grover P (2004). Genotoxic evaluation of welders occupationally exposed to chromium and nickel using the Comet and micronucleus assays. *Mutagenesis*, 19(1):35–41. doi:10.1093/mutage/geh001 PMID:14681311

Ding X, Zhang Q, Wei H, Zhang Z (2011). Cadmium-induced renal tubular dysfunction in a group of welders. *Occup Med (Lond)*, 61(4):277–9. doi:10.1093/occmed/kqr034 PMID:21511812

Doherty MJ, Healy M, Richardson SG, Fisher NC (2004). Total body iron overload in welder's siderosis. *Occup Environ Med*, 61(1):82–5. PMID:14691279

Domínguez Odio A, Rojas Vázquez EI, Romero García LI, Rodríguez Tito JC, Pérez Andrés I (2005). [Buccoepithelial cytologic lesions in workers exposed to chemical products.] *Rev Med Inst Mex Seguro Soc*, 43(3):221–7. [Spanish] PMID:16138456

Dominici L, Villarini M, Fatigoni C, Monarca S, Moretti M (2011). Genotoxic hazard evaluation in welders occupationally exposed to extremely low-frequency magnetic fields (ELF-MF). *Int J Hyg Environ Health*, 215(1):68–75. doi:10.1016/j.ijheh.2011.07.010 PMID:21862403

Dufresne A, Bégin R, Dion C, Jagirdar J, Rom WN, Loosereewanich P, et al. (1997). Angular and fibrous particles in lung are markers of job categories. *Sci Total Environ*, 206(2-3):127–36. doi:10.1016/S0048-9697(97)80004-6 PMID:9394479

Edmé JL, Shirali P, Mereau M, Sobaszek A, Boulenguez C, Diebold F, et al. (1997). Assessment of biological chromium among stainless steel and mild steel welders in relation to welding processes. *Int Arch Occup Environ Health*, 70(4):237–42. doi:10.1007/s004200050213 PMID:9342623

El-Zein M, Malo JL, Infante-Rivard C, Gautrin D (2003). Incidence of probable occupational asthma and changes in airway calibre and responsiveness in apprentice welders. *Eur Respir J*, 22(3):513–8. doi:10.1183/09031936.03.00000903 PMID:14516144

Elias Z, Mur JM, Pierre F, Gilgenkrantz S, Schneider O, Baruthio F, et al. (1989). Chromosome aberrations in peripheral blood lymphocytes of welders and characterization of their exposure by biological samples analysis. *J Occup Med*, 31(5):477–83. PMID:2715858

Ellingsen DG, Chashchin M, Berlinger B, Konz T, Zibarev E, Aaseth J, et al. (2014). Biomarkers of iron status and trace elements in welders. *J Trace Elem Med Biol*, 28(3):271–7. doi:10.1016/j.jtemb.2014.03.004 PMID:24703374

Ellingsen DG, Chashchin V, Haug E, Chashchin M, Tkachenko V, Lubnina N, et al. (2007). An epidemiological study of reproductive function biomarkers in male welders. *Biomarkers*, 12(5):497–509. doi:10.1080/13547500701366496 PMID:17701748

Ellingsen DG, Dubeikovskaya L, Dahl K, Chashchin M, Chashchin V, Zibarev E, et al. (2006). Air exposure assessment and biological monitoring of manganese

and other major welding fume components in welders. *J Environ Monit*, 8(10):1078–86. doi:10.1039/b605549d PMID:17240914

Erdely A, Antonini JM, Salmen-Muniz R, Liston A, Hulderman T, Simeonova PP, et al. (2012). Type I interferon and pattern recognition receptor signaling following particulate matter inhalation. *Part Fibre Toxicol*, 9(1):25. doi:10.1186/1743-8977-9-25 PMID:22776377

Erdely A, Antonini JM, Young SH, Kashon ML, Gu JK, Hulderman T, et al. (2014). Oxidative stress and reduced responsiveness of challenged circulating leukocytes following pulmonary instillation of metal-rich particulate matter in rats. *Part Fibre Toxicol*, 11(1):34. doi:10.1186/s12989-014-0034-8 PMID:25123171

Erdely A, Hulderman T, Salmen-Muniz R, Liston A, Zeidler-Erdely PC, Chen BT, et al. (2011b). Inhalation exposure of gas-metal arc stainless steel welding fume increased atherosclerotic lesions in apolipoprotein E knockout mice. *Toxicol Lett*, 204(1):12–6. doi:10.1016/j.toxlet.2011.03.030 PMID:21513782

Erdely A, Salmen-Muniz R, Liston A, Hulderman T, Zeidler-Erdely PC, Antonini JM, et al. (2011a). Relationship between pulmonary and systemic markers of exposure to multiple types of welding particulate matter. *Toxicology*, 287(1-3):153–9. doi:10.1016/j.tox.2011.06.008 PMID:21708214

Etienne CE, Hooftman RN, de Raat WK, Reuzel PGJ, van der Sluis HH, Wilmer JWGM (1986). The assessment of the carcinogenicity of chromium- and nickel-containing welding fumes. Phase I: in vitro and in vivo genotoxicity and cytotoxicity studies. Final report (ECSC-TNO Contract 7248/22/020). Luxembourg: Commission of the European Communities.

Falcone LM, Erdely A, Meighan TG, Battelli LA, Salmen R, McKinney W, et al. (2017). Inhalation of gas metal arc-stainless steel welding fume promotes lung tumorigenesis in A/J mice. *Arch Toxicol*, 91(8):2953–62. doi:10.1007/s00204-016-1909-2 PMID:28054104

Fan T, Fang SC, Cavallari JM, Barnett IJ, Wang Z, Su L, et al. (2014). Heart rate variability and DNA methylation levels are altered after short-term metal fume exposure among occupational welders: a repeated-measures panel study. *BMC Public Health*, 14(1):1279. doi:10.1186/1471-2458-14-1279 PMID:25512264

Fang SC, Cassidy A, Christiani DC (2010b). A systematic review of occupational exposure to particulate matter and cardiovascular disease. *Int J Environ Res Public Health*, 7(4):1773–806. doi:10.3390/ijerph7041773 PMID:20617059

Fang SC, Cavallari JM, Eisen EA, Chen JC, Mittleman MA, Christiani DC (2009). Vascular function, inflammation, and variations in cardiac autonomic responses to particulate matter among welders. *Am J Epidemiol*, 169(7):848–56. doi:10.1093/aje/kwn405 PMID:19153215

Fang SC, Eisen EA, Cavallari JM, Mittleman MA, Christiani DC (2008). Acute changes in vascular function among welders exposed to metal-rich particulate matter. *Epidemiology*, 19(2):217–25. doi:10.1097/EDE.0b013e31816334dc PMID:18300696

Fang SC, Eisen EA, Cavallari JM, Mittleman MA, Christiani DC (2010a). Circulating adhesion molecules after short-term exposure to particulate matter among welders. *Occup Environ Med*, 67(1):11–6. doi:10.1136/oem.2008.043794 PMID:19736177

Fidan F, Unlü M, Köken T, Tetik L, Akgün S, Demirel R, et al. (2005). Oxidant-antioxidant status and pulmonary function in welding workers. *J Occup Health*, 47(4):286–92. doi:10.1539/joh.47.286 PMID:16096352

Fuortes L, Schenck D (2000). Marked elevation of urinary zinc levels and pleural-friction rub in metal fume fever. *Vet Hum Toxicol*, 42(3):164–5. PMID:10839322

Graczyk H, Lewinski N, Zhao J, Concha-Lozano N, Riediker M (2016b). Characterization of tungsten inert gas (TIG) welding fume generated by apprentice welders. *Ann Occup Hyg*, 60(2):205–19. doi:10.1093/annhyg/mev074 PMID:26464505

Graczyk H, Lewinski N, Zhao J, Sauvain JJ, Suarez G, Wild P, et al. (2016a). Increase in oxidative stress levels following welding fume inhalation: a controlled human exposure study. *Part Fibre Toxicol*, 13(1):31. doi:10.1186/s12989-016-0143-7 PMID:27286820

Grigg J, Miyashita L, Suri R (2017). Pneumococcal infection of respiratory cells exposed to welding fumes; Role of oxidative stress and HIF-1 alpha. *PLoS One*, 12(3):e0173569. doi:10.1371/journal.pone.0173569 PMID:28278175

Gube M, Ebel J, Brand P, Göen T, Holzinger K, Reisgen U, et al. (2010). Biological effect markers in exhaled breath condensate and biomonitoring in welders: impact of smoking and protection equipment. *Int Arch Occup Environ Health*, 83(7):803–11. doi:10.1007/s00420-010-0516-4 PMID:20130903

Halasova E, Matakova T, Musak L, Polakova V, Letkova L, Dobrota D, et al. (2012). Evaluating chromosomal damage in workers exposed to hexavalent chromium and the modulating role of polymorphisms of DNA repair genes. *Int Arch Occup Environ Health*, 85(5):473–81. doi:10.1007/s00420-011-0684-x PMID:21858514

Halatek T, Stanislawska M, Kaminska I, Cieslak M, Swiercz R, Wasowicz W (2017). The time-dependent health and biochemical effects in rats exposed to stainless steel welding dust and its soluble form. *J Environ Sci Health A Tox Hazard Subst Environ Eng*, 52(3):265–73. doi:10.1080/10934529.2016.1253397 PMID:27901646

Han SG, Kim Y, Kashon ML, Pack DL, Castranova V, Vallyathan V (2005). Correlates of oxidative stress and free-radical activity in serum from asymptomatic

shipyard welders. *Am J Respir Crit Care Med*, 172(12):1541–8. doi:10.1164/rccm.200409-1222OC PMID:16166614

Hansen K, Stern RM (1985). Welding fumes and chromium compounds in cell transformation assays. *J Appl Toxicol*, 5(5):306–14. doi:10.1002/jat.2550050509 PMID:4056308

Harisa GI, Attia SM, Ashour AE, Abdallah GM, Omran GA, Touliabah HE (2014). Cigarette smoking and hyperglycemia increase renal response to low levels of cadmium in welders: cystatin C as a sensitive marker. *Biol Trace Elem Res*, 158(3):289–96. doi:10.1007/s12011-014-9939-1 PMID:24652630

Hemminki K, Jiang Y, Ma X, Yang K, Egevad L, Lindblad P (2002). Molecular epidemiology of VHL gene mutations in renal cell carcinoma patients: relation to dietary and other factors. *Carcinogenesis*, 23(5):809–15. doi:10.1093/carcin/23.5.809 PMID:12016154

Heo JD, Oh JH, Lee K, Kim CY, Song CW, Yoon S, et al. (2010). Gene expression profiling in the lung tissue of cynomolgus monkeys in response to repeated exposure to welding fumes. *Arch Toxicol*, 84(3):191–203. doi:10.1007/s00204-009-0486-z PMID:19936710

Hjollund NH, Bonde JP, Jensen TK, Ernst E, Henriksen TB, Kolstad HA, et al. (1998). Semen quality and sex hormones with reference to metal welding. *Reprod Toxicol*, 12(2):91–5. doi:10.1016/S0890-6238(97)00156-1 PMID:9535501

Hoffmeyer F, Raulf-Heimsoth M, Lehnert M, Kendzia B, Bernard S, Berresheim H, et al.; Weldox Group (2012a). Impact of different welding techniques on biological effect markers in exhaled breath condensate of 58 mild steel welders. *J Toxicol Environ Health A*, 75(8-10):525–32. doi:10.1080/15287394.2012.675303 PMID:22686312

Hoffmeyer F, Raulf-Heimsoth M, Weiss T, Lehnert M, Gawrych K, Kendzia B, et al.; WELDOX Study Group (2012b). Relation between biomarkers in exhaled breath condensate and internal exposure to metals from gas metal arc welding. *J Breath Res*, 6(2):027105. doi:10.1088/1752-7155/6/2/027105 PMID:22622358

Hossain MB, Li H, Hedmer M, Tinnerberg H, Albin M, Broberg K (2015). Exposure to welding fumes is associated with hypomethylation of the F2RL3 gene: a cardiovascular disease marker. *Occup Environ Med*, 72(12):845–51. doi:10.1136/oemed-2015-102884 PMID:26395445

Hudson NJ, Evans AT, Yeung CK, Hewitt PJ (2001). Effect of process parameters upon the dopamine and lipid peroxidation activity of selected MIG welding fumes as a marker of potential neurotoxicity. *Ann Occup Hyg*, 45(3):187–92. doi:10.1016/S0003-4878(00)00053-3 PMID:11295141

Husgafvel-Pursiainen K, Kalliomäki PL, Sorsa M (1982). A chromosome study among stainless steel welders. *J Occup Med*, 24(10):762–6. PMID:7143122

Huvinen M, Oksanen L, Kalliomäki K, Kalliomäki PL, Moilanen M (1997). Estimation of individual dust exposure by magnetopneumography in stainless steel production. *Sci Total Environ*, 199(1-2):133–9. doi:10.1016/S0048-9697(97)05505-8 PMID:9200856

IARC (1990). Chromium, nickel and welding. *IARC Monogr Eval Carcinog Risks Hum*, 49:1–648. Available from: http://publications.iarc.fr/67 PMID:2232124

Iarmarcovai G, Sari-Minodier I, Chaspoul F, Botta C, De Méo M, Orsière T, et al. (2005). Risk assessment of welders using analysis of eight metals by ICP-MS in blood and urine and DNA damage evaluation by the comet and micronucleus assays; influence of XRCC1 and XRCC3 polymorphisms. *Mutagenesis*, 20(6):425–32. doi:10.1093/mutage/gei058 PMID:16234265

Iarmarcovai G, Sari-Minodier I, Orsière T, De Méo M, Gallice P, Bideau C, et al. (2006). A combined analysis of XRCC1, XRCC3, GSTM1 and GSTT1 polymorphisms and centromere content of micronuclei in welders. *Mutagenesis*, 21(2):159–65. doi:10.1093/mutage/gel010 PMID:16551674

Ibfelt E, Bonde JP, Hansen J (2010). Exposure to metal welding fume particles and risk for cardiovascular disease in Denmark: a prospective cohort study. *Occup Environ Med*, 67(11):772–7. doi:10.1136/oem.2009.051086 PMID:20581417

Jara-Ettinger AC, López-Tavera JC, Zavala-Cerna MG, Torres-Bugarín O (2015). Genotoxic evaluation of Mexican welders occupationally exposed to welding-fumes using the micronucleus test on exfoliated oral mucosa cells: a cross-sectional, case-control study. *PLoS One*, 10(8):e0131548. doi:10.1371/journal.pone.0131548 PMID:26244938

Jelmert O, Hansteen IL, Langård S (1994). Chromosome damage in lymphocytes of stainless steel welders related to past and current exposure to manual metal arc welding fumes. *Mutat Res*, 320(3):223–33. doi:10.1016/0165-1218(94)90049-3 PMID:7508088

Jelmert O, Hansteen IL, Langård S (1995). Cytogenetic studies of stainless steel welders using the tungsten inert gas and metal inert gas methods for welding. *Mutat Res*, 342(1-2):77–85. doi:10.1016/0165-1218(95)90092-6 PMID:7885396

Kalliomäki PL, Alanko K, Korhonen O, Mattsson T, Vaaranen V, Koponen M (1978). Amount and distribution of welding fume lung contaminants among arc welders. *Scand J Work Environ Health*, 4(2):122–30. doi:10.5271/sjweh.2715 PMID:684387

Kalliomäki PL, Junttila ML, Kalliomäki K, Lakomaa EL, Kivelä R (1983b). Comparison of the retention and clearance of different welding fumes in rat lungs. *Am Ind Hyg Assoc J*, 44(10):733–8. doi:10.1080/15298668391405652 PMID:6650394

Kalliomäki PL, Junttila ML, Kalliomäki KK, Lakomaa E-L, Kivelä R (1983a). Comparison of the behavior of stainless and mild steel manual metal arc welding

fumes in rat lung. *Scand J Work Environ Health*, 9(2 Spec No):176–80. PMID:6648415

Kalliomäki PL, Kalliomäki K, Korhonen O, Nordman H, Rahkonen E, Vaaranen V (1982). Respiratory status of stainless steel and mild steel welders. *Scand J Work Environ Health*, 8(Suppl 1):117–21. PMID:7100838

Kalliomäki PL, Olkinuora M, Hyvärinen HK, Kalliomäki K (1984). Kinetics of nickel and chromium in rats exposed to different stainless-steel welding fumes. *IARC Sci Publ*, (53):385–93. PMID:6532989

Kile ML, Fang S, Baccarelli AA, Tarantini L, Cavallari J, Christiani DC (2013). A panel study of occupational exposure to fine particulate matter and changes in DNA methylation over a single workday and years worked in boilermaker welders. *Environ Health*, 12(1):47. doi:10.1186/1476-069X-12-47 PMID:23758843

Kim EA, Cheong HK, Joo KD, Shin JH, Lee JS, Choi SB, et al. (2007). Effect of manganese exposure on the neuroendocrine system in welders. *Neurotoxicology*, 28(2):263–9. doi:10.1016/j.neuro.2006.07.013 PMID:16950514

Kim JY, Chen JC, Boyce PD, Christiani DC (2005). Exposure to welding fumes is associated with acute systemic inflammatory responses. *Occup Environ Med*, 62(3):157–63. doi:10.1136/oem.2004.014795 PMID:15723880

Kim JY, Mukherjee S, Ngo LC, Christiani DC (2004). Urinary 8-hydroxy-2′-deoxyguanosine as a biomarker of oxidative DNA damage in workers exposed to fine particulates. *Environ Health Perspect*, 112(6):666–71. doi:10.1289/ehp.6827 PMID:15121508

Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ (1987). Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol*, 59(4):256–62. doi:10.1016/0002-9149(87)90795-8 PMID:3812275

Knudsen I (1980). The mammalian spot test and its use for the testing of potential carcinogenicity of welding fume particles and hexavalent chromium. *Acta Pharmacol Toxicol (Copenh)*, 47(1):66–70. doi:10.1111/j.1600-0773.1980.tb02027.x PMID:7395526

Knudsen LE, Boisen T, Christensen JM, Jelnes JE, Jensen GE, Jensen JC, et al. (1992). Biomonitoring of genotoxic exposure among stainless steel welders. *Mutat Res*, 279(2):129–43. doi:10.1016/0165-1218(92)90255-X PMID:1375338

Kolarzyk E, Stepniewski M, Mendyk A, Kitlinski M, Pietrzycka A (2006). The usefulness of artificial neural networks in the evaluation of pulmonary efficiency and antioxidant capacity of welders. *Int J Hyg Environ Health*, 209(4):385–92. doi:10.1016/j.ijheh.2006.03.004 PMID:16702030

Koshi K, Yagami T, Nakanishi Y (1984). Cytogenetic analysis of peripheral blood lymphocytes from stainless steel welders. *Ind Health*, 22(4):305–18. doi:10.2486/indhealth.22.305 PMID:6526704

Lai CY, Lai CH, Chuang HC, Pan CH, Yen CC, Lin WY, et al. (2016). Physicochemistry and cardiovascular toxicity of metal fume PM2.5: a study of human coronary artery endothelial cells and welding workers. *Sci Rep*, 6(1):33515. doi:10.1038/srep33515 PMID:27641436

Leonard SS, Chen BT, Stone SG, Schwegler-Berry D, Kenyon AJ, Frazer D, et al. (2010). Comparison of stainless and mild steel welding fumes in generation of reactive oxygen species. *Part Fibre Toxicol*, 7(1):32. doi:10.1186/1743-8977-7-32 PMID:21047424

Li GJ, Zhang LL, Lu L, Wu P, Zheng W (2004). Occupational exposure to welding fume among welders: alterations of manganese, iron, zinc, copper, and lead in body fluids and the oxidative stress status. *J Occup Environ Med*, 46(3):241–8. doi:10.1097/01.jom.0000116900.49159.03 PMID:15091287

Li H, Hedmer M, Kåredal M, Björk J, Stockfelt L, Tinnerberg H, et al. (2015b). A cross-sectional study of the cardiovascular effects of welding fumes. *PLoS One*, 10(7):e0131648. doi:10.1371/journal.pone.0131648 PMID:26147298

Li H, Hedmer M, Wojdacz T, Hossain MB, Lindh CH, Tinnerberg H, et al. (2015a). Oxidative stress, telomere shortening, and DNA methylation in relation to low-to-moderate occupational exposure to welding fumes. *Environ Mol Mutagen*, 56(8):684–93. doi:10.1002/em.21958 PMID:26013103

Littorin M, Högstedt B, Strömbäck B, Karlsson A, Welinder H, Mitelman F, et al. (1983). No cytogenetic effects in lymphocytes of stainless steel welders. *Scand J Work Environ Health*, 9(3):259–64. doi:10.5271/sjweh.2411 PMID:6612267

Liu HH, Shih TS, Huang HR, Huang SC, Lee LH, Huang YC (2013). Plasma homocysteine is associated with increased oxidative stress and antioxidant enzyme activity in welders. *Scientific World Journal*, 2013:370487. doi:10.1155/2013/370487 PMID:24106453

Lombardi DA, Pannala R, Sorock GS, Wellman H, Courtney TK, Verma S, et al. (2005). Welding related occupational eye injuries: a narrative analysis. *Inj Prev*, 11(3):174–9. doi:10.1136/ip.2004.007088 PMID:15933411

Luo JC, Hsu KH, Shen WS (2009). Inflammatory responses and oxidative stress from metal fume exposure in automobile welders. *J Occup Environ Med*, 51(1):95–103. doi:10.1097/JOM.0b013e31818f756e PMID:19136878

Marongiu A, Hasan O, Ali A, Bakhsh S, George B, Irfan N, et al. (2016). Are welders more at risk of respiratory infections? Findings from a cross-sectional survey and analysis of medical records in shipyard workers: the WELSHIP project. *Thorax*, 71(7):601–6. doi:10.1136/thoraxjnl-2015-207912 PMID:27030577

McNeilly JD, Heal MR, Beverland IJ, Howe A, Gibson MD, Hibbs LR, et al. (2004). Soluble transition metals cause the pro-inflammatory effects of welding fumes in vitro.

Toxicol Appl Pharmacol, 196(1):95–107. doi:10.1016/j.taap.2003.11.021 PMID:15050411

McNeilly JD, Jiménez LA, Clay MF, MacNee W, Howe A, Heal MR, et al. (2005). Soluble transition metals in welding fumes cause inflammation via activation of NF-kappaB and AP-1. *Toxicol Lett*, 158(2):152–7. doi:10.1016/j.toxlet.2005.03.005 PMID:16039403

Medeiros MG, Rodrigues AS, Batoréu MC, Laires A, Rueff J, Zhitkovich A (2003). Elevated levels of DNA-protein crosslinks and micronuclei in peripheral lymphocytes of tannery workers exposed to trivalent chromium. *Mutagenesis*, 18(1):19–24. doi:10.1093/mutage/18.1.19 PMID:12473731

Mocevic E, Kristiansen P, Bonde JP (2015). Risk of ischemic heart disease following occupational exposure to welding fumes: a systematic review with meta-analysis. *Int Arch Occup Environ Health*, 88(3):259–72. doi:10.1007/s00420-014-0965-2 PMID:25047981

Mukherjee S, Palmer LJ, Kim JY, Aeschliman DB, Houk RS, Woodin MA, et al. (2004). Smoking status and occupational exposure affects oxidative DNA injury in boilermakers exposed to metal fume and residual oil fly ash. *Cancer Epidemiol Biomarkers Prev*, 13(3):454–60. PMID:15006923

Myślak M, Kośmider K (1997). [Frequency of sister chromatid exchanges (SCE)in peripheral blood lymphocytes from stainless steel welders.] *Med Pr*, 48(4):399–406. [Polish] PMID:9471487

Nakata A, Araki S, Park SH, Park JT, Kim DS, Park HC, et al. (2006). Decreases in CD8+ T, naive (CD4+CD45RA+) T, and B (CD19+) lymphocytes by exposure to manganese fume. *Ind Health*, 44(4):592–7. doi:10.2486/indhealth.44.592 PMID:17085920

Nersesyan A, Kundi M, Atefie K, Schulte-Hermann R, Knasmüller S (2006). Effect of staining procedures on the results of micronucleus assays with exfoliated oral mucosa cells. *Cancer Epidemiol Biomarkers Prev*, 15(10):1835–40. doi:10.1158/1055-9965.EPI-06-0248 PMID:17035390

Niu Q, Shuchang H, Sheng W, Di Gioacchino M, Verna N, Volpe AR, et al. (2004). Neurobehavioral functions, serum prolactin and plasma renin activity of manganese-exposed workers. *Int J Immunopathol Pharmacol*, 17(2 Suppl):17–24. doi:10.1177/03946320040170S204 PMID:15345187

Nuernberg AM, Boyce PD, Cavallari JM, Fang SC, Eisen EA, Christiani DC (2008). Urinary 8-isoprostane and 8-OHdG concentrations in boilermakers with welding exposure. *J Occup Environ Med*, 50(2):182–9. doi:10.1097/JOM.0b013e31815cf6cc PMID:18301175

OECD (2016). In vitro mammalian cell micronucleus test. Test No. 487. Paris:, France Organisation for Economic Co-operation and Development.

Oh JH, Yang MJ, Heo JD, Yang YS, Park HJ, Park SM, et al. (2012). Inflammatory response in rat lungs with recurrent exposure to welding fumes: a transcriptomic approach. *Toxicol Ind Health*, 28(3):203–15. doi:10.1177/0748233711410906 PMID:21730038

Oh JH, Yang MJ, Yang YS, Park HJ, Heo SH, Lee EH, et al. (2009). Microarray-based analysis of the lung recovery process after stainless-steel welding fume exposure in Sprague-Dawley rats. *Inhal Toxicol*, 21(4):347–73. doi:10.1080/08958370802464281 PMID:19235613

Ong TM, Stewart J, Wen YF, Whong WZ (1987). Application of SOS umu-test for the detection of genotoxic volatile chemicals and air pollutants. *Environ Mutagen*, 9(2):171–6. doi:10.1002/em.2860090207 PMID:2434323

Palmer KT, Cullinan P, Rice S, Brown T, Coggon D (2009). Mortality from infectious pneumonia in metal workers: a comparison with deaths from asthma in occupations exposed to respiratory sensitisers. *Thorax*, 64(11):983–6. doi:10.1136/thx.2009.114280 PMID:19703831

Palmer KT, McNeill Love RM, Poole JR, Coggon D, Frew AJ, Linaker CH, et al. (2006). Inflammatory responses to the occupational inhalation of metal fume. *Eur Respir J*, 27(2):366–73. doi:10.1183/09031936.06.00053205 PMID:16452594

Palmer KT, Poole J, Ayres JG, Mann J, Burge PS, Coggon D (2003). Exposure to metal fume and infectious pneumonia. *Am J Epidemiol*, 157(3):227–33. doi:10.1093/aje/kwf188 PMID:12543622

Park JD, Chung YH, Kim CY, Ha CS, Yang SO, Khang HS, et al. (2007a). Comparison of high MRI T1 signals with manganese concentration in brains of cynomolgus monkeys after 8 months of stainless steel welding-fume exposure. *Inhal Toxicol*, 19(11):965–71. doi:10.1080/08958370701516108 PMID:17849280

Park JD, Kim KY, Kim DW, Choi SJ, Choi BS, Chung YH, et al. (2007b). Tissue distribution of manganese in iron-sufficient or iron-deficient rats after stainless steel welding-fume exposure. *Inhal Toxicol*, 19(6-7):563–72. doi:10.1080/08958370701276554 PMID:17497534

Pasanen JT, Gustafsson TE, Kalliomäki PL, Tossavainen A, Järvisalo JO (1986). Cytotoxic effects of four types of welding fumes on macrophages in vitro: a comparative study. *J Toxicol Environ Health*, 18(1):143–52. doi:10.1080/15287398609530855 PMID:3701879

Patterson L, Irvine N, Wilson A, Doherty L, Loughrey A, Jessop L (2015). Outbreak of invasive pneumococcal disease at a Belfast shipyard in men exposed to welding fumes, Northern Ireland, April–May 2015: preliminary report; pp.3–5.

Pedersen P, Thomsen E, Stern RM (1983). Detection by replica plating of false revertant colonies induced in the Salmonella-mammalian microsome assay by hexavalent chromium. *Environ Health Perspect*, 51:227–30. PMID:6357773

Pesch B, Lotz A, Koch HM, Marczynski B, Casjens S, Käfferlein HU, et al. (2015). Oxidatively damaged guanosine in white blood cells and in urine of welders: associations with exposure to welding fumes and body iron stores. *Arch Toxicol*, 89(8):1257–69. doi:10.1007/s00204-014-1319-2 PMID:25107450

Popp W, Vahrenholz C, Schmieding W, Krewet E, Norpoth K (1991). Investigations of the frequency of DNA strand breakage and cross-linking and of sister chromatid exchange in the lymphocytes of electric welders exposed to chromium- and nickel-containing fumes. *Int Arch Occup Environ Health*, 63(2):115–20. doi:10.1007/BF00379074 PMID:1889880

Popstojanov R, Antonini JM, Salmen R, Ye M, Zheng W, Castranova V, et al. (2014). Alterations in cardiomyocyte function after pulmonary treatment with stainless steel welding fume in rats. *J Toxicol Environ Health A*, 77(12):705–15. doi:10.1080/15287394.2014.888692 PMID:24786677

Quievryn G, Goulart M, Messer J, Zhitkovich A (2001). Reduction of Cr (VI) by cysteine: significance in human lymphocytes and formation of DNA damage in reactions with variable reduction rates. *Mol Cell Biochem*, 222(1-2):107–18. doi:10.1023/A:1017923609175 PMID:11678591

Racette BA, Criswell SR, Lundin JI, Hobson A, Seixas N, Kotzbauer PT, et al. (2012). Increased risk of parkinsonism associated with welding exposure. *Neurotoxicology*, 33(5):1356–61. doi:10.1016/j.neuro.2012.08.011 PMID:22975422

Raulf M, Weiss T, Lotz A, Lehnert M, Hoffmeyer F, Liebers V, et al. (2016). Analysis of inflammatory markers and metals in nasal lavage fluid of welders. *J Toxicol Environ Health A*, 79(22-23):1144–57. doi:10.1080/15287394.2016.1221370 PMID:27924706

Reuzel PGJ, Beems RB, De Raat WK, Lohman PMH (1986). Carcinogenicity and in vitro genotoxicity of the particulate fraction of two stainless steel welding fumes. In: Stern RM, Berlin A, Fletcher AC, Jarvisalo J, editors. Health hazards and biological effects of welding fumes and gases. *Excerpta Med Int Congr Ser,* Volume 676; pp.329–332.

Rim KT, Park KK, Sung JH, Chung YH, Han JH, Cho KS, et al. (2004). Gene-expression profiling using suppression-subtractive hybridization and cDNA microarray in rat mononuclear cells in response to welding-fume exposure. *Toxicol Ind Health*, 20(1-5):77–88. doi:10.1191/0748233704th200oa PMID:15807411

Rossbach B, Buchta M, Csanády GA, Filser JG, Hilla W, Windorfer K, et al. (2006). Biological monitoring of welders exposed to aluminium. *Toxicol Lett*, 162(2-3):239–45. doi:10.1016/j.toxlet.2005.09.018 PMID:16280209

Sardas S, Omurtag GZ, Tozan A, Gül H, Beyoglu D (2010). Evaluation of DNA damage in construction-site workers occupationally exposed to welding fumes and solvent-based paints in Turkey. *Toxicol Ind Health*, 26(9):601–8. doi:10.1177/0748233710374463 PMID:20542926

Scheepers PT, Heussen GA, Peer PG, Verbist K, Anzion R, Willems J (2008). Characterisation of exposure to total and hexavalent chromium of welders using biological monitoring. *Toxicol Lett*, 178(3):185–90. doi:10.1016/j.toxlet.2008.03.013 PMID:18455331

Sellappa S, Prathyumnan S, Keyan KS, Joseph S, Vasudevan BS, Sasikala K (2010). Evaluation of DNA damage induction and repair inhibition in welders exposed to hexavalent chromium. *Asian Pac J Cancer Prev*, 11(1):95–100. PMID:20593913

Sener C, Eroglu HE (2013). The in vitro determination of genotoxicity in peripheral lymphocytes of welders exposed to fumes from metal arc welding. *Turk J Med Sci*, 43:411–6.

Sharifian A, Gharavi M, Pasalar P, Aminian O (2009). Effect of extremely low frequency magnetic field on antioxidant activity in plasma and red blood cells in spot welders. *Int Arch Occup Environ Health*, 82(2):259–66. doi:10.1007/s00420-008-0332-2 PMID:18504600

Singh Z, Chadha P (2016). Assessment of DNA damage as an index of genetic toxicity in welding microenvironments among iron-based industries. Toxicol Ind Health, 32(10):1817–24. doi:10.1177/0748233715590518 PMID:26088556

Sjögren B, Elinder CG, Lidums V, Chang G (1988). Uptake and urinary excretion of aluminum among welders. *Int Arch Occup Environ Health*, 60(2):77–9. doi:10.1007/BF00381484 PMID:3346084

Sjögren B, Lidums V, Håkansson M, Hedström L (1985). Exposure and urinary excretion of aluminum during welding. *Scand J Work Environ Health*, 11(1):39–43. doi:10.5271/sjweh.2255 PMID:3992220

Slagor RM, La Cour M, Bonde JP (2016). The risk of cataract in relation to metal arc welding. *Scand J Work Environ Health*, 42(5):447–53. doi:10.5271/sjweh.3572 PMID:27243234

Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, et al. (2016). Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environ Health Perspect*, 124(6):713–21. PMID:26600562

Solano-Lopez C, Zeidler-Erdely PC, Hubbs AF, Reynolds SH, Roberts JR, Taylor MD, et al. (2006). Welding fume exposure and associated inflammatory and hyperplastic changes in the lungs of tumor susceptible a/j mice. *Toxicol Pathol*, 34(4):364–72. doi:10.1080/01926230600815122 PMID:16844664

Sriram K, Jefferson AM, Lin GX, Afshari A, Zeidler-Erdely PC, Meighan TG, et al. (2014). Neurotoxicity following acute inhalation of aerosols generated during resistance spot weld-bonding of carbon steel. *Inhal Toxicol*, 26(12):720–32. doi:10.3109/08958378.2014.954654 PMID:25265048

Sriram K, Lin GX, Jefferson AM, Roberts JR, Andrews RN, Kashon ML, et al. (2012). Manganese accumulation in nail clippings as a biomarker of welding fume exposure and neurotoxicity. *Toxicology*, 291(1-3):73–82. doi:10.1016/j.tox.2011.10.021 PMID:22085607

Sriram K, Lin GX, Jefferson AM, Roberts JR, Chapman RS, Chen BT, et al. (2010). Dopaminergic neurotoxicity following pulmonary exposure to manganese-containing welding fumes. *Arch Toxicol*, 84(7):521–40. doi:10.1007/s00204-010-0525-9 PMID:20224926

Stark M, Zubareb J, Jacovovitz R, Schwartz Y, Lerman Y, Grinberg N, et al. (2009). HO-1 and VEGF gene expressions are time dependant during exposure to welding fumes. *Cytokine*, 46(2):290–5. doi:10.1016/j.cyto.2009.02.012 PMID:19303319

Stern RM, Hansen K, Madsen AF, Olsen KM (1988). In vitro toxicity of welding fumes and their constituents. *Environ Res*, 46(2):168–80. doi:10.1016/S0013-9351(88)80030-6 PMID:3402405

Stridsklev IC, Hemmingsen B, Karlsen JT, Schaller KH, Raithel HJ, Langård S (1993). Biologic monitoring of chromium and nickel among stainless steel welders using the manual mental arc method. *Int Arch Occup Environ Health*, 65(4):209–19. doi:10.1007/BF00381193 PMID:8144230

Sudha S, Kripa SK, Shibily P, Joseph S, Balachandar V (2011). Biomonitoring of genotoxic effects among shielded manual metal arc welders. *Asian Pac J Cancer Prev*, 12(4):1041–4. PMID:21790248

Sung JH, Choi BG, Maeng SH, Kim SJ, Chung YH, Han JH, et al. (2004). Recovery from welding-fume-exposure-induced lung fibrosis and pulmonary function changes in sprague dawley rats. *Toxicol Sci*, 82(2):608–13. doi:10.1093/toxsci/kfh289 PMID:15456923

Suri R, Periselneris J, Lanone S, Zeidler-Erdely PC, Melton G, Palmer KT, et al. (2016). Exposure to welding fumes and lower airway infection with Streptococcus pneumoniae. *J Allergy Clin Immunol*, 137(2):527–534.e7. doi:10.1016/j.jaci.2015.06.033 PMID:26277596

Szram J, Schofield SJ, Cosgrove MP, Cullinan P (2013). Welding, longitudinal lung function decline and chronic respiratory symptoms: a systematic review of cohort studies. *Eur Respir J*, 42(5):1186–93. doi:10.1183/09031936.00206011 PMID:23258779

Taylor MD, Roberts JR, Leonard SS, Shi X, Antonini JM (2003). Effects of welding fumes of differing composition and solubility on free radical production and acute lung injury and inflammation in rats. *Toxicol Sci*, 75(1):181–91. doi:10.1093/toxsci/kfg173 PMID:12832661

Toniolo P, Zhitkovich A, Costa M (1993). Development and utilization of a new simple assay for DNA-protein crosslinks as a biomarker of exposure to welding fumes. *Int Arch Occup Environ Health*, 65(1 Suppl):S87–9. doi:10.1007/BF00381313 PMID:8406945

Torén K, Qvarfordt I, Bergdahl IA, Järvholm B (2011). Increased mortality from infectious pneumonia after occupational exposure to inorganic dust, metal fumes and chemicals. *Thorax*, 66(11):992–6. doi:10.1136/thoraxjnl-2011-200707 PMID:21856701

Tutkun E, Abuşoğlu S, Yılmaz H, Gündüzöz M, Gıynas N, Bal CD, et al. (2014). Prolactin levels in manganese-exposed male welders. *Pituitary*, 17(6):564–8. doi:10.1007/s11102-013-0545-6 PMID:24337778

Umukoro PE, Fan T, Zhang J, Cavallari JM, Fang SC, Lu C, et al. (2016). Long-term metal PM2.5 exposures decrease cardiac acceleration and deceleration capacities in welders. *J Occup Environ Med*, 58(3):227–31. doi:10.1097/JOM.0000000000000661 PMID:26949871

Wang C, Lu JP, Jiang YM, Ma NH, Qin WP, Luo HL, et al. (2011). [Effects of low level manganese exposure on the serum neuroendocrine hormones in the welders] *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi*, 29(2):94–7. [Chinese] PMID:21619835

Wang Z, Neuberg D, Su L, Kim JY, Chen JC, Christiani DC (2008). Prospective study of metal fume-induced responses of global gene expression profiling in whole blood. *Inhal Toxicol*, 20(14):1233–44. doi:10.1080/08958370802192874 PMID:18951227

Wang Z, Neuburg D, Li C, Su L, Kim JY, Chen JC et al. (2005). Global gene expression profiling in whole-blood samples from individuals exposed to metal fumes. *Environ Health Perspect*, 113(2):233–41. doi:10.1289/txg.7273 PMID:15687063

Wang ZP, Larsson K, Malmberg P, Sjögren B, Hallberg BO, Wrangskog K (1994). Asthma, lung function, and bronchial responsiveness in welders. *Am J Ind Med*, 26(6):741–54. doi:10.1002/ajim.4700260603 PMID:7892825

Wei Y, Wang Z, Chang CY, Fan T, Su L, Chen F, et al. (2013). Global metabolomic profiling reveals an association of metal fume exposure and plasma unsaturated fatty acids. *PLoS One*, 8(10):e77413. doi:10.1371/journal.pone.0077413 PMID:24143234

Weiss T, Pesch B, Lotz A, Gutwinski E, Van Gelder R, Punkenburg E, et al.; WELDOX Group (2013). Levels and predictors of airborne and internal exposure to chromium and nickel among welders–results of the WELDOX study. *Int J Hyg Environ Health*, 216(2):175–83. doi:10.1016/j.ijheh.2012.07.003 PMID:22926021

Werfel U, Langen V, Eickhoff I, Schoonbrood J, Vahrenholz C, Brauksiepe A, et al. (1998). Elevated DNA single-strand breakage frequencies in lymphocytes of welders exposed to chromium and nickel. *Carcinogenesis*, 19(3):413–8. doi:10.1093/carcin/19.3.413 PMID:9525274

Wergeland E, Iversen BG (2001). Deaths from pneumonia after welding. *Scand J Work Environ Health*, 27(5):353. doi:10.5271/sjweh.625 PMID:11712617

White LR, Hunt J, Richards RJ, Eik-Nes KB (1982). Biochemical studies of rat lung following exposure to potassium dichromate or chromium-rich welding fume

particles. *Toxicol Lett*, 11(1-2):159–63. doi:10.1016/0378-4274(82)90122-9 PMID:6896394

White LR, Marthinsen AB, Jakobsen K, Eik-Nes KB (1983). Response of bovine alveolar macrophages in vitro to welding fume particles. *Environ Health Perspect*, 51:211–5. doi:10.1289/ehp.8351211 PMID:6315362

Wong A, Marrie TJ, Garg S, Kellner JD, Tyrrell GJ; SPAT Group (2010). Welders are at increased risk for invasive pneumococcal disease. *Int J Infect Dis*, 14(9):e796–9. doi:10.1016/j.ijid.2010.02.2268 PMID:20637673

Wong JY, De Vivo I, Lin X, Grashow R, Cavallari J, Christiani DC; SPAT Group (2014c). The association between global DNA methylation and telomere length in a longitudinal study of boilermakers. *Genet Epidemiol*, 38(3):254–64. doi:10.1002/gepi.21796 PMID:24616077

Wong JY, De Vivo I, Lin X, Christiani DC (2014b). Cumulative PM(2.5) exposure and telomere length in workers exposed to welding fumes. *J Toxicol Environ Health A*, 77(8):441–55. doi:10.1080/15287394.2013.875497 PMID:24627998

Wong JY, De Vivo I, Lin X, Fang SC, Christiani DC (2014a). The relationship between inflammatory biomarkers and telomere length in an occupational prospective cohort study. *PLoS One*, 9(1):e87348. doi:10.1371/journal.pone.0087348 PMID:24475279

Wultsch G, Nersesyan A, Kundi M, Jakse R, Beham A, Wagner KH, et al. (2014). The sensitivity of biomarkers for genotoxicity and acute cytotoxicity in nasal and buccal cells of welders. *Int J Hyg Environ Health*, 217(4-5):492–8. doi:10.1016/j.ijheh.2013.09.005 PMID:24698449

Xu Y, Li H, Hedmer M, Hossain MB, Tinnerberg H, Broberg K, et al. (2017). Occupational exposure to particles and mitochondrial DNA - relevance for blood pressure. *Environ Health*, 16(1):22. doi:10.1186/s12940-017-0234-4 PMID:28274239

Yang MJ, Yang YS, Sung JH, Kim JS, Cho KH, Lim CW, et al. (2009). Recurrent exposure to welding fumes induces insufficient recovery from inflammation. *Inhal Toxicol*, 21(4):337–46. doi:10.1080/08958370802448979 PMID:19235612

Yu IJ, Park JD, Park ES, Song KS, Han KT, Han JH, et al. (2003). Manganese distribution in brains of Sprague-Dawley rats after 60 days of stainless steel welding-fume exposure. *Neurotoxicology*, 24(6):777–85. doi:10.1016/S0161-813X(03)00046-9 PMID:14637372

Yu IJ, Song KS, Maeng SH, Kim SJ, Sung JH, Han JH, et al. (2004). Inflammatory and genotoxic responses during 30-day welding-fume exposure period. *Toxicol Lett*, 154(1-2):105–15. doi:10.1016/j.toxlet.2004.07.009 PMID:15475184

Zamanian Z, Mortazavi SM, Asmand E, Nikeghbal K (2015). Assessment of health consequences of steel industry welders' occupational exposure to ultraviolet radiation. *Int J Prev Med*, 6(1):123. doi:10.4103/2008-7802.172379 PMID:26900437

Zeidler-Erdely PC, Battelli LA, Salmen-Muniz R, Li Z, Erdely A, Kashon ML, et al. (2011a). Lung tumor production and tissue metal distribution after exposure to manual metal ARC-stainless steel welding fume in A/J and C57BL/6J mice. *J Toxicol Environ Health A*, 74(11):728–36. doi:10.1080/15287394.2011.556063 PMID:21480047

Zeidler-Erdely PC, Battelli LA, Stone S, Chen BT, Frazer DG, Young SH, et al. (2011b). Short-term inhalation of stainless steel welding fume causes sustained lung toxicity but no tumorigenesis in lung tumor susceptible A/J mice. *Inhal Toxicol*, 23(2):112–20. doi:10.3109/08958378.2010.548838 PMID:21309664

Zeidler-Erdely PC, Erdely A, Antonini JM (2012). Immunotoxicology of arc welding fume: worker and experimental animal studies. *J Immunotoxicol*, 9(4):411–25. doi:10.3109/1547691X.2011.652783 PMID:22734811

Zeidler-Erdely PC, Kashon ML, Battelli LA, Young SH, Erdely A, Roberts JR, et al. (2008). Pulmonary inflammation and tumor induction in lung tumor susceptible A/J and resistant C57BL/6J mice exposed to welding fume. *Part Fibre Toxicol*, 5(1):12. doi:10.1186/1743-8977-5-12 PMID:18778475

Zeidler-Erdely PC, Kashon ML, Li S, Antonini JM (2010). Response of the mouse lung transcriptome to welding fume: effects of stainless and mild steel fumes on lung gene expression in A/J and C57BL/6J mice. *Respir Res*, 11(1):70. doi:10.1186/1465-9921-11-70 PMID:20525249

Zeidler-Erdely PC, Meighan TG, Erdely A, Battelli LA, Kashon ML, Keane M, et al. (2013). Lung tumor promotion by chromium-containing welding particulate matter in a mouse model. *Part Fibre Toxicol*, 10(1):45. doi:10.1186/1743-8977-10-45 PMID:24107379

Zeidler-Erdely PC, Meighan TG, Erdely A, Fedan JS, Thompson JA, Bilgesu S, et al. (2014). Effects of acute inhalation of aerosols generated during resistance spot welding with mild-steel on pulmonary, vascular and immune responses in rats. *Inhal Toxicol*, 26(12):697–707. doi:10.3109/08958378.2014.944287 PMID:25140454

Zhu CQ, Lam TH, Jiang CQ (2001). Lymphocyte DNA damage in bus manufacturing workers. *Mutat Res*, 491(1-2):173–81. doi:10.1016/S1383-5718(01)00141-3 PMID:11287310

Zhu YG, Zhou JF, Shan WY, Zhou PS, Tong GZ (2004). Potential oxidative stress in the bodies of electric arc welding operators: effect of photochemical smog. *Biomed Environ Sci*, 17(4):381–9. PMID:15745241

5. SUMMARY OF DATA REPORTED

5.1 Exposure data

Welding is a broad term for the process of joining metals through coalescence. Approximately 11 million people worldwide are estimated to have the occupational title of welder, and approximately 110 million workers (3% of the worldwide economically active population) may incur welding-related exposures in the workplace. Many types of welding are used in occupational settings, including oxyfuel (gas) and arc welding. Arc welding includes manual metal arc (MMA), gas metal arc (GMA), flux-cored arc (FCA), and gas tungsten arc (GTA) welding. Electric resistance (ER) welding is also used. Most welding is carried out on stainless steel (SS) and mild steel (MS).

Welding results in concurrent exposures including welding fumes, gases, ionizing and non-ionizing radiation, and co-exposures such as asbestos and solvents.

Welding fumes are produced when metals are heated above their melting point, vaporize, and condense into fumes of predominantly fine solid particles with an aerodynamic diameter of less than 1 μm. These fumes are a complex mixture of particles from the wire or electrode, base metal, or any coatings on the base metal. They consist mainly of metallic oxides, silicates, and fluorides.

Measured exposures to fumes from welding on SS or MS range from less than 1 mg/m^3 to over 50 mg/m^3. The welding process, type of metal welded, use of local ventilation, degree of enclosure, and use of personal protection are the major determinants of exposure. Concentrations of welding fumes in western Europe declined during 1983–2003 by 4% per annum. FCA welding generates the highest concentration of welding fumes, followed by GMA and MMA. GTA welding consistently generates lower concentrations of welding fumes, but produces the highest number of ultrafine particles (aerodynamic diameter, < 0.1 μm).

Fumes generated from SS welding could contain up to ten times more chromium and nickel than those generated from MS welding. For SS, the highest total chromium concentrations could exceed 1 mg/m^3 from MMA welding, but concentrations are lower from GMA and GTA welding. Chromium VI concentrations are about a factor of ten lower than total chromium. Nickel concentrations generated by GMA and GTA welding are similar to total chromium, but are lower when performing MMA welding.

Exposure to various gases also occurs during welding. Measured nitrogen oxide (NO_x) concentrations are generally relatively low, but reported maximum concentrations approach or exceed occupational exposure limits. Carbon monoxide exposure as high as 1.5 ppm has been reported for GMA and MMA welding.

Welders can also be exposed to various forms of radiation such as ultraviolet (UV), extremely low-frequency electromagnetic fields (ELF-EMF), and alpha radiation from thorium-232. The level of UV radiation associated with

arc welding is in general much higher than for other artificial processes generating UV radiation, and typically orders of magnitude higher than that from natural sunlight. Welders and bystanders can also be exposed to UV radiation indirectly from other welding operations. Welders can experience exposures to ELF-EMF at higher levels than electric power transmission line workers. Thorium oxide has been used in GTA welding electrodes, but the estimated yearly effective doses resulting from this exposure are mostly below the current general population limit.

Welders (shipbuilding welders in particular) might also experience exposure to asbestos, as it has been used as an insulating material in ships and covered rod electrodes, in the cylinders holding acetylene gas, and in heat-protective equipment used by welders. The use of chlorinated solvents for cleaning metal in tandem with welding may result in exposures to hydrogen chloride, and possibly result in phosgene exposure.

The exposure assessments in epidemiological studies considered by the Working Group which relied on a welding-specific questionnaire or a 'welding exposure matrix' were most informative, followed by studies applying general job-exposure matrices and those based on self-reported welding-related exposures. Studies that looked at job titles alone were considered less informative.

5.2 Human carcinogenicity data

5.2.1 Ocular melanoma

Fewer than ten partially overlapping case–control studies and two independent census-based cohort studies reported on ocular melanoma related to welding. For the case–control studies, the exposure was generally characterized as having worked as a welder often based on a full occupational history collected by questionnaire; for the cohort studies, exposure was based on self-reported job as a welder at the time of census. Most of the case–control studies showed positive associations, generally in the range of twofold and up to tenfold. Two of the three studies that evaluated risk by duration of employment as a welder showed positive trends, whereas the third study showed an overall increased risk but no trend. One of two cohort studies showed relative risk (RR) estimates close to unity for ocular melanoma, whereas the other showed a modest increased risk in welders based on 5 cases but no increased risk in occasional welders. None of the studies characterized exposure to UV from welding, but two studies provided some evidence of associations with proxies for UV exposure, i.e. increased ocular melanoma risk associated with eye burns. One of these studies also reported a positive exposure–response relationship for cumulative occupational exposure to artificial UV radiation, including welding. For most studies the risk estimates were related to an unspecified group of welders, and only three of the studies specified the relative risk estimates for arc welding. This specification by type of welding was not considered highly informative as welders often perform multiple types of welding over their work history, and any welder can be exposed to UV radiation from arc welding being conducted nearby. The Working Group also considered that UV radiation from the sun as well as artificial UV radiation from UV-emitting tanning devices are both risk factors for ocular melanoma in humans (*IARC Monographs*, Volume 100D). Several studies collected information on sun exposure and/or sun bed use, but adjustment for these indicated that the observed associations for welding could not be explained by these sources of UV exposure.

5.2.2 Cancer of the lung

Most of the more than 20 available case–control studies reported elevated risks of cancer of the lung for workers employed as welders reporting welding as their job task, or classified as or reporting to be exposed to welding fumes. The same was true for the majority of the more than 20 cohort studies that assessed the association between welding and cancer of the lung in several industries, and for 6 population-based cohort studies. Furthermore, these studies consistently observed positive associations for both arc and gas welding. In view of the constancy of these associations across different study designs, occupational settings, countries, and time periods, as well as the high quality of several positive studies, chance, information bias, or selection bias are unlikely to explain the results.

Studies used several metrics to assess a possible exposure–effect relationship between exposure to welding fumes and risk of cancer of the lung. Cohort studies mostly reported the duration of employment as a welder. Other studies, mostly case–control in design, calculated more complex cumulative exposure indices that included estimates of intensity, probability, and/or frequency of exposure to welding fumes. Several case–control and cohort studies observed an increasing risk of cancer of the lung with longer employment as a welder. Two large, high-quality case–control studies and four cohort studies using indices of exposure to welding fumes observed associations; two of the higher-quality studies observed associations compatible with a dose–effect relationship. Exposure effects were not consistent across studies but there is difficulty in quantifying exposure to welding fumes retrospectively, particularly for those relying on self-reporting by respondents. Despite these limitations, the observed patterns of risk estimates by cumulative exposure and by duration add support to the association between exposure to welding fumes and increased risk of cancer of the lung.

Tobacco smoking was considered an important potential confounder. However, smoking is unlikely to explain all of the observed excess risk of lung cancer among welders. Positive associations were found in the majority of cohort and case–control studies that adjusted for smoking in multivariable analyses, and with internal analyses of some cohort studies that rendered confounding by lifestyle factors such as smoking unlikely. Furthermore, positive associations were found in analyses restricted to non-smokers or infrequent smokers.

Occupational exposure to asbestos is another potential confounder entailed by many welding jobs. However, asbestos co-exposure is unlikely to explain the excess of lung cancer among welders. Excess lung cancer was observed among welders in cohorts with low or minimal asbestos exposure. Furthermore, almost all studies that adjusted for asbestos exposure, including some with a detailed and high-quality assessment of asbestos exposure, still found substantially elevated risks of lung cancer after adjustment. For example, in one study the relative risk was reduced from 2.25 to 1.93 after adjustment for occupational exposure to asbestos. Similarly, internal analyses which found positive associations within groups of welders may have indirectly adjusted for exposure to asbestos.

Increased risks of cancer of the lung were observed regardless of the material or the welding method in both case–control and cohort studies. The reviewed studies provide no evidence that these increased risks are limited to welding SS base metals or to specific welding processes. Several studies with detailed assessment of welding tasks tended to report higher odds ratios (ORs) for gas welding compared with arc welding. However, although two of these studies distinguished between welders exclusively exposed to gas welding fumes and those exclusively exposed to arc welding fumes, the majority of welders

rarely use only one type of welding exclusively; the observed results might therefore reflect other underlying differences such as temporal trends, characteristics of the workplace, or related work practices such as gas cutting.

Gas and arc welding inherently produce fumes. Although welding fumes were not measured directly in the reviewed studies, exposure to fumes was assessed indirectly through indicator variables such as welding process, welding materials, branch of industry, job title, expert assessment or self-report. Since the association with lung cancer was observed for both gas and arc welding and could not be explained by other exposures that occur with these two predominant welding procedures, the Working Group concluded that increased risk of lung cancer among welders can be attributed to exposure to welding fumes.

5.2.3 Cancer of the kidney

The Working Group evaluated several cohort studies (each reporting on ≥ 5 exposed cases or deaths) and independent case–control studies (10 studies for each design) that reported on associations between increased risk of cancer of the kidney and exposure to welding fumes. All six cohort studies found positive associations between occupation as a welder and increased risk of kidney cancer. Two large census-based population cohorts conducted in Canada and the Nordic countries reported statistically significant increased risks of 1.2–1.3. Risk estimates were generally higher (ranging from ~1.4 to 3.8), but less precise for the four industrial cohorts (welders in diverse industries in Europe, shipyard welders in Italy, boiler welders in Norway, and metal welders in the USA). The Norwegian study of boiler welders and the Italian shipyard study of welders reported statistically significant estimates of effect. None of the cohort studies adjusted for tobacco smoking or other potential confounders related to lifestyle, but the Canadian population-based cohort study also found a significantly increased risk of cancer of the kidney when the analysis was restricted to "blue-collar" workers, which may reduce the effects of potential confounders. The Working Group also considered that tobacco smoke is a weak kidney carcinogen and that most other non-occupational risk factors for cancer of the kidney would not be expected to be associated with welding, and therefore unlikely to explain the observed associations.

The case–control studies support the findings of the cohort studies. Six of the eight studies reported increased relative risks of cancer of the kidney (ranging from 1.2 to ~5.5). Increased risks were found in studies reporting risk estimates for welding as an occupation and exposure to welding fumes. Three studies evaluated associations for different categories of exposure to welding fumes (e.g. low, high, substantial), but clear exposure–response relationships were not observed. A hospital-based case–control study in Germany reported statistically significant odds ratios for exposure to welding fumes; however, subjects were potentially exposed to high levels of trichloroethylene, a known human kidney carcinogen. Since several case–control studies adjusted for tobacco, smoking was excluded as an explanation for the observed elevated relative risks.

Overall, there were consistent findings of elevated risks in several studies in different geographical areas and occupational settings, and using different study designs. However, not all findings were statistically significant, most studies had only a few exposed cases, and there was little evidence of an exposure–effect relationship; alternative explanations, such as bias and confounding, cannot therefore be reasonably ruled out.

5.2.4 Leukaemia

The Working Group evaluated four case–control studies, a nested case–control study, and three cohort studies (with number of exposed cases > 2) on welding that reported findings for leukaemia or specific subtypes of leukaemia. Almost all case–control and cohort studies reported elevated odds ratios for all types of leukaemia combined and occupation as a welder; however, most risk estimates were small (relative risks increased by 10–30%) and imprecise. The only study reporting a statistically significant risk estimate was the nested case–control study of welders in the Portsmouth Naval Shipyard monitored for radiation exposure; all cases were electric resistance welders and may have been exposed to solvents, including benzene (ORs were adjusted for solvents in general and for radiation). The evidence for myeloid leukaemia is somewhat stronger than for all types of leukaemia combined. All six studies evaluating this type of leukaemia reported elevated odds ratios, two of which were statistically significant, and the Nordic population-based cohort study reported a standardized incidence ratio of 1.23 (95% CI, 0.99–1.52, for male welders). Risk estimates were higher for myeloid leukaemia than combined leukaemia in the three studies that evaluated both. There were concerns about the two studies reporting statistically significant risk estimates: one was the nested case–control study of welders monitored for radiation exposure and the other was a Californian case–control study that reported a very high odds ratio (> 25) for chronic myeloid leukaemia. The only study (with more than 1 exposed case) for lymphoid leukaemia found an odds ratio close to unity. In New Zealand, a study of risk of combined leukaemia (acute myeloid leukaemia and acute lymphoid leukaemia) found a statistically significant association with occupation as a welder or flame cutter.

5.2.5 Non-Hodgkin lymphoma

The Working Group evaluated numerous independent case–control studies (including one pooled case–control study) and four cohort studies on welding that reported findings for non-Hodgkin lymphoma (NHL), including chronic lymphocytic leukaemia and subsets of B-cell lympho-haematopoietic cancers, including multiple myeloma. Classification and coding systems for NHL and its subtypes have changed considerably over the past 20 years, which may introduce heterogeneity between studies because of differences in lymphoma groupings.

Elevated risks for all NHL were found for those with the occupation welder in most of the 13 case–control studies, and were statistically significant in 4 studies. Importantly, one study found a significant association with daily exposure to welding after controlling for occupational co-exposures (benzene, pesticides, ELF-EMF), and medical and lifestyle factors (medical history, education, smoking); risks were higher among daily welders versus often welders (i.e. those who weld at least once per week, but less than once per day). Although a pooled analysis of 10 case–control studies did not find an association with all NHL, it did find an association with the NHL subtype of diffuse large B-cell lymphoma (DLBCL). A USA-based case–control study also found a significant association with DLBCL, and a Canadian case–control study found a significant association with diffuse small cleaved-cell lymphoma. Findings were inconsistent across five small studies on multiple myeloma. The cohort studies were limited in their ability to evaluate risk due to the paucity of studies reporting an estimate, the small numbers of exposed cases in the industrial studies, and the cruder exposure assessments in the population-based cohorts (compared with the case–control studies). A non-significant excess risk of NHL was found in the IARC multicentre cohort; the highest risk was observed among those who had held the

occupation of welder for 30 years. Risk estimates for NHL or its subtypes were close to or below unity in two population-based cohort studies and a cohort study of Norwegian boiler welders.

Overall, the case–control studies suggest a small excess risk of NHL among welders, but the evidence is not consistent across study design and was not observed in some of the larger studies. It is reasonable that the inconsistency across studies could be explained by the fact that risk factors for NHL could differ by subtype; however, the current database is inadequate for evaluating the association between welding and specific NHL subtypes.

5.2.6 Cancer of the bladder

More than 18 case–control studies and more than 10 cohort studies reported on the association between cancer of the bladder and exposure to welding fumes. The case–control studies were considered more informative than the cohort studies because they typically had a larger number of exposed cases, had stronger methods for exposure assessment, and adjusted for smoking while the cohort studies did not. The possibility of confounding by smoking in the cohort studies could not be excluded by the Working Group as a possible explanation for the moderately higher relative risk estimates reported by the cohort studies compared with the case–control studies. The Working Group noted that, despite a large number of case–control studies of adequate size, including several that were of relatively high quality, most reported relative risk estimates that were close to unity. Three case–control studies reported estimates by duration of welding or exposure to welding fumes, but the trend was inconsistent across studies. Several cohort studies reported elevated relative risk estimates for welding, although they were generally based on a small number of welder cases. One large multicentre cohort study of over 11 000 welders in Europe reported an elevated standardized mortality ratio for bladder cancer, while the risk estimate was lower, but still greater than unity, for incidence of bladder cancer.

5.2.7 Cancer of the brain

Four case–control studies and more than five cohort studies reported on the association between cancer of the brain and exposure to welding fumes. Three of the case–control studies reported odds ratios of less than or close to unity, all based on small numbers of exposed cases. A fourth case–control study reported an odds ratio of 1.26 (95% CI, 0.98–1.45) and weak evidence for a higher risk being associated with longer duration of welding. Several cohort studies reported elevated relative risk estimates, although generally based on small numbers of welder cases, and some of these were deemed to be of low quality and therefore uninformative. There were two large census-based cohort studies that showed inconsistent results: a study from Canada reported an increased risk of cancer of the brain in welders in an internal analysis (RR, 1.16; 95% CI, 0.83–1.63), while a study based on the Nordic cancer registries showed no association.

None of the studies adjusted for occupational exposure to ionizing radiation, so potential confounding could not be excluded.

Two case–control studies reported on welding in relation to incidence of meningioma. A study from China reported elevated odds ratios for both men and women exposed to “welding rod”, although each was based on small numbers of exposed cases. A much larger international case–control study on meningioma that assessed exposure to welding fumes through a job-exposure matrix reported an odds ratio of 1.79 (95% CI, 0.78–4.1; 12 exposed cases) for women and 1.15 (95% CI, 0.86–1.54; 82 exposed cases) for men. Trends according to categories of cumulative exposure and duration (years) of exposure to welding fumes were not observed.

5.2.8 Cancers of the head and neck

The Working Group considered case–control studies as being more informative than cohort studies when examining the association between welding and cancers of the head and neck. Due to the relatively low incidence of these cancers, either the number of cases was small or no relative risks were reported in many of the cohort studies. The evaluated case–control studies also controlled for smoking and alcohol drinking, the major risk factors for cancers of the oral cavity, pharynx, and larynx. However, the studies were hampered in their ability to evaluate these cancers by specific site because of the small numbers of exposed cases. Although positive associations were observed in some studies, these limitations prevented the Working Group from drawing any conclusions.

For sinonasal cancer, three out of the four case–control studies that reported on welding found positive associations. In one study that reported results by histological type the association was limited to squamous cell carcinoma, and a significant trend with duration was observed. However, no association with exposure to welding fumes was found in the largest case–control study for any histological type of sinonasal cancer. A pooled analysis of 12 case–control studies on sinonasal cancer also found no evidence of an elevated risk of sinonasal squamous cell carcinoma among welders. Only four cohort studies report on sinonasal cancer. No deaths from sinonasal cancer were observed in a large European study of welders, whereas non-significant increases in risk were found in a Danish study of boiler welders and in two census-based cohorts.

5.2.9 Other cancer sites

Associations between exposure to welding fumes and several other cancers, including cancers of the pancreas, colorectum, stomach, oesophagus, prostate, and testis, as well as between parental welding exposure and diverse cancers in offspring, were each examined in a few studies. The Working Group concluded that the data for these cancer sites did not permit any conclusion to be drawn with respect to the carcinogenicity of exposures related to welding.

5.3 Animal carcinogenicity data

No long-term studies on the effects of exposure to welding fumes in experimental animals treated by inhalation were available to the Working Group. One short-term inhalation study and two oropharyngeal aspiration studies examined the carcinogenicity of welding fumes in male A/J mice, and one intratracheal instillation study was conducted in male hamsters. The Working Group judged an intrabronchial implantation study in rats to be inadequate for the evaluation. The short-term inhalation study in male A/J mice exposed to GMA-SS welding fumes gave negative results. One oropharyngeal aspiration study in male A/J mice exposed to GMA-SS, MMA-SS, or GMA-MS welding fumes gave negative results. A second oropharyngeal aspiration study in male A/J mice exposed to MMA-SS welding fumes also gave negative results. The study in male hamsters exposed to low and high concentrations of MMA-SS welding fumes by intratracheal instillation reported two malignant lung tumours (a single tumour in each group); the Working Group deemed the study to be inconclusive, however, because of the comparison with undocumented historical controls. An oropharyngeal aspiration initiation–promotion study and an inhalation initiation–promotion study in male A/J mice examined exposure to GMA-SS welding fumes as a lung tumour promoter after initiation with 3-methylcholanthrene. Both studies showed a significant promoter effect of GMA-SS welding fumes on lung tumorigenicity.

5.4 Mechanistic and other relevant data

Toxicokinetic data from exposed humans concerned metals, and data regarding the deposition and clearance of particulate matter from welding fumes were sparse. All types of welding are associated with siderosis, a pulmonary accumulation of iron. In studies of MS welders, metals (chromium, nickel, and manganese) were measured in blood and urine, demonstrating absorption and excretion. Many studies in SS welders measured chromium in the blood and urine, and several also evaluated nickel and aluminium, demonstrating absorption and excretion. In rats, lung deposition of these same metals (chromium, nickel, and manganese) was demonstrated, followed by tissue distribution (e.g. to brain, lymph nodes, heart, kidney, spleen, and liver), and one study demonstrated urinary excretion. Comparable results were found between a study in non-human primates and a study in mice. Manganese distribution to specific brain regions was shown in multiple studies in rats and in one non-human primate study.

With respect to the key characteristics of human carcinogens, adequate data were available to evaluate if welding fumes: induce chronic inflammation; are immunosuppressive; are genotoxic; induce oxidative stress; alter cell proliferation, cell death, and nutrient supply; and modulate receptor-mediated effects.

There is *strong* evidence that welding fumes induce chronic inflammation and are immunosuppressive. More than 20 panel studies in humans with short-term exposure to various arc welding fumes reported increases in biomarkers of lung and systemic inflammation, some with exposure–response relationships. Other studies reported the similar or more pronounced effects of exposure to SS welding fumes. Several studies demonstrated increases in mediators of chronic inflammation in arc welders exposed to MS welding fumes. No information was available concerning whether the effects are sustained after exposure cessation. Several epidemiological studies of different design showed an increased risk of infection (pneumonia) in welders as a consequence of exposure-related immune suppression, while one molecular epidemiology investigation provided a plausible mechanism involving platelet-activating factor receptor. In a few toxicogenomic and metabolomic studies of arc welders exposed to MS fumes, changes were observed in eicosanoid levels and inflammatory pathways.

In numerous studies in male rats and mice, short-term and subchronic exposure to welding fumes (SS but not MS) stimulated cellular influx primarily of alveolar macrophages, neutrophils, and lymphocytes when evaluated immediately after exposure, or after subchronic (in rats and mice) or chronic (in mice) observation periods. Cellular infiltration was associated with an accumulation of inflammatory cytokines in the bronchoalveolar lavage fluid (BALF). In the few available studies in vitro, results were mixed.

Fewer experimental animal studies were available for immune suppression. Subchronic exposure to SS or MS welding fumes impaired resolution of pulmonary infection in several studies of male rats or female mice, with evidence of systemic as well as local immunosuppression. In lung gene-expression arrays, SS welding fumes dysregulated pathways signalling a strong immunological response in rats and mice, and perturbed immunosuppression pathways in non-human primates. Two studies in vitro reported impaired function in mouse immune cells.

There is *moderate* evidence that welding fumes are genotoxic. In exposed humans, the results of studies on genotoxicity are heterogeneous. Both positive and negative results were obtained, especially for chromosomal aberrations and sister-chromatid exchange rates in lymphocytes. Studies on micronucleus formation in lymphocytes and exfoliated cells generally had

methodological concerns, such as having scored an inadequate number of cells. Studies on DNA damage (two of which compared measurements before and after exposure) generally gave positive results. Evidence was found for an increase in 8-hydroxy-2′-deoxyguanosine (8-OHdG) in blood plasma and in urine, with two studies of controlled crossover exposure and two field studies showing an effect during the welding work shift. Few data from experimental animals were available, with largely positive results for DNA damage in rats and in assays for genotoxicity in bacteria.

There is *moderate* evidence that welding fumes induce oxidative stress. All five identified short-term panel studies of exposure to various types of welding fumes in humans (including TIG/GTA welding on Al; arc welding on MS) reported increases in 8-OHdG in urine and in hydrogen peroxide in exhaled breath or urine. Four of these studies observed exposure–response relationships with particulate matter of diameter less than 2.5 μm ($PM_{2.5}$) or particle number concentrations. In several cross-sectional observational studies, exposure to various types of welding fumes was associated with increases in oxidative stress markers and decrements in antioxidant status (glutathione, superoxide dismutase activity) in the blood and urine. In three studies in male Sprague-Dawley rats, SS welding fumes increased markers of lung oxidative stress. Gene expression arrays in male mice showed that SS and MS welding fumes activated stress-response pathways in the lungs. In numerous studies of primary and immortalized cells in vitro, both SS and MS welding fumes induced production of reactive oxygen species (ROS). In acellular systems, SS and MS fumes generated ROS and oxidized macromolecules. No experimental studies of inhalation exposure, or studies demonstrating experimental challenge, were identified.

There is *moderate* evidence that welding fumes alter cell proliferation or death. Few data were available from exposed humans. In numerous studies in both male rats and mice, short-term and subchronic durations of exposure to primarily SS welding fumes increased BALF albumin levels and/or lactate dehydrogenase activity measured immediately after exposure, or after subchronic (in rats and mice) or chronic (in mice) observation periods. Proliferative pulmonary lesions were induced. In the few available gene-expression array studies, SS welding fumes perturbed pathways related to cell proliferation in non-human primates and rodents, while MS welding fumes induced circadian rhythm signalling and cell survival pathways in mice. Both SS and MS welding fumes induced cytotoxicity and/or altered mitochondrial function in a variety of mammalian cells in vitro.

There is *weak* evidence that welding fumes modulate receptor-mediated effects. Data from exposed humans were inconsistent and several studies had methodological weaknesses. No information was available from experimental systems.

There were no data on cancer susceptibility.

In exposed humans, pulmonary, cardiovascular, ocular, and neurological effects were observed, as well as renal effects when cadmium is present. In experimental systems, pulmonary, cardiovascular, and neurological effects were observed.

6. EVALUATION

6.1 Cancer in humans

There is *sufficient evidence* in humans for the carcinogenicity of welding fumes. Welding fumes cause cancer of the lung. Positive associations have been observed with cancer of the kidney.

There is *sufficient evidence* in humans for the carcinogenicity of ultraviolet radiation from welding. Ultraviolet radiation from welding causes ocular melanoma.

6.2 Cancer in experimental animals

There is *limited evidence* in experimental animals for the carcinogenicity of gas metal arc stainless steel welding fumes.

6.3 Overall evaluation

Welding fumes are *carcinogenic to humans* (Group 1).

Ultraviolet radiation from welding is *carcinogenic to humans* (Group 1).

MOLYBDENUM TRIOXIDE

1. Exposure Data

1.1 Identification

Chem. Abstr. Serv. Reg. No.: 1313-27-5

Chem. Abstr. Serv. Name: Molybdenum trioxide

IUPAC systematic name: Trioxomolybdenum (ECHA, 2016a)

Other common names: Molybdenum oxide, molybdenum (VI) oxide, molybdenum (VI) trioxide, molybdic acid anhydride, molybdic anhydride, molybdic oxide, molybdite

Molecular formula: MoO_3

Relative molecular mass: 143.94

Density: 4.69 g/cm^3 at 26 °C (HSDB, 2017)

Melting point: 795 °C (HSDB, 2017)

Boiling point: 1155 °C, sublimes (HSDB, 2017)

Solubility in water: 1.0 g/L at 20 °C (ECHA, 2016a). It is slightly soluble in water at room temperature, the saturated solution being acid (pH 2.5) (ECHA, 2016a).

Molybdenum trioxide (MoO_3) is a white solid at room temperature (HSDB, 2017).

Technical-grade molybdenum trioxide (see Section 1.2.1) typically contains 80% molybdenum trioxide, 6% molybdenum suboxides, 4% iron molybdates, 3% quartz, 1% calcium molybdate, 0.45% copper compounds, 0.03% lead compounds, and 0.012% arsenic compounds (Christensen et al., 2015).

1.2 Production and use

1.2.1 Production process

Molybdenum trioxide occurs naturally as the rare mineral molybdite (Anthony et al., 2001–2005), but is obtained commercially almost exclusively from molybdenite (molybdenum (IV) sulfide, MoS_2) (Sebenik et al., 2012). Molybdenite ore is crushed, ground, and passed through flotation cells to obtain about 90% molybdenum (IV) sulfide (Steifel, 2010). The remainder is mainly silica, with small amounts of aluminium, copper, and iron. Impure molybdenum trioxide, also called technical-grade or roasted molybdenum sulfide (CAS No. 86089-09-0), is obtained by roasting the molybdenum (IV) sulfide concentrate in air in a multiple-hearth furnace at a temperature of 600–650 °C (Sebenik et al., 2012). Pure molybdenum trioxide is obtained by sublimation or by wet chemical methods (Steifel, 2010). Other methods of molybdenum trioxide production exist. Hydrometallurgical routes, including solvent extraction, ion exchange, membrane-based separation, and precipitation,

have the advantage of producing molybdenum trioxide without emission of sulfur dioxide (Lasheen et al., 2015).

1.2.2 Production volume

World molybdenum (as Mo metal) mine production was estimated at 281 000 tonnes for 2014 (Polyak, 2016). Table 1.1 lists the mine production by country (more specific information about MoO_3 is not available). About half of the total amount of mine production is converted into and used as molybdenum trioxide (Christensen et al., 2015). National production volume of molybdenum trioxide in the USA was estimated at 83 290 tonnes for 2014 (EPA, 2016).

Molybdenum trioxide is a high production volume chemical. High production volume chemicals "are produced or imported at levels greater than 1,000 tonnes per year in at least one member country/region" of the Organisation for Economic Co-operation and Development (OECD, 2009).

1.2.3 Use

Technical-grade molybdenum trioxide is primarily and directly used in steel production. The rest is used in the synthesis of various molybdate salts (Stiefel, 2011).

In 2014 in the USA, metallurgical applications (corrosion inhibitor) accounted for ~88% of consumption. Christensen et al. (2015) estimated the world consumption of molybdenum trioxide to be divided between: ~80–90% for various steel applications; ~10% for catalysts (mainly for refineries); and ~5% for super alloys.

The lead REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) registrant for molybdenum trioxide lists the current uses for this chemical as: catalyst manufacturing, an intermediate in the manufacture of molybdenum chemicals, surface treatment substances, molybdenum metal, frits and enamels (blue dye), liquid industrial paints, pigments, water treatment chemicals, lubricant additives, lubricants and greases, and an intermediate for reduction to molybdenum dioxide in steel and alloy production and in steel and alloy powder production (CLIMAX, 2016).

Furthermore, recent research initiatives indicate that uses of molybdenum trioxide may increase in the future due to its interesting properties in new technologies, for example: solar energy harvesting and storing, and biocidal activity on material surfaces (Zollfrank et al., 2012; Lou et al., 2014). Some applications (catalyst, coatings, and ceramics) are facilitated by the use of molybdenum trioxide in the form of nanoparticles or nanotubes in combination with other molybdenum compounds (Jin et al., 2016).

Table 1.1 Mine production of molybdenum, by country, 2014

Country	Production (tonnes)
China	103 000
USA	68 200
Chile	48 770
Peru	17 018
Mexico	14 370
Canada	9 698
Armenia	7 100
Russian Federation	4 800
Islamic Republic of Iran	4 000
Mongolia	1 999
Turkey	1 300
Uzbekistan	530

Adapted from Polyak (2016)

1.3 Measurement and analysis

Molybdenum trioxide is measured by the analyte molybdenum in air, blood, tissue, urine, or water samples (Table 1.2). Air sampling to determine molybdenum can be performed using the National Institute for Occupational Safety and Health (NIOSH) Method 7300 or 7303 for elements by inductively coupled plasma.

Table 1.2 Analytical methods for molybdenum in different matrices

Sample matrix	Assay procedure	Limit of detection	Method/reference
Air	ICP-AES	0.8 ng/mL	NIOSH 7300, NIOSH 7303
Blood (plasma or whole blood)	ICP-AES	10 µg/10 mL	NIOSH 8005
Plasma	ICP-MS		Keyes & Turnlund (2002)
Tissue	ICP-AES	10 µg/g	NIOSH 8005
Urine	ICP-AES	2.0 µg/50 mL	NIOSH 8310
Water (drinking, surface, and domestic and industrial wastewaters)	ICP-AES	12 µg/L	EPA 200.7
Water	AAS	0.1 mg/L	Franson (1985)

AAS, atomic absorption spectrometry; AES, atomic emission spectrometry; ICP, inductively coupled plasma; MS, mass spectrometry

Molybdenum can be determined in other matrices by inductively coupled plasma mass spectrometry.

1.4 Occurrence and exposure

Molybdenum trioxide occurs naturally as the rare mineral molybdite. However, environmental levels of molybdenum trioxide have not been reported in the literature; it is therefore total elemental molybdenum that is discussed here.

1.4.1 Environmental occurrence

Environmental exposure to molybdenum is negligible for most people.

(a) Water/air

Most natural water worldwide contains low concentrations of molybdenum of < 2–3 µg/L. Around areas of molybdenum mining or other industrial manufacturing of molybdenum, concentration in water may reach up to 400 µg/L in surface water and up to 25 000 µg/L in groundwater (Barceloux & Barceloux, 1999). Molybdenum concentration in water can vary widely over short distances, but waters with an elevated pH will have increased solubility of molybdenum and increased leaching of molybdenum from soil to water (Runnells et al., 1977). Molybdenum in ambient air is typically very low, with concentrations in urban areas of 0.01–0.03 µg/m^3 and approximately 10 times lower in rural areas, except where molybdenum mining or manufacturing occurs (Barceloux & Barceloux, 1999). Molybdenum trioxide could be present in waste water, with the majority coming from industrial sites that use molybdenum trioxide in catalysts or alloys. However, in countries where recycling facilities exist, molybdenum is often recycled due to its economic value. For this reason, it is generally believed that molybdenum trioxide in wastewater streams is typically low in developed countries (Danish Ministry of the Environment, 2015). For the majority of people worldwide, ambient air and drinking-water exposures to molybdenum are negligible compared with dietary intake, especially for exposures to molybdenum trioxide (Lener & Bíbr, 1984).

(b) Soil

The typical range of molybdenum concentrations found in soil is 1–2 mg/kg (Barceloux & Barceloux, 1999). The concentration of molybdenum varies considerably with the type of soil, however (Runnells et al., 1977); sedimentary soils contain higher concentrations of molybdenum than acidic soils, with molybdenum at concentrations of > 0.7 mg/kg and < 0.2 mg/kg, respectively (Barceloux & Barceloux, 1999).

(c) Food

Diet is the major source of exposure to molybdenum for most people. Dietary analysis of 56 adults in Germany found molybdenum intake to be < 100 µg/day (Anke et al., 1991). Studies in the USA found a range of intakes over 120–240 µg/day for adults (Tsongas et al., 1980). Similarly, the European Food Safety Authority reported that dietary intake in European adults ranges over 58–57 µg/day, and the United States Institute of Medicine reported a range of 120–240 µg/day in the USA (Institute of Medicine, 2001; EFSA, 2013). Health Canada reported similar intakes in adults; during 1993–1999, average dietary intake of molybdenum for Canadians of all ages was estimated at 2.66 µg/kg body weight (bw) per day (Health Canada, 2011). Foods with the highest molybdenum content include legumes, leafy vegetables, beans, cereal grains, kidney, liver, and milk. Only small quantities are found in fruits, sugar-rich foods, and meat. The United States Institute of Medicine has established recommended dietary allowances, which is the average daily intake sufficient to meet nutrient requirements of healthy people, based on age and sex. These range from 2 µg/day in infants to 45 µg/day in adult men and women (Institute of Medicine, 2001). Molybdenum deficiency is extremely rare, as is molybdenum overdose due solely to dietary intake. A tolerable upper intake level for molybdenum was determined by the European Food Safety Authority to be 0.01 mg/kg bw per day, equivalent to 0.6 mg/person per day for adults (EFSA, 2006).

1.4.2 Exposure of the general population

The general population will typically only be exposed to molybdenum through diet, including drinking-water, with negligible exposure due to ambient air or soil. The United States National Health and Nutrition Examination Survey (NHANES) measures molybdenum in urine of the general USA population. In 484 people aged 18–55 years sampled for NHANES during 2011–2012, geometric mean urine molybdenum was 41.5 µg/L; no samples fell below the analytical limit of detection (Lewis & Meeker, 2015). The Canadian Health Measures Survey (CHMS) also measures for molybdenum in urine and blood in the general Canadian population. In all 5319 subjects aged 6–79 years measured during 2007–2009, the geometric mean urine molybdenum was 36.3 µg/L in urine and 0.68 µg/L in blood. In adults aged 20–79 years, the geometric mean urine and blood molybdenum were 32.9 µg/L and 0.67 µg/L, respectively (Health Canada, 2011). During 2012–2013 11 healthy men in China with no occupational history of working with metals gave multiple urine samples over a 3-month period. Mean molybdenum was 98.5 µg/L in 529 spot urine samples collected, with the first morning sample having a higher mean molybdenum concentration of 122.8 µg/L (Wang et al., 2016).

The molybdenum content in human breast-milk ranges from < 0.1 µg/L to > 60 µg/L, depending on days postpartum and mothers' diet. Infant formulas have more molybdenum than breast-milk (Gunshin et al., 1985; Casey & Neville, 1987; Yoshida et al., 2008; Mohd-Taufek et al., 2016).

1.4.3 Occupational exposures

See Table 1.3

Common occupations with exposure to molybdenum trioxide include mining and metallurgy works, steel foundries, and welding and other hot work processes using steel.

Exposure to respirable molybdenum dust was measured for 25 male workers in a molybdenite roasting plant in Denver, Colorado in the 1970s, at which stationary dust samples were collected from three locations. Results showed that the 8-hour time-weighted average molybdenum concentration ranged over 1.02–4.49 mg/m^3. All 25 workers gave a plasma

Table 1.3 Occurrence of molybdenum in facilities using molybdenum trioxide

Reference	Location, collection date	Occupation description	Sampling matrix, *n*	Exposure level[a]	Exposure range	Comments/additional data
Walravens et al. (1979)	USA, 1979	Roasting plant miners	Respirable air, *n* = 3	NR	1.02–4.49 mg/m³	Samples taken at three different locations in plant: base of roaster (1.02 mg/m³), first tier (1.58 mg/m³), and second tier (4.49 mg/m³) Total dust stationary samples collected at the first tier and second tier of the roasting plant 18 people not in the roasting plant
			Total dust, environmental, *n* = 2	NR	9.11–33.28 mg/m³	
			Plasma, *n* = 25	NR	9–365 µg/L	
		Student/research personnel	Urine, *n* = 14	1790 µg/L	120–11 000 µg/L	
			Urine, *n* = 18	53.66 µg/L	20–230 µg/L	
			Plasma, *n* = 24	NR	< LOD–34 µg/L	
Kucera et al. (2001)	NS	Stainless steel vessel production welders	Total dust, personal, *n* = 15, 8 h	2.25 µg/m³	0.27–9.7 µg/m³	Closed-face cassette with 0.8 µm pores
		Stainless steel vessel production drillers, cutters, assemblers	Total dust, personal, *n* =15, 8 h	0.34 µg/m³	0.14–0.60 µg/m³	
		Stainless steel vessel production polishers	Total dust, personal, *n* = 9, 8 h	1.86 µg/m³	0.03–4.2 µg/m³	
Huvinen et al. (2002)	Finland, 1999	Stainless steel production, steel melting shop	Air, personal, *n* = 6	Median 0.3 µg/m³	Maximum 2.3 µg/m³	Details on sampling method not specified

[a] Arithmetic mean unless indicated otherwise

LOD, limit of detection; NR, not reported; NS, not specified

sample, and 14 workers gave a urine sample. Plasma molybdenum concentrations ranged over 9–365 µg/L and urine molybdenum concentrations over 120–11 000 µg/L (Walravens et al., 1979). These urine values are greater than those found by NHANES and Health Canada in the general population (see Section 1.4.2).

Twenty stainless steel vessel production workers were monitored for exposure to molybdenum in dust in a study published in 2001. The stainless steel used in the plant contained an average of 2.0–2.5% molybdenum. Workers were divided into groups defined by occupational task: welding, polishing, or other (drilling, cutting, or assembling). Molybdenum exposure for each group had a mean value of 0.3–2 µg/m^3 over the range 0.03–9.7 µg/m^3 (see Table 1.3; Kucera et al., 2001).

Another study of occupational exposure published in 2002 took personal and area samples of molybdenum in a steel melting shop. From 6 personal samples and 17 stationary samples, the median molybdenum concentration was 0.3 µg/m^3 (maximum value: 2.3 µg/m^3) and 0.6 µg/m^3 (maximum value: 4 µg/m^3), respectively (Huvinen et al., 2002).

[The Working Group noted that air exposures to molybdenum were about three orders of magnitude higher at the Colorado roasting plant compared with the metal working shops. However, the samples at the roasting plant were acquired several decades earlier than those from the metalworking shops.]

1.5 Regulations and guidelines

A specific limit value for occupational exposure to molybdenum trioxide of 0.5 mg/m^3 as an 8-hour total weight average (TWA) concentration only exists in Finland. No values for short-term limit exist (GESTIS, 2017).

For insoluble molybdenum compounds in general, many countries have limit values ranging over 3–15 mg/m^3 as an 8-hour TWA concentration. Corresponding short-term limit values range over 10–60 mg/m^3. For soluble molybdenum compounds these ranges are 0.5–5 mg/m^3 (8-hour TWA) and 10–20 mg/m^3 (short-term limit value as Mo) (GESTIS, 2017).

Molybdenum trioxide has an official harmonized classification in the EU Classification and Labelling Regulation. In Regulation (EC) No. 1272/2008, it is classified as a Category 2 Carcinogen H351: "Suspected of causing cancer" as well as STOT SE 3: H335: "May cause respiratory irritation" and H319: "Causes serious eye irritation" (ECHA, 2016b).

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

3.1 Mouse

See Table 3.1

3.1.1 Inhalation

In a well-conducted good laboratory practice (GLP) study, groups of 50 male and 50 female B6C3F$_1$ mice (age, 6 weeks) were exposed by whole-body inhalation to molybdenum trioxide (purity, ~99%; mass median aerodynamic diameter, 1.3–1.8 µm) at concentrations of 0, 10, 30, or 100 mg/m^3 for 12 min (T_{90}) plus 6 hours per day, 5 days per week for up to 105 weeks on study (NTP, 1997; Chan et al., 1998). The body weights of the female mice were generally greater than those of the control group from week 11 until the end of the study. The survival of treated male and female mice was similar to that of controls. The incidence of metaplasia of the alveolar epithelium was significantly increased in all exposed groups of males and females. The incidences of

Table 3.1 Studies of carcinogenicity with molybdenum trioxide in experimental animals

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence or multiplicity of lung tumours	Significance	Comments
Full carcinogenicity Mouse, B6C3F$_1$ (M) 6 wk 105 wk NTP (1997)	Inhalation (whole-body exposure) MoO_3, ~99% Clean air 0, 10, 30, 100 mg/m^3 6 h + 12 min (T90)/d, 5 d/wk 50, 50, 50, 50 36, 33, 25, 37	Bronchioloalveolar adenoma 9/50, 14/50, 10/49, 9/50 Bronchioloalveolar carcinoma 2/50, 16/50, 14/49, 10/50 Bronchioloalveolar adenoma or carcinoma (combined) 11/50, 27/50, 21/49, 18/50	NS $P < 0.001$ (low dose), $P < 0.001$ (mid-dose), $P = 0.017$ (high dose) $P = 0.001$ (low dose), $P = 0.020$ (mid-dose)	Principal strengths: GLP study; physiological exposure route; both sexes used Statistical test: logistic regression test
Full carcinogenicity Mouse, B6C3F$_1$ (F) 6 wk 105 wk NTP (1997)	Inhalation (whole-body exposure) MoO_3, ~99% Clean air 0, 10, 30, 100 mg/m^3 6 h + 12 min/d, 5 d/wk 50, 50, 50, 50 25, 31, 33, 35	Bronchioloalveolar adenoma 1/50, 4/50, 8/49, 9/49 Bronchioloalveolar carcinoma 2/50, 2/50, 0/49, 6/49 Bronchioloalveolar adenoma or carcinoma (combined) 3/50, 6/50, 8/49, 15/49	$P = 0.018$ (trend), $P = 0.036$ (mid-dose), $P = 0.016$ (high dose) $P = 0.024$ (trend) $P < 0.001$ (trend), $P = 0.003$ (high dose)	Principal strengths: GLP study; physiological exposure route; both sexes used Historical control incidence for NTP studies: adenoma, 61/939 (6.5 ± 3.2%) [range, 0–14%]; carcinoma, 38/939 (4.1 ± 3.2%) [range, 0–12%]; adenoma or carcinoma (combined), 97/939 (10.3 ± 3.7%) [range, 0–16%] Statistical test: logistic regression test
Full carcinogenicity Mouse, A/J (M+F combined) 6–8 wk 30 wk Stoner et al. (1976)	Intraperitoneally MoO_3, > 97% Saline 0, 950, 2735, 4750 mg/kg bw 19 times 20, 20, 20, 20 19, 13, 19, 15	Tumour [presumably adenomas] incidence 7/19, 4/13, 7/19, 10/15 Tumour multiplicity 0.42 ± 0.10, 0.30 ± 0.08, 0.50 ± 0.13, 1.13 ± 0.20*	[NS] *$P < 0.05$ (Student's *t* test)	Principal limitations: limited histopathological examination Equal number of M and F; incidences for M and F were combined

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence or multiplicity of lung tumours	Significance	Comments
Full carcinogenicity Rat, F344/N (M) 6 wk 106 wk NTP (1997)	Inhalation (whole-body exposure) MoO_3, ~99% Clean air 0, 10, 30, 100 mg/m^3 6 h + 12 min/d, 5 d/wk 50, 50, 50, 50 17, 10, 16, 17 Inhalation (whole-body exposure) MoO_3, ~99% Clean air 0, 10, 30, 100 mg/m3 6 h + 12 min/d, 5 d/wk 50, 50, 50, 50 28, 24, 24, 23	Bronchioloalveolar adenoma 0/50, 0/50, 0/50, 3/50 Bronchioloalveolar carcinoma 0/50, 1/50, 1/50, 1/50 Bronchioloalveolar adenoma or carcinoma (combined) 0/50, 1/50, 1/50, 4/50 Bronchioloalveolar adenoma or carcinoma (combined) 0/50, 2/50, 0/50, 2/50	 $P = 0.017$ (trend) NS $P = 0.034$ (trend) NS	Principal strengths: GLP study; physiological exposure route; both sexes used Principal limitations: poor survival of exposed and control animals Historical control incidence at laboratory: adenoma, 16/347 (4.6 ± 4.0%) [range, 0–10%]; carcinoma, 4/347 (1.2 ± 1.1%) [range, 0–2%]; adenoma or carcinoma (combined), 20/347 (5.8 ± 3.7%) [range, 0–10%] Adjusted incidences: adenoma, 0.0, 0.0, 0.0, 14.8%; adenoma or carcinoma (combined), 0.0, 5.3, 4.3, 17.4% Terminal rate: adenoma, 0/17, 0/10, 0/16, 1/17; adenoma or carcinoma (combined), 0/17, 0/10, 0/16, 1/17 Statistical test: logistic regression test

bw, body weight; d, day(s); F, female; GLP, good laboratory practice; M, male; min, minute(s); MoO_3, molybdenum trioxide; NS, not significant; NTP, National Toxicology Program; wk, week(s)

carcinoma of the bronchioloalveolar were significantly increased in male mice (2 out of 50, 16 out of 50, 14 out of 49, and 10 out of 50) for all treated groups, and there was a significant positive trend in the incidence in females (2 out of 50, 2 out of 50, 0 out of 49, and 6 out of 49). The incidences of adenoma of the bronchioloalveolar were significantly increased in female mice (with a significant positive trend) exposed to 30 mg/m^3 and 100 mg/m^3 (1 out of 50, 4 out of 50, 8 out of 49, and 9 out of 49) and the incidences of adenoma or carcinoma (combined) of the bronchioloalveolar were significantly increased in female mice exposed to 100 mg/m^3 (3 out of 50, 6 out of 50, 8 out of 49, and 15 out of 49) and in male mice exposed to 10 mg/m^3 and 30 mg/m^3 (11 out of 50, 27 out of 50, 21 out of 49, and 18 out of 50). [The Working Group noted the strengths of the study: this was a GLP study, a physiological exposure route was employed, and both sexes were used.]

3.1.2 Intraperitoneal injection

Four groups of 20 A/J mice (equal numbers of male and female mice; age, 6–8 weeks) were given intraperitoneal injections of 0 (vehicle control), 950, 2735, or 4750 mg/kg bw (total doses) reagent-grade molybdenum trioxide (purity > 97%; impurities unspecified) in saline three times per week for a total of 19 injections (except saline controls: 24 injections). After 30 weeks, 13, 19, and 15 animals were still alive in the three treated groups. At that time, these animals and 19 surviving vehicle controls were killed and their lungs examined macroscopically for tumour induction; a few of the grossly visible nodules were examined microscopically to confirm the typical appearance of adenomas of the lung. The incidences of mice with lung tumours were 7 out of 19, 4 out of 13, 7 out of 19, and 10 out of 15 [no statistically significant differences], and the average number of lung tumours per mouse (multiplicity) was 0.42 ± 0.10, 0.30 ± 0.08, 0.50 ± 0.13, and 1.13 ± 0.20 (average ± standard error) for the 0, 950, 2735, or 4750 mg/kg bw groups, respectively. Lung tumour multiplicity in the 4750 mg/kg bw group was significantly ($P < 0.05$) higher than the vehicle control group (Stoner et al., 1976). [The Working Group noted the limitations of the study: the non-physiological route of exposure, the limited histopathological examination, and the combination of tumour incidences for male and female mice.]

3.2 Rat

See Table 3.1

3.2.1 Inhalation

In a well-conducted GLP study, groups of 50 male and 50 female Fischer 344/N rats (age, 6 weeks) were exposed by whole-body inhalation to molybdenum trioxide (purity, ~99%; mass median aerodynamic diameter, 1.3–1.8 μm) at concentrations of 0, 10, 30, or 100 mg/m^3 for 6 hours plus 12 min per day, 5 days per week for 106 weeks on study (NTP, 1997; Chan et al., 1998). Mean body weights of male and female exposed rats were similar to those of controls throughout the study. The survival of exposed and control rats was poor, but survival of male and female exposed rats was similar to those of their respective controls. The incidence of chronic inflammation of the alveolar was significantly increased in male and female treated rats. The incidences of adenoma of the bronchioloalveolar (0 out of 50, 0 out of 50, 0 out of 50, and 3 out of 50 for 0, 10, 30, and 100 mg/m^3, respectively) and of adenoma or carcinoma (combined) of the bronchioloalveolar (0 out of 50, 1 out of 50, 1 out of 50, and 4 out of 50) were increased in male rats with a significant positive trend ($P = 0.017$ and $P = 0.034$, respectively); these incidences were within historical control incidence ranges. The incidences of carcinoma of the bronchioloalveolar were 0 out of 50, 1 out of 50, 1 out of 50, and 1 out of 50 in male rats. No significant increase

in the incidence of lung neoplasms occurred in female rats. [The Working Group noted the strengths of the study: this was a GLP study, a physiological exposure route was employed, and both sexes were used. The Working Group also noted the poor survival of exposed and control male and female rats.]

4. Mechanistic and Other Relevant Data

4.1 Toxicokinetic data

4.1.1 Humans

No studies on molybdenum trioxide (MoO_3) in exposed humans were available to the Working Group.

Regarding elemental molybdenum (Mo), several publications from the same laboratory reported on toxicokinetics of radiolabelled elemental molybdenum following exposure to four healthy men. Turnlund and colleagues used a compartmental model based on isotope excretion patterns to determine molybdenum absorption, distribution, and elimination (Turnlund et al., 1995, 1998, 1999; Thompson & Turnlund, 1996; Novotny & Turnlund, 2006). Four healthy men were fed a low-molybdenum diet (22 µg/day or 0.23 µmol/day) for 102 days, followed by a high-molybdenum diet (467 µg/day or 4.9 µmol/day) for 18 days. Molybdenum was very efficiently absorbed, distributed, and excreted, primarily in the urine (Turnlund et al., 1995; Thompson & Turnlund, 1996).

4.1.2 Experimental systems

Exposure-dependent increases in blood molybdenum concentrations were seen in male and female F344/N rats and $B6C3F_1$ mice exposed to 0, 10, 30, or 100 mg/m³ molybdenum trioxide via inhalation for 106 and 105 weeks, respectively (NTP, 1997; Chan et al., 1998; see Section 3). Blood concentrations of molybdenum were greater in exposed male rats than in exposed female rats. [The Working Group noted that the reported effects on respiratory tract tissues of male rats and female mice suggest distribution of molybdenum to lungs, although this was not directly examined in these studies.]

Metabolism and excretion of molybdenum were not reported in either of these studies.

4.2 Mechanisms of carcinogenesis

The sections that follow summarize the evidence for key characteristics of carcinogens (Smith et al., 2016), addressing whether molybdenum trioxide is genotoxic and induces inflammation. There were insufficient data for the evaluation of other key characteristics of human carcinogens.

4.2.1 Genetic and related effects

See Table 4.1

No data in exposed humans, human cells in vitro, or in experimental systems in vivo were available to the Working Group.

Molybdenum trioxide did not induce sister-chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells in vitro (NTP, 1997). Molybdenum trioxide was not mutagenic in the five tested strains of *Salmonella typhimurium*. All tests were conducted with and without S9 metabolic activation enzymes (NTP, 1997).

4.2.2 Chronic inflammation

In a 106-week chronic inhalation study in male and female F344/N rats, molybdenum trioxide increased the incidence and severity of inflammation in the lung (NTP, 1997; Chan et al., 1998; Ozaki et al., 2002; see Section 3). This effect was not observed in mice.

Table 4.1 Genetic and related effects of molybdenum trioxide in experimental systems in vitro

Species	Tissue, cell line	End-point	Test	Results		Concentration (LEC or HIC)	Reference
				Without metabolic activation	With metabolic activation		
Chinese hamster	CHO cells	Chromosomal damage	Chromosomal aberrations	–	–	HIC, 10 µg/mL	NTP (1997)
Chinese hamster	CHO cells	Chromosomal damage	Sister-chromatid exchange	–	–	HIC, 10 µg/mL	NTP (1997)
Prokaryote (bacteria)	Null TA100, TA1535, TA1537, TA97, TA98	Mutation	Reverse mutation	–	–	HIC, 10 000 µg/plate	NTP (1997)

–, negative; CHO, Chinese hamster ovary; HIC, highest ineffective concentration; LEC, lowest effective concentration

4.2.3 Other mechanisms

Data on other key characteristics of carcinogens were sparse, and no such data were available to the Working Group from exposed humans or from experimental systems in vivo.

Molybdenum trioxide nanoplates were more cytotoxic to the invasive MCF-7 breast cancer cells than the MCF-7 parental cell line, with significant differences in cytotoxicity starting at 50 µg/mL (Anh Tran et al., 2014).

In a mouse germline stem cell model, molybdenum trioxide nanoparticles were more cytotoxic than soluble molybdenum salts. The nanoparticulate molybdenum exerted its cytotoxic effects via cellular metabolic activity, but only at higher doses (≥ 50 µg/mL); very low concentrations (5–10 µg/mL) induced membrane leakage (Braydich-Stolle et al., 2005).

Molybdenum trioxide gave positive results in the assay for cell transformation in the Syrian hamster embryo, requiring a dose of ≥ 75 µg/mL to demonstrate morphological transformation (Kerckaert et al., 1996).

Lewis et al. (1996) noted that molybdenum trioxide has been predicted to generate oxygen radicals due to its metal ion redox potential (Lewis et al., 1996).

4.3 Cancer susceptibility

No data were available to the Working Group.

4.4 Other adverse effects

In a chronic (106-week) inhalation study in male F344/N rats, molybdenum trioxide exposure (100 mg/m^3 dose only) induced fibrosis and metaplasia in the lung (NTP, 1997; Ozaki et al., 2002).

5. Summary of Data Reported

5.1 Exposure data

Molybdenum trioxide (MoO_3) is a white solid with rare natural occurrence in the form of the mineral molybdite. It is obtained commercially almost exclusively from roasting molybdenite (molybdenum sulfide). Molybdenum trioxide is a high production volume chemical. Globally, more than 100 000 tonnes of molybdenum trioxide are estimated to be produced annually, the majority for direct use in steel production. Other significant uses include catalysts and super alloys, and upcoming developments include the harvesting and storing of solar energy, and biocidal activity

on material surfaces. Environmental exposures to molybdenum trioxide are negligible. Occupational exposures may occur mainly in mining and metallurgy works, steel foundries, and welding and other hot work processes using steel. Molybdenum air concentrations measured in a plant producing molybdenum trioxide in the 1970s ranged from 1.02 to 4.49 mg/m^3, and associated plasma and urine molybdenum concentrations were significantly higher than in the general population. In contrast, in two recent studies of metal workers, molybdenum air concentrations were all < 0.01 mg/m^3.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Two well-conducted carcinogenicity studies under GLP conditions are described in Sections 3.1.1 and 3.2.1: an inhalation study in male and female mice and an inhalation study in male and female rats, respectively. Section 3.1.2 describes an intraperitoneal injection study in male and female strain A mice.

In the inhalation study in mice, molybdenum trioxide significantly increased the incidence of carcinoma of the bronchioloalveolar in male mice (with a significant positive trend), the incidence of adenoma of the bronchioloalveolar in female mice (with a significant positive trend), and the incidence of adenoma or carcinoma (combined) of the bronchioloalveolar in female (with a significant positive trend) and male mice. There was also a positive trend in the incidence of carcinoma of the bronchioloalveolar in female mice. In the inhalation study in rats, there was no statistically significant increase in tumour incidence in male and female rats. In male rats, however, there was a significant positive trend in the incidence of adenoma and adenoma or carcinoma (combined) of the bronchioloalveolar; the incidences were within historical control ranges. In the intraperitoneal injection study in mice, molybdenum trioxide increased the multiplicity (but not the incidence) of lung tumours (presumably adenomas) in male and female mice combined.

5.4 Mechanistic and other relevant data

No toxicokinetic studies of molybdenum trioxide in humans or in experimental animals were available.

With respect to the key characteristics of human carcinogens, there is *weak* evidence that molybdenum trioxide is genotoxic or induces chronic inflammation. No data were available in exposed humans. Data on other key characteristics of carcinogens were sparse.

No in vivo genotoxicity assay data were available. In vitro, molybdenum trioxide was positive in an assay for cell transformation but was not genotoxic in Chinese hamster ovary cells or in several *Salmonella* strains.

Molybdenum trioxide increased the incidence and severity of chronic lung inflammation in a 2-year inhalation study in both male and female rats, but not in mice. An analysis of the male rats from this bioassay showed increased incidence of lung fibrosis and metaplasia.

6. Evaluation

6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of molybdenum trioxide.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of molybdenum trioxide.

6.3 Overall evaluation

Molybdenum trioxide is *possibly carcinogenic to humans (Group 2B).*

References

Anh Tran T, Krishnamoorthy K, Song YW, Cho SK, Kim SJ (2014). Toxicity of nano molybdenum trioxide toward invasive breast cancer cells. *ACS Appl Mater Interfaces*, 6(4):2980–6. doi:10.1021/am405586d PMID:24417578

Anke M, Groppel B, Krause U, Arnhold W, Langer M (1991). Trace element intake (zinc, manganese, copper, molybdenum, iodine and nickel) of humans in Thuringia and Brandenburg of the Fed. Rep. of Germany. *J Trace Elem Electrolytes Health Dis*, 5(2):69–74. PMID:1821712

Anthony JW, Bideaux RA, Bladh KW, Nichols MC (2001–2005). Handbook of Mineralogy. Tucson (AZ), USA: Mineral data publishing. Online version, Mineralogical Society of America, Chantilly, VA. Available from: http://www.handbookofmineralogy.org/pdfs/molybdite.pdf, accessed 17 August 2016.

Barceloux DG, Barceloux D (1999). Molybdenum. *J Toxicol Clin Toxicol*, 37(2):231–7. doi:10.1081/CLT-100102422 PMID:10382558

Braydich-Stolle L, Hussain S, Schlager JJ, Hofmann MC (2005). In vitro cytotoxicity of nanoparticles in mammalian germline stem cells. *Toxicol Sci*, 88(2):412–9. doi:10.1093/toxsci/kfi256 PMID:16014736

Casey CE, Neville MC (1987). Studies in human lactation 3: molybdenum and nickel in human milk during the first month of lactation. *Am J Clin Nutr*, 45(5):921–6. doi:10.1093/ajcn/45.5.921 PMID:3578094

Chan PC, Herbert RA, Roycroft JH, Haseman JK, Grumbein SL, Miller RA et al. (1998). Lung tumor induction by inhalation exposure to molybdenum trioxide in rats and mice. *Toxicol Sci*, 45(1):58–65. doi:10.1093/toxsci/45.1.58 PMID:9848111

Christensen FM, Warming M, Kjølholt J, Lau Heckmann L-H, Nilsson NH (2015). Survey of molybdenum trioxide. Environmental project No. 1716. Copenhagen, Denmark: Danish Environmental Protection Agency; Available from: http://mst.dk/service/publikationer/publikationsarkiv/2015/jul/survey-of-molybdenum-trioxide/

CLIMAX (2016). Chemical safety report: molybdenum trioxide. Rotterdam, The Netherlands: Climax Molybdenum BV. Available from: http://www.molybdenumconsortium.org/assets/files/Uses/MoTriox-2ndUpdateFeb2016-IdentifiedUses.pdf, accessed 15 December 2016.

Danish Ministry of the Environment (2015). Survey of molybdenum trioxide. Environmental project No. 1716, 2015. Available from: http://mst.dk/service/publikationer/publikationsarkiv/2015/jul/survey-of-molybdenum-trioxide/

ECHA (2016a). Molybdenum trioxide. Helsinki, Finland: European Chemicals Agency. Available from: https://www.echa.europa.eu/en/web/guest/registration-dossier/-/registered-dossier/15499/1, accessed 11 October 2016, Registration dossier.

ECHA (2016b). Harmonised classification - Annex VI of Regulation (EC) No. 1272/2008 (CLP Regulation). Available from: https://www.echa.europa.eu/fr/web/guest/information-on-chemicals/cl-inventory-database/-/discli/details/68763

EFSA (2006). Tolerable upper intake levels for vitamins and minerals. Scientific Committee on Food, Scientific Panel on Dietetic Products, Nutrition and Allergies, European Food Safety Authority, February 2006. Available from: http://www.efsa.europa.eu/sites/default/files/efsa_rep/blobserver_assets/ndatolerableuil.pdf

EFSA (2013). Scientific opinion on dietary reference values for molybdenum. *EFSA J.*, 11(8):3333 doi:10.2903/j.efsa.2013.3333

EPA (2016). ChemView [online database]. Washington (DC), USA: United States Environmental Protection Agency, Office of Pollution Prevention and Toxics. Available from: https://chemview.epa.gov/chemview, accessed 8 March 2018.

Franson MA (1985). Standard methods for the examination of water and wastewater.p. 174. [cited 2016 October 10]. Available from: Available from https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@rn+@rel+1313-27-5

GESTIS (2017). GESTIS Substance Database. IFA (Institut fur Arbeitsschutz). Available from: http://limitvalue.ifa.dguv.de/, accessed 17 January 2017.

Gunshin H, Yoshikawa M, Doudou T, Kato N (1985). Trace elements in human milk, cow's milk, and infant formula. *Agric Biol Chem*, 49(1):21–6.

Health Canada (2011). Dietary intakes of contaminants & other chemicals for different age-sex groups of Canadians. Canadian Total Diet Study. Available from: http://www.hc-sc.gc.ca/fn-an/surveill/total-diet/intake-apport/index-eng.php accessed 23 October 2016.

HSDB (2017). Hazardous Substances Data Bank. [online database]. TOXNET toxicology data network. Bethesda

(MD), USA: United States National Library of Medicine. Available from: https://toxnet.nlm.nih.gov/

Huvinen M, Uitti J, Oksa P, Palmroos P, Laippala P (2002). Respiratory health effects of long-term exposure to different chromium species in stainless steel production. *Occup Med (Lond)*, 52(4):203–12. doi:10.1093/occmed/52.4.203 PMID:12091586

Institute of Medicine (2001). DRI. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc: a report of the panel on micronutrients and of interpretation and uses of dietary reference intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Washington (DC) USA: National Academy Press.

Jin B, Zhou X, Huang L, Lickleder M, Yang M, Schmuki P (2016). Aligned MoOx/MoS2 core-shell nanotubular structures with a high density of reactive sites based on self-ordered anodic molybdenum oxide nanotubes. *Angew Chem Int Ed Engl*, 55(40):12252–6. doi:10.1002/anie.201605551 PMID:27599478

Kerckaert GA, LeBoeuf RA, Isfort RJ (1996). Use of the Syrian hamster embryo cell transformation assay for determining the carcinogenic potential of heavy metal compounds. *Fundam Appl Toxicol*, 34(1):67–72. doi:10.1006/faat.1996.0176 PMID:8937893

Keyes WR, Turnlund JR (2002). Determination of molybdenum and enriched Mo stable isotope concentrations in human blood plasma by isotope dilution ICP-MS. *J Anal At Spectrom*, 17(9):1153–6. doi:10.1039/b202250h

Kucera J, Bencko V, Pápayová A, Saligová D, Tejral J, Borská L (2001). Monitoring of occupational exposure in manufacturing of stainless steel constructions. Part I: Chromium, iron, manganese, molybdenum, nickel and vanadium in the workplace air of stainless steel welders. *Cent Eur J Public Health*, 9(4):171–5. PMID:11787242

Lasheen TA, El-Ahmady ME, Hassib HB, Helal AS (2015). Molybdenum metallurgy review: Hydrometallurgical routes to recovery of molybdenum from ores and mineral raw materials. *Miner Process Extr Metall Rev*, 36(3):145–73. doi:10.1080/08827508.2013.868347

Lener J, Bíbr B (1984). Effects of molybdenum on the organism (a review). *J Hyg Epidemiol Microbiol Immunol*, 28(4):405–19. PMID:6396329

Lewis DF, Ioannides C, Parke DV (1996). COMPACT and molecular structure in toxicity assessment: a prospective evaluation of 30 chemicals currently being tested for rodent carcinogenicity by the NCI/NTP. *Environ Health Perspect*, 104:Suppl 5: 1011–6. doi:10.1289/ehp.96104s51011 PMID:8933049

Lewis RC, Meeker JD (2015). Biomarkers of exposure to molybdenum and other metals in relation to testosterone among men from the United States National Health and Nutrition Examination Survey 2011-2012. *Fertil Steril*, 103(1):172–8. doi:10.1016/j.fertnstert.2014.09.020 PMID:25439796

Lou SN, Ng YH, Ng C, Scott J, Amal R (2014). Harvesting, storing and utilising solar energy using MoO3: modulating structural distortion through pH adjustment. *ChemSusChem*, 7(7):1934–41. doi:10.1002/cssc.201400047 PMID:24811956

Mohd-Taufek N, Cartwright D, Davies M, Hewavitharana AK, Koorts P, Shaw PN et al. (2016). The simultaneous analysis of eight essential trace elements in human milk by ICP-MS. *Food Anal Methods*, 9(7):2068–75. doi:10.1007/s12161-015-0396-z

National Toxicology Program(1997). NTP toxicology and carcinogenesis studies of molybdenum trioxide (CAS No. 1313-27-5) in F344 rats and B6C3F1 mice (inhalation studies). *Natl Toxicol Program Tech Rep Ser*, 462:1–269. PMID:12587014

Novotny JA, Turnlund JR (2006). Molybdenum kinetics in men differ during molybdenum depletion and repletion. *J Nutr*, 136(4):953–7. doi:10.1093/jn/136.4.953 PMID:16549456

OECD (2009). The 2007 OECD List of High Production Volume Chemicals. ENV/JM/MONO40. OECD Environment, Health and Safety Publications Series on Testing and Assessment Number 112. Environment Directorate Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology. Paris: Organisation for Economic Co-operation and Development.

Ozaki K, Haseman JK, Hailey JR, Maronpot RR, Nyska A (2002). Association of adrenal pheochromocytoma and lung pathology in inhalation studies with particulate compounds in the male F344 rat–the National Toxicology Program experience. *Toxicol Pathol*, 30(2):263–70. doi:10.1080/019262302753559605 PMID:11950170

Polyak DE (2016). Molybdenum [advance release]. 2014 Minerals Yearbook. Washington (DC), USA: United States Geological Survey.

Runnells DD, Kaback DS, Thurman EM (1977). Geochemistry molybdenum 237 and sampling of molybdenum in sediments, soils, and plants in Colorado. In: Chappell WR, Peterson KK editors. Molybdenum in the environment. Volume 2. New York, USA: Elsevier Science Publishing Co.

Sebenik RF, Burkin AR, Dorfler RR, Laferty JM, Leichtfried G, Meyer-Grünow H et al. (2012). Molybdenum and molybdenum compounds. Ullmann's encyclopedia of industrial chemistry. Volume 23. Weinheim: Wiley-VCH.

Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I et al. (2016). Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environ Health Perspect*, 124(6):713–21. PMID:26600562

Steifel EI (2010). Molybdenum and molybdenum alloys. Kirk-Othmer encyclopedia of chemical technology. Hoboken (NY), USA: John Wiley & Sons.

Stiefel EI (2011). Molybdenum compounds. Kirk-Othmer encyclopedia of chemical technology. Hoboken (NY), USA: John Wiley & Sons.

Stoner GD, Shimkin MB, Troxell MC, Thompson TL, Terry LS (1976). Test for carcinogenicity of metallic compounds by the pulmonary tumor response in strain A mice. *Cancer Res*, 36(5):1744–7. PMID:1268831

Thompson KH, Turnlund JR (1996). Kinetic model of molybdenum metabolism developed from dual stable isotope excretion in men consuming a low molybdenum diet. *J Nutr*, 126(4):963–72. doi:10.1093/jn/126.4.963 PMID:8613900

Tsongas TA, Meglen RR, Walravens PA, Chappell WR (1980). Molybdenum in the diet: an estimate of average daily intake in the United States. *Am J Clin Nutr*, 33(5):1103–7. doi:10.1093/ajcn/33.5.1103 PMID:7369160

Turnlund JR, Keyes WR, Peiffer GL (1995). Molybdenum absorption, excretion, and retention studied with stable isotopes in young men at five intakes of dietary molybdenum. *Am J Clin Nutr*, 62(4):790–6. doi:10.1093/ajcn/62.4.790 PMID:7572711

Turnlund JR, Thompson KH, Scott KC (1998). Key features of copper versus molybdenum metabolism models in humans. *Adv Exp Med Biol*, 445:271–81. doi:10.1007/978-1-4899-1959-5_17 PMID:9781395

Turnlund JR, Weaver CM, Kim SK, Keyes WR, Gizaw Y, Thompson KH et al. (1999). Molybdenum absorption and utilization in humans from soy and kale intrinsically labeled with stable isotopes of molybdenum. *Am J Clin Nutr*, 69(6):1217–23. doi:10.1093/ajcn/69.6.1217 PMID:10357742

Walravens PA, Moure-Eraso R, Solomons CC, Chappell WR, Bentley G (1979). Biochemical abnormalities in workers exposed to molybdenum dust. *Arch Environ Health*, 34(5):302–8. doi:10.1080/00039896.1979.10667421 PMID:496425

Wang YX, Feng W, Zeng Q, Sun Y, Wang P, You L et al. (2016). Variability of metal levels in spot, first morning, and 24-hour urine samples over a 3-month period in healthy adult Chinese men. *Environ Health Perspect*, 124(4):468–76. PMID:26372665

Yoshida M, Takada A, Hirose J, Endô M, Fukuwatari T, Shibata K (2008). Molybdenum and chromium concentrations in breast milk from Japanese women. *Biosci Biotechnol Biochem*, 72(8):2247–50. doi:10.1271/bbb.80283 PMID:18685182

Zollfrank C, Gutbrod K, Wechsler P, Guggenbichler JP (2012). Antimicrobial activity of transition metal acid MoO(3) prevents microbial growth on material surfaces. *Mater Sci Eng C*, 32(1):47–54. doi:10.1016/j.msec.2011.09.010 PMID:23177771

INDIUM TIN OXIDE

1. Exposure Data

1.1 Identification

Chem. Abstr. Serv. Reg. No.: 50926-11-9

Chem. Abstr. Serv. Name: indium tin oxide

IUPAC systematic name: indium tin oxide

Other common names: ITO, tin indium oxide, tin doped indium oxide

Molecular formula: In_2O_3; SnO_2

Indium tin oxide (ITO) is a yellow-green solid mixture of indium oxide (In_2O_3, CAS No. 1312-43-2) and stannic (or tin) oxide (SnO_2, CAS No. 18-282-10-5) (Indium Corporation, 2014). The proportion of indium oxide is typically 90% (Hines et al., 2013), but can vary over the range 80–95% (NTP, 2009). As the physicochemical properties of ITO depend on the relative proportions of indium and tin oxides, they are presented below separately for both compounds. As an illustration, the properties for one commercial formula (exact proportion of In_2O_3 not available) are also provided.

Relative molecular mass: 277.64 (In_2O_3); 150.71 (SnO_2) (HSDB, 2017); 264.94 (commercial formula) (Indium Corporation, 2008)

Density: 7.179 g/cm^3 (In_2O_3); 6.95 g/cm^3 (SnO_2) (HSDB, 2017); 7.16 g/cm^3 (commercial formula) (Indium Corporation, 2008)

Melting point: volatilizes at 850 °C (In_2O_3) (Weast, 1970); 1630 °C (SnO_2) (HSDB, 2017); volatilizes at 1910 °C (commercial formula) (Indium Corporation, 2008)

Boiling point: volatilizes at 850 °C (In_2O_3) (Weast, 1970); sublimes at 1800–1900 °C (SnO_2) (HSDB, 2017); sublimes at 982 °C (commercial formula) (Indium Corporation, 2008)

Solubility in water: insoluble (In_2O_3; SnO_2; ITO) (HSDB, 2017)

One manufacturer reported that ITO particle size varies over the range 0.1–1.0 μm depending on grade, with agglomerates varying over the range 7–31 μm (Indium Corporation, 2014).

ITO may contain impurities in small quantities. In the commercial product line of one ITO fabricator, the total concentration of impurities (aluminium, antimony, bismuth, chromium, copper, iron, lead, magnesium, nickel, potassium, sodium, titanium, zinc) does not exceed 100 ppm (UMICORE, 2013).

1.2 Production and use

1.2.1 Production process

ITO can be sintered or unsintered, but typically the occupational exposure is to the sintered form. Sintering uses heat and pressure to combine indium oxide and tin oxide powders to

Table 1.1 Analytical methods for indium in different matrices

Sample matrix	Assay procedure	Limit of detection	Method/reference
Air	ICP-AES	0.015 µg/mL	NIOSH 7303
Plasma	ICP-MS	0.3 µg/L	Cummings et al. (2016)
Serum	ICP-MS	0.1 µg/L	Hamaguchi et al. (2008)
Urine	ICP-MS	0.02 µg/L	Hoet et al. (2012)

AES, atomic emission spectrometry; ICP, inductively coupled plasma; MS, mass spectrometry

form compressed disks called sputtering targets (Cummings et al., 2012a). The process introduces a high density of free electrons and oxygen vacancies in the indium oxide crystal structure, imparting the specific electronic properties of ITO (Lison et al., 2009).

1.2.2 Production volume

ITO production statistics are not publicly available. Indium metal world production was estimated at 755 tonnes for 2015, down from 844 tonnes in 2014 (USGS, 2016). Since ITO production accounts for most (> 70%) of the global indium consumption (NTP, 2009), ITO worldwide production can be estimated for 2015 at more than 529 tonnes. In descending order of importance, China, Republic of Korea, Japan, Canada, and France are the five main indium metal refiners (USGS, 2016).

1.2.3 Use

The main use of ITO is in producing transparent conductive films on glass or plastic panels used in electronic devices and other products, including touch panels, plasma displays, flat panel displays, solar panels, cathode-ray tubes, energy efficient windows, gas sensors, and photovoltaics (NTP, 2009). The sputtering targets (ITO disks or blocks) are bombarded with energetic ions which extract metallic atoms that are deposited as thin films on the desired substrate (Lippens & Muehlfeld, 2012).

1.3 Measurement and analysis

1.3.1 Detection and quantification

Current analytical methods only allow for the quantification of total elemental indium, and cannot quantify ITO. Exposure to humans may occur via inhalation or dermal exposure, and indium is minimally absorbed after ingestion. Inhalation is the primary route for occupational exposures.

Air sampling to determine indium can be performed using the United States National Institute for Occupational Safety and Health (NIOSH) Method 7303 for elements by inductively coupled plasma (ICP). Indium can also be determined in serum, plasma, or urine samples (Table 1.1) by ICP mass spectrometry.

1.3.2 Biological markers

Indium levels in plasma and serum samples are highly correlated (Harvey et al., 2016). Indium air concentrations and biological levels (in urine and plasma) of workers at an indium ingot production plant showed no correlation however (Hoet et al., 2012), but the number of subjects was small (9 current and 5 former workers, and 20 controls). A study in an ITO production facility reported that plasma indium had a stronger relationship with cumulative (r = 0.77) than current exposure (r = 0.54) (based on personal sampling of respirable indium). This finding was driven by workers with a longer tenure (≥ 1.9 years) (Cummings et al., 2016). Hoet et al. (2012) found that neither plasma nor urine levels increased

significantly during the day (before vs after shift) or during the week. Biological levels in former workers (3.5–14 years since last exposure) were still higher than in unexposed controls (Hoet et al., 2012). Nakano et al. (2009) also reported that former indium-exposed workers (2–200 months since last exposure) had similar serum indium levels to currently exposed workers and significantly higher levels than unexposed workers (Nakano et al., 2009). Biological levels of indium therefore appear to better reflect chronic exposures rather than recent, due to accumulation in the body.

1.4 Occurrence and exposure

1.4.1 Environmental occurrence

ITO does not occur naturally; however, elemental indium is present naturally as a small percentage (estimated range, 50–250 ppb) in the Earth's crust. Indium is produced mainly from zinc ore processing, but is also found in small amounts in iron, lead, and copper ores (Alfantazi & Moskalyk, 2003; Enghag, 2007). Elemental indium has been characterized in seawater at 0.2–0.7 ppb, in air at 43 ng/m^3, and in rainwater at 0.59 µg/L (IARC, 2006; Enghag, 2007; Schwarz-Schampera, 2014).

1.4.2 Exposure to the general population

The average daily human intake of indium has been estimated as 8–10 µg/day from dietary sources, which is considered a minimal dietary exposure (Scansetti, 1992).

1.4.3 Occupational exposure

Exposure to ITO primarily occurs in occupational settings where ITO is produced or processed, or where elemental indium is recycled and recovered from ITO; these exposures are summarized in Table 1.2.

No data are available to estimate the number of workers exposed to ITO.

During 2009–2011, NIOSH contacted indium-using companies in the USA to characterize where and how indium is used. ITO was reported to be used primarily as a transparent conductive oxide on polymer substrates, or in the manufacture of sputter targets or photovoltaic cells (Hines et al., 2013). At a company that sputters indium-containing thin films onto polymer, NIOSH task-based sampling data (2010) were combined with company sampling data (2004); air indium concentration varied over the range 0.018–9.8 mg/m^3 by job task and ventilation controls. Combining task-based NIOSH and company sampling data at two photovoltaic companies, indium in air varied over the range 0.072–5.4 mg/m^3 by job task and reported exposure controls (Hines et al., 2013).

ITO became an occupational exposure of interest in the early 2000s, when several case reports related to indium exposure appeared in the literature. In a series of three case reports from Japan, three workers involved in wet-surface grinding of ITO all presented with interstitial pulmonary disease and serum indium concentrations of 40, 99, and 127 µg/L (Taguchi & Chonan, 2006). At another ITO processing facility in Japan, a worker with a serum indium concentration of 290 µg/L died from pulmonary fibrosis (Homma et al. 2003). These serum indium measurements were at the upper end of the exposure distribution reported in other workplaces for multiple workers (Tanaka et al., 2010a; Omae et al., 2011).

Several studies have used biological monitoring to assess indium exposures in workplaces using ITO (see Table 1.2). Liu et al. (2012) measured serum in exposed workers at four ITO manufacturing plants in Taiwan, China, and unexposed administrative controls at the same plants. The exposed workers had a geometric mean serum indium concentration of 1.26 µg/L (maximum 18.4 µg/L), whereas the geometric

Table 1.2 Measurement of indium in facilities producing or processing indium tin oxide

Reference	Location, collection date	Occupation	Sampling matrix; *n* (duration)	Exposure level	Exposure range	Comments
Homma et al. (2003)	Japan, 2000	ITO processing	Serum; *n* = 1	290 µg/L		Case report of ITO worker who presented for pulmonary dysfunction
Homma et al. (2005)	Japan, 2002	Transparent conductive film manufacturing	Serum; *n* = 1	51 µg/L		Case report of ITO worker who presented for pulmonary dysfunction
Taguchi and Chonan (2006)	Japan, NR	ITO manufacturing plant	Serum; *n* = 3	40, 127, and 99 µg/L		Three case reports of interstitial pneumonia, reported by Tanaka et al. (2010a); originally reported by Taguchi and Chonan (2006)
Cummings et al. (2010)	USA, 2005	ITO-producing facility	Lung; *n* = 1	29.3 µg/g lung tissue	NR	Case report of ITO worker who presented for pulmonary dysfunction
Liu et al. (2012)	Taiwan, China NR	ITO manufacturing plants	Serum; *n* = 170	1.26 µg/L (geometric mean)	Maximum, 18.4 µg/L	
		Administrative controls at same ITO plant as exposed	Serum; *n* = 132	0.72 µg/L (geometric mean)	NR	
Chonan et al. (2007)	Japan, 2002	ITO manufacturing plant, formerly exposed	Serum; *n* = 27	8.3 µg/L (geometric mean)	NR	
		ITO manufacturing plant, currently exposed	Serum; *n* = 78	7.8 µg/L (geometric mean)	NR	
		Administrative controls at same ITO plant as exposed	Serum; *n* = 38	0.3 µg/L (geometric mean)	NR	
		ITO manufacturing plant	Total dust; *n* = 8 locations (≥ 10 min)	10–50 µg/m^3 (geometric mean)	Maximum, 360 µg/m^3	Range of geometric means found at the eight stationary locations (it is unclear how many samples were taken at each location); sampling occurred for at least 10 min using a low-volume sampling pump

Table 1.2 (continued)

Reference	Location, collection date	Occupation	Sampling matrix; *n* (duration)	Exposure level	Exposure range	Comments
Hamaguchi et al. (2008)	Japan, 2003–2004	ITO manufacturing or recycling plants	Serum; *n* = 93	8.25 µg/L (geometric mean)	< 0.1–116.9 µg/L	
		Administrative controls	Serum; *n* = 93	0.25 µg/L (geometric mean)	< 0.1–1.3 µg/L	
Nakano et al. (2009)		ITO factories and research laboratory, currently exposed	Serum; *n* = 465	8.35 µg/L (arithmetic mean)	< 0.1–116.9 µg/L	Includes data from Chonan et al. (2007) and Hamaguchi et al. (2008)
		ITO factories and research laboratory, formerly exposed	Serum; *n* = 127	9.63 µg/L (arithmetic mean)	< 0.1–126.8 µg/L	
		Administrative controls at same ITO factories as exposed	Serum; *n* = 169	0.56 µg/L (arithmetic mean)	< 0.1–3.0 µg/L	
Cummings et al. (2012a)	USA, 2002–2010	ITO production	Blood; *n* = 42	3.8 µg/L (median)	< 5–63 µg/L	*n* = 21 subjects had a blood In concentration above the LOD; median blood In concentration was 12 µg/L with a range of 5.1–63 µg/L
			Total dust; *n* = 11 (full shift)	NR	9–136 µg/m^3	Total dust area samples taken at four locations in the plant: In_2O_3 production area, ITO tile-making area, grinding area, and reclaim area using open-faced 37 mm cassettes Respirable In of 2–42 µg/m^3 measured at the same locations using cyclones with 37 mm cassettes
Harvey et al. (2016)	USA, 2014	ITO production facility	Plasma; *n* = 50	3.48 µg/L (arithmetic mean)	NR	
			Serum; *n* = 50	3.90 µg/L (arithmetic mean)	NR	
			Blood; *n* = 50	4.66 µg/L (arithmetic mean)	NR	

Table 1.2 (continued)

Reference	Location, collection date	Occupation	Sampling matrix; *n* (duration)	Exposure level	Exposure range	Comments
Nogami et al. (2008)	Japan, NR	In recycling facility	Serum; *n* = 40	2.23 µg/L (arithmetic mean)	NR	Research conducted by Nogami et al. (2008), published in Japanese; reported by Omae et al. (2011)
Cummings et al. (2016)	USA, 2012	ITO facility workers	Respirable air; personal; *n* = 110 (full shift)	NR	0.4–108.4 µg/m^3	Respirable samples collected using the GK2.69 cyclone
Choi et al. (2013)	Republic of Korea, 2012	ITO manufacturing and reclaiming factories	Serum; *n* = 34	10.9 µg/L (geometric mean)	< LOD–125.8 µg/L	
Iwasawa et al. (2017)	Japan, 2013–2014	ITO processing plant	Respirable air; personal; NR (251–483 min)	NR	0.004–24.0 µg/m^3	Samples standardized to 8 h TWA; respirable sample collected using GS-3 respirable dust cyclone or TR sampler (PM4 NWPS-254)
			Serum; *n* = 64 (251–483 min)	NR	< 0.1–8.5 µg/L	
Hoet et al. (2012)	Belgium, NR	In ingot production plant	Inhalable air; personal; NR	175 µg/m^3 (arithmetic mean)	10–1030 µg/m^3	Plant where workers are mainly exposed to In_2O_3 but also to $In(OH)_3$, In metal, and $InCl_3$; personal air samples collected using IOM samplers for inhalable fraction

Table 1.2 (continued)

Reference	Location, collection date	Occupation	Sampling matrix; *n* (duration)	Exposure level	Exposure range	Comments
Liu et al. (2016)	Japan, 2010–2012	ITO sputter target manufacturing plant	Respirable air; personal; $n = 54$ (average 365 min)	NR	2–3 μg/m^3	Personal respirable samples collected using a cyclone; geometric means presented for the respirable samples by year
			Total dust; personal; $n = 40$ (average 365 min)	NR	21–34 μg/m^3	Personal total dust samples collected using a closed-face sampling cassette; geometric means presented for the total dust samples by year
			Outside PAPR; personal; $n = 15$ (average 85 min)	53 μg/m^3 (arithmetic mean)	24–105 μg/m^3	15 samples were collected inside and outside a PAPR simultaneously
			Inside PAPR; personal; $n = 15$ (average 85 min)	3 μg/m^3 (arithmetic mean)	2–8 μg/m^3	

In, indium; $InCl_3$, indium chloride; In_2O_3, indium oxide; $In(OH)_3$, indium hydroxide; IOM, Institute of Occupational Medicine; ITO, indium tin oxide; LOD, limit of detection; NR, not reported; PAPR, powered air-purifying respirator; TWA, time-weighted average

mean for the unexposed workers was 0.72 µg/L (Liu et al., 2012). Exposed workers at an ITO manufacturing plant in Japan had a geometric mean serum indium concentration of 7.8 µg/L, while unexposed administrative controls from the same plant had a geometric mean serum indium concentration of 0.3 µg/L (Chonan et al., 2007). Another study from Japan compared serum indium in currently exposed, formerly exposed, and unexposed workers at ITO factories and a research laboratory using ITO. Those currently exposed had a mean serum indium concentration of 8.35 µg/L (range, < limit of detection (LOD) to 116.9 µg/L), those formerly exposed had a mean serum indium concentration of 9.63 µg/L (range, < LOD–126.8 µg/L), and those unexposed to ITO had a mean serum indium concentration of 0.56 µg/L (range, < LOD–3.0 µg/L) (Nakano et al., 2009).

Despite these studies measuring serum indium (or, less commonly, blood or plasma) in workplaces using ITO, and studies measuring airborne indium exposures in workplaces using ITO, few studies have compared biological markers of indium exposure with indium exposure in workplace air. Cummings et al. (2016) compared respirable and cumulative airborne exposure to indium with plasma indium concentration in 87 ITO facility workers. Table 1.3 summarizes personal respirable indium air samples by department in the ITO facility; all samples taken were personal samples with the exception of one area sample. Personal respirable indium (110 samples from 49 workers) measured over a full work shift varied over the range 0.4–796.6 µg/m^3; the highest exposure levels were for workers in the reclaim area, followed by those in the ITO department, grinders, and in research and development. The background level in the administrative department was 0.4 µg/m^3. Cumulative exposures to indium ranged from 0.4 to 923 µg-year/m^3, based on individual job tasks and time in each job. Median plasma for the 87 workers was reported as 1 µg/L. The respirable concentrations of indium reported by Cummings et al. (2016) were comparable to previous reports of indium in air (in total dust, and inhalable and respirable fractions) in occupational settings using ITO (Chonan et al., 2007; Cummings et al., 2012a, 2016).

Liu et al. (2016) measured indium in air both inside and outside of powered air-purifying respirators (PAPRs) on 15 ITO sputter target manufacturing workers and found that the use of a PAPR reduced exposures to indium by an average of 93.4%. These workers also showed a decrease in geometric mean serum indium and urine indium 10 months after implementation of PAPRs in the workplace, with geometric mean serum decreasing from 5.28 to 4.05 µg/L, and geometric mean urine indium decreasing from 0.81 to 0.74 µg/g creatinine (Liu et al. 2016).

1.5 Regulations and guidelines

No specific limit values for occupational exposure to ITO exist. Almost 20 countries do have 8-hour time-weighted average (TWA) limit values for exposure to indium and compounds (as In) which are set across the board at 0.1 mg/m^3. Corresponding short-term limit values do exist in a few countries and range from 0.2 to 0.3 mg/m^3 (GESTIS, 2017). The Japan Society for Occupational Health (JSOH) recommended an occupational exposure limit based on the biological monitoring of indium in serum of 3 µg/L in 2007 (Iwasawa et al., 2017).

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

See Table 3.1

Table 1.3 Personal respirable indium exposure levels by department at a facility producing indium tin oxide

Department	*n*	Mean indium exposure (μg/m³)	Range of indium exposure (μg/m³)
ITO	25	81.9	9.9–518.3
Planar bond	5	9.1	3.2–17.6
Planar grind	8	27.2	4.6–148.4
Reclaim	12	108.4	4.8–796.6
Refinery	6	26.3	10.9–40.9
Rotary bond	9	3.7	0.7–6.4
Rotary grind	4	39.4	20.9–59.3
Engineering	9	4.9	1.7–23.2
Maintenance and facilities	8	8.6	2.2–16.0
Forming	8	5.7	1.3–12.4
Quality control laboratory	6	3.5	1.9–5.4
Research and development	8	35.5	2.1–111.1
Shipping and receiving	2	1.9	1.7–2.1
Administrative (area sample)	1	0.4	NR

ITO, indium tin oxide; NR, not reported
Adapted from: Cummings et al. (2016), with permission of John Wiley & Sons

3.1 Mouse

3.1.1 Inhalation

In the study by Nagano et al. (2011a), groups of 50 male and 50 female B6C3F$_1$/Crlj mice (age, 6 weeks) were exposed to sintered ITO (90.06% In_2O_3 + 9.74% SnO_2, median aerodynamic particle diameter of 1.8–2.4 μm) or clean air via whole-body inhalation (6 hours per day, 5 days per week) under good laboratory practice (GLP) conditions. Mice were killed after 104 weeks of exposure. The ITO exposure concentrations were 0 (air control), 0.01, 0.03, or 0.1 mg/m³. In females, there was a significant positive trend in the incidence of adenoma of the lung and of adenoma or carcinoma (combined) of the lung at week 104 after exposure to ITO. The incidences of bronchioloalveolar adenoma in female mice were 1/50, 0/50, 2/50, and 4/47, and the incidences of bronchioloalveolar adenoma or carcinoma (combined) were 3/50, 0/50, 3/50, and 7/47 at the 0, 0.01, 0.03, and 0.1 mg/m³ ITO exposure concentrations, respectively. There was no significant increase in the incidence of bronchiolo-alveolar carcinoma in female mice or in the incidence of any type of lung tumours in male mice after ITO exposure. [The Working Group noted that study strengths were the 2-year GLP bioassay for chronic toxicity, use of a physiologically relevant exposure route, testing of sintered ITO at a 90:10 (In_2O_3:SnO_2) ratio, and use of both sexes.]

3.2 Rat

3.2.1 Inhalation

In the study by Nagano et al. (2011a), groups of 50 male and 50 female F344 rats/DuCrlCrlj (age, 6 weeks) were exposed to sintered ITO (90.06% In_2O_3 + 9.74% SnO_2, median aerodynamic particle diameter of 1.8–2.4 μm) or clean air via whole-body inhalation (6 hours per day, 5 days per week) under GLP conditions. Rats were killed after 104 weeks of exposure. The ITO exposure concentrations were 0 (air control), 0.01, 0.03, or 0.1 mg/m³. For the highest tested

Table 3.1 Studies of carcinogenicity with indium tin oxide in experimental animals

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of lung tumours	Significance	Comments
Full carcinogenicity Mouse, B6C3F$_1$ (M) 6 wk 104 wk Nagano et al. (2011a)	Inhalation (whole-body exposure) ITO, 99.8% Clean air 0, 0.01, 0.03, 0.1 mg/m^3 6 h/d, 5 d/wk 50, 50, 50, 50 31, 33, 28, 30	Bronchioloalveolar adenoma 5/50, 4/50, 5/50, 5/50 Bronchioloalveolar carcinoma 7/50, 1/50, 4/50, 5/50 Combined all lung tumours 12/50, 5/50, 9/50, 10/50	 NS NS NS	Principal strengths: full 2-year GLP long-term study; physiological exposure route (inhalation); used sintered ITO at a 90:10 (In_2O_3:SnO_2) ratio; used both sexes All lung tumours were bronchioloalveolar adenomas or carcinomas
Full carcinogenicity Mouse, B6C3F$_1$ (F) 6 wk 104 wk Nagano et al. (2011a)	Inhalation (whole-body exposure) ITO, 99.8% Clean air 0, 0.01, 0.03, 0.1 mg/m^3 6 h/d, 5 d/wk 50, 50, 50, 50 38, 32, 34, 34	Bronchioloalveolar adenoma 1/50*, 0/50, 2/50, 4/47 Bronchioloalveolar carcinoma 2/50, 0/50, 1/50, 3/47 Combined all lung tumours 3/50**, 0/50, 3/50, 7/47	 Trend test, *P < 0.05 (Peto test) NS Trend test, **P < 0.01 (Peto test)	
Full carcinogenicity Rat, F344 (M) 6 wk 104 wk Nagano et al. (2011a)	Inhalation (whole-body exposure) ITO, 99.8% Clean air 0, 0.01, 0.03, 0.1 mg/m^3 6 h/d, 5 d/wk for 26 wk (0.1 mg/m^3) or 104 wk 50, 50, 50, 50 39, 38, 41, 40	Bronchioloalveolar adenoma 3/49*, 5/50, 10/50*, 12/50* Bronchioloalveolar carcinoma 0/49*, 4/50, 5/50*, 5/50*	 Trend test, *P < 0.05 (Peto test) Pairwise, *P < 0.05 (Fisher test) Trend test, *P < 0.05 (Peto test) Pairwise, *P < 0.05 (Fisher test)	Principal strengths: full 2-year GLP long-term study; physiological exposure route (inhalation); used sintered ITO at a 90:10 (In_2O_3:SnO_2) ratio; used both sexes Historical control incidence of adenosquamous carcinoma at the laboratory, 0/2399

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of lung tumours	Significance	Comments
Nagano et al. (2011a) (cont.)		Adenosquamous carcinoma 0/49, 1/50, 0/50, 0/50 Combined malignant lung tumours 0/49*, 5/50*, 5/50*, 5/50* Combined all lung tumours 3/49**, 10/50*, 15/50**, 16/50**	NS Trend test, *$P < 0.05$ (Peto test) Pairwise, *$P < 0.05$ (Fisher test) Trend test, **$P < 0.01$ (Peto test) Pairwise, **$P < 0.01$ (Fisher test)	
Full carcinogenicity Rat, F344 (F) 6 wk 104 wk Nagano et al. (2011a)	Inhalation (whole-body exposure) ITO, 99.8% Clean air 0, 0.01, 0.03, 0.1 mg/m^3 6 h/d, 5 d/wk for 26 wk (0.1 mg/m^3) or 104 wk 50, 50, 50, 50 41, 42, 41, 43	Bronchioloalveolar adenoma 1/50, 5/49, 6/50, 7/49* Bronchioloalveolar carcinoma 0/50**, 1/49, 9/50**, 5/49* Adenosquamous carcinoma 0/50, 1/49, 0/50, 0/49 Squamous cell carcinoma 0/50, 1/49, 0/50, 1/49 Combined malignant lung tumours 0/50**, 3/49, 9/50**, 6/49*	Trend test, *$P < 0.05$ (Peto test) Pairwise, *$P < 0.05$ (Fisher test) Trend test, *$P < 0.05$ and **$P < 0.01$ (Peto test) Pairwise, *$P < 0.05$ and **$P < 0.01$ (Fisher test) NS NS Trend test, *$P < 0.05$ and **$P < 0.01$ (Peto test) Pairwise, *$P < 0.05$ and **$P < 0.01$ (Fisher test)	Principal strengths: full 2-year GLP chronic study; physiological exposure route (inhalation); used sintered ITO at a 90:10 (In_2O_3:SnO_2) ratio; used both sexes Historical control incidence of: adenosquamous carcinoma at the laboratory, 1/2197; and squamous cell carcinoma at the laboratory, 0/2197

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of lung tumours	Significance	Comments
Nagano et al. (2011a) (cont.)		Combined all lung tumours 1/50**, 8/49*, 14/50**, 13/49**	Trend test, $^{**}P < 0.01$ (Peto test) Pairwise, $^{**}P < 0.01$ (Fisher test)	
Full carcinogenicity Hamster, Syrian golden (M) 8 wk Up to 86 wk Tanaka et al. (2010b)	Intratracheal instillation ITO, 74.4% In and 7.8% Sn by weight Distilled water 0, 0, 6, 6 mg/kg bw 2×/wk for 8 wk 7–8, 6–8, 8, 7–8 7, 6, 8, 7	Bronchioloalveolar adenoma 0/7 (wk 48), 0/6 (wk 86), 1/8 (wk 48), 2/7 (wk 86)	NS	Principal limitations: only one sex; small number of animals per group; NR if ITO 90:10 (In_2O_3:SnO_2); NR if ITO sintered; non-physiological exposure route

bw, body weight; d, day; F, female; In, indium; GLP, good laboratory practice; ITO, indium tin oxide; M, male; NR, not reported; NS, not significant; Sn, tin; wk, week(s)

concentration (0.1 mg/m^3), rats were exposed to ITO for 26 weeks followed by air for the remaining 78 weeks. At week 104, the incidences of preneoplastic lesions (bronchioloalveolar hyperplasia) were significantly increased in male and female exposed rats. The incidences of bronchioloalveolar adenoma in male rats were 3/49, 5/50, 10/50, and 12/50, and in female rats 1/50, 5/49, 6/50, and 7/49 at the 0, 0.01, 0.03, and 0.1 mg/m^3 ITO exposure concentrations, respectively. The increases in the incidence of bronchioloalveolar adenoma with ITO at 0.03 and 0.1 mg/m^3 were significant in male rats (with a significant positive trend) and significant at 0.1 mg/m^3 ITO in female rats. The incidences of bronchioloalveolar carcinoma in male rats were 0/49, 4/50, 5/50, and 5/50, and in female rats 0/50, 1/49, 9/50, and 5/49 at the 0, 0.01, 0.03, and 0.1 mg/m^3 ITO exposure concentrations, respectively. Bronchioloalveolar carcinomas of the observed in exposed rats were often accompanied by proliferative fibrous connective tissue, not commonly seen in spontaneous bronchioloalveolar carcinomas observed in control F344 rats. The increases in the incidences of bronchioloalveolar carcinoma were significant in male and female rats at ITO concentrations of 0.03 and 0.1 mg/m^3, respectively, with a significant positive trend. In one male and one female rat given ITO at a concentration of 0.01 mg/m^3, there was an adenosquamous carcinoma of the lung. At ITO doses of 0.01 and 0.1 mg/m^3, there was a squamous cell carcinoma of the lung in one female rat. There was a significant increase in the incidence of combined malignant lung tumours (with a significant positive trend) for all groups of exposed male rats (0/49, 5/50, 5/50, and 5/50 at the 0, 0.01, 0.03, and 0.1 mg/m^3 ITO exposure concentrations, respectively) and for the 0.03 mg/m^3 and 0.1 mg/m^3 groups of ITO-exposed female rats. There was a significant increase in the incidence of combined (all) lung tumours (with a significant positive trend) for all groups of exposed male and female rats. [The Working Group noted that male and female rats exposed only for 26 weeks to the high dose had a significant increase in the incidence of bronchioloalveolar carcinoma. In addition, males at the lowest dose had a significant increase in the incidence of combined malignant lung tumours. Study strengths were noted as: the 2-year GLP chronic bioassay, use of a physiologically relevant exposure route, testing of sintered ITO at a 90:10 (In_2O_3:SnO_2) ratio, and use of both sexes.]

3.3 Hamster

3.3.1 Intratracheal instillation

In a study conducted by Tanaka et al. (2010b), male Syrian golden hamsters (age, 8 weeks) were exposed to ITO (74.4% indium and 7.8% tin by weight; mean particle diameter, 0.95 ± 2.42 μm) or indium oxide (In_2O_3 > 99.99%; mean particle diameter, 0.14 μm), or exposed as vehicle controls (sterile distilled water; n = 40) via intratracheal instillation twice per week for 8 weeks. The initial ITO treatment groups (3 mg/kg body weight (bw), n = 40; or 6 mg/kg bw, n = 40) and indium oxide treatment groups (2.7 mg/kg bw, n = 23; or 5.4 mg/kg bw, n = 23) were selected so that equimolar indium was given for each (4.5 mg/kg bw indium for the highest exposure level, 2.2 mg/kg bw indium for the lowest). Groups of 6–8 vehicle control, indium oxide, and ITO-exposed hamsters were killed at 48 or 86 weeks. Body weights were decreased in the ITO treatment group at 6 mg/kg bw (vs controls). Relative lung weights were increased for all exposed groups (vs controls). Severe inflammation (including infiltration of alveolar macrophages and neutrophils) and bronchioloalveolar cell hyperplasia were observed at week 86 for both ITO exposure levels. For the 6 mg/kg bw ITO and both indium oxide groups, there were low incidences of localized alveolar or bronchiolar cell proliferating lesions. Bronchioloalveolar adenomas were observed in the 6 mg/kg bw ITO-exposed groups at 48 weeks (1/8) and 86

weeks (2/7); the combined incidence (3/15) was low and not statistically significant. No bronchioloalveolar adenomas were observed in 48-week and 86-week vehicle controls (0/7 and 0/6, respectively) or in hamsters exposed to indium oxide (0/8 and 0/8 in the 48-week groups; week 86 was not assessed). [The Working Group noted that this 'chronic' study actually involved subchronic exposure only with an extended observation phase. All deaths due to cannibalization or emaciation were excluded from the evaluation. Limitations were noted as: use of a non-physiological 'bolus' exposure route, testing of only one sex, lack of information regarding whether the ITO was sintered and at a 90:10 (In_2O_3:SnO_2) ratio (most relevant to occupational exposures), the low number of animals per group for tumour evaluation, and the combination of groups from different time points for the purpose of statistical analyses. The Working Group concluded this was an uninformative study.]

4. Mechanistic and Other Relevant Data

4.1 Toxicokinetic data

Data on metabolism and excretion of ITO are sparse. Elemental indium (In) has been measured in exposed humans and in experimental systems, and a few rodent studies have shown that inhaled or intratracheally instilled ITO is slowly dissolved, systemically available, widely distributed, and slowly eliminated over a period of years. The distribution of indium to tissues suggests indium dissolution from ITO particles. The precise form of indium in tissues was not reported in any of the studies, and the excretion of indium was not well characterized.

4.1.1 Humans

In a cross-sectional study, 93 workers from 2 ITO manufacturing plants and 2 ITO recycling plants where ITO (> 50%) was the major indium species in the dust had an overall serum indium geometric mean concentration of 8.25 µg/L (maximum, 116.9 µg/L) compared with 0.25 µg/L in 93 unexposed workers (Hamaguchi et al., 2008). [The Working Group noted possible confounding by exposure to other indium compounds in dusts, including indium oxide (approximately 40%) and indium (approximately 10%).]

In 170 workers from 2 ITO-producing plants in Taiwan, China, the mean indium serum concentration (1.26 µg/L) was significantly higher than that in 132 administrators who served as controls (Liu et al., 2012). [The Working Group noted that it was not specified whether those workers who showed serum concentrations above 3 µg/L, the occupational exposure limit set by JSOH, were in the exposed group.]

Several case reports of workers at the same Japanese worksite provided data on serum indium concentrations. The indium serum concentration of a 27-year-old Japanese man engaged in wet-surface polishing of ITO targets, 3 years after stopping work at the facility and 1 year before his death, was 290 µg/L compared with a mean of 0.1 µg/L reported for 377 healthy workers (Homma et al., 2003). A 30-year-old man exposed to ITO aerosols who was diagnosed with pulmonary fibrosis, most likely due to ITO exposure [as reported in the study], had a serum indium concentration of 51 µg/L (compared with a normal value of < 0.1 µg/L) (Homma et al., 2005). Another 3 additional workers (out of 115 ITO workers) had high serum indium concentrations (40, 127, and 99 µg/L) (Taguchi & Chonan, 2006; Omae et al., 2011). In another report of 108 men at the same Japanese worksite, the range of serum indium concentrations was observed to increase with increasing number of years of exposure (Chonan et al., 2007).

4.1.2 Experimental systems

Several inhalation studies have analysed ITO deposition and biodistribution in rodents. In male Sprague-Dawley rats exposed to ITO particles (average size, < 50 nm) via nose-only inhalation for 4 weeks (~1 mg/m^3 of indium by mass concentration), indium was mainly deposited in the lungs, eliminated slowly, and distributed, in descending order of concentration, to the spleen, liver, and brain (Lim et al., 2014). Indium also distributed to the blood and serum. [The Working Group noted that measurements of indium were only reported for lungs; for other tissues, precise concentrations of indium were not reported.] In male and female F344 rats exposed to ITO aerosols for 6 hours per day, 5 days per week for 2 weeks (0, 0.1, 1, 10, or 100 mg/m^3) and 13 weeks (0, 0.1, or 1 mg/m^3), ITO particles deposited in the lung and, to a lesser extent, in the bronchus-associated lymphoid tissue, mediastinal lymph nodes, and nasal-associated lymphoid tissue (Nagano et al., 2011b). All ITO doses had a mass concentration of indium of 75–80%. [The Working Group noted that the number of mice with particles, but not concentrations of the particles, was reported.] Indium contents in blood and lung were elevated in a dose-dependent manner in both the 2-week and 13-week studies. The group exposed to 0.1 mg/m^3 over 13 weeks were then exposed to clean air for 26 weeks; indium contents in the lung were found to be reduced by 60% and blood contents were elevated approximately 1.3-fold compared with concentrations at 13 weeks of exposure (Nagano et al., 2011b).

In male Sprague-Dawley (Hla:(SD) CVF) rats, particles from both indium oxide and sintered ITO (SITO) induced time-dependent increases in plasma indium concentrations, with SITO particles causing a much greater increase (85.3 µg/L) compared with indium oxide (< 2.0 µg/L) (Badding et al., 2016). Plasma indium from ventilation dust installations peaked after 1 week of exposure, inducing concentrations (93.5 µg/L) similar to those of SITO at 90 days of exposure. The rats were given intratracheal instillations of 3 different particle samples (In_2O_3 and SITO at doses of 1 and 5 mg per rat, and ventilation dust at doses of 0.5 and 1.0 mg per rat) collected at various production stages throughout an ITO facility for 90 days (Badding et al., 2016).

In F344/DuCrlCrlj rats and B6C3F$_1$/Crlj mice of both sexes, ITO particles were deposited mainly in the lung [half-life not calculated] and, to a lesser extent, in the mediastinal lymph node, nasal-associated lymphoid tissue, and bronchus-associated lymphoid tissue (Nagano et al., 2011c). Rats (0, 0.01, or 0.03 mg/m^3 ITO) and mice (0, 0.01, 0.03, or 0.1 mg/m^3) were exposed by aerosol for 6 hours per day, 5 days per week, for 104 weeks. Male and female rats were also exposed to 0.1 mg/m^3 ITO for 26 weeks followed by exposure to clean air for 78 weeks. In the rats exposed to 0.1 mg/m^3, indium was also detected in the spleen, kidney, liver, bone marrow, ovary, pancreas, testis, epididymis, and blood. Blood contents of indium in rats exposed to 0.01 and 0.03 mg/m^3 ITO increased in a dose-dependent manner. In mice, indium was only detected in those given the 0.1 mg/m^3 dose (both sexes) and in females given the 0.03 mg/m^3 dose. In general, blood indium content was higher in female mice than in males (Nagano et al., 2011c).

In male and female B6C3F$_1$ mice exposed to ITO aerosols for 6 hours per day, 5 days per week for 2 weeks (0, 0.1, 1, 10, or 100 mg/m^3) or 13 weeks (0, 0.1, or 1.0 mg/m^3), indium was deposited in the lungs and, to a lesser extent, the mediastinal lymph nodes (Nagano et al., 2011a). Mean indium contents in the lungs of groups exposed to doses of 0.1 and 1 mg/m^3 (13-week exposure) were 11.5 and 77.4 µg/g for male mice and 7.8 and 74.9 µg/g for female mice, respectively. Pooled blood contents of indium (1 mg/m^3 group) were 0.58 and 0.90 µg/L for male and female mice, respectively (Nagano et al., 2011a).

In male Syrian golden hamsters, indium concentrations gradually increased from the end

of exposure at 8 weeks to 78 weeks after intratracheal instillations of 3 or 6 mg/kg of ITO particles containing indium at 2.2 or 4.5 mg/kg twice per week for 8 weeks (Tanaka et al., 2010b, 2015). Concentrations reached 0.237 and 0.436 μg/L in the serum, 8.37 and 14.42 μg/L in the liver, 9.362 and 17.773 μg/L in the kidney, and 2.91 and 5.682 μg/L in the spleen at the end of the observation period, for the groups at 3 and 6 mg/kg, respectively. Indium content in the lungs slowly decreased, with elimination half-lives of approximately 142 and 124 weeks for the 3 and 6 mg/kg doses, respectively (Tanaka et al., 2010b, 2015).

4.2 Mechanisms of carcinogenesis

The sections that follow summarize the evidence for the "key characteristics" of carcinogens (Smith et al., 2016). Sections 4.2.1–4.2.4 address whether: ITO induces chronic inflammation; is genotoxic; alters cell proliferation, cell death, and nutrient supply; and induces oxidative stress. There were insufficient data for the evaluation of other key characteristics of human carcinogens.

4.2.1 Chronic inflammation

(a) Humans

In the case reports of ITO-exposed workers with interstitial lung disease, also called indium lung disease (Homma et al., 2003, 2005; Cummings et al., 2010, 2012b), increased accumulation of inflammatory cells including alveolar macrophages, lymphocytes, and plasma cells in the airways/lung was described.

In a study in vitro, SITO particles were readily taken up by human bronchial epithelial (BEAS-2B) cells and induced proinflammatory signalling via nuclear factor-kappa B (NFκB) activation within 3 hours of exposure. ITO also induced production of the proinflammatory cytokines IL-6 and IL-8 by BEAS-2B cells at 24 hours, but did not induce nod-like receptor protein 3 (NLRP3) inflammasome activation (Badding et al., 2015).

In a study in vitro by Tabei et al. (2016), sample B ('indium release ITO') induced increased proinflammatory IL-8 expression by A549 cells. Treatment of activated human blood derived monocytes (THP-1 cells) with ITO nanoparticles (NPs) induced increased production of TNFα and IL-1β (Naji et al., 2016).

(b) Experimental systems in vivo

(i) Rats

In the chronic study by Nagano et al. (2011a), as previously described in Section 3.2.1, extensive inflammation was observed in the lungs of ITO-exposed F344 rats (both sexes) at weeks 26 and 104.

Lung inflammation was also observed in male and female F344 rats in an experiment in which exposure was to ITO at 0.1 mg/m^3 for 13 weeks (6 hours per day and 5 days per week) and then to air for 26 weeks (Nagano et al., 2011a). When F344 rats were exposed to SITO (0.1, 1, 10, or 100 mg/m^3), indium oxide, or clean air via whole-body inhalation for 6 hours per day and 5 days per week, and killed after 2 weeks of exposure, lung inflammation was observed in SITO-exposed rats of both sexes, as was increased infiltration of alveolar macrophages (Nagano et al., 2011a).

In male Sprague-Dawley rats exposed via intratracheal instillation to SITO, indium oxide, or vehicle and killed 1, 7, or 90 days later (Badding et al., 2016), total cells (including macrophages and neutrophils) and proinflammatory cytokines (TNFα, IL-6 and IL-1β) were increased in bronchioloalveolar lavage fluid (BALF), predominantly for ITO. The doses tested were 1 or 5 mg per rat.

Lung inflammation was observed in female Wistar-Han rats 60 days after a single dose of SITO (2 mg or 20 mg) via oropharyngeal aspiration, compared with exposures to non-sintered ITO (non-SITO) (2 mg or 20 mg), indium oxide

(1.8 mg or 18 mg), stannic oxide (0.2 mg or 2 mg), or saline vehicle (Lison et al., 2009). Three days after exposure, acute airway/lung inflammation was evident in SITO-treated rats compared with the other treatment groups, including non-SITO and indium oxide. Acute alveolitis and inflammatory nodules were also observed in the lung, and total cells were increased in the BALF, 3 days after exposure to SITO (Lison et al., 2009).

Total cells (including neutrophils) in BALF were significantly increased for all groups (vs air-only control) of male Sprague-Dawley rats exposed to indium oxide (< 4000 nm or < 100 nm) or ITO 50 (< 50 nm) containing 1 mg/m^3 indium via nose-only inhalation for 6 hours per day, 5 days per week for 4 weeks (some rats were held an additional 4 weeks without further treatment) (Lim et al., 2014). The greatest increases were for rats exposed to ITO 50 compared with the other exposure groups at both time points. Perivascular inflammation (including alveolar macrophages) in the lung was also present to some extent in all indium-exposed groups, but was highest for the rats exposed to ITO 50 at both time points (Lim et al., 2014).

(ii) Mice

In the chronic study by Nagano et al. (2011a), as previously described in Section 3.1.1, extensive inflammation was observed in the lungs of ITO-exposed B6C3F$_1$ male and female mice at week 104.

Lung inflammation was also observed 2 or 13 weeks after exposure to SITO in male and female B6C3F$_1$ mice (Nagano et al., 2011a). Mice were exposed to SITO, indium oxide, or clean air via whole-body inhalation, as described in Section 3.2.1 for rats (Nagano et al., 2011b).

Treatment of Balb/c mice with ITO NPs via intraperitoneal injection induced NLRP3 inflammasome-dependent peritonitis with increased recruitment of neutrophils and production of proinflammatory IL-1β (Naji et al., 2016).

(iii) Hamsters

In the long-term study by Tanaka et al. (2010b) described in Section 3.3.1, severe inflammation (including infiltration of alveolar macrophages and neutrophils) was observed in the lungs of ITO-exposed hamsters at week 86 for both ITO exposure levels (3 and 6 mg/kg bw).

Mild inflammation (including accumulation of alveolar macrophages and neutrophils) was observed in the lungs of ITO-treated male Syrian golden hamsters (Tanaka et al., 2002). The hamsters were exposed to ITO at 6 mg/kg bw (or In at 4.5 mg/kg bw) or vehicle control via intratracheal instillation once per week for 16 weeks (16 doses total), and animals were killed the day after the final dose.

(c) Experimental systems in vitro

SITO particles were readily taken up by mouse macrophages (RAW 264.7 cells) and induced proinflammatory signalling via NFκB activation within 3 hours of exposure (Badding et al., 2015). ITO induced production of the proinflammatory cytokines TNFα and IL-1β by RAW 264.7 cells at 24 hours, as well as increased caspase-1 activity. Activation of caspase-1, together with increased IL-1β production, was indicative of NLRP3 inflammasome activation within ITO-treated RAW 264.7 cells (Badding et al., 2015). Treatment of mouse peritoneal macrophages or alveolar macrophages (MH-S cells) with ITO NPs induced increased production of TNFα and/or IL-1β (Naji et al., 2016).

4.2.2 Genetic and related effects

(a) Humans

Indium concentrations were increased in the serum of ITO-exposed workers who also exhibited increased DNA damage in whole blood as measured by comet assay in a cross-sectional study (Liu et al., 2012). A reduction in exposure was found to decrease the DNA damage by comet assay (Liu et al., 2016).

ITO-exposed workers exhibited increased urinary and leukocyte 8-hydroxy-2′-deoxyguanosine (8-OHdG) (Liu et al., 2012; Liou et al., 2016, 2017) as well as increased exhaled breath condensate 8-isoprostane (Liou et al., 2017), biomarkers of oxidative damage to DNA.

In an assay for micronucleus formation in human peripheral lymphocytes in vitro, ITO NPs increased the frequency of micronuclei (Akyıl et al., 2016).

ITO NPs were readily taken up by the human lung adenocarcinoma cell line A549 within 24 hours of exposure and induced DNA damage at 24–72 hours by comet assay (Alkahtane, 2015; Tabei et al., 2015). In the study by Tabei et al. (2016), A549 cells were exposed to two types of SITO NPs: sample A (720 μg/mL In_2O_3 + 70 μg/mL SnO_2) or sample B (200 μg/mL In_2O_3 + 15 μg/mL SnO_2). Based on transmission electron microscopy and measurements of intracellular indium concentrations by ICP-MS at 24 hours, sample B was taken up better (into lysosomal structures) than sample A. Sample B was solubilized within the cells, resulting in indium release extracellularly (as measured by ICP-MS at 24 hours), and was therefore called "indium release ITO"; sample A was solubilized within the cells, resulting in tin release, and therefore called "tin release ITO". The highest concentration of genotoxicity (as measured by comet assay) was induced in A549 cells by sample B (indium release ITO) at 24 hours (Tabei et al., 2016).

(b) Experimental systems

Positive results in the micronucleus assay were observed in rat type II pneumocytes collected 3 days after treatment with SITO via oropharyngeal aspiration at a dose of 2 mg per rat (Lison et al., 2009).

ITO NPs were not mutagenic in an Ames test using *Salmonella typhimurium* strains TA98 and TA100 (Akyıl et al., 2016), but gave positive results in comet assay using *Allium cepa* root cells (Ciğerci et al., 2015).

4.2.3 Altered cell proliferation, cell death, or nutrient supply

(a) Humans

No data in exposed humans were available to the Working Group.

In vitro, ITO particles were cytotoxic to BEAS-2B cells based on an assay for 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) viability at 24 and 48 hours (Badding et al., 2014). In studies using A549 cells, ITO NPs induced cytotoxicity at 48 hours with increased caspase activity and the formation of condensed chromosomal bodies indicative of apoptosis (Alkahtane, 2015). In the study by Tabei et al. (2016), exposure to sample B (indium release ITO) also decreased A549 cell viability (by WST-1 assay) and cell proliferation/colony formation. Treatment of activated human blood derived monocytes (THP-1 cells) with ITO NPs induced cell death (Naji et al., 2016).

(b) Experimental systems

Alveolar epithelial hyperplasia was observed in the lungs of ITO-treated rats and mice (Nagano et al., 2011a, b; Lim et al., 2014; Badding et al., 2016) as well as in hamsters (Tanaka et al., 2002, 2010b).

In rat alveolar macrophages (NR8383 cells), but not rat lung epithelial cells, treatment with SITO for 24 hours resulted in the phagocytic uptake of particles and cytotoxicity via measurements of increased lactate dehydrogenase (LDH) release (Lison et al., 2009). In studies by Gwinn et al. (2013, 2015), non-SITO and SITO particles were readily phagocytosed by RAW 264.7 cells. Particle solubilization, cytotoxicity (based on assays for MTT viability and LDH release), and the extracellular release of indium (μg/L; as measured by atomic absorption spectroscopy) were seen at 24 hours. In addition, ITO particles were phagocytosed by mouse alveolar epithelial (LA-4) cells but did not induce cytotoxicity or indium release at 24 hours, although

particle-induced alveolar epithelial cell cytotoxicity was increased at 48 hours. Cytochalasin D (an inhibitor of phagocytosis) or bafilomycin A1 (an inhibitor of phagolysosomal acidification) blocked particle-induced cytotoxicity and indium release in RAW 264.7 cells, indicating that solubilization of ITO particles, via the phagolysosomal pathway, is linked to particle-induced cytotoxicity (Gwinn et al. 2013, 2015). ITO particles were cytotoxic to RAW 264.7 cells, based on an assay for MTT viability at 24 and 48 hours (Badding et al., 2014). ITO also induced caspase 3/7 activation in RAW 264.7 cells, indicative of apoptosis. Treatment of mouse peritoneal macrophages or alveolar macrophages (MH-S cells) with ITO NPs induced cell death (Naji et al., 2016).

4.2.4 Oxidative stress

(a) Humans

The antioxidants glutathione peroxidase and superoxide dismutase were decreased in the study of ITO-exposed workers noted above (see Section 4.2.2) (Liou et al., 2016, 2017). Use of PAPRs in an interventional study reduced serum indium concentrations in ITO-exposed workers as well as biomarkers of oxidative stress, including lipid peroxidation (based on MDA assay) and glutathione *S*-transferase in plasma as well as 8-OHdG in urine (Liu et al., 2016).

In several in vitro studies, ITO NPs induced increased intracellular production of reactive oxygen species (ROS) and expression of haem oxygenase 1 mRNA, most noticeably at 72 hours, in A549 cells (Tabei et al., 2015). Additionally, ITO NPs decreased glutathione and increased lipid hydroperoxide, superoxide activity, and ROS production by A549 cells (Alkahtane, 2015). In the study by Tabei et al. (2016), increased MTIIA and haem oxygenase 1 mRNA concentrations, as well as increased intracellular ROS production, were induced at 24 hours in A549 cells by sample B (indium release ITO).

(b) Experimental systems

No data from experimental systems in vivo were available to the Working Group.

In vitro, treatment of zebrafish liver cells with ITO NPs for 24 hours increased production of ROS and expression of oxidative stress-related genes including mt2 (Brun et al., 2014). Using a cell-free system, SITO was shown to generate ROS (Lison et al., 2009).

4.3 Cancer susceptibility

No data were available to the Working Group.

4.4 Other adverse effects

4.4.1 Humans

The characteristics of indium lung disease in individuals exposed occupationally to ITO included impaired pulmonary function associated with alveolar proteinosis, fibrosis, and emphysematous changes (Bomhard, 2016). Serum indium concentrations, as well as biomarkers of interstitial lung injury such as Krebs von den Lungen-6 (KL-6) glycoprotein, surfactant protein (SP)-A, SP-D, LDH, and Clara cell (CC16) protein, were also increased in the serum of ITO-exposed workers (Bomhard, 2016).

In two workers (a non-smoker aged 49 years and a smoker aged 39 years) exposed to airborne ITO dust at an ITO-producing facility in the USA, pulmonary alveolar proteinosis and indium in lung tissue specimens were seen (Cummings et al., 2010). A case of pulmonary alveolar proteinosis was also reported in a Chinese male aged 29 years working with an ITO spraying process; his indium serum concentration was 151.8 µg/L (Xiao et al., 2010).

4.4.2 Experimental systems

In male and female ITO-treated rats at 104 weeks, increased relative lung weights, hyperplasia of the alveolar epithelium, alveolar wall fibrosis, infiltration of alveolar macrophages, pleural wall thickening, alveolar proteinosis, and inflammation in the lung were observed (Nagano et al., 2011a, b; Lim et al., 2014; Badding et al., 2016; Section 3). Granulomas were also described in these studies in the bronchus-associated lymphoid tissue (BALT) and lung-draining mediastinal lymph nodes (MLNs). LDH activity and total protein concentrations, which are indicative of airway damage, were increased in the BALF of ITO-treated rats (Lison et al., 2009; Lim et al., 2014).

In ITO-treated mice, alveolar wall fibrosis, pleural thickening, and alveolar proteinosis were observed in the lungs (Nagano et al., 2011a, c). BALT and MLN hyperplasia, as well as extramedullary haematopoiesis in the spleen, were also described in these studies. Immune activation based on increased lymphocyte proliferation (T-cell mediated responses) in a local lymph node assay was induced in female Balb/c mice exposed to non-SITO NPs dermally or via intradermal injection (Brock et al., 2014).

In ITO-treated hamsters, alveolar wall and pleural thickening as well as expansion of the alveolar spaces were observed in the lungs (Tanaka et al., 2002, 2010b). Testicular toxicity in the form of epithelial vacuolization of the seminiferous tubules was described in male Syrian Golden hamsters treated with ITO with 6 mg/kg bw via intratracheal instillation once per week for 16 weeks (Omura et al., 2002).

5. Summary of Data Reported

5.1 Exposure data

Indium tin oxide (ITO) is a mixture of indium oxide (In_2O_3) and stannic oxide (SnO_2), not naturally occurring. ITO is a low production volume chemical, the main use of which is in producing transparent conductive films on glass or plastic panels used in electronic devices and other products. Exposure to ITO occurs primarily in occupational settings where ITO is produced or processed, or where elemental indium is recycled and recovered from ITO. Current analytical methods can only quantify total elemental indium, not ITO. A serum indium concentration was reported at 290 µg/L in a case of pulmonary dysfunction in an ITO worker. Mean serum indium concentrations of up to 11 µg/L have been reported among exposed workers.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

One well-conducted inhalation study in male and female mice and one well-conducted inhalation study in male and female rats were performed under good laboratory conditions. One intratracheal instillation study in male hamsters was conducted.

ITO exposure significantly increased the incidences of bronchioloalveolar adenoma, bronchioloalveolar carcinoma, combined malignant lung tumours, and combined (all) lung tumours in male and female rats, often with a significant positive trend. In female mice, there was a significant positive trend in the incidence of bronchioloalveolar adenoma and bronchioloalveolar adenoma or carcinoma (combined), but there was no significant increase in the incidences

of bronchioloalveolar adenoma, carcinoma, or adenoma or carcinoma (combined) by pairwise comparison. There was no significant increase in tumour incidence in male mice.

The intratracheal study in hamsters was uninformative.

5.4 Mechanistic and other relevant data

Elemental indium (In) has been measured in exposed humans, in rodents, and in vitro after ITO exposure, but the metabolism of ITO has not been well characterized. A few rodent studies showed that inhaled or intratracheally instilled ITO is slowly dissolved, made systemically available, widely distributed, and slowly eliminated over a period of years. ITO deposited in the lung can be distributed to blood, serum, and multiple tissues (liver, spleen, and brain), and is excreted in urine. The distribution of indium to tissues suggests dissolution from ITO particles. Exposure to ITO can result in substantial levels of indium in biofluids (e.g. blood, urine, and serum), and particle solubilization has been demonstrated in vitro. The excretion of indium has not been well characterized.

With respect to the key characteristics of human carcinogens, adequate data were available to evaluate whether ITO induces chronic inflammation, is genotoxic, alters cell proliferation or death, and induces oxidative stress. Only a few studies from exposed humans were available.

The evidence that ITO induces chronic inflammation is *strong*, based on findings in experimental systems. In the few case reports available, increased inflammation in the airways and lung was observed in ITO-exposed workers with interstitial lung disease. In the 2-year ITO study in both sexes of rats and mice, as well as in a long-term study in hamsters, chronic lung inflammation was seen. Numerous subchronic studies in multiple strains of rats and mice also showed inflammatory responses. Several in vitro studies in human and mouse cells showed that ITO induced proinflammatory signalling and cytokine production.

The evidence that ITO is genotoxic is *moderate*. Two studies in exposed humans from the same investigators showed increased DNA damage in blood cells and increased urinary 8-OHdG. An independent study in exposed humans showed that ITO increased 8-OHdG in leukocytes and in urine. One in vivo study in rats showed increased frequency of micronuclei in type II pneumocytes after exposure to sintered ITO by oropharyngeal aspiration. In several in vitro studies, ITO increased the frequency of micronuclei in human peripheral lymphocytes and induced DNA damage in human lung adenocarcinoma cells and in plant root cells. Ames assay results were negative.

The evidence that ITO alters cell proliferation or death is *moderate*. No data in exposed humans were available. Alveolar epithelial hyperplasia was reported in exposed rats, mice, and hamsters. ITO induced cell death in multiple studies using human or rodent cells in vitro.

The evidence that ITO induces oxidative stress is *weak*. There were a few studies in exposed humans, showing that ITO increased 8-isoprostane in exhaled breath, increased lipid peroxidation in plasma, and decreased plasma antioxidant enzymes. No in vivo studies were available in experimental systems. In vitro, ITO increased biomarkers of oxidative stress in human A549 cells.

There were no data on cancer susceptibility.

In exposed humans, ITO induced interstitial lung disease associated with alveolar proteinosis and fibrosis. Similar effects were seen in exposed rats, mice, and hamsters.

6. Evaluation

6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of indium tin oxide.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of indium tin oxide.

6.3 Overall evaluation

Indium tin oxide is *possibly carcinogenic to humans (Group 2B)*.

References

Akyıl D, Eren Y, Konuk M, Tepekozcan A, Sağlam E (2016). Determination of mutagenicity and genotoxicity of indium tin oxide nanoparticles using the Ames test and micronucleus assay. *Toxicol Ind Health*, 32(9):1720–8. doi:10.1177/0748233715579804 PMID:25907664

Alfantazi AM, Moskalyk RR (2003). Processing of indium: a review. *Miner Eng*, 16(8):687–94. doi:10.1016/S0892-6875(03)00168-7

Alkahtane A (2015). Indium tin oxide nanoparticles-mediated DNA fragmentation and cell death by apoptosis in human lung epithelial cells. *Toxicol Environ Chem*, 97(8):1086–98. doi:10.1080/02772248.2015.1086111

Badding MA, Fix NR, Orandle MS, Barger MW, Dunnick KM, Cummings KJ, et al. (2016). Pulmonary toxicity of indium-tin oxide production facility particles in rats. *J Appl Toxicol*, 36(4):618–26. doi:10.1002/jat.3253 PMID:26472246

Badding MA, Schwegler-Berry D, Park JH, Fix NR, Cummings KJ, Leonard SS (2015). Sintered indium-tin oxide particles induce pro-inflammatory responses in vitro, in part through inflammasome activation. *PLoS One*, 10(4):e0124368 doi:10.1371/journal.pone.0124368 PMID:25874458

Badding MA, Stefaniak AB, Fix NR, Cummings KJ, Leonard SS (2014). Cytotoxicity and characterization of particles collected from an indium-tin oxide production facility. *J Toxicol Environ Health A*, 77(20):1193–209. doi:10.1080/15287394.2014.920757 PMID:25208660

Bomhard EM (2016). The toxicology of indium tin oxide. *Environ Toxicol Pharmacol*, 45:282–94. doi:10.1016/j.etap.2016.06.011 PMID:27343753

Brock K, Anderson SE, Lukomska E, Long C, Anderson K, Marshall N, et al. (2014). Immune stimulation following dermal exposure to unsintered indium tin oxide. *J Immunotoxicol*, 11(3):268–72. doi:10.3109/1547691X.2013.843620 PMID:24164313

Brun NR, Christen V, Furrer G, Fent K (2014). Indium and indium tin oxide induce endoplasmic reticulum stress and oxidative stress in zebrafish (Danio rerio). *Environ Sci Technol*, 48(19):11679–87. doi:10.1021/es5034876 PMID:25188630

Choi S, Won YL, Kim D, Yi GY, Park JS, Kim EA (2013). Subclinical interstitial lung damage in workers exposed to indium compounds. *Ann Occup Environ Med*, 25(1):24. doi:10.1186/2052-4374-25-24 PMID:24472147

Chonan T, Taguchi O, Omae K (2007). Interstitial pulmonary disorders in indium-processing workers. *Eur Respir J*, 29(2):317–24. doi:10.1183/09031936.00020306 PMID:17050566

Ciğerci İH, Liman R, Özgül E, Konuk M (2015). Genotoxicity of indium tin oxide by Allium and Comet tests. *Cytotechnology*, 67(1):157–63. doi:10.1007/s10616-013-9673-0 PMID:24337653

Cummings KJ, Donat WE, Ettensohn DB, Roggli VL, Ingram P, Kreiss K (2010). Pulmonary alveolar proteinosis in workers at an indium processing facility. *Am J Respir Crit Care Med*, 181(5):458–64. doi:10.1164/rccm.200907-1022CR PMID:20019344

Cummings KJ, Nakano M, Omae K, Takeuchi K, Chonan T, Xiao YL, et al. (2012b). Indium lung disease. *Chest*, 141(6):1512–21. doi:10.1378/chest.11-1880 PMID:22207675

Cummings KJ, Suarthana E, Day GA, Stanton ML, Saito R, Kreiss K (2012a). An evaluation of preventive measures an an indium-tin oxide production facility. Health Hazard Evaluation Report. HETA 2009-0214-3153. Rhode Island, USA: Department of Health and Human Services, National Institute for Occupational Safety and Health.

Cummings KJ, Virji MA, Park JY, Stanton ML, Edwards NT, Trapnell BC, et al. (2016). Respirable indium exposures, plasma indium, and respiratory health among indium-tin oxide (ITO) workers. *Am J Ind Med*, 59(7):522–31. doi:10.1002/ajim.22585 PMID:27219296

Enghag P (2007). Gallium, indium and thallium. In: Encyclopedia of the elements. Wiley-VCH Verlag GmbH & Co., pp. 845–867.

GESTIS (2017). Indium tin oxide. GESTIS Substance Database. IFA (Institut fur Arbeitsschutz). Available from: http://www.dguv.de/ifa/gestis/gestis-stoffdatenbank/index-2.jsp/, accessed 17 January 2017.

Gwinn WM, Qu W, Bousquet RW, Price H, Shines CJ, Taylor GJ, et al. (2015). Macrophage solubilization and cytotoxicity of indium-containing particles as in vitro correlates to pulmonary toxicity in vivo. *Toxicol Sci*, 144(1):17–26. doi:10.1093/toxsci/kfu273 PMID:25527823

Gwinn WM, Qu W, Shines CJ, Bousquet RW, Taylor GJ, Waalkes MP, et al. (2013). Macrophage solubilization and cytotoxicity of indium-containing particles in vitro. *Toxicol Sci*, 135(2):414–24. doi:10.1093/toxsci/kft154 PMID:23872580

Hamaguchi T, Omae K, Takebayashi T, Kikuchi Y, Yoshioka N, Nishiwaki Y, et al. (2008). Exposure to hardly soluble indium compounds in ITO production and recycling plants is a new risk for interstitial lung damage. *Occup Environ Med*, 65(1):51–5. doi:10.1136/oem.2006.029124 PMID:17626138

Harvey RR, Virji MA, Edwards NT, Cummings KJ (2016). Comparing plasma, serum and whole blood indium concentrations from workers at an indium-tin oxide (ITO) production facility. *Occup Environ Med*, 73(12):864–7. doi:10.1136/oemed-2016-103685 PMID:27456157

Hines CJ, Roberts JL, Andrews RN, Jackson MV, Deddens JA (2013). Use of and occupational exposure to indium in the United States. *J Occup Environ Hyg*, 10(12):723–33. doi:10.1080/15459624.2013.836279 PMID:24195539

Hoet P, De Graef E, Swennen B, Seminck T, Yakoub Y, Deumer G, et al. (2012). Occupational exposure to indium: what does biomonitoring tell us? *Toxicol Lett*, 213(1):122–8. doi:10.1016/j.toxlet.2011.07.004 PMID:21771645

Homma S, Miyamoto A, Sakamoto S, Kishi K, Motoi N, Yoshimura K (2005). Pulmonary fibrosis in an individual occupationally exposed to inhaled indium-tin oxide. *Eur Respir J*, 25(1):200–4. doi:10.1183/09031936.04.10012704 PMID:15640342

Homma T, Ueno T, Sekizawa K, Tanaka A, Hirata M (2003). Interstitial pneumonia developed in a worker dealing with particles containing indium-tin oxide. *J Occup Health*, 45(3):137–9. doi:10.1539/joh.45.137 PMID:14646287

HSDB (2017). NIH Toxnet. Toxicology Data Network. Available from: https://toxnet.nlm.nih.gov/

IARC (2006). Cobalt in hard metals and cobalt sulfate, gallium arsenide, indium phosphide and vanadium pentoxide. *IARC Monogr Eval Carcinog Risks Hum*, 86:1–294. Available from: http://publications.iarc.fr/104 PMID:16906675

Indium Corporation (2008). Indium tin oxide. Material safety data sheet No. MSDS-IB011. Available from: http://www.indium.com/technical-documents/safety-data-sheets/english

Indium Corporation (2014). Product data sheet: indium tin oxide (ITO) - In_2O_3:SnO_2. Utica (NY), USA: Indium Corporation. Form No. 97550(A4):R11.

Iwasawa S, Nakano M, Miyauchi H, Tanaka S, Kawasumi Y, Higashikubo I, et al. (2017). Personal indium exposure concentration in respirable dusts and serum indium level. *Ind Health*, 55(1):87–90. doi:10.2486/indhealth.2016-0015 PMID:27644848

Lim CH, Han JH, Cho HW, Kang M (2014). Studies on the toxicity and distribution of indium compounds according to particle size in Sprague-Dawley rats. *Toxicol Res*, 30(1):55–63. doi:10.5487/TR.2014.30.1.055 PMID:24795801

Liou SH, Chen YC, Liao HY, Wang CJ, Chen JS, Lee HL (2016). Increased levels of oxidative stress biomarkers in metal oxides nanomaterial-handling workers. *Biomarkers*, 21(7):600–6. doi:10.3109/1354750X.2016.1160432 PMID:27010249

Liou SH, Wu WT, Liao HY, Chen CY, Tsai CY, Jung WT, et al. (2017). Global DNA methylation and oxidative stress biomarkers in workers exposed to metal oxide nanoparticles. *J Hazard Mater*, 331:329–35. doi:10.1016/j.jhazmat.2017.02.042 PMID:28273583

Lippens P, Muehlfeld U (2012). Indium tin oxide (ITO): sputter deposition processes. In: Chen J, Cranton W, Fihn M, editors. Handbook of visual display technology. Berlin: Springer-Verlag. doi:10.1007/978-3-540-79567-4_54

Lison D, Laloy J, Corazzari I, Muller J, Rabolli V, Panin N, et al. (2009). Sintered indium-tin-oxide (ITO) particles: a new pneumotoxic entity. *Toxicol Sci*, 108(2):472–81. doi:10.1093/toxsci/kfp014 PMID:19176593

Liu H-H, Chen C-Y, Chen G-I, Lee L-H, Chen H-L (2012). Relationship between indium exposure and oxidative damage in workers in indium tin oxide production plants. *Int Arch Occup Environ Health*, 85(4):447–53. doi:10.1007/s00420-011-0688-6 PMID:21833746

Liu HH, Chen CY, Lan CH, Chang CP, Peng CY (2016). Effects of a powered air-purifying respirator intervention on indium exposure reduction and indium related biomarkers among ITO sputter target manufacturing workers. *J Occup Environ Hyg*, 13(5):346–55. doi:10.1080/15459624.2015.1125487 PMID:26771526

Nagano K, Gotoh K, Kasai T, Aiso S, Nishizawa T, Ohnishi M et al. (2011b). Two- and 13-week inhalation toxicities of indium-tin oxide and indium oxide in rats. *J Occup Health*, 53(2):51–63. doi:10.1539/joh.L10128 PMID:21233592

Nagano K, Nishizawa T, Eitaki Y, Ohnishi M, Noguchi T, Arito H, et al. (2011c). Pulmonary toxicity in mice by 2- and 13-week inhalation exposures to indium-tin oxide and indium oxide aerosols. *J Occup Health*, 53(3):234–9. doi:10.1539/joh.10-0053-BR PMID:21422720

Nagano K, Nishizawa T, Umeda Y, Kasai T, Noguchi T, Gotoh K, et al. (2011a). Inhalation carcinogenicity and chronic toxicity of indium-tin oxide in rats and mice. *J Occup Health*, 53(3):175–87. doi:10.1539/joh.10-0057-OA PMID:21471693

Naji A, Muzembo BA, Yagyu K, Baba N, Deschaseaux F, Sensebé L, et al. (2016). Endocytosis of indium-tin-oxide nanoparticles by macrophages provokes pyroptosis requiring NLRP3-ASC-Caspase1 axis that can be prevented by mesenchymal stem cells. *Sci Rep*, 6(1):26162. doi:10.1038/srep26162 PMID:27194621

Nakano M, Omae K, Tanaka A, Hirata M, Michikawa T, Kikuchi Y, et al. (2009). Causal relationship between indium compound inhalation and effects on the lungs. *J Occup Health*, 51(6):513–21. doi:10.1539/joh.L9077 PMID:19834281

Nogami H, Shimoda T, Shoji S, Nishima S (2008). [Pulmonary disorders in indium-processing workers.] *Nihon Kokyuki Gakkai Zasshi*, 46(1):60–4. [Japanese] PMID:18260313

NTP (2009). Chemical information profile for indium tin oxide [CAS No. 50926-11-9]. Research Triangle Park (NC), USA: National Toxicology Program, National Institute of Environmental Health Sciences, National Institutes of Health, United States Department of Health and Human Services.

Omae K, Nakano M, Tanaka A, Hirata M, Hamaguchi T, Chonan T (2011). Indium lung–case reports and epidemiology. *Int Arch Occup Environ Health*, 84(5):471–7. doi:10.1007/s00420-010-0575-6 PMID:20886351

Omura M, Tanaka A, Hirata M, Inoue N, Ueno T, Homma T, et al. (2002). Testicular toxicity evaluation of indium-tin oxide. *J Occup Health*, 44(2):105–7. doi:10.1539/joh.44.105

Scansetti G (1992). Exposure to metals that have recently come into use. *Sci Total Environ*, 120(1–2):85–91. doi:10.1016/0048-9697(92)90218-H PMID:1641643

Schwarz-Schampera U (2014). Indium. In: Critical metals handbook. John Wiley & Sons: pp. 204–229.

Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, et al. (2016). Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environ Health Perspect*, 124(6):713–21. PMID:26600562

Tabei Y, Sonoda A, Nakajima Y, Biju V, Makita Y, Yoshida Y, et al. (2015). In vitro evaluation of the cellular effect of indium tin oxide nanoparticles using the human lung adenocarcinoma A549 cells. *Metallomics*, 7(5):816–27. doi:10.1039/C5MT00031A PMID:25781390

Tabei Y, Sonoda A, Nakajima Y, Biju V, Makita Y, Yoshida Y, et al. (2016). Intracellular accumulation of indium ions released from nanoparticles induces oxidative stress, proinflammatory response and DNA damage. *J Biochem*, 159(2):225–37. doi:10.1093/jb/mvv098 PMID:26378248

Taguchi O, Chonan T (2006). [Three cases of indium lung.] *Nihon Kokyuki Gakkai Zasshi*, 44(7):532–6. [Japanese] PMID:16886812

Tanaka A, Hirata M, Homma T, Kiyohara Y (2010b). Chronic pulmonary toxicity study of indium-tin oxide and indium oxide following intratracheal instillations into the lungs of hamsters. *J Occup Health*, 52(1):14–22. doi:10.1539/joh.L9097 PMID:19940388

Tanaka A, Hirata M, Kiyohara Y, Nakano M, Omae K, Shiratani M, et al. (2010a). Review of pulmonary toxicity of indium compounds to animals and humans. *Thin Solid Films*, 518(11):2934–6. doi:10.1016/j.tsf.2009.10.123

Tanaka A, Hirata M, Matsumura N, Kiyohara Y (2015). Tissue distribution of indium after repeated intratracheal instillations of indium-tin oxide into the lungs of hamsters. *J Occup Health*, 57(2):189–92. doi:10.1539/joh.14-0123-BR PMID:25735506

Tanaka A, Hirata M, Omura M, Inoue N, Ueno T, Homma T, et al. (2002). Pulmonary toxicity of indium-tin oxide and indium phosphide after intratracheal instillations into the lung of hamsters. *J Occup Health*, 44(2):99–102. doi:10.1539/joh.44.99 PMID:20110621

UMICORE (2013). Indium tin oxide (ITO) for deposition of transparent conductive oxide layers. High density ceramic TCO sputtering targets. BV868857/3/2013/1000. Balzers, Liechtenstein: Umicore Thin Film Products AG.

USGS (2016). Indium. Mineral commodity summaries. Washington (DC), USA: United States Geological Survey.

Weast RC, editor (1970). CRC Handbook of Chemistry and Physics. Cleveland (OH), USA: The Chemical Rubber Company.

Xiao YL, Cai HR, Wang YH, Meng FQ, Zhang DP (2010). Pulmonary alveolar proteinosis in an indium-processing worker. *Chin Med J (Engl)*, 123(10):1347–50. PMID:20529594

LIST OF ABBREVIATIONS

%DNA	percentage DNA in tail
•OH	hydroxyl radical
3-MC	3-methylcholanthrene
8-OH-dG	8-hydroxy-2′-deoxyguanosine
8-oxodGuo	8-oxo-7,8-dihydro-2′-deoxyguanosine
ACGIH	American Conference of Governmental Industrial Hygienists
Al	aluminium
ALL	acute lymphoblastic leukaemia
AM	alveolar macrophage
AML	acute myeloid leukaemia
ApoJ	apolipoprotein J
Ar	argon
BALF	bronchoalveolar lavage fluid
BALT	bronchus-associated lymphoid tissue
Be	beryllium
Ca	calcium
$CaCrO_4$	calcium chromate
CANJEM	Canadian job-exposure matrix
Cd	cadmium
CFU	colony-forming unit
CHMS	Canadian Health Measures Survey
CI	confidence interval
CLL	chronic lymphocytic leukaemia
CLU	clusterin
CO	carbon monoxide
Co	cobalt
Cr	chromium
Cr(VI)	hexavalent chromium
CRP	C-reactive protein
Cu	copper
dGuo	deoxyguanosine
DLBCL	diffuse large B-cell lymphoma
ECRHS	European Community Respiratory Follow-up Survey

ELF-EMF	extremely low frequency electromagnetic fields
EPIC	European Prospective Investigation into Cancer and Nutrition
ER	electric resistance
FCA	flux-cored arc
Fe	iron
Fe_2O_3	iron oxide
FINJEM	Finnish job-exposure matrix
FSH	follicle-stimulating hormone
GLP	good laboratory practice
GMA	gas metal arc
GPX	glutathione peroxidase
GSH	glutathione
GTA	gas tungsten arc
H_2O_2	hydrogen peroxide
He	helium
HR	hazard ratio
HRV	heart rate variability
HS	hard-surfacing
IARC	International Agency for Research on Cancer
ICARE	Investigation of Occupational and Environmental Causes of Respiratory Cancers
ICNIRP	International Commission on Non-Ionizing Radiation Protection
ICP	inductively coupled plasma
IEC	International Electrochemical Commission
IFNγ	interferon gamma
IgA	immunoglobulin A
IgM	immunoglobulin M
IL	interleukin
In	indium
In_2O_3	indium tin oxide
iNOS	inducible nitrite oxide synthase
IPUMS	Integrated Public Use Microdata Series
ISO	International Organization for Standardization
ITO	indium tin oxide
JEM	job-exposure matrix
JSOH	Japan Society for Occupational Health
KL-6	Krebs von den Lungen-6
LALN	lung-associated lymph node
LDH	lactate dehydrogenase
LH	luteinizing hormone
LINE-1	long interspersed nuclear element-1
LOD	limit of detection
LPS	lipopolysaccharide
MAG	metal active gas
MAPP	methylacetylene-propadiene
MDA	malondialdehyde
Mg	magnesium
MIG	metal inert gas
MLN	mediastinal lymph node
MMA	manual metal arc
Mn	manganese

MN	micronucleus
MnSOD	manganese superoxide dismutase
Mo	molybdenum
MoO_3	molybdenum trioxide
MOR	mortality odds ratio
MoS_2	molybdenum (IV) sulfide
MS	mild steel
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
N	nitrogen
β-NAG	β-*N*-acetyl-glucosaminidase
NFκB	nuclear factor kappa-light-chain-enhancer of activated B cells
NHANES	United States National Health and Nutrition Examination Survey
NHL	non-Hodgkin lymphoma
Ni	nickel
NIOSH	United States National Institute for Occupational Safety and Health
NLRP3	NACHT, LRR and PYD domains-containing protein 3
NLST	National Lung Screening Trial
NO	nitric oxide
NO_2	nitrogen dioxide
NO_X	nitrogen oxides
NP	nanoparticle
O	oxygen
O_3	ozone
OR	odds ratio
PAFR	platelet-activating factor receptor
PAH	polycyclic aromatic hydrocarbon
PAPR	powered air-purifying respirator
Pb	lead
PBMC	peripheral blood mononuclear cell
$PM_{2.5}$	particulate matter of diameter < 2.5 μm
PM_4	particulate matter of diameter < 4 μm
PMN	polymorphonuclear leukocytes
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
ROS	reactive oxygen species
RR	relative risk
SA	submerged arc
SAA	serum amyloid A
SIR	standardized incidence ratio
SITO	sintered indium tin oxide
SLL	small lymphocytic lymphoma
SMR	standardized mortality ratio
SnO_2	stannic oxide
SOD	superoxide dismutase
SP	surfactant protein
SRBC	sheep red blood cell
SS	stainless steel
TCC	transitional cell carcinoma
TCE	trichloroethylene
Th	thorium
TIG	tungsten inert gas

TiO_2	titanium dioxide
TIP	total inhalable particulate
TNFα	tumour necrosis factor alpha
TRH	TSH-releasing hormone
TSH	thyroid-stimulating hormone
TWA	time-weighted average
UFP	ultrafine particles
UV	ultraviolet
VHL	von Hippel–Lindau tumour suppressor
vs	versus
wt%	percentage by weight
Zn	zinc

IARC MONOGRAPHS

This volume of the *IARC Monographs* provides evaluations of the carcinogenicity of welding and welding fumes, molybdenum trioxide, and indium tin oxide.

Worldwide, an estimated 11 million workers have a job title of welder, and around 110 million additional workers probably incur welding-related exposures. Welding can involve exposures to fumes, gases, ultraviolet radiation and electromagnetic fields, and co-exposures to asbestos and solvents. The extent and type of exposure can depend on the process used, the material welded, ventilation, degree of enclosure, and use of personal protection.

Molybdenum trioxide, which occurs rarely naturally, is a chemical with a high production volume that is mainly used in steel manufacture, but also in biocides and in photovoltaic technology. Most occupational exposures occur in mining and metallurgy, steel foundries, welding, and other high-temperature processes using steel.

Indium tin oxide, which does not occur naturally, is a chemical with a low production volume that is a mixture of indium oxide and stannic oxide. It is mainly used in producing transparent conductive films on glass or plastic panels used in electronic devices. Exposure to indium tin oxide occurs mainly in occupational settings, during production and processing, or during recycling of elemental indium. As the use, recycling, and disposal of electronics increases worldwide, exposures to indium in low- and middle-income countries where informal e-recycling occurs are also expected to increase.

An *IARC Monographs* Working Group reviewed epidemiological evidence, animal bioassays, and mechanistic and other relevant data to reach conclusions as to the carcinogenic hazard to humans due to exposure to these agents.