REVIEW AND EVALUATION OF IARC'S MONOGRAPH OF WELDING FUMES

RAMBØLL

CONTENTS

ACRONYMS AND ABBREVIATIONS

8-OHdG	8-hydroxy-2'-deoxyguanosine
ACGIH	American Conference of Governmental Industrial Hygienists
As	Arsenic
AWS	American Welding Society
CEI	Cumulative exposure index
Cd	Cadmium
CI	Confidence interval
CO_2	Carbon dioxide
Cr	Chromium
Cr VI	Hexavalent chromium
CSI	Cumulative smoking index
FCA	Flux core arc
Fe	Iron
FINJEM	Finnish job-exposure matrix
GMA	Gas metal arc
GMA-MS	Gas metal arc- mild steel
GMA-SS	Gas metal arc- stainless steel
GTA	Gas tungsten arc
HR	Hazard ratio
IARC	International Agency for Research on Cancer
JEM	Job-exposure matrix
MIG-SS	Metal inert gas – stainless steel
MMA	Manual metal arc
MMA-SS	Manual metal arc – stainless steel
MMA-HS	Manual metal arc – hard-surfacing
Mn	Manganese
Ni	Nickel
NIOSH	National Institute for Occupational Safety and Health
OR	Odds ratio
OSHA	Occupational Safety and Health Administration
$PM_{2.5}$	Particulate matter less than 2.5 micrometers in diameter
PPE	Personal protective equipment
ROS	Reactive oxygen species
SIR	Standardized incidence ratio
SMR	Standardized mortality ratio
SMA	Shielded metal arc
TEM	Time exposure matrix
TIG	Tungsten inert gas
UV	Ultraviolet
VOC	Volatile organic compound
WF	Welding fume

1 INTRODUCTION

On behalf of the American Welding Society (AWS), Ramboll conducted an evaluation of the most recent International Agency for Research on Cancer's Monograph related to the carcinogenic risks to humans from welding fume exposures (IARC, 2018). The carcinogenicity of welding fumes was last evaluated in 1989, when IARC determined that welding was "possibly carcinogenic to humans (Group 2B)" based on limited evidence in humans and inadequate evidence in animals (IARC, 1990). Based on new evidence published since then, IARC determined that welding is "carcinogenic to humans (Group 1)" (IARC, 2018). This determination was based on measured exposures to UV radiation generated from arc welding and from studies of the effects of exposure to welding fume. Ultraviolet (UV) radiation is a risk factor for a rare type of ocular melanoma. According to IARC (2018) exposure to welding fume was assessed in connection with increased lung and kidney cancers in more than 20 case-control studies and over 30 occupational or population-based studies that mostly reported positive associations. Co-exposures to lung and kidney carcinogens, including asbestos and solvents, as well as differences in welding processes (e.g., GMA, MMA, TIG) and materials (mild and stainless steel) were assessed. Lastly, IARC (2018) found that evidence from animal studies was limited, but concluded that mechanistic studies support the hypothesis that welding fumes induce chronic inflammation and can be immunosuppressive, both of which are implicated in carcinogenesis. In its review of the available literature, IARC concluded that there was sufficient evidence that welding fumes cause lung cancer in humans, and limited evidence for kidney cancer.

Ramboll evaluated the evidence IARC identified as being most informative for concluding that welding fumes were lung carcinogens, focusing on key epidemiological and toxicological studies that IARC identified as the strongest evidence of carcinogenic effects. The IARC review process is briefly described in Section 1. Section 2 provides a summary of the epidemiological evidence and conclusions by IARC, as well as Ramboll's assessment of the evidence. Section 3 describes the toxicological evidence that IARC evaluated including IARC's conclusions and Ramboll's assessment of the evidence. Concluding remarks are provided in Section 4.

2 IARC EVALUATION METHODS

The objectives, scope and methods used in developing the IARC Monographs are described in detail in the Preamble for the Monograph (IARC, 2018). We briefly summarize the methodology, including the types of evidence considered, selection of studies, and the criteria used in the evaluation.

2.1 Background

The goal of the IARC Monograph program is to identify potential causes of cancer in humans. The IARC Monograph program was established in 1965 and in 1970 it began compiling monographs that summarized the carcinogenic risks of chemicals. IARC evaluations have since been broadened to include groups of related chemicals, complex mixtures and physical and biological agents. The first criteria for IARC Monographs were established in 1971, but these criteria have been updated, most recently in 2006. As noted in the Preamble, the scientific criteria are not a specific list of procedures that the Working Group implements, and therefore no specific procedures are detailed in the Preamble. Instead, general criteria are summarized, and the detailed procedures of each Monograph are left to the prerogative of the Individual Working Group.

The Monograph is meant to represent the first step in a cancer risk assessment (i.e., the hazard evaluation), which includes an evaluation of all relevant information and the strength of the scientific evidence for carcinogenicity of the agent. IARC identifies "agents" for review that are potentially carcinogenic on the basis of potential human exposures. These agents can include specific chemicals, groups of related chemicals, mixtures, occupational or environmental agents, biological or physical agents. IARC also makes the distinction of cancer hazard vs. cancer risk. Cancer risk is the estimate of a cancer effect from a certain level of exposure to the agent, whereas cancer hazard is the carcinogenic effect at any exposure level. IARC evaluates cancer hazards even when cancer risks may be very low at low exposure levels.

The data reviewed in each Monograph includes pertinent epidemiological studies and animal carcinogenicity studies. If a study is deemed inadequate it may be cited but not summarized. Mechanistic studies are also reviewed, but not all of these studies may be evaluated and included in the Monograph. Only studies that have been published in peer-reviewed journals will be considered by IARC, but IARC may consider data from government agencies or theses in their final form that are publicly available. Exposure data and other information regarding production and use of an agent are also reviewed and summarized by IARC and for this information both published and unpublished sources are included. Lastly, inclusion of a study in the Monograph does not indicate that the study is adequate for consideration. IARC uses brackets to comment on the adequacy of any particular study.

IARC selects a group of specialists with knowledge on the agent being evaluated and with no conflicts of interest and this group is known as the "Working Group" and is responsible for conducting the IARC evaluation for a particular agent. In addition, IARC may call on specific experts in areas that may be required to supplement the review.

The following sections are included in each Monograph:

- 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" is included at the beginning of each Monograph volume. A brief summary of what is included in each Monograph section and of the IARC general procedures is provided below.

2.2 Exposure data

Each Monograph includes general information on the agent that varies depending on the availability of this information. For example, the information summarized in this section of the Monograph includes production and use (when applicable), measurement methods of analysis and detection, occurrence, and sources and routes of human occupational and environmental exposures. In addition, IARC summarizes available regulations and guidelines. For welding fumes, the Monograph covers the major welding processes and materials emphasizing the different processes and materials and the impact on various exposures. Exposures include welding fumes (a complex mix of suspended particles, such as various metals), gases (nitrogen oxides, carbon monoxide, and ozone), and ionizing and nonionizing radiation. The most common processes that are described in the Monograph include manual metal arc (MMA), gas metal arc (GMA), flux-cored arc (FCA), and gas tungsten arc (GTA). Other processes such as electric resistance welding are also described. The Monograph also describes welding materials including the commonly used mild steel (MS) and stainless steel (SS). MS contains small amounts of manganese (Mn, <1.6%), while SS contains up to 25% chromium (Cr), 7% nickel (Ni), and 4% molybdenum.

The Monograph also summarizes the populations potentially exposed to welding fumes worldwide, noting that it is difficult to quantify the number of welders worldwide, because of differences in survey methodologies, including how jobs are coded. Based on available data, IARC (2018) estimated that welders represent about 0.3% of the active working population, which yields approximately 11 million welders worldwide. In addition to full-time welders (listing welding as primary occupation) there are a large number of other occupations that involve more intermittent welding (e.g., sheet metal workers, pipe fitters, blacksmiths, etc.).

The exposure section details extensive literature on measurement data related to welding fumes and associated exposures to particulate, gases, and metals.

2.3 Studies of cancer in humans

IARC considers several types of epidemiological studies including cohort studies, case–control studies, correlation (or ecological) studies and intervention studies. IARC may also consider case reports and case series. The most common studies are cohort and case–control studies that relate individual exposures to the occurrence of cancer in individuals and provide an estimate of cancer risk (such as relative risk). Although intervention studies, where exposures are removed and disease rates decrease, provide strong evidence for causal inferences, these studies are rare.

Correlation studies are also common and typically involve whole populations (e.g. particular geographical areas or particular time points), and cancer frequency is evaluated in relation to a summary measure of the exposure of the population to the agent. As noted by IARC, because individual exposures are not documented in correlation studies, these studies are more prone to confounding bias and are generally less informative for making causal inferences. Similarly, case reports and case series lack complete information regarding the population at risk and therefore are inadequate to form causal conclusions. However, IARC does consider this evidence if there is also evidence from more robust cohort and case-control studies.

In evaluating the quality of epidemiological studies, IARC notes that it considers the possible roles of bias, confounding and chance in the interpretation of these studies and whether these factors affected the association between an agent and disease (i.e., actual effects could be stronger or weaker). Confounding occurs when the association between exposure and disease appears stronger or weaker than it actually is because of the association between the actual causal factor and another factor that is associated with the disease; inclusion of this factor in the analyses will result in a significant reduction or increase in the observed effect. The role of a chance finding is related to the influence of sample size on the precision of estimates of effect.

IARC evaluates the extent to which bias has been minimized in any individual study by considering the design and analysis as described in the study. According to IARC, if a study does not clearly address bias it reduces its credibility and it is given less weight in the final evaluation.

The general study quality criteria provided in the Monograph include:

1) How the study defines the study population, disease (or diseases) and exposure
2) Consideration of confounding in the study design or analysis (i.e., variables that are risk factors of the disease and also may be related to the exposure such as higher smoking rates in welders vs. non-welders. Confounding can be reduced by study design (matching) or by statistical adjustments. In cohort studies, internal comparisons of individuals by level of exposure can reduce confounding related to differences between an external reference group and the study population.
3) All data that form the bases of the conclusions should be reported by the authors, including number of exposed/unexposed cases and control (case-control study) or the number of observed and expected cases (cohort study). Temporal factors are also important (i.e., time since exposure). To reduce reporting bias, information on all cancer sites or all causes of death should be provided, and in case-control studies alternative factors (other than the exposure of interest) should also be explored.
4) All statistical methods used to obtain effect estimates (e.g., relative risks or rates of cancer), confidence intervals, and significance tests should be clearly stated by the authors.

After completion of the study quality, IARC makes a judgement concerning the strength of evidence that the agent is carcinogenic to humans. IARC applies the Bradford Hill criteria that are commonly used to make causality judgements (Hill, 1965). For example, stronger associations (e.g. large risk estimates) are more likely causal compared to weak associations. Similarly, associations replicated in several studies of the same design, but different population groups, or that use different epidemiological methods or applied to different exposure scenarios are more likely to be causal than observations from a single

study. Inconsistent results are evaluated to determine possible reasons (e.g., differences in exposure), and results of higher quality studies are given more weight. A strong indication of a dose-response (risk increases with the exposure) are considered to be an indication of causality, but IARC notes that the absence of a dose-response does not necessarily indicate a lack of a causal relationship. Lastly, the temporality (exposure prior to effect), precision of estimates of effect, biological plausibility and coherence of the overall database are considered. Biomarker studies may be considered in an assessment of the biological plausibility.

An ideal study for assessing causality is a randomized trial that would be able to show different rates of cancer among exposed and unexposed individuals, but these types of studies are rarely available. IARC also considers studies that show no association between exposure and cancer, and a group of studies may show evidence of a lack of carcinogenicity. These studies must meet the quality criteria described above to be considered for determination of a lack of carcinogenicity. Of note, IARC highlights that human carcinogenicity is associated with a latency period (the period from first exposure to the development of clinical cancer) that can be 20 years or more. If a study does not consider latency, i.e., because follow-up is too short, it may not be able to provide evidence of carcinogenicity. Details on the epidemiological studies related to welding fume exposures and evaluated by IARC are provided in Section 3.

2.4   Studies of cancer in experimental animals

Sufficient animal evidence of carcinogenicity usually consists of long-term animal studies of cancer of the agent. High quality studies include an assessment of the nature and extent of any impurities or contaminants present in the agent. In addition, the authors should specify the 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 tumors (incidence, latency, severity or multiplicity of neoplasms).

In general, IARC considers that any agent with sufficient animal data indicating carcinogenicity in animals is likely to also be carcinogenic to humans, although IARC acknowledges that animal data cannot establish that all agents that cause cancer in animals also cause cancer in humans

As with epidemiological evidence, IARC evaluates whether studies considered dose-responses (evidence of an increased incidence of tumors with increasing levels of exposure strengthens the causal association). The shape of the dose-response, however, may vary depending on the mechanism of action. Details on the animal studies related to the carcinogenicity of welding fumes and evaluated by IARC are provided in Section 4.

2.5   Mechanistic and other relevant data

IARC considers mechanistic data and other relevant data as supporting information for evidence of carcinogenicity and also for providing biological plausibility to the findings of cancer in animals and in humans. IARC does not always consider all mechanistic studies. Relevant studies may include toxicokinetics, mechanisms of carcinogenesis, susceptible individuals, populations and life-stages, other relevant data and other adverse effects.

Biomarker data may also be included in the mechanistic section. Details on the mechanistic studies related to welding fume exposures and evaluated by IARC are provided in Section 4.

2.6   Summary and rationale

The strength of the evidence from human and animal data, as well as any relevant mechanistic data, is evaluated and IARC categorizes the evidence into one of four classifications: Sufficient evidence of carcinogenicity, Limited evidence of carcinogenicity, Inadequate evidence of carcinogenicity or evidence suggesting a lack of carcinogenicity. The criteria for each classification vary for human and animal/mechanistic data (see IARC, 2018).

For example, in human studies:

Sufficient evidence of carcinogenicity:

IARC applies this criteria when it has determined that a causal relationship has been established between exposure to the agent and human cancer, where 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. IARC specifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans.

Limited evidence of carcinogenicity:

IARC applies this criteria when it has determined that a positive association has been observed between exposure to the agent and cancer, but chance, bias or confounding could not be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity:

IARC applies this criteria when it has determined that 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:

IARC applies this criteria when it has determined that there are several adequate studies covering the full range of levels of exposure that humans could encounter, which show consistently *no* positive association between exposure to the agent and any studied cancer.

IARC then considers the body of evidence as a whole to reach an overall evaluation of the carcinogenicity of the agent to humans and classifies the agent as Group 1, Group 2A or 2B, Group 3 or Group 4. The criteria for each category are described below.

Group 1: The agent is carcinogenic to humans.

IARC applies this category when there is *sufficient evidence of carcinogenicity* in humans. It is applied in rare circumstances when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in animal studies and strong evidence that the agent acts through a relevant mechanism of carcinogenicity.

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

IARC applies this category in cases where there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in animals. In some cases, an agent may

have *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in animals together with strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Rarely, an agent may have *limited evidence of carcinogenicity* in humans, but this classification may be applied based on mechanistic considerations, or if it belongs 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.

IARC applies this category to agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in animals; also, if there is *inadequate evidence of carcinogenicity* in humans, but *sufficient evidence of carcinogenicity* in animals. In some instances, when 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 or 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.

IARC uses this category for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in animals. Rarely, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in animals, but there is strong evidence that the mechanism of carcinogenicity in animals does not operate in humans. Also, it is used for agents that do not fall into any other group.

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

IARC uses this category when there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some cases, IARC uses this category when there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in animals, together with a broad range of mechanistic and other relevant data.

In the Rationale section, IARC summarizes the evidence across all lines, human, animal and mechanistic data and provides a concise judgement for the selection of the agent's category. The IARC conclusions and rationale regarding welding fume exposures and lung cancer are summarized in Section 6.

3 WELDING STUDIES OF CANCER IN HUMANS

3.1 Introduction

IARC reviewed a large body of epidemiological literature on cancer risks from welding jobs or exposures to welding fumes, primarily from cohort and case-control studies (IARC, 2018). IARC noted that the number of published epidemiological studies has greatly increased since the evaluation in 1989 (IARC, 1990). The focus of the IARC review was on studies that reported risk estimates associated with occupation as a welder (and not other associated jobs such as pipefitter or plumber) or exposure to welding fumes, which primarily was based on occupation or welding as a job task rather than any quantitative estimate of welding fume exposure. Specifically, the exposure assessments in some epidemiological studies relied on a welding-specific questionnaire or a welding exposure matrix, and these studies were considered by IARC to be the most informative. Studies that applied a general job-exposure matrix and those based on self-reported welding-related exposures were considered somewhat less informative, and studies that looked at only job titles were considered the least informative. Most studies focused on lung cancer, but evidence of associations with other cancers was also evaluated.

Several studies considered the type of welding process and specifically the type of metal welded, such MS or SS, IARC noted that SS welding may contribute to higher exposures to Ni and Cr, which are recognized lung carcinogens. Co-exposures to other non-welding activities in the welding environment are also important to consider as these may be important confounders (e.g., metal grinders, coatings on welded metal, or compounds used to prepare the metal for welding). Asbestos is also a common co-exposure typically from heat-protective materials or insulating materials. Lastly, smoking is a key confounder that needs to be considered for lung cancers. According to IARC, the prevalence of smoking among welders has been shown to be higher than in the general population. IARC considered studies with information on welding material, welding process, and co-exposures to asbestos and smoking to be the most informative.

We provide a general overview of IARC's evaluation of the epidemiological literature related to welding exposures and lung cancer, and provide a more detailed evaluation on six studies highlighted by Guha et al. (2017) in their discussion of IARC's conclusions related to welding exposure and lung cancer risk. Four studies, two cohort (Sorensen et al. 2007, Siew et al. 2008) and two case-control (Matrat et al. 2016, 't Mannetje et al. 2012), were described as being large and of high quality and also reporting exposure-response associations of longer or greater cumulative exposure to welding fumes. An additional two studies were highlighted for their consideration of key confounders (Kendzia et al. 2013, Steenland et al. 2002). The IARC Working Group reported finding more than twenty relevant case-control studies in addition to several industrial cohort studies (see IARC, 2018 Table 2.3) and population-based cohort studies (see IARC 2018 Table 2.1). We discuss the key studies and limitations in the following sections.

3.2 General Overview of IARC's Evaluation of the Epidemiological Evidence

IARC discusses cohort studies by groups of related studies, including industry cohorts such as the large multi-center study that was coordinated by IARC – hereafter the "IARC cohort studies" (summarized in IARC, 2018, Table 2.3) and population-based studies (summarized in IARC, 2018, Table 2.1). The IARC cohort studies are comprised of over 11,000 welders

employed across 135 companies in eight European countries (Denmark, England, Finland, France, Germany, Italy, Norway, Scotland, and Sweden) (Simonato et al., 1991). The cohort includes welders in many different industries that use different welding materials and processes. A special welding matrix was developed to assign welders to 13 combinations of welding process and metals that were matched to average exposures level including total welding fumes, total Cr, hexavalent chromium, and Ni. In addition, welders were assigned to different groups – shipyard welders, only MS welders, or ever SS welders. Mortality and incidence were compared to national rates. Overall the study found increased lung cancer risks for the full cohort (SMR: 1.34, 95% CI 1.1-1.6), but there was no indication of a dose-response as SMRs did not increase with time since first employment. Analyses by welding type also showed positive, but not statistically significant increased risks of lung cancer, except for MS welders (SMR: 1.78, 95% CI 1.27-2.43), but still no indication of a dose-response. IARC noted that the size of the cohort was a particular strength, as well as the analyses by welding process. However, there was little information on smoking as a potential confounder, and the large number of reported mesotheliomas indicated potential asbestos exposures.

After the IARC study, there were several IARC subcohort analyses that were conducted with extended follow-up times or more detailed analyses of individual country cohorts including the Denmark cohort (Hansen et al., 1996; Lauritsen and Hansen, 1996; Sorensen et al., 2007), the French cohort (Moulin et al., 1993), the German cohort (Becker, 1999), and the Swedish cohort (Milatou-Smith et al., 1997). Details of these studies can be found in IARC (2018) Table 2.4. As discussed in more detail in the next Section, IARC considered the study by Sorensen et al. (2007) to be the superior study because of adjustments for asbestos and smoking. Other subcohort analyses were deemed to be less informative because they were generally much smaller in size. In several of the studies, and in particular the German study (Becker, 1999), asbestos exposure was believed to explain some or all of the lung cancer risks.

In addition to details regarding the IARC cohort and subcohorts, IARC summarizes results from seven cohort studies of shipyard workers including studies in Norway, Italy, and the US. Overall, IARC noted several limitations associated with these studies, including potential for confounding from asbestos and smoking, limited follow-up time (potential cancers may have been missed), and lack of detailed evaluation of welding fume exposures. IARC also evaluated cohort studies of welders in other industries including heavy equipment manufacturing plants, automobile assembly, stamp and engine plants, foundries, metal shops, telephone line workers, and nuclear plants. Of these studies, IARC found the study by Steenland et al. (2002) to be the most informative of these studies (see details in next section).

IARC, also evaluated population-based studies (see IARC (2018) Table 2.1), but in general considered the exposure assessment in these studies to be weaker than in occupational studies. Of these studies, IARC considered the study by Siew et al. (2008) to be the highest quality study (see details in the next section).

IARC identified over 20 case-control studies that evaluated associations between welding and lung cancer. Details of these studies can be found in IARC (2018) Tables 2.5 and 2.6. Overall, IARC reported that case-control studies found elevated risks for lung cancer in welders, but they noted that for many studies results were not statistically significant

(potentially due to small sample sizes). In addition, they noted that some, but not all, studies adjusted for smoking and/or asbestos exposures. As discussed in more detail in the next section, IARC identified three key case-control studies that it considered to be the highest quality studies, 't Mannetje et al. (2012), Matrat et al. (2016), and Kendzia et al. (2013).

3.3 Evaluation of Key Epidemiological Studies

3.3.1 't Mannetje et al. (2012)

Study Summary:

't Mannetje et al. (2012) examined welding employment and lung cancer in 2,197 male incident lung cancer cases and 2,295 controls from 15 centers in Romania, Hungary, Poland, Russia, Slovakia, the Czech Republic, and the UK between 1998 and 2001. Hospital based controls were selected from all but two centers where population-based controls were used; 15.9% of cases and 15.0% of controls were not included. Face-to-face, an interviewer gathered data on occupations lasting for more than one year and other "lifestyle factors" (e.g. tobacco use). A welding specific questionnaire was administered to those who responded that they had been employed as a welder; 17 questionnaires were available for those who had worked in other occupational fields. Experts evaluated exposure to 70 agents for each job (possible, probable, certain confidence in presence of exposure; percent of working time exposed; low, medium, high intensity of exposure). Arc welding fumes and gas welding fumes were defined separately.[1] Total years working in an occupation with welding fumes was captured. The authors assessed how well the experts agreed with each other through the use of a Kappa statistic where values closer to 1 indicate high agreement and those closer to 0 indicate little agreement. They reported that agreement was high between the experts for welding fumes (Kappa 0.9), but lower for welding-related exposures (Kappa 0.3 for asbestos and Cr). Lifetime exposure to welding fumes was examined as duration, weighted duration, and cumulative exposure. Models were adjusted in multiple steps for 1) age, center (i.e. study location), tobacco use, education; 2) lifetime occupational exposure to asbestos, silica, plastics pyrolysis fumes, ionizing radiation; 3) exposure to Cr, Ni, cadmium (Cd), and arsenic (As) unrelated to welding fume and exposure to these agents related to welding fumes.

In a model adjusted for age, center, education, tobacco use, the odds ratio was 1.37 (95% CI 1.01-1.87) for ever having worked as a welder/flame cutter and 1.19 (95% CI 1.02-1.39) for ever being exposed to welding fumes. Adjustment for asbestos, silica and metals in jobs not involving welding fumes (Cr, Ni, Cd, and As) did not appreciably change the results. Further adjustment for welding-related exposure from Cr, Ni, and Cd reduced the odds ratios to 1.18 (95% CI 0.84, 1.66) for ever having worked as a welder/flame cutter and 1.10 (95% CI 0.92, 1.32) for ever being exposed to welding fumes. The odds ratio for lung cancer in those with more than 25 years of exposure to welding fumes was 1.38 (95% CI 1.09-1.75) in a model adjusted for age, center, education, smoking, asbestos, and silica

---

[1] The authors defined arc welding fumes as fumes "generated during the joining or cutting of metals using arc welding techniques (a process in which the heat of fusion is obtained by striking an electric arc between an electrode and the metal work piece), " and gas welding fumes "fumes generated during the joining or cutting of metals using gas welding techniques (a process in which the heat of fusion is obtained from the combustion of oxygen and one of several gases such as acetylene, methyl-acetylene-propadiene, propane, or hydrogen)." ('t Mannetje et al., 2012)

and Cr exposure not related to welding. The estimate was reduced to 1.29 (95% CI 1.00, 1.67) when Cr exposure that was welding-related was added. The p value for trend for duration of exposure to welding fumes and lung cancer was 0.01 (statistically significant), which became non-statistically significant (p value = 0.11) when Cr exposure that was welding-related was added to the model. The exposure-response relationship was less pronounced for weighted duration (lifetime hours) and was less consistent for cumulative exposure; both tests for trend became non-statistically significant once Cr exposure was included in the model. The authors also explored welding fumes with and without Cr, reporting an elevated OR of 1.34 (95% CI 1.04, 1.71) for exposure to welding fumes with Cr and an OR of 1.14 (95% CI 0.95, 1.36) for exposure to welding fumes without Cr. Furthermore, the authors explored exposure to only arc welding fumes and only gas welding fumes. The odds ratio was higher for exposure to gas welding fumes only (OR 1.31, 95% CI 0.93, 1.85) than arc welding fumes only (OR 1.05, 95% CI 0.82, 1.33); they noted that this difference between the odds ratios was not statistically significant. The authors concluded that welding fume exposures increased the risk of lung cancer independently of asbestos exposure and smoking.

Ramboll comments:

The sample size of this study was a particular strength with 2,197 male incident lung cancer cases and 2,295 controls, and the number of cases and controls were adequate for the large majority of analyses. The study included separate analyses for arc welding and gas welding fumes and also examined exposure to welding fumes with and without Cr.

- *Exposure assessment*: IARC considered this to be one of the better case-control studies as far as exposure assessment because they used a welding-specific questionnaire and can account for information regarding job title, type of industry, time period, welding type and materials and control measures, the questionnaire can also collect information that allows for examining how worker exposures vary within the same job. IARC does note that this method has limitations because it relies on worker histories and self-reported welding exposure details. Self-reported information can be susceptible to recall bias.

- *Confounding by tobacco:* The authors offered little detail on the tobacco use variable. The authors only described it as a "continuous variable for cumulative lifetime tobacco use." Without more detail it is difficult to assess whether the information is reliable, however, the authors presumably included this in the questionnaire as an additional self-reported question.

- *Confounding by asbestos:* The authors reported that the reliability between experts was low for evaluating exposures to asbestos (Kappa agreement was 0.3 for asbestos). As noted by the authors this could mean that there is misclassification of asbestos exposure and the potential for residual confounding.

- *Conclusions:* We note that the risk estimates are low, and the study appears to show that there are increased risks only for gas welding fumes compared to arc welding fumes. This study also shows increased risks for welding fumes that contain Cr compared to welding fumes with no Cr and this could be indicative of differences between MS and SS welding. Also, while the authors adjusted for both tobacco use and asbestos exposure, it is unclear if these could still be contributing to confounding, especially because the risks were so small (i.e., there is a great chance for confounding effects that could explain small risks).

3.3.2   Matrat et al. (2016)

Study Summary:

Matrat et al. (2016) conducted a population-based case-control study in France between 2001 and 2007. The study included 2,276 male cases and 2,780 male controls. During face-to-face interviews, occupational history was collected for each job lasting one month or longer using a general questionnaire and 20 job-specific questionnaires. In the general questionnaire, participants were asked "during this job period, were you exposed to welding/brazing/gas cutting?" and if more than 5% of worktime was spent doing this, then the job-specific questionnaire was used to gather "process of welding, the type of metals welded, the type of coating covering the metal, the treatments applied before welding and the use of protective clothing." The authors distinguished between "regular welders," who had at least one job period as a welder, and "occasional welders," who responded in the affirmative at least once to the general question above. A task exposure matrix (TEM) and job exposure matrix (JEM) were used to develop a cumulative exposure index (CEI) for asbestos exposure. A cumulative smoking index (CSI) combining total smoking duration, time since cessation and intensity (average cigarettes smoked per day) was used to assess lifelong cigarette smoking. Multivariable logistic regression models were used to examine regular and occasional welding separately following adjustment for age, department, CSI, CEI for asbestos, and total number of working periods.

No statistically significant associations or clear patterns were observed among the occasional welders. In the regular welders, the odds ratio for lung cancer was elevated in those who welded more that 5% of the time (1.67, 95% CI 1.10-2.54). Also in regular welders whose time since their first welding exposure was greater than 35 years and for those that had worked for more than 10 years the risks were elevated (OR 2.05, 95% CI 1.08 to 3.91) compared to those who had worked for 10 years or less (OR 1.64, 95% CI 0.75, 3.62). In regular welders whose time since first welding exposure was *less* than 35 years, the odds ratios were 1.08 (95% CI 0.38, 3.01) for those who worked 10 years or less and 1.54 (95% CI 0.62, 3.79) among those who worked more than 10 years. The odds ratio for those with 10-20 years since last welding was highest (OR 2.53, 95% CI 1.01 to 6.37) and decreased in those in the 20+ year categories. Among regular welders, odds ratios were statistically significantly elevated for ever soldering (2.62, 95% CI 1.20 to 5.72), ever gas welding[2] (1.98, 95% CI 1.20 to 3.29) and ever arc welding[2] (1.99, 95% CI 1.21 to 3.26), but not ever brazing, ever spot welding, or ever doing other types of welding. Among the occasional welders, odds ratios were not statistically elevated for any of these welding categories. However, due to a larger pool of cases and controls who were occasional welders, the authors were able to examine exclusive time spent doing different welding activities. Of note, the odds ratio for exclusive gas welding was non-statistically significantly elevated (OR 1.64 95% CI 0.69, 3.90); the odds ratio for exclusive time arc welding was 0.89 (95% CI 0.39, 2.04).

In the regular welders, the odds ratios for lung cancer were statistically significantly elevated in those who reported the presence of grease or paint on the piece to be welded (OR 1.98, 95% CI 1.15, 3.43) or who reported cleaning the surface to be welded with a chemical or mechanical preparation (OR 2.79, 95% CI 1.35, 5.77). In the regular welders, the odds ratios for welding and the three histological lung cancer types were similar (squamous cell carcinoma: 1.8, 95% CI 1.1, 3.0; small cell carcinoma: 1.6, 95% CI 0.8, 3.1; and adenocarcinoma: 1.6, 95% CI 1.0, 2.8; p=0.4). The authors concluded that there

---

[2] Gas and arc welding were not defined by the authors

was a clear dose-response relationship between exposures to welding fumes and lung cancer, and that it appeared that both the type of welding (gas vs. arc welding) and the presence of other products (grease or paint) on the welding materials influenced the lung cancer risks.

Ramboll comments:

- *Sample size*: The sample size was adequate overall, but some of the subgroup analyses had few sample size numbers. For example, among the regular welders, there are only 5 controls and 8 cases that weld <=5% of the time. Also, for the regular welders, sample sizes are low in the time since last welding models.

- *Welding type/process:* The authors categorized welders into groups of: regular welders, occasional welders, and never welders. They analyzed welding type separately (e.g. gas welding vs. arc welding) and also analyzed risk according to the preparation or covering on the welding surface (e.g. grease, paint, chemical preparation) and according to the chemicals used to clean the welding surface (e.g. gasoline, acid). They attempted to examine lung cancer risk according to type of welded metal, but they reported that it was not possible to "isolate groups of workers that had welded a unique type of metal." Risk estimates by type of metal were "homogeneous" (range of 1.05–1.75), not significant, and not presented. The authors reported differences in cancer risk by type of welding and also if the welding materials had other products on the surface. Differential risks by welding type are consistent with the findings by 't Mannetje et al. (2012).

- *Exposure assessment*: IARC considered this to be one of the better case-control studies as far as exposure assessment because they used a welding-specific questionnaire. However, as with other studies, effects are not specifically correlated to any actual exposure measurements. IARC noted that a particular strength of the study was the distinction between regular and occasional welders. It is worth noting that occasional welders were not found to have an increased risk of lung cancer. In addition, while recall bias is an issue in case-control studies, Matrat et al. (2012) noted that they addressed this issue. Specifically they had knowledge of the entire occupational history of the workers, and for occasional welders they also found that welding activity was similarly self-reported by cases and controls (23%). In contrast, the authors noted that regular welders were significantly more represented among cases than among controls, and therefore it is likely that cases were overestimated as regular welders.

- *Confounding by tobacco use:* Matrat et al. (2012) used a cumulative smoking index (CSI), which captures the entire smoking history. This was a particular strength of the data although it is also based on recall.

- *Confounding by asbestos exposure*: Asbestos exposure was gathered by questionnaires, which were used in a TEM. By using a TEM, the authors are able to assign individuals their own exposure rather than rely on the exposure associated with a particular job (as is done using a JEM). Therefore, the authors were confident that the assessment of asbestos exposures was conducted as accurately as possible.

- *Conclusions*: This study had many strengths including the most complete assessment of both tobacco use and asbestos exposure in the workers. The authors also distinguished between occasional and regular welders. The most interesting results from this study included analyses comparing gas vs arc welding, and analyses

that accounted for the presence of other products on welding materials. The authors specifically made note of these findings as they may indicate significant differences in lung cancer risk depending on the type of welding as well as the materials used. These results were consistent with those of 't Mannetje et al. (2012).

3.3.3 Sorensen et al. (2007)

Study Summary:

Sorensen et al. (2007) followed 4,539 male welders (3,085 stainless steel (SS), 1,454 mild steel (MS)) from 74 Danish companies (excluding shipyards due to the potential for asbestos exposure) who had worked for at least one year between 1964 and 1984, were born before 1965, and alive as of April 1968. Participants were followed for primary cancer diagnosis from 1968 to 2003; seventy-five lung cancers were identified. A questionnaire completed in 1986 gathered information on "direct" asbestos exposure and "duration, timing, type, and amount of daily tobacco smoking." Details about welding activities including first and last year were also gathered and divided into 1960-69, 1970-79 and 1980-86. A welding exposure matrix was used to calculate a summary measure of exposure to welding fume particulates over the lifetime. Gender-, age- and calendar-specific national rates were used to calculate standardized incidence ratios (SIR). Hazard rate ratios (HRR) adjusted for age, asbestos exposure (yes/no) and tobacco smoking (never smoker, ex-smoker in 1986 or current smoker in 1986) were calculated using Cox regression analyses.

SIRs for lung cancer were statistically significantly elevated for "ever welding" (1.35, 95% CI 1.06-1.70), for welding that began in 1960-1969 (1.41, 95% CI 1.04-1.87), MS or SS welding for 21 or more years (3.69, 95% CI 1.77-6.79), and only SS welding for 21 or more years (3.69, 95% CI 1.77-6.79). In the internal analysis with adjustments for potential confounders, risk was not elevated in the SS welders compared to the MS welders (HRR 0.86, 95% CI 0.52-1.42). No clear dose-response was detected for the duration of welding variables in MS workers. In SS welders with 11 or more years of accumulated exposure, workers had an increased risk of lung cancer compared to those with 0-5 years (HRR 2.34, 95% CI 1.03-5.28). The authors concluded that their findings support a lung cancer risk in welders, and suggest that SS welders may have an increased risk compared to MS welders.

Ramboll comments:

- *Cohort follow-up and sample size:* The follow-up period for the cohort was adequate spanning from 1968 to 2003. The SS welders had a mean age of 37.3 (SD 9.8) and the MS welders had a mean age of 43.1 (12.4) at baseline in 1986, so they would be in their late 50s to early 60s on average at the end of follow up. Sample size was adequate overall, but for some subcohorts (e.g., duration and cumulative exposure models) the sample sizes were small.

- *Welding type/process:* SS and MS welders considered.

- *Exposure assessment*: IARC judged this study to be among the studies having the strongest exposure assessment. The study used a welding specific job-exposure matrix (JEM). However, IARC also noted limitations with the exposure assessment including issues with retrospective recall of details regarding welding processes and the lack of full job histories of the workers.

- *Confounding by asbestos*: A questionnaire administered in 1986 was used to determine whether the worker had been directly exposed to asbestos. No additional

detail was provided. This was captured as yes or no in the internal analysis, which appears to be a crude measure of asbestos exposure.

- *Confounding by tobacco*: Smoking history was also assessed by questionnaire in 1986, which captured "duration, timing, type, and amount of daily tobacco smoking." In the internal analysis, this was captured as current smoker in 1986, ex-smoker in 1986, or never smoker.

- *Conclusions*: Although IARC considered this study to be the most informative of the IARC cohort studies because of the longer follow-up period, better exposure assessment (based on a JEM and using exposure measurements available), and adjustment for tobacco use and exposure to asbestos, the study had important limitations including in both the exposure assessment and in the adjustments for smoking and asbestos exposures. In addition, the overall risks were generally small, and the study suggests that not all welders are equal risk from welding exposures, with SS welders at a potentially increased risk.

3.3.4   Siew et al. (2008)

Study Summary:

Siew et al. (2008) evaluated associations between exposure to iron (Fe) and welding fumes and the incidence of lung cancer among Finnish men. Risk of lung cancer and exposure to welding fumes ("occupational inhalation exposure to fumes from welding") and Fe fumes and dust ("occupational inhalation exposure to Fe dust or fumes from welding, smelting, grinding, or other processing of steel and other materials containing iron", including metallic Fe and all Fe compounds) was examined. All "economically active" men born between 1906 and 1945 who had taken part in the 1970 census were included and followed for mortality from 1971 to 1995. The longest held occupation as recorded in the census was used to calculate cumulative exposure estimates using the Finnish job-exposure matrix (FINJEM). Individual-level smoking information was not available. Instead, information from yearly health behaviors surveys conducted in the Finnish population between 1978-1991 were used to determine the proportion of daily smokers in a given occupation. Exposure estimates for asbestos, silica, Ni, Cr, lead (Pb), benzo(a)pyrene, and smoking were included in the FINJEM. A total of 30,137 lung cancer cases occurred in the 1.2 million men. Poisson regression was used to examine exposure-response relationships in models adjusted for smoking, exposure to asbestos and silica, socioeconomic status, age, and periods of follow-up. The authors also examined risks associated with lung cancer subtypes (squamous cell, small cell and adenocarcinoma).

The results of the analyses are shown in Table 1. In the internal analysis, the risk of lung cancer was statistically significantly increased for 50 mg/m^3-years or more of cumulative exposure to Fe fumes or dust (RR 1.35, 95% CI 1.05, 1.73). Risk of lung cancer was mildly elevated, but not statistically significantly for the highest cumulative exposure category of ≥200 mg/m^3-years of welding fumes (RR 1.15, 95% CI 0.90–1.46). When specific lung cancer subtypes were examined, an increased risk of squamous cell carcinoma was seen for both exposure to Fe or dust fume and exposure to welding fume. Compared to those with no exposure to welding fumes, the RR were 1.07 (95% CI 0.99–1.15), 1.26 (95% CI 1.04–1.53), and 1.55 (95% CI 1.08–2.24) for 0.1–10, 10.1–49.9 and ≥50 mg/m^3-years of exposure to welding fumes, respectively. For exposure to 0.1 to 10, 10.1 to 49.9 and 50+ mg/m^3-years of Fe or dust fumes, the relative risks were 1.08 (95% CI 1.00, 1.16), 1.16 (95% CI 0.95, 1.41), 1.94 (95% CI 1.35, 2.78), respectively, compared to no exposure. Clear patterns were not seen for small-cell carcinoma or adenocarcinoma. The authors

concluded that exposure to Fe and welding fumes was associated with an increase in lung cancer risk (primarily squamous-cell carcinoma), but they could not determine the independent role for each of the agents because of the simultaneous exposure to both agents.

Table 1. Summary of Results by Job Category

Job Category	SIR	95% CI
welder and flame cutter (stainless steel >10%)	0.95	0.78–1.15
welder (shipyard)	1.05	0.69–1.55
welders (building)	1.31	0.84–1.95
welders (not elsewhere classified)	1.39	1.14–1.69

Notes: SIR – standardized incidence ratio; CI – confidence interval

Ramboll comments:
- *Cohort follow-up*: The follow-up appears to be adequate (from 1971 to 1995) although the mean age at baseline was not provided.

- *Welding type/process:* The authors evaluated different occupational categories for welder and flame cutter (stainless steel >10%), welder (shipyard), welders (building), and welders (not elsewhere classified), but otherwise did not assess welding by specific type or process.

- *Exposure assessment:* The authors used a general JEM, which was judged by IARC to be less informative than a welding specific exposure matrix. In addition, exposure duration was based on information regarding the occupations that were held for the longest time according to the 1970 census. Specifically, the authors noted that "[s]tability is relatively high in most occupations, and therefore the cross-sectional information on occupation corresponds rather well to life-long occupational history." Furthermore, the authors noted that the correspondence is even higher for older populations in Finland, where turnover rate between occupations is low.

- *Confounding by tobacco*: Adjustment for smoking was crude. As reported by the authors, smoking was based on the proportion of people in a certain occupation who smoked, and these data were obtained from annual health behavior surveys of the Finnish adult population in 1978–1991. The authors further note that the smoking data based on the years 1978–1991 are likely to be too recent to assess any causation for lung cancers diagnosed between 1971 and 1995. Therefore, an adjustment based on these smoking data might bias the relative risk estimates if the smoking habits do not correlate with those in earlier decades. The authors acknowledged that residual confounding may have had an effect on the relative risk estimates.

- *Confounding by asbestos*: The FINJEM provides exposure estimates for asbestos.

- *Conclusions:* This was a very large cohort, but the exposure assessment was not necessarily specific to welding (general job-exposure matrix). Further uncertainty was introduced as the job duration (cumulative exposure) was assumed based on the longest occupation that was held until 1970 (which could mean an incomplete job history) – and this affects both welding fume exposures and other important exposures such as asbestos and silica. The relative risks, which we adjusted for age, smoking, socioeconomic status, and exposure to asbestos and silica, were generally positive except for SS welders and only statistically significant for welders that could not be classified into welders in the building industry or shipyards. The authors did find increasing risks with increased cumulative exposures. IARC noted that the study strengths included the large number of workers, the exposure assessment, and data on confounders. However, it is important to note that both exposure assessment and the adjustment for confounding was limited, and residual confounding is likely.

3.3.5 Kendzia et al. (2013)

Study Summary:

Kendzia et al. (2013) conducted a pooled analysis of case-control studies that included occupational and smoking histories to evaluate the risk of lung cancer from welding exposures. The authors identified 15,483 male cases and 18,388 male controls from the SYNERGY project, which combines data from 16 studies conducted in Europe, Canada, China, and New Zealand between 1985 and 2010. Response rates were 85% for cases and 77% for controls. Interviews on occupational and smoking history were face-to-face 81% of the time. 94% of cases and 93% of controls were alive at the time of the interview. Individuals with a job title of "welder" lasting for one or more years were categorized as welders. Individuals with job titles that may involve welding activities or involve welding on occasion were categorized as occasional welders (e.g. plumbers, sheet-metal workers, fitters). Welders and occasional welders were categorized as ever holding the position or as it being the longest held position. Welders and occasional welders were also stratified by industries commonly involving welding (e.g. ship building and repair, construction and related building services). Logistic regression models were adjusted in three steps. Model 1 was adjusted for age and study center. Model 2 was additionally adjusted for smoking captured as "log (pack-years + 1), time-since-quitting smoking cigarettes (current smokers, ever other types of tobacco only, stopped smoking 2–7, 8–15, 16–25, or ≥ 26 years before interview/diagnosis, or never smokers)." Those who smoked fewer than 10 pack-years were considered to be light smokers. Model 3 further adjusted for "List A" jobs or those in "occupations associated with risk of lung cancer, excluding welding-related occupations."

The odds ratio for ever welding was statistically significantly elevated for both welders (1.44, 95% CI 1.25, 1.67) and in those in occupations occasionally involving welding (1.19, 95% CI 1.10, 1.28). When examined by lung cancer type, the odds ratios for adenocarcinoma (1.23 0.99, 1.53), squamous cell (1.58, 95% CI 1.32, 1.89) and small cell (1.41, 95% CI 1.09, 1.82) were elevated in welders and adenocarcinoma (1.22, 95% CI 1.09, 1.37) and squamous cell (1.14, 95% CI 1.03, 1.25) in occasional welders. Odds ratios for lung cancer increased as years working as a welder increased compared with never welders :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). The authors concluded that their study provides additional support for an increased risk of lung cancer in welders.

Ramboll comments:

- *Sample size:* The sample size was adequate.

- *Welding type/process:* The authors did not specify the welding type or process. Welders or occasional welders were identified by job titles.

- *Exposure assessment:* The authors categorized workers as welders or occasional welders. IARC noted that exposure assessment based on job title only does not provide information on level of exposure, so it is less informative.

- *Confounding by tobacco*: Smoking information was collected primarily though face-to-face interviews. It was included in the models as log(pack-years + 1) AND time-since-quitting smoking cigarettes (current smokers, ever other types of tobacco only, stopped smoking 2–7, 8–15, 16–25, or ≥ 26 years before interview/diagnosis, or never smokers). Recall bias is generally an issue when collecting this information.

- *Confounding by asbestos*: The authors did not adjust specifically for asbestos exposure. Instead, they adjusted for ever working in "List A" jobs, which are occupations that involve risk of lung cancer (excluding welding-related occupations). Kendzia et al. (2013) justified their decision to not adjust for asbestos exposure by citing studies that found no influence on the relative risks when asbestos exposure was included. They concluded that welding fumes exert an independent risk for lung cancer.

- *Conclusions:* This was a large case control study that overlapped with the study by 't Mannetje et al. (2012) but was evaluated separately by IARC because of additional analyses not included in Kendzia et al. (2013). The limitations of this study as noted above include an exposure assessment that was based solely on job title and the lack of adjustment specifically for asbestos exposures. The authors did report a significant trend with duration of occupation as a welder and a stronger risk associated with squamous cell lung cancer (consistent with Siew et al., 2008). Overall, it is difficult to exclude potential confounding by asbestos or other air pollutants commonly associated with welding fume exposures.

3.3.6 Steenland et al. (2002)

Study Summary:

Steenland et al. (2002) evaluated the mortality risk from lung cancer in 4,459 male mild steel (MS) welders and 4,286 never welders from three heavy equipment plants in the US from 1989 to 1998, extending follow up from the mid-1950s to 1988 (from a prior study Steenland, 1991). The welder cohort included production welders (arc welders) or welder helpers (welder cleaners) and the non-welder cohort included "assemblers, inspectors, packers, janitors, or electric forklift drivers"; all workers had been employed for two or more years in their respective areas at the plants. SMRs were calculated using age-, race-, and calendar- time specific rates for the welders and non-welders separately.

A total of 1,969 deaths (23% of the cohort) including 108 lung cancer deaths in the welders and 128 in the non-welders were reported. The SMR for lung cancer was statistically significantly elevated in welders (1.46, 95% CI 1.20–1.76) and was smaller in non-welders (1.18, 95% CI 0.98–1.40); the standardized rate ratio for the welders compared to the non-welders was 1.22 (95% CI 0.93, 1.59). A 15-year lag did not markedly modify the results. No clear trends emerged for duration of exposure or latency. The authors concluded that

the findings were suggestive but not conclusive for an association between MS welding and lung cancer.

Ramboll comments:

- *Follow up:* Follow-up was adequate for lung cancer. The first study had a follow up from the mid-1950s to 1988 (Steenland, 1991), and this study extended the follow-up from 1989 to 1998.

- *Welding type/process:* The study included only MS welders. Shielded metal arc welding (stick welding) was the main method up to the mid-1960s. From then until the time of the study, continuous wire shielded with inert or neutral gas (often carbon dioxide) was the main process. Other than a shield, respiratory protection was not common. The workers primarily welded unpainted steel (Steenland, 1991.)

- *Exposure assessment:* Workers were categorized as welders or non-welders in the analysis. Personal exposure monitoring was conducted from 1974-1987 in the welders. Also, exposure monitoring was conducted in 28 non-welders to confirm non-exposed status. However, none of these measurements were used in the analysis. Cr, Pb, and Mn levels were generally undetectable. Exposures to welders tended to be within acceptable levels (based on the OSHA total dust standard of 15 mg/m^3, for iron oxide OSHA standard of 10 mg/m^3 and the ACGIH standard of 5.0 mg/m^3). In addition, they reported that the concentrations of components of welding fumes (e.g., Cr and Ni), which have health-based occupational standards, were very low or undetectable. Non-welders had minimal to no exposure (Steenland, 1991.). Overall, however, analyses were based on job title and not measured levels of welding fume exposures.

- *Confounding by tobacco:* The authors did not use any individual measures for tobacco use in the analysis. Instead, the authors stated that they assumed that welders and non-welders from the same plant were "likely to have smoked similar amounts." The authors reported results from a company survey taken in 1985 that showed that the two groups were similar in terms of the percentage of nonsmokers, but that the welders were more likely to be current smokers. The authors did attempt to determine the effect of confounding by smoking and concluded that there was a "modest excess" in the welders compared to the non-welders which is beyond that explained by tobacco. The authors estimated that the difference in the rate ratio between welders and non-welders would be approximately 1.08 due to smoking differences alone, compared to the rate ratios of 1.22 for welders versus non-welders. The authors caveat these calculations, however, by noting that the smoking data were limited and "did not provide a basis for solid inference about the effects of smoking versus exposure on lung cancer rates."

- *Confounding by asbestos*: The authors did not control for asbestos exposure in the analysis. However, this was a population reported to have low asbestos exposure. Steenland et al. (2002) specifically included a cohort of MS workers and of never welders from the same plants to reduce the confounding impact from both asbestos (typical of shipyard welding) or Ni and Cr (present in SS welding). Steenland et al. (2002) also reported that there were no asbestosis or nonspecific pneumoconiosis deaths in the welders or non-welders, which suggests minimal asbestos exposure and there was only one mesothelioma death in a welder who had "20 years of prior

employment in a brewery, an industry with potential asbestos exposure." In addition, the authors reported that the continuous wire welding method used starting in the mid-1969s did not involve asbestos exposure. Welding rods coated with asbestos could have been used in past, but even still the exposure to asbestos would likely have been minimal (Steenland, 1991.). The authors did report that they did not have work histories of the workers who were currently employed at the time of the data collection in the mid-1980s (14% of the cohort). A full record of work histories could contribute to bias because of potential asbestos exposures in prior jobs.

- *Conclusions:* This was a large cohort which extended the follow-up from a previous study by 10 years. The workers were only MS welders that were compared to non-welders, and were not exposed to asbestos, Ni or Cr in their current jobs. No information, however, was provided for prior jobs that may have included these potential exposures. Although the authors found statistically significant increased lung cancer risks compare to the general population, in an internal analysis compared to non-welders the risks were significantly less and were not statistically significant (standardized rate ratio (SRR), 1.22; 95% CI, 0.93–1.59). Also, trends for years of exposure were not significant. Although the authors attempted to evaluate smoking risks relative to welding fume risks, the analysis was crude, and the authors found that both welders and non-welders smoked more than the general population. As noted by IARC, the major limitation was the lack of any quantitative or even semi-quantitative exposure assessment to welding fumes. We would add that the study lacked full employment history (with any potential for prior asbestos exposure) and there was no formal adjustment for smoking. As noted by the authors the results are suggestive, but not conclusive for an association between welding and lung cancer.

4   TOXICOLOGICAL EVIDENCE

4.1   Studies in Animals

- A previous IARC Monograph conducted in 1989 found that there was *inadequate evidence* for the carcinogenicity of welding fumes in experimental animals (IARC, 1990).

- One short-term inhalation study exposed male A/J mice for 6 or 10 days (N= 45 and N=55, respectively) for 3 hours per day to gas metal arc stainless steel (GMA-SS) fumes (40 mg/m^3) and measured lung tumor incidence and multiplicity 78 weeks after exposure. The results for the exposed group were not significantly different from those of the control (nonexposed) group. The study was limited by the study design with of short duration and applied only a single exposure. The dose was considered a low dose, equivalent to about 50 days of exposure in a 75 kg person working an 8-hour shift using the time-weighted average of 5 mg/m^3 for welding fumes (Zeidler-Erdely et al., 2011a as cited in IARC, 2018).

- One well-designed study exposed GMA-SS, manual metal arc stainless steel (MMA-SS), and gas metal arc mild steel (GMA-MS) welding fumes to male A/J mice (N=25) via oropharyngeal aspiration (dosed every 3 days, 340 µg) and evaluated tumor incidence and multiplicity after 48 and 78 weeks. There was no significant difference between the exposed mice and the nonexposed controls. However, there was a small number of animals in each group and no way to evaluate a dose-response effect as only one dose was tested (Zeidler-Erdely et al., 2008 as cited in IARC, 2018).

- Another study exposed male A/J mice (N=11) to MMA-SS welding fumes (20 mg/kg body weight) via oropharyngeal aspiration once per month for 4 months and evaluated lung tumor incidence and multiplicity. As with the other oropharyngeal study, the results were negative. The study was limited in that there was only one dose tested, and the sample size was small (Zeidler-Erdeley et al., 2011b as cited in IARC, 2018).

- One study exposed male hamsters to metal inert gas stainless steel (MIG-SS) and MMA-SS welding fumes via intratracheal instillation. Two doses of MMA-SS (0.5 and 2.0 mg) and one dose of MIG-SS (2.0 mg) along with a saline vehicle control were tested on 35 hamsters per group. Two malignant lung tumors were observed after 100 weeks of exposure in the MMA-SS exposed hamsters. However, this study was determined inconclusive by IARC due to the lack of detailed histopathology, survival data, statistics, clear methodology reporting, and historical controls (Reuzel et al., 1986 as cited in IARC, 2018).

- Two studies investigated whether welding fumes had a lung tumor promoter effect. In one quality study, male A/J mice were exposed to GMA-SS welding fumes via whole-body inhalation after initiation with 3-methylcholanthrene and evaluated for lung tumor incidence and multiplicity. A significant promoter effect was observed. However, a dose-response effect could not be evaluated due to the single dose tested in the study (Falcone et al. 2017 as cited in IARC 2018). The other initiation-promotion study exposed male A/J mice to a low (340 ug) and high (680 ug) dose of GMA-SS welding fumes via oropharyngeal aspiration once per week for 5 weeks, 1 week following initiation with 3-methylcholanthrene (Zeidler-Erdely et al., 2013 as

cited in IARC, 2018). The cumulative doses of GMA-SS were estimated to be equivalent to approximately 450 days and 900 days of exposure in a 75-kg human working an 8-hour shift. The animals were evaluated for tumor incidence and multiplicity 30 weeks after exposure. Both groups exposed to GMA-SS welding fumes with the initiator had significantly increased lung tumor multiplicity compared with the sham control. There was no significant difference in results between the low and high dose, though the lower dose trended lower in all measures.

- Another initiation-promotion experiment where mice were exposed to GMA-SS and its components via oropharyngeal aspiration examined the pulmonary toxicity and tumorigenic potential of welding fume as well as of the individual metal oxide components (Falcone et al., 2018 as cited in Zeidler-Erdeley et al., 2019). GMA-SS welding fume induced the most lung toxicity in the animals; Fe and Cr showed toxicity in the animals, but Ni did not. Fe (as Fe_2O_3) significantly promoted lung tumors in the presence of the initiator 3-methylcholanthrene but the Cr mixture and Ni alone did not. Zeidler-Erdeley et al. (2019) suggest that iron could be the primary component causes lung cancer down the line.

- No long-term studies on the effects of exposure to welding fumes in experimental animals treated by inhalation were available.

- *Overall conclusions:* Based on these animal studies only, there is inconclusive evidence for welding fumes causing lung cancer. No long-term studies were available and reviewed by IARC. One short-term inhalation study and two oropharyngeal aspiration studies had negative results. Three initiation-promotion studies showed evidence for GMA-SS welding fumes having a significant promoter effect on lung tumorigenicity, one of which had evidence for iron oxide being a primary mediator in the process.

4.2 Mechanistic Studies

4.2.1 Absorption, distribution, and excretion

- All types of welding are associated with siderosis of the lung, also known as welder's lung, and caused by inhalation of iron oxide (Doherty et al., 2004 as cited in IARC, 2018). Numerous studies of welders demonstrate the absorption and excretion of metals as measured in blood and urine: Cr, Ni, and Mn (among MS welders, including MMA and TIG processes) (Kalliomaki et al., 1982, Kalliomaki et al., 1978, Edme et al., 1997, Cena et al., 2015, Scheepers et al., 2008, Dufresne et al., 1997 as cited in IARC, 2018), Cr, Ni, and aluminum (among SS welders, including GMA, FCA, TIG and SMA with stick electrodes processes) (Weiss et al., 2013, Ellingsen et al., 2006, 2004, Rossbach et al., 2006, Brand et al., 2010, Bonde & Ernst 1992, Stridsklev et al., 1993, Sjogren et al. 1988, Sjogren et al., 1985, Huvinen et al., 1997, Fuortes & Schenck, 2000 as cited in IARC, 2018).

- Two rat studies where animals were exposed by inhalation to MMA-MS or MMA-SS welding fumes, Fe and Mn were absorbed from the lung, though the alveolar retention of the MS fumes was lower and had faster clearance (Kalliomaki et al., 1983 a, b as cited in IARC, 2018). One rat study showed urinary excretion of these same metals (Kalliomaki et al., 1982a, b, 1984 as cited in IARC, 2018). Two studies exposed male Sprague-Dawley rats to GMA-MS and MMA-HS (hard-surfacing) welding fumes via intratracheal instillations and showed lung deposition and

absorption of metals (Cr, Ni, Mn, and Fe) with varying rates of clearance (no copper clearance was reported) and all four metals examined had evidence of distribution to various tissues (brain, lymph nodes, heart, kidney, spleen, liver) (Antonini et al., 2010, Sriram et al., 2012 as cited in IARC, 2018). One rat study showed urinary excretion.

- A dose-dependent increase in lung Mn concentration was observed in a study where six male cynomolgus monkeys were exposed to whole-body inhalation to MMA-SS welding fumes for 2 hours per day for 240 days (Park et al., 2007a as cited in IARC, 2018). Increases in Mn concentrations were seen in the liver, kidneys, testes, and a dose-dependent increase in Mn was seen in the globus pallidus. However, this study lacked power in a sample size of six animals.

- Mn was also shown to have dose- and time-dependent distribution to specific regions in the brain, lungs, and liver of male Sprague-Dawley rats after exposure to MMA-SS welding fumes for 60 days (Yu et al., 2003 as cited in IARC, 2018).

- Several other studies exposing rats and mice to welding fumes showed absorption and distribution of metals including Mn, Fe, and Cr. One study measured urinary excretion of Cr and Ni and reported that almost all of the metals were excreted, but was limited because the metal concentrations were not corrected for creatinine.

- *Overall conclusions:* The studies that have assessed the absorption and distribution of metals from welding fume exposures indicate that exposures result in absorption and distribution of these metals in the body. The rate of absorption, distribution and clearance appears to vary depending on the dose and timing of exposure as well as type of metal fume (e.g., MS and SS) and this could impact the relative toxicity of these metals.

4.2.2 Mechanisms of carcinogenesis

Induction of chronic inflammation

- The IARC Working Group concluded that there is strong evidence that welding fumes induce chronic inflammation.

- Numerous studies in occupational cohorts show increases in biomarkers of lung inflammation, oxidative stress, and systemic inflammation.

- Acutely exposed boilermakers (exposed to GTA, SMA, or GMA welding) are associated with a blunting of systemic inflammation at the end of their work shifts. Statistically significant increase in 8-OHdG (a measure of systemic inflammation) from pre- to post-shift have been observed. However, the post-shift to bedtime change in 8-OHdG had an unexpected inverse relationship with $PM_{2.5}$. Chronically exposed workers had a higher biomarker measured value consistent with chronic inflammation at the start of their shift (Nuernberg et al., 2008 as cited in IARC, 2018).

- Long-term exposure is associated with an increase in markers of tissue damage rather than system inflammation.

- Some exposure-response relationships are observed. In a study of 27 welders who were exposed long-term to welding fumes, an increase in blood eosinophil and basophils was seen (Palmer et al., 2006 as cited in IARC, 2018). Another study of chronic exposure to Mn fumes, welders with high concentrations of blood Mn had

significantly lower levels of immune cells (CD8+ T and CD10+ B lymphocytes) compared with workers with lower blood Mn concentrations (Nakata et al., 2006 as cited in IARC 2018).

- Seven repeated measure panel studies in boilermakers with ST exposure to welding fumes were identified by the Working Group (Kim et al., 2005, Wang et al., 2005, 2008, Fang et al., 2008, 2009, 2010a, Nuernberg et al., 2008 as cited in IARC, 2018). In these studies, exposure assessment of welding fumes within the individuals' breathing zones and assessment of biological variability between individuals was conducted. Exposure of high levels of welding fumes induced acute systemic inflammation (i.e., increased leukocyte and neutrophil counts) among healthy workers, but there is evidence for smoking as a modifier of effect.

- In toxicogenomic and metabolomic studies of welders (Wang et al., 2008, Wei et al., 2013 as cited in IARC, 2018), there were changes in inflammatory pathways and eicosanoid levels with evidence of a time-dependent or exposure-response relationship, respectively.

- There were numerous studies in rats and mice demonstrating changes in the inflammatory response. Lung inflammation and bronchoalveolar lavage fluid cellular content was increased. Short-term and subchronic exposure to SS welding fumes stimulated cellular influx of alveolar macrophages, neutrophils, lymphocytes, which were not seen in MS welding fumes (Zeidler-Erdely et al., 2012 as cited in IARC, 2018). Inhalation exposure to MMA-SS or GMA-SS welding fumes was associated with inflammatory cytokines in bronchoalveolar lavage fluid (Yu et al., 2004, Sung et al., 2004, Yang et al., 2009, Antonini et al., 2007, Halatek et al., 2017 as cited in IARC, 2018). Short-term inhalation exposure to GMA-MS fumes did not have a notable effect on BALF or lymph nodes associated with the lungs (Antonini et al., 2009a, Zeidler-Erdely et al., 2014 as cited in IARC, 2018).

- The Working Group reviewed some in vitro studies, but results were mixed. In vitro studies may not be the best way to observe chronic inflammation, as noted by IARC.

- There were no studies observing past short-term exposure, and if the inflammatory effect continues after exposure ceases.

- *Conclusions:* While studies indicate evidence of an inflammatory response from welding fume exposures all the studies were short-term studies and do not provide information on long-term effects that would ultimately contribute to carcinogenicity. Effects are also dose and timing dependent, and are likely modified by other factors (e.g., smoking).

Immunosuppression

- The Working Group concluded that there is strong evidence that welding fumes are immunosuppressive.

- Welders are known to have higher risk of pneumococcal pneumonia in epidemiological studies (Coggon et al., 1994, Wergeland and Iversen, 2001, Palmer et al., 2003 as cited in IARC, 2018). This is evidence for immune suppression due to welding fume exposure.

- A plausible mechanism for the increase of pneumonia involves platelet-activating factor receptor (PAFR) (Suri et al., 2016, Grigg et al., 2017 as cited in IARC, 2018).

Respiratory cells exposed to welding fumes can cause upregulation of PAFR-dependent pneumococcal infection.

- Several animal studies observing subchronic exposure to welding fumes were reviewed by the Working Group. Subchronic exposure to SS or MS welding fumes impaired resolution of pulmonary infection.

- Gene-expression arrays of the lung showed that SS welding fumes interfered with immunological response pathways in rats and mice; there was also evidence for welding fumes interfering with immunological pathways in a primate study.

- Two in vitro studies showed decreased immune functions in mouse immune cells when exposed to welding fumes.

- *Conclusions*: Although increased susceptibility for pneumococcal pneumonia in welders is suggestive on immunosuppression of welding exposures, we found the evidence to be limited and inconclusive overall. In particular gene-expression assays and in vitro assays are generally very non-specific.

Genotoxicity

- The Working Group concluded there is moderate evidence that welding fumes are genotoxic.

- Among humans, the results of studies on genotoxicity (chromosomal aberrations and sister-chromatid exchange rates in lymphocytes) are mixed. Most micronuclei studies had positive findings, but some studies had methodological issues. The majority of DNA strand break studies in lymphocytes and buccal cells were positive. The three DNA-protein cross-linking studies had positive results, but the studies had small sample sizes of five to 21 exposed subjects.

- Of three inhalation exposure studies in rats, two studies had positive results for DNA damage in lung cells or strand breaks in leukocytes, kidney, and liver cells (Yu et al. 2004, Chuang et al. 2010 as cited in IARC 2018) and one study reported no increase in chromosomal aberrations or sister-chromatid exchanges. All three in vitro assays for genotoxicity identified by the Working Group were positive for genotoxicity (Leonard et al. 2010, Pedersen et al. 1983, Ong et al. 1987 as cited in IARC 2018).

- An increase in 8-hydroxy-2'-deoxyguanosine (8-OHdG) in blood plasma and urine, a measure of oxidative damage to DNA, was observed in two studies of controlled crossover exposure and two field studies showing an effect during the work shift of boilermakers (Nuernberg et al. 2008, Kim et al. 2004 as cited in IARC 2018). An exposure-response relationship was seen with PM2.5 or particle number concentrations in four of the studies (Kim et al. 2004, Lai et al. 2016, Graczyk et al. 2016a, b as cited in IARC 2018). These studies were all small cohort or controlled crossover studies with around 20-40 exposed subjects. One study of 118 shipyard tungsten inert gas (TIG) welders and 45 office workers showed that 8-OHdG levels in the urine were higher at the end of 5 working days than at the start for all subjects, but 8-OHdG concentrations among welders were significantly higher at the end of the study period than those of the office workers (Lai et al. 2016 as cited in IARC 2018).

- Three cross-sectional studies had mixed findings; a relationship between welding fume exposure and urinary 8-OHdG or 8-oxo-guanosine was unclear (Liu et al., 2013, Li et al., 2015a, Pesch et al., 2015 as cited in IARC, 2018). Cross-sectional studies are less informative, especially with small sample sizes.

- *Conclusions*: Results were generally mixed and inconclusive for this outcome.

Oxidative stress

- The Working Group concluded that there was moderate evidence that welding fumes induce oxidative stress.

- Short-term studies of exposure to various types of welding fumes reported increases in 8-OHdG in urine (see Genotoxicity section) and increases in hydrogen peroxide in exhaled breath or urine (Graczyk et al., 2016a, Gube et al., 2010 as cited in IARC 2018).

- In cross-sectional studies of welders, exposure to welding fumes was associated with increases in oxidative stress markers (8-isoprostane) and decrements in antioxidant status (glutathione, superoxide dismutase activity) in blood and urine.

- In three studies in which male Sprague-Dawley rats were exposed to SS welding fumes, markers of lung oxidative stress were observed (Taylor et al. 2003, Antonini et al., 2004a, Erdely et al., 2014 as cited in IARC, 2018). However, one study in male Wistar rats reported no change in serum concentrations of lipid peroxidation measures (Halatek et al., 2017 as cited in IARC, 2018).

- SS and MS welding fumes did not activate stress-response pathways in gene expression arrays of the lungs of male mice. The welding fumes used to expose these mice were not freshly generated, which may have an impact on the potential oxidative effect of the fumes (Zeidler-Erdely et al. 2008 as cited in IARC 2018).

- In vitro studies (in both primary cells and immortalized cell lines) showed that both SS and MS welding fumes induced oxidative stress in the form of reactive oxygen species production (Antonini et al., 1997, 1999, Change et al., 2013, Leonard et al., 2010 as cited in IARC, 2018).

- In biochemical acellular systems, SS and MS fumes generated ROS and oxidized dopamine, ascorbate, and glutathione.

- No inhalation exposure experiments or experimental challenge studies in humans were identified in the Working Group's review.

- *Conclusions:* Study results were somewhat mixed, but suggestive of the oxidative potential of welding fume exposures. It remains unclear if these biomarkers of effect would result in carcinogenicity based on short-term studies.

Alterations to cell proliferation and cell death

- The Working Group concluded that there was *moderate* evidence that welding fumes alter cell proliferation or death.

- There was little data from exposed humans. One study reported nuclear anomalies in the buccal and nasal cells of TIG welders (Wultsch et al., 2014 as cited in IARC, 2018). An *in vitro* study that exposed human lung cells to SS welding fumes reported cytotoxicity (McNeilly et al., 2004 as cited in IARC 2018).

- Short term and subchronic exposures to welding fumes increased BALF albumin levels and/or lactate dehydrogenase activity in Sprague-Dawley rats (Taylor et al., 2003, Antonini et al., 2004a as cited in IARC, 2018). Studies in mice who were exposed short-term to GMA-SS fumes reported increases in proliferative lesions and persistent lung cytotoxicity (Falcone et al., 2017 as cited in IARC, 2018) and several

studies exposing mice to welding fumes reported changes in BALF albumin levels and lactate dehydrogenase activity for a period of time after exposure.

- In gene-expression array studies, SS welding fumes disrupted pathways related to cell proliferation in primates and rodents. In another gene-expression array study, MS welding fumes induced circadian rhythm signaling and cell survival pathways in mice (Zeidler-Erdeley et al., 2010 as cited in IARC, 2018).

- In several studies, MS and SS welding fumes induced cytotoxicity and/or altered mitochondrial function in mammalian cells. SS fumes had the most potent cytotoxicity.

- *Conclusions:* Evidence from these studies is suggestive of the potential for cytotoxicity of welding fumes, particularly for SS welding. No studies in humans were available, and only short-term animal studies were available. It is unclear how these observed changes, if they are transient and not persistent, contribute to cancer.

Modulation of receptor-mediated effects

- The Working Group concluded *weak* evidence that welding fumes modulate receptor-mediated effects.

- Studies evaluating the effects of welding fumes on the levels of sex hormones (testosterone, luteinizing hormone, and follicle-stimulating hormone), serum prolactin and inhibin B in occupational cohorts had mixed findings. Some studies had methodological issues or improper statistical analyses.

- There were no experimental studies reported.

- *Conclusions*: Studies were generally limited and inconclusive for this outcome.

Other mechanisms of carcinogenesis

- Studies of welders (mostly MMA-MS) reported decrease in telomere length and increased LINE-1 methylation, potential markers of increased risk of cancer. Two studies of welders reported that $PM_{2.5}$ was significantly associated with increased methylation (Fan et al., 2014, Kan et al., 2013 as cited in IARC, 2018). Another study where 48 welders (mostly MMA-MS welding) were followed for 8 years reported a statistically significant decrease in relative telomere length. The study also reported that genomic damage to leukocyte telomeres was correlated with recent occupational $PM_{2.5}$ exposure (Wong et al., 2014b as cited in IARC, 2018).

- Some studies found that genetic damage was associated with exposure to respirable dust and length of time working as a welder (Li et al., 2015a, Hossain et al., 2015 as cited in IARC 2018).

- *Conclusions*: There is some suggestive evidence of genetic damage from welding fume exposures or occupational exposure to $PM_{2.5,}$ but these studies fall short of making conclusive links between welding exposures and cancer.

5 Conclusions

IARC (2018) concluded that welding fumes are *carcinogenic to humans* (Group 1) based on *sufficient evidence* in humans for the carcinogenicity of welding fumes, specifically for cancer of the lung (more limited evidence for cancer of the kidney). There is *limited evidence* in experimental animals for the carcinogenicity of welding fumes.

IARC (2018) based its conclusions of lung carcinogenicity on over 20 available case–control studies, which mostly reported positive lung cancer risks based on welding as their job task, or classified as or reporting to be exposed to welding fumes. Similarly, IARC noted that most of the 20 plus cohort studies that assessed the association between welding and cancer of the lung also reported positive findings. IARC did not find convincing evidence of differences between arc and gas welding. They found that the studies rated to be of the highest quality (as discussed in detail in Section 3) eliminated chance and bias as contributing to the findings. Lastly, IARC found convincing evidence of an exposure-response relationship between exposure to welding fumes and lung cancer.

IARC considered tobacco smoking an important potential confounder, but found that it was unlikely to explain all of the observed excess lung cancer risk in the epidemiological studies, noting that several of the higher quality studies adjusted for smoking. Similarly, with respect to asbestos exposure, IARC also determined that asbestos exposure was unlikely to explain all of the lung cancer risk. Although asbestos has not been used in several decades, the occupational cohorts may have had historical exposures to asbestos that contributed to lung cancer in the decades after exposure, as there is a long lag time between exposure and the development of disease.

Also, IARC noted that there was insufficient evidence to conclude that lung cancer risks were limited to specific welding materials or the welding methods, for example SS welders.

In general, IARC determined that the animal studies were limited, primarily because there were no long-term studies on the effects of exposure to welding fumes in animals treated by inhalation. The few short-term studies provided inconclusive evidence of carcinogenicity. IARC did find that the initiation–promotion studies provided evidence of promoter effects of GMA-SS welding fumes on lung tumorigenicity.

IARC also found that there was adequate data with respect to the key characteristics of human carcinogens including induction of chronic inflammation, immunosuppression, genotoxicity, induction of oxidative stress; alteration of cell proliferation, cell death, and modulation of receptor-mediated effects.

Ramboll found that the evidence for lung cancer effects from welding fume exposures remains inconsistent and that confounding by smoking, asbestos, and other lung toxicants was not sufficiently accounted for even in the most rigorous, higher quality studies. These limitations preclude clear causal inference. Exposure assessment remains a major limitation in these occupational studies, as individual level exposures are not used to assess cancer risks. Exposure-response relationships were inconsistent across the higher quality studies, and risks were low and often not statistically significant. In fact, in the 1990 IARC monograph, IARC (1990) concluded that "[i]n the absence of an increasing trend with duration of exposures a relative risk for lung cancer lower than about 1.5 should be interpreted with caution." Although relative risks in the more recent epidemiological studies remain in this range, IARC did not include similar language in the more recent evaluation. Epidemiologists generally agree that such weak correlations make causation difficult to

establish because there is a higher likelihood that unmeasured or residual confounding would explain the observations (e.g., Boffetta et al., 2008; Flewell et al. 2007).

In addition, several of the higher quality studies found evidence of the potential for differential risks by welding type (arc vs. gas welding) and welding material (MS vs SS). We also note that some of the authors of the key epidemiological and animal studies held important positions in the IARC Working group, which may present a real or perceived conflict of interest when evaluating the scientific evidence in an objective manner.

Based on the available literature, Ramboll found that data are generally lacking to provide any definite causal conclusions regarding welding fume exposures and cancer. In particular, there is a lack of long-term animal studies that could be conducted to evaluate carcinogenesis of well-characterized welding fume exposures (i.e., from different processes, and including composition of welding fume components). In addition, there is a need to evaluate occupational exposures in epidemiological studies, such that cancer risks are based on actual or modelled welding fume exposure concentrations (i.e., rather than job type) or on biomonitoring results, and should be stratified by welding processes or welding fume composition. In addition, the IARC evaluation is limited to cancer, and a similar evaluation of non-cancer risks from welding fume exposures is needed.

Lastly, an important limitation of the IARC evaluation is that IARC does not quantify the level of risk or provide guidelines or health-based exposure limits that could be used for implementation of adequate process controls. In light of the lack of clear guidelines, Ramboll offers the following recommendations:

- Updating hazard communication materials to inform workers of IARC's new classification of welding fume as a Group 1 carcinogen,
- Documenting and better characterizing welding fume exposures in the workplace for both workers and nearby workers (not engaged in welding):
  - Exposure data can be used in future epidemiological studies
  - Exposure data can be used to evaluate current exposures and identify areas for improvement of process controls as well as tracking of progress, and
- Assess areas of improvement for reducing exposures and implement controls that maximize reductions per NIOSH guidelines for carcinogens that aim to make exposures as low as feasible.

6   REFERENCES

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.

Boffetta P, McLaughlin JK, La Vecchia C, Tarone RE, Lipworth L, Blot WJ. 2008. False-positive results in cancer epidemiology: a plea for epistemological modesty. *J Natl Cancer Inst.* 16;100(14):988-95.

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):848-856.

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):217-225.

Fewell Z, Davey Smith G, Sterne JA. 2007. The impact of residual and unmeasured confounding in epidemiologic studies: a simulation study. *Am J Epidemiol*. 15;166(6):646-55.

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):373-382.

Hill, AB. 1965. The environment and disease: association or causation? *Proceedings of the Royal Society of Medicine* 58:295-300.

International Agency for Research on Cancer (IARC). 1990. Chromium, Nickel and Welding. IARC Monographs of the Evaluation of Carcinogenic Risks to Humans. Volume 49. Lyon, France.

Interntional Agency for Research on Cancer (IARC). 2018. Welding, Molybdenum Trioxide, and Indium Tin Oxide. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 118. Lyon, France.

Jockel, KH, Ahrens, W, Pohlabeln, H, Bolm-Audorff, U, Muller, KM. 1998. Lung cancer risk and welding: results from a case-control study in Germany. *Am J Ind Med* 33(4):313-320.

Kendzia, B, Behrens, T, Jockel, KH, Siemiatycki, J, Kromhout, H, Vermeulen, R, . . . Bruning, T. 2013. Welding and lung cancer in a pooled analysis of case-control studies. *Am J Epidemiol* 178(10):1513-1525.

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):383-391.

Matrat, M, Guida, F, Mattei, F, Cenee, S, Cyr, D, Fevotte, J, . . . Icare Study, G. 2016. Welding, a risk factor of lung cancer: the ICARE study. *Occup Environ Med* 73(4):254-261.

Meguellati-Hakkas, D, Cyr, D, Stucker, I, Fevotte, J, Pilorget, C, Luce, D, Guenel, P. 2006. Lung cancer mortality and occupational exposure to asbestos among telephone

linemen: a historical cohort study in France. *J Occup Environ Med* 48(11):1166-1172.

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):128-131.

Moulin, JJ, Wild, P, Haguenoer, JM, Faucon, D, de Gaudemaris, R, Mur, JM, . . . Birembaut, Y. 1993. A mortality study among mild steel and stainless steel welders. *Br J Ind Med* 50(3):234-243.

Pukkala, E, Martinsen, JI, Lynge, E, Gunnarsdottir, HK, Sparen, P, Tryggvadottir, L, . . . Kjaerheim, K. 2009. Occupation and cancer - follow-up of 15 million people in five Nordic countries. *Acta Oncologica* 48(5):646-790.

Siew, SS, Kauppinen, T, Kyyronen, P, Heikkila, P, Pukkala, E. 2008. Exposure to iron and welding fumes and the risk of lung cancer. *Scand J Work Environ Health* 34(6):444-450.

Simonato, L, Fletcher, AC, Andersen, A, Anderson, K, Becker, N, Chang-Claude, J, . . . Hansen, KS. 1991. A historical prospective study of European stainless steel, mild steel, and shipyard welders. *Br J Ind Med* 48(3):145-154.

Sorensen, AR, Thulstrup, AM, Hansen, J, Ramlau-Hansen, CH, Meersohn, A, Skytthe, A, Bonde, JP. 2007. Risk of lung cancer according to mild steel and stainless steel welding. *Scand J Work Environ Health* 33(5):379-386.

Steenland, K. 2002. Ten-year update on mortality among mild-steel welders. *Scand J Work Environ Health* 28(3):163-167.

't Mannetje, A, Brennan, P, Zaridze, D, Szeszenia-Dabrowska, N, Rudnai, P, Lissowska, J., . . . Boffetta, P. 2012. Welding and lung cancer in Central and Eastern Europe and the United Kingdom. *Am J Epidemiol* 175(7): 706-714.