# Health Effects from Welding: 2014 Literature Update

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# 1 Introduction

The American Welding Society (AWS) asked Gradient to conduct a comprehensive literature search and summary of studies related to the health effects of welding for 2014, providing an update to previous summaries that have been conducted for 2010-2013. In this update, we included literature published in 2014, following the same methodology as in our previous reviews. This report describes the literature search methods, provides a summary of the results of our searches (*e.g.*, how many articles we identified), and explains how we identified relevant articles to include in the report (Section 2). We also present brief summaries of the exposure-related studies in Section 3, and more detailed summaries of relevant health effects studies in Section 4. Lastly, in Appendix A we present a brief overview of recent studies that have focused specifically on exposures to welding and lung cancer.

# 2 Methods

We searched the PubMed, Toxline, NIOSHTIC-2, and SCOPUS databases for articles relevant to welding exposures and health effects resulting from those exposures, as described below.

## 2.1 Search Strategy

1. To capture all the potentially relevant literature, the initial keyword searches included the word "welding" or "welders."
2. To narrow the search and identify specific articles related to "health," specific terms and their variants were applied, as necessary, in conjunction with the general terms welding and welders. Search terms included: toxicology, risk, epidemiology, morbidity, mortality, inhalation, cancer, lung(s), lung inflammation, respiratory, cardiovascular, bronchitis, Parkinson's, asthma, neurological/neurotoxicity, metal fume fever, and occupational lung disease. The details of how these terms were applied are provided in Section 2.2.
3. To narrow the general results and identify specific articles related to "exposure," specific terms and their variants were applied, as appropriate, in conjunction with the general terms welding and welders. The search terms included: exposure monitoring, exposure characterization, occupation(al), workers, workplace, laborers, cohort, dose, particle characterization, inhalable, respirable, and sampling. The details of how these terms were applied are provided in Section 2.2.
4. Literature searches were limited to documents published in 2014 (either electronically or in print). Articles included in previous reviews were excluded from this review.

## 2.2 Database Searches

### 2.2.1 PubMed

An initial search for "welders" or "welding" in all fields or in Medical Subject Headings (MeSH) terms was conducted. Results were filtered for the year 2014, yielding 217 citations. The search results were then filtered for citations relevant to health and exposure (as described in Section 2.1). Any citations that were excluded were reviewed to ensure that no relevant articles were missed. An Excel file was created with the remaining citations and reviewed. Any additional non-relevant articles (*e.g.*, materials processing, nano-synthesis, prosthetics, and chemical structure or analysis) were removed at this stage. A total of 54 articles were retained in the Excel spreadsheet for further review.

### 2.2.2 TOXLINE

The TOXLINE database was searched for articles containing "welders" or "welding" that were published in 2014. No relevant citations were identified.

### 2.2.3 SCOPUS

The SCOPUS database was queried for articles containing "welders" or "welding" in the title, abstract, or key that were published in 2014, and the results of that query were filtered using the search terms that included the health and exposure terms described in Section 2.1. This method yielded 58 articles, which were exported to an Excel spreadsheet.

The results of these searches overlapped significantly. After removing the overlapping studies, one additional relevant study remained from the SCOPUS query.

## 2.3 Literature Review

We sorted the results from the literature search by PubMed identification number (PMID) and excluded additional duplicates that were identified. We also excluded case reports, commentaries, conference presentations, and any foreign studies that were deemed to be of little or no relevance. The remaining citations were retained in the Excel spreadsheet, and the article titles and abstracts were reviewed for relevance and sorted into the following categories:

- Particle characterization and exposure data
- Epidemiology and controlled human exposure studies
- Animal studies
- Cell/*in vitro*/mechanistic studies
- Reviews

The breakdown of the number of articles by category is listed in Table 2.1.

**Table 2.1 Breakdown of Abstracts Reviewed by Study Category**

| Study Category | PubMed 2014 Totals | SCOPUS 2014 Totals |
|---|---|---|
| Particle characterization and exposure | 22 | |
| Epidemiology and controlled human exposure | 21 | 1 |
| Animal | 6 | |
| Cell/*in vitro*/mechanistic | 1 | |
| Reviews | 4 | |
| **Overall Total** | **54** | **1** |

We provided a brief summary of abstracts for exposure-related studies in Section 3, and summarized the abstracts for all health-related studies by health endpoint in Section 4.

# 3 Exposure Studies

We identified 22 exposure-related publications from 2014 (*i.e.*, particle characterization and exposure data). Several studies were published online in 2014 (*i.e.*, 2014 was the "epub date") but were published in print in 2015; these were included in our summary. Articles that were not relevant or were included in a prior AWS updates (*e.g.*, epub date in 2013) were excluded. A brief summary of the exposure abstracts is provided below for all the relevant studies; links to complete abstracts are provided in the reference list.

- Afshari *et al.* (2014 PMID: 25140455) developed an inhalation exposure system to characterize exposure to aerosols during resistance spot welding. This system can be used to help identify which components of spot welding emissions might be associated with specific health effects.
- Aiba *et al.* (2014 PMID: 25212435) conducted interviews of 38 male arc welders regarding their use of a respirator. Survey results showed that the subjects' respirator use was adequate and appropriate, but the participants were not aware of the frequency of filter replacement in the respirators.
- Arrandale *et al*. (2015 – epub 2014 PMID: 25359273) collected urine samples from female and male welders in order to compare urinary metal concentrations by gender and task or type of welding. In multiple regression analyses, little relation was found between urinary metals and task or type of welding, except for cadmium where lower levels were seen in those reporting semi-automatic manual welding (after adjustment for age and smoking). The authors reported lower manganese (Mn) and copper (Cu) exposures in male welders.
- Baker *et al.* (2015a epub 2014 PMID: 24916793) collected blood, plasma, and urine samples from nine newly exposed apprentice welders over a 3-month period in order to assess inter- and within-subject variability in Mn concentrations. In blood, the majority of the variance in Mn concentration was between subjects, whereas in plasma and urine the majority of the variance was within subjects, demonstrating the importance of longitudinal designs with repeated exposures when assessing biomarkers of exposure and the spurious associations that could result from cross-sectional analyses.
- Casjens *et al*. (2014 PMID: 25223225) compared concentrations of iron (Fe) in the blood serum (serum ferritin) with respirable concentrations of iron in the breathing zone of welders during welding shifts. Concentrations of respirable iron were a significant indicator of serum ferritin.
- Cate *et al.* (2014 PMID: 24515892) evaluated the accuracy and cost effectiveness of microfluidic paper-based analytical devices (µPADs), a new method of measuring metals in welding fumes. The acid-extractable concentrations of Fe, Cu, nickel (Ni), and chromium (Cr) in fumes from shielded metal arc, metal inert gas, and tungsten inert gas welding measured by the µPADs were compared to the concentrations detected using inductively coupled plasma-optical emission spectroscopy (ICP-OES). The authors concluded that the µPAD sensors are a viable and inexpensive alternative to traditional analytic methods for hazard surveillance of metals in welding fume particulate matter (PM).
- Cena *et al.* (2014 PMID: 24824154) evaluated the accuracy of collecting Mn, Ni, Cr, and Cr(VI) in welding fumes with nanoparticle respiratory deposition samplers, in order to develop a new method of measuring respiratory deposition of metal nanoparticles. The results indicated that a large portion of the collected mass of the various metal species may have been contributed by the nano-sized particle range, but validation of the method in occupational settings is still needed.

- Driscoll *et al.* (2014 PMID: 25018282) used data collected in the Australian Work Exposures Study (AWES) project survey to quantify the prevalence of exposure to lead (Pb) in the workforce. The authors reported larger than expected exposures to Pb in Australian workers.

- Gomes *et al.* (2014 PMID: 25072724) evaluated the source of aluminum (Al) particles emitted and their deposition in the alveoli during friction stir welding. Both nano- and micro-particles were measured, and the authors noted that nanosized particles are likely due to tool wear.

- Guerreiro *et al.* (2014 PMID: 24730680) analyzed the metal composition of particles emitted during metal active gas welding and determined that the amount of emitted particles (measured by particle number and alveolar deposited surface area) are dependent on the distance to the welding front, the current intensity, and heat input. Fine particle emissions increased with the current intensity, and higher emissions were observed with higher carbon dioxide ($CO_2$) content.

- Hulo *et al.* (2014 PMID: 24508310) compared the concentrations of four metals (Mn, Ni, Fe, Cr) in exhaled breath condensate (EBC) to concentrations in urine to determine the viability of exhaled breath condensate as a potential biomarker for exposure to fumes produced during metal inert gas welding. The authors found concentrations of Mn and Ni in EBC were significantly higher in welders compared to controls, but they were not correlated with their respective levels in urine. The results suggest that EBC can be a useful biomarker for exposure to Mn and Ni from welding fumes.

- Keane *et al.* (2014 PMID: 24515891) assessed the emissions generation rate of nine gas metal arc welding processes for mild steel, shielded metal arc welding, and flux-cored arc-welding processes by collecting emissions in a fume chamber and analyzing total metals with inductively coupled atomic emission spectroscopy (ICP-AES). The study identified which processes had lower emission rates and provided information to aid in choosing the best process for minimizing fume emissions and costs while satisfying the weld requirements.

- Keane (2014 PMID: 25574138) compared the emission rates measured in the aforementioned Keane *et al*. (2014 PMID: 24515891) study with the costs per meter length of a weld in order to identify the method with the lowest emissions and relative labor and capital costs. The results show that any of the gas metal arc welding processes (and flux-cored welding) could substantially reduce fume and Cr(VI) emissions, and greatly reduce costs relative to shielded-metal arc welding.

- Lin *et al.* (2015 epub 2014 PMID: 25327301) measured the particle size distribution and metal concentration of emissions produced during welding and other processes in a fitness equipment manufacturing plant. This study observed bimodal distribution in the size of welding fume in the ranges of 0.7-1 µm and 15-21 µm. Particle size distributions were not consistent across work areas in the plant.

- Park *et al.* (2014 PMID: 25097299) evaluated the spark discharge system as a new method to simulate welding fumes for future toxicology and emissions studies related to welding. The results of this study showed that the spark discharge system can produce stable fumes that are similar to actual welding fumes, which may be useful for exposure and toxicological studies.

- Persoons *et al.* (2014 PMID: 25223250) collected post-shift urine samples from 137 welders at the end of a week and analyzed them for metals to determine the relevance of a biomonitoring program. Both welding parameters (nature of base metal, welding technique) and working conditions (confinement, welding and grinding durations, mechanical ventilation and welding experience) were predictive of occupational exposure. The results suggest that biomonitoring can be an effective tool for assessing and managing risks from welding fume exposures and for small- and medium-sized enterprises.

- Pesch *et al.* (2014a PMID: 25018273) used data compiled in the German MEGA database from 1988-2009 to assess the magnitude of Cr(VI) exposures in occupations with known Cr(VI) exposures. Cr(VI) exposure was assessed for eight out of 30 jobs tasks; the majority of measurements (53%) were collected in welders (N = 1930), which were further detailed by welding technique. Exposure to Cr(VI) varied by occupation and job task, particularly between welding techniques, but less over time

- Pouzou *et al.* (2015 epub 2014 PMID: 25245587) assessed how various parameters influenced welders' exposure to welding emissions. Welding method, the proximity of the welder's head to the fume, and air mixing were significantly associated with the welder's exposure, while other characteristics of dilution ventilation did not produce appreciable differences in exposure level. The authors found that ventilation was often inadequate for reducing emission exposures in confined spaces.

- Stam (2014 PMID: 24557933) searched scientific databases and related websites for occupational exposure data on electromagnetic field exposure, in order to determine occupations with exposure levels exceeding the revised European directive. The authors reported that magnetic flux densities exceeding action levels for peripheral nerve stimulation were reported for workers involved in several occupations, including welding.

- Wong *et al.* (2014 PMID: 24627998) assessed the association between $PM_{2.5}$ exposure and telomere length, a biomarker of mitotic history and genomic damage, in 48 broiler makers. At any follow-up time, there was a statistically significant decrease in relative telomere length of -0.04 units for each milligram per cubic meter per hour increase in cumulative $PM_{2.5}$ exposure in the prior month. The authors found that there was a more consistent association between genomic damage and recent $PM_{2.5}$ exposures compared to cumulative exposures.

- Yuasa *et al.* (2015 epub 2014 PMID: 25382381) recorded the breathing patterns of welders using an electromechanical breathing simulator and a respiration sampling device developed for the study to assess respirator performance. The system was applied to record the breathing patterns of workers engaging in welding, and successfully reproduced the breathing patterns.

- Zoppetti *et al.* (2015 epub 2014 PMID: 24936022) reviewed and assessed the current guidelines and standards for assessing welders' exposure to magnetic fields generated during arc welding, outlining their strengths and limitations.

# 4 Health Effects Studies

## 4.1 Studies in Humans

We identified 22 studies in humans that assessed various health effects related to welding fume exposures. These health effects included neurological effects (three studies), respiratory effects (ten studies), cardiovascular effects (two studies), cancer (one study), effects on the eyes (one study), immune function effects (one study), renal function effects (two studies), developmental effects (one study), and other effects (one study on heat stress). Summaries of these studies are provided below; links to study abstracts are provided in the reference list.

### 4.1.1 Neurological Effects

Baker *et al*. (2015b epub 2014 PMID: 25380186) evaluated apprentice welders with no prior welding experience every 3 months for five quarters, administering central nervous system function assessments to the entire group as well as magnetic resonance imaging (MRI) scans to a subset of welders. Personal exposure to welding fume was quantified using a mixed-model estimate. No association was measured between Unified Parkinson's Disease Rating Scale (UPDRS3) score or Grooved Pegboard time and cumulative exposure to welding fumes; however, increased Mn exposure was associated with increases in signal intensity observed in the basal ganglia, the region of the central nervous system associated with motor skills and procedural learning. These results suggest that effects on the brain may be detected before deficits can be clinically diagnosed.

Nielsen *et al*. (2014 PMID: 25018322) conducted a nested-case control study on three groups of welders: welders without Parkinsonism, welders with Parkinsonism, and welders with an intermediate UPDRS3 score of 6-15. Both the groups with Parkinsonism and intermediate UPDRS3 scores had lower levels of methylation of the nitric oxide synthase 2 (NOS2) gene (significantly decreased in welders with Parkinsonism). This study suggests that inflammation mediated by NOS2 gene expression may underlie the pathophysiology of Parkinsonism in Mn-exposed welders.

Giorgianni *et al*. (2014 PMID: 22914260) compared the blood levels of Al, zinc (Zn), Mn, Pb, and Cr of 86 male Al welders and administered three neurological function assessments (the Wechsler Memory Scale, the Colour Word Test, or Stroop Test, and the Test of Attention Matrixes). The average value of environmental Al, recorded in the workplace, was 19.5 $mg/m^3$. The results of these assessments were compared to a control group with no Al welding exposure. Test scores showed an association between decreased attention and memory performance and Al welding exposure.

### 4.1.2 Respiratory Effects

Ahn and Jeong (2014 PMID: 25408577) reviewed the characteristics of cases of lung cancer compensated by the Industrial Accident Compensation Insurance Law between 1994 and 2011. Cr(VI) was the third most common carcinogenic exposure, and welding was the third most common occupation among the reported cancer cases, reinforcing the need for proper surveillance systems.

Al-Otaibi (2014 PMID: 25374466) collected spirometry metrics (*i.e.*, lung function measurements) and information on respiratory symptoms *via* questionnaires from 41 welders and 41 comparable controls. While spirometry indices did not vary significantly between welders and controls, welders reported significantly higher rates of morning phlegm and chronic bronchitis compared to controls. Based on the questionnaire results, welders had 70% greater odds of developing chronic bronchitis compared to controls. However, the difference in cough, shortness of breath and lung function was statistically insignificant when the welders were compared with the nonexposed group.

Andujar *et al*. (2014 PMID: 24885771) conducted a multitude of scans of the lungs of 21 welders and 21 controls in order to assess nanoparticle deposition in lung tissue. Nanoparticles related to welding fume exposure were enriched in Fe, Mn, and Cr oxides. This nanoparticle profile was then externally synthesized in order to assess its effects on lung immune system cells in *in vitro* models. Exposure to the nanoparticles induced secretion of pro-inflammatory secretome from the cells in the *in vitro* lung model. Results suggest that pulmonary inflammation observed in welders may result from inhalation of nanoparticles.

Antonini *et al*. (2014 PMID: 25392698) conducted an *in vivo* and *in vitro* bioassay to assess the lung tissue toxicity of welding fumes generated from Ni- and Cu-based consumables. Exposure to Ni-Cu fumes was consistently associated with increased lung injury and inflammation compared to exposure to other welding fumes. The authors postulated that this increase in lung injury is a result of the direct cytotoxic effect of the metals rather than generation of secondary reactive oxygen species.

Hansell *et al*. (2014 PMID: 24327054) conducted multiple regression analyses on data collected from 1,017 individuals regarding respiratory disease and occupational exposures in the Wellington Respiratory Survey of New Zealand. Self-reported exposure to welding was significantly associated with chronic bronchitis symptoms. Higher predicted $FEV_1$% (forced expiratory volume in the first second of expiration, a measure of lung function) measurements were associated with exposure to welding fumes, but results were limited by the small number of cases identified in the study.

Kauppi *et al*. (2015 epub 2014 No PMID) administered lung inflammation challenge tests to 16 patients with suspected occupational asthma using mild steel and stainless steel welding fumes. Immune biomarkers of inflammation in blood and pulmonary function measurements were collected following exposure to the welding fumes. Biomarkers of inflammation in the blood increased following exposure to both kinds of welding fumes. Five of the patients were diagnosed with occupational asthma.

Koh *et al*. (2015 epub 2014 PMID: 25324483) collected pulmonary function measurements and questionnaire data from 240 male welders working at two shipyards in Korea to assess the relationship between welding fume exposure and chronic obstructive pulmonary disease (COPD). Exposure concentrations were derived from 884 air metal concentrations measured at one of the shipyards between 2002 and 2009, and subjects were divided into low, medium, and high exposure groups for regression analyses. No significant correlations between pulmonary function results and exposure were found. Fifteen percent of the welding subjects had COPD. The odds of developing COPD were significantly higher in the medium and high exposure groups compared to the low exposure group.

Mao *et al*. (2014 PMID: 25579026) followed 136 Chinese welders diagnosed with pneumoconiosis for up to 6 years. Based on a decrease in round opacities observed on patient radiographs, lung damage decreased and welder conditions improved during the follow-up time after diagnosis. Mao *et al*. postulated that the observed lung damage was likely due to siderosis (*i.e.*, the deposition of Fe in lung tissue).

Marongiu *et al*. (2014 PMID: 25018220) collected pulmonary function measurements and behavioral and exposure data from male shipyard workers in the Middle East, 397 of whom were exposed to welding fumes and 127 who were not. Details about measurements or how exposed *vs.* non-exposed workers were defined were not included in abstract. No differences in pulmonary function measurements were reported for the exposed compared to the non-exposed groups of workers. The study did not control for smoking behavior or past occupational exposure.

In order to assess the relationship between parental occupational exposures, chemical exposures during infancy, and childhood onset of respiratory disease, McCarty *et al*. (2014 PMID: 24566356) administered a standardized questionnaire and lung function tests to primary school children in Perth, Western Australia. Regression analyses were conducted to assess the correlation between respiratory symptoms and chemical exposures, including from welding. No significant associations were found between respiratory health and parental occupational or a child's exposures to chemicals, with the exception of current smoking in the home and exposure to smoking during the first year of life.

### 4.1.3 Cardiovascular Effects

Fan *et al*. (2014 PMID: 25512264) measured resting heart rate variation and DNA methylation in blood cells for 66 welders before and after a work shift in which welding activities were conducted. Ambient concentrations of $PM_{2.5}$ were monitored during welding activities. $PM_{2.5}$ exposure was significantly associated with DNA methylation (increased blood methylation level of LINE-1). However the data show a non-significant positive association between LINE-1 methylation level and heart rate variability (HRV), so the results are not statistically significant but suggest a link between DNA methylation and adverse cardiac outcomes.

Brand *et al*. (2014 PMID: 24327055) exposed 12 healthy subjects to fumes generated during metal inert gas brazing in order to determine the concentration at which no effects on high-sensitivity C-reactive protein in the blood were observed. High-sensitivity C-reactive protein in the blood is often used as a biomarker for inflammation and the resulting risk of cardiovascular disease in human subjects. Results suggest that the air concentration at which no effect is expected is between 0.90 and 1.20 $mg/m^3$.

### 4.1.4 Cancer

Pesch *et al*. (2014b PMID: 25107450) collected post-shift blood and urine samples from 238 welders in order to assess the association between exposure to metals in welding fumes and oxidative damage to white blood cells. Higher levels of oxidative damage were significantly associated with blood Fe and Mn stores. Urinary Cr and Ni concentrations were also significantly correlated with the urinary biomarkers of oxidative damage to DNA (genetic material) in the cells, which may increase the risk of cancer.

### 4.1.5 Effects on the Eye

Li and Zhang (2014 PMID: 25533367) administered ophthalmologic examinations to 86 welders in order to assess the effects of risk factors such as age, welding duration, job duration, and the use of personal protection on the incidence of phototoxic maculopathy. Thirty-two percent of the patients had phototoxic maculopathy. Risk factors associated with the onset of phototoxic maculopathy were length of service, time spent operating welding machinery, and use of personal protective equipment. Subjects that were administered lutein, a caratenoid postulated to reduce oxidative damage in the eyes, had the best visual acuity, serum lutein concentrations, macular pigment optical density (MPOD), and contrast and glare sensitivity. The age of a welder was not associated with the onset of phototoxic maculopathy.

### 4.1.6 Immune Function Effects

Gube *et al*. (2014 PMID: 24854261) exposed 12 healthy, male non-welders to either ambient air (controls) or welding fumes from resistance spot welding of Zn-coated material for 6 hours. Biomarkers of inflammation were measured before and after exposure. The authors found no difference in inflammatory biomarker levels between the exposed and unexposed groups at the observed exposure of 100 $\mu g/m^3$.

### 4.1.7 Renal Effects

Aminian *et al*. (2014 PMID: 24833825) conducted a case control study in which cases of bladder cancer were identified in an Iranian hospital between 2007-2009. Occupational exposure history data was collected from the patients. Patients with no reported occupational exposures had a significantly lower risk of developing urinary tract stones compared to patients with occupational exposure. Patients with a history of welding and metal manufacturing exposure had a significantly higher risk of bladder cancer compared to controls.

Harisa *et al*. (2014 PMID: 24652630) assessed the viability of using cystatin C, a protein produced by all cells throughout the body and commonly used as a biomarker of renal injury, as an early biomarker of cadmium (Cd)-induced renal injury. Plasma levels of cystatin C were compared for nonwelders, welders, welders who smoke, diabetic welders, and diabetic welders who smoke. Plasma levels of cystatin C were significantly higher in welders compared to nonwelders. Other biomarkers of exposure to Cd or renal injury, such as whole blood Cd and protein oxidation products, were collected and were significantly higher in welders compared to nonwelders. Cystatin C levels and other potential biomarker proteins, such as creatinine, were higher in welders who were smokers or had hyperglycemia. These results indicate that cystatin C may be a viable biomarker of Cd-induced renal injury.

### 4.1.8 Developmental Effects

Ali *et al*. (2014 PMID: 24859222) conducted a case-control study on musculoskeletal congenital malformation in newborns and paternal exposure to potential hazards during the preconception period. Paternal exposure was determined through a questionnaire conducted by a trained physician. Congenital malformations were significantly associated with paternal exposure to welding fumes, pesticides, and solvents.

### 4.1.9 Other Health Effects

Lutz *et al*. (2014 PMID: 24495958) measured the continuous core body temperature, heart rate, urine, specific gravity, and body mass index of 31 miners working in an underground metal mine in order to assess the effects of job tasks and health conditions on the incidence of occupational heat strain. Welding was significantly ($p < 0.05$) associated with a higher core body temperature, maximum heart rate, and increased postshift urine specific gravity. This study confirms that job task, body type, and shift are risk factors for heat strain.

## 4.2 Animal Studies

We identified six animal studies that evaluated the potential effects of welding fumes.

Erdely *et al*. (2014 PMID: 25123171) exposed rats to welding fumes *via* intratracheal instillation to assess the effects of exposure to welding fumes on the immune system. Exposure to welding fumes was associated with oxidative stress and an increase in circulating immune cells, known as leukocytes, indicating the potential for impairment of the respiratory immune system.

Popstojanov *et al*. (2014 PMID: 24786677) exposed rats to welding fumes generated by manual metal arc hard surfacing welding *via* inhalation once a week for 7 weeks to assess effects on the cardiac system. Rats exposed to welding fumes exhibited signs of weakened cardiac functioning, which the authors postulated was likely due to inefficient calcium utilization.

Sivakumar *et al*. (2014 PMID: 24530425) exposed pregnant rats to doses of potassium dichromate, a Cr(VI) compound, in drinking water in order to assess potential developmental effects of exposure to Cr(VI). The offspring of the experimentally exposed rats exhibited higher rates of apoptosis (*i.e.*, cell death) and breakdown of key reproductive cells. Smaller litter sizes and early reproductive senescence (*e.g.*, reduced reproductive function) were also observed in the offspring of exposed rats when compared to controls.

Sriram *et al*. (2015 epub 2014 PMID: 25549921) exposed rats to fumes generated by gas-metal arc welding using stainless steel electrodes (GMA-SS) at standard/regular voltage or high voltage in order to assess the effects of the voltage used in welding on health outcomes. The welding fumes produced at a high voltage contained a larger fraction of ultrafine particles; however, no differences in biomarkers of neurotoxicity were observed between the two exposure groups.

Sriram *et al*. (2014 PMID: 25265048) exposed rats to fumes generated by either weld-bonding with sparking or without sparking in order to assess differences in neurotoxicity. Fumes produced with sparking have high metal concentrations but low concentrations of volatile organic compounds, while those produced without sparking have low metal concentrations and high concentrations of volatile organic compounds. Short-term exposure to both fumes caused neurotoxicity in the study rats; however, the effects on biomarkers of neurotoxicity and mechanism of toxicity varied between exposure groups.

Zeidler-Erdely *et al*. (2014 PMID: 25140454) exposed rats to fumes generated by mild-steel spot welding aerosols with sparking or without sparking in order to assess differences in cardiovascular, lung, and immune system toxicity. The fumes produced with sparking induced detrimental effects to the vascular system, while fumes produced without sparking were found to impair immune system biomarkers. Effects on the lungs were minimal, with only mild inflammation of the lungs and no effects on airway reactivity. `The authors concluded that acute inhalation of mild-steel spot welding fumes at occupationally relevant concentrations may act as an irritant as evidenced by the increased lung resistance and result in endothelial dysfunction, but otherwise had minor effects on the lung.

## 4.3 Mechanistic Studies

We identified only one mechanistic study that evaluated the potential effects of welding fumes. Badding *et al*. (2014 PMID: 24977413) compared the cytotoxic effects of exposure to fumes generated by welding of Ni- and Cu-based materials (Ni-Cu WF) with effects produced by exposure to fumes generated by gas metal arc welding using mild steel (GMA-MS) or GMA-SS. The authors exposed the macrophages of RAW 264.7 mice to the three welding fumes for 24 hours and assessed cell viability, reactive oxygen species (ROS) production, phagocytic function, and cytokine production. Although exposure to GMA-MS and GMA-SS welding fumes generated more ROS species, the Ni-Cu WF induced more cell death, mitochondrial dysfunction, and impaired macrophage function. The Ni-Cu WF were deemed to be more cytotoxic in this assay, suggesting that reduction of Ni and Cu may be necessary to decrease the hazard associated with exposure to welding fumes.

## 4.4 Reviews

We identified four reviews of health effects of exposures to welding fumes.

Baker *et al*. (2014 PMID: 24579750) reviewed 24 published studies on exposure to Mn in which data on Mn in air and blood were collected. Correlation analyses were conducted to assess associations between concentrations of Mn in air and blood. Concentrations of Mn in air and blood were significantly correlated at Mn air concentrations exceeding 10 $\mu g/m^3$, although interpretation is limited by largely cross-sectional data, study design variability, and differences in exposure monitoring methods.. The authors hypothesized that the lack of correlation at air concentrations less than 10 $\mu g/m^3$ is due to dietary Mn exposure dominating blood Mn concentrations until air Mn exposures are large enough to affect Mn in blood.

Mocevic *et al*. (2015 epub 2014 PMID: 25047981) searched Medline and EMBASE databases for published studies of ischemic heart disease mortality and exposure to welding fumes. A meta-analysis was conducted on the pooled data from 18 epidemiology studies after the studies were evaluated for potential sources of bias and confounding. While analyses showed that workers with welding fume exposure were at a slightly greater risk of ischemic heart disease, authors note that bias and confounding reduce the certainty of the results.

In order to assess potential modes of action for Cr(VI)-induced cancer, Proctor *et al*. (2014 PMID: 25174529) reviewed published toxicology studies conducted on rodents, humans, and *in vitro* models. Data from these studies indicate that, at high Cr(VI) exposure levels, cells are unable to clear Cr(VI), which tends to accumulate and get absorbed by the cells. This results in oxidative stress as well as protein and DNA damage.

Wardhana and Datau (2014 PMID: 25348190) reviewed existing literature on metal fume fever in galvanized steel welders. The causes, the mechanism of action, symptoms, diagnosis methods, and possible treatments for metal fume fever are reviewed.

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# Appendix A : Exposure to Welding and Lung Cancer

Gradient identified four key studies that have recently been published and that address exposures to welding fumes and lung cancer risk (Ambroise *et al*., 2006; Sørensen *et al*., 2007; Commission VIII, 2010; Kendzia *et al*., 2013). These studies present key new information that will likely be used by the World Health Organization's International Agency for Research on Cancer (IARC) to assess the cancer risks from welding fume exposures. Specifically, IARC recently released a "Report of the Advisory Group to Recommend Priorities for the IARC Monographs during 2015-2019,"[1] which included welding and welding fumes as a high priority chemical group to evaluate. Currently IARC classifies welding fumes as a Group 2B carcinogen, "possibly carcinogenic to humans" because, at the time, IARC considered human evidence to be limited and animal studies inadequate. Specifically, in 1990 IARC found that there was evidence of excess cancer risks in occupational exposed workers, but an absence of an association with duration of employment or cumulative exposures. In the most recent report, IARC indicate new epidemiology evidence and experimental evidence could bolster a case for carcinogenicity, and therefore, IARC could potentially upgrade its cancer classification for welding fumes. If IARC re-classifies welding fumes as a probable or known human carcinogen this could have implications for the regulation of welding fumes in the workplace.

In 2010, Commission VIII released a report that summarized, commented, and provided conclusions regarding the factors that contribute to excess risks of lung cancer that have been observed among welders in epidemiology studies. Its review of the published scientific literature ratified a 2003 Statement concluding that the prime causative agents (namely welding fume, asbestos dust, and tobacco smoke) remain the same and that a clear cause has yet to be identified. The commission recommends that all efforts be made to reduce welding fume exposures at least to national standards, prevent asbestos dust, and help to minimize tobacco smoke exposures.

The commission report focused on summarizing the evidence of lung cancer risk associated with specific agents including welding fumes in general, iron compounds, chromium compounds, nickel compounds, asbestos dust, tobacco smoke, ionizing radiation, ultrafine particles, and other unidentified agents.

For welding fumes, the Commission briefly summarized the findings from IARC published in 1990 and discussed findings from several recent epidemiology studies and some supporting evidence from *in vitro* and *in vivo* studies, noting generally that more research is needed. With regards to other specific agents, the commission noted that for all of the metals (iron, chromium, and nickel) more research was needed to support a causative link. In contrast, both asbestos exposure and exposure to tobacco smoke were likely contributors to the excess cancer observed in epidemiology studies, although there remained some conflicting evidence. For ionizing radiation, the commission concluded that risks were likely to be low, and research was too limited to make conclusions regarding ultrafine particles. In general, it appeared that the Commission concluded that for most lines of evidence, further review was needed to help draw appropriate conclusions.

One of the limitations of this review is that it was unclear how the literature search was conducted and whether it was comprehensive. Only a limited number of studies were cited, and the Commission did not discuss the strengths and limitations of the different lines of evidence (*i.e.*, epidemiology and/or toxicology studies). Importantly, there was little discussion on whether different lines of evidence

[1] http://monographs.iarc.fr/ENG/Publications/internrep/14-002.pdf

presented consistent and coherent findings, both within and across studies (although there was some indication that it wasn't). While it will be important for IARC to consider this review, it may not be compelling enough to impact any IARC decision. Therefore, a more rigorous review of the literature, which focuses on the evidence for welding fumes, may be needed for consideration by IARC.

Three other key studies have recently been published, and two of these were cited in the Commission VIII 2010 report (Ambroise *et al*., 2006; Sørensen *et al*., 2007). These recent reviews include a recent meta-analysis of published occupational studies investigating excess lung cancer risks from welding fume exposures (Ambroise *et al*., 2006), an update to a large cohort study in Danish welders (Sørensen *et al*., 2007), and a pooled analysis of case-control studies (Kendzia *et al*., 2013). These studies all add to the body of evidence that will be considered by IARC, but they do not necessarily represent a comprehensive review that incorporates all lines of evidence (*e.g.*, epidemiology and toxicology evidence) or do they represents the most current literature. These studies are summarized below with a brief discussion of their strengths and limitations.

The study by Ambroise *et al*. (2006) was an updated meta-analysis that incorporated 24 new studies and 28 more data points that in their previous study conducted in 1994. This more recent analysis included the period between 1954 and 2004. This study also included more sophisticated analyses of heterogeneity in the underlying studies as well as an assessment of publication bias. The literature search was comprehensive and the authors did an appropriate extraction of all relevant information from the studies. The study also used appropriate statistics to analyze the data. According to the authors, the large number of studies identified for this analysis reflects the efforts that have been made in recent years to assess lung cancer risks for different welding processes and to better account for smoking.

The results from this analyses indicate that welding exposure was associated with excess in lung cancers of 21-32% compared to the general population, with no significant difference in risk between the types of welding (when these data were reported by the authors). The authors note that the study findings confirm results from a previous meta-analysis (Moulin, 1997). The authors reported that publication bias was present in their analyses, and therefore restricted their analyses to studies that did not appear to have a positive bias (*i.e.*, studies that only reported positive findings). The authors also noted that based on studies that provided estimates that controlled for smoking, the analyses indicated that the excess lung cancers could not be attributed to smoking alone. However, the authors also noted that some of the findings were surprising, particularly the finding of similar cancer risks among shipyard welders as factory welders, given the increased asbestos exposures in shipyard workers. The authors suggested that asbestos co-exposure could not be ruled out as a causal agent in these studies, although the authors were not able to specifically evaluate the role asbestos in their analyses.

The strengths of this analysis were that it was comprehensive and included a large number of studies and data points. The authors did not find a large amount of heterogeneity in the risk estimates, which was surprising given the large variation in the study designs, welding categories, countries where study was conducted, and analytical approaches. The limitations include the inability to account for asbestos confounding in the analysis, the potential that publication bias is still present despite efforts to control for it, and inadequate control for smoking because of limited data. The study also suggested no difference in the risks between stainless steel workers and mild steel workers which contradicts the findings of other studies (*e.g.*, Sørensen *et al*., 2007 discussed below).

A study in Denmark of a large cohort of welders by Sørensen *et al*. (2007) includes a long follow-up period, spanning about 35 years. In this study the authors also reported an excess number of lung cancers of 35% compared to expected numbers. The results indicated an increased risk of lung cancer with increasing years of welding or cumulative welding fume exposure, but only among the stainless steel welders and not the mild steel welders. Also of note was that within the group of stainless steel welders the lung cancer risks was only elevated among the MMA welders. The authors hypothesized that this may be due to higher exposures to hexavalent chromium in MMA welding. The authors also noted that welders that smoked for more than 35 years had an increased risk of cancer that was 8 times higher than nonsmokers (after adjusting for age, asbestos, and welding fume exposure).

The studies strengths included the long follow-up period (35 years, from 1968-2003) and large size of the cohort (over 6000 welders). In addition, the authors had information of individual smoking habits and asbestos exposure, as well as a comprehensive quantitative exposure assessment. There were, however, several limitations. To minimize selection bias, the authors had to restrict the analysis to welders that started work in 1960 or later (as no cancer diagnoses were available before 1968), which reduced the size of the cohort by almost 30%. The authors also assumed that there would be no increased risk of lung cancer within the first 8 years of exposure. With regards to the exposure assessment, work histories were often provided for work that was completed 20 years prior and thus the accuracy of the recall with respect to specific welding activities, time spent and, and work conditions may have impacted the exposure estimates. In fact, the authors noted that there was a large amount on unaccounted for variability in the estimated exposure levels. The authors believed that group estimates are still reliable, however. In addition, the authors noted that exposure estimates are only valid for the period between 1950 and 1985 as the questionnaire was administered in 1986. There was no data regarding welding activity after 1986. Exposure estimates exceeded current occupational threshold limits in Denmark, which are 0.5 $mg/m^3$ for MMA stainless steel welding, 1.1 $mg/m^3$ for TIG stainless steel welding, and 1.6-1.7 $mg/m^3$ for mild steel welding (depending on the process), and actions to reduce welding fume exposures started around 1980. Therefore, it may be that exposure estimates are higher than actual levels. Overall, the authors concluded that their data corroborates earlier studies and that an excess cancer risk exists even after controlling for asbestos exposure and smoking. The data from this study specifically pointed to a risk for stainless steel welders, specifically MMA stainless steel welding. There is biological plausibility for this finding because of the potential for increased exposures to hexavalent chromium. There is less support for a cancer risk for mild steel welders based on the study findings.

In the most recent epidemiology assessment, Kendzia *et al*. (2013) evaluated data from 16 studies conducted in Europe, Canada, China and New Zealand from 1985 to 2010. The studies were mostly case-control studies that included both men and women, although the analysis was restricted to men because of the low number of women welders. Cases were recruited from hospitals or cancer registries and controls from the general population. Occupational and smoking histories were assessed by face-to-face interviews for the majority of subjects. Subjects were considered to be exposed if the job title was welder for at least one year or the subject was identified as an "occasional welders" based on their job (*e.g.*, plumber, fitter, sheet-metal worker). Subjects were also divided by industry (*e.g.*, shipbuilding and repair, construction, manufacturing, other). The authors conducted separate analyses to assess the interaction between exposures to welding fumes and smoking.

The study reported that among welders there was a significant increased risk of lung cancer of 42%, and for occasional welders the excess risk was 19%. Risks varied by industry, with the highest risk for welders in the shipbuilding industry. Risks also increased with the number of years working as a welder. With regards to the analysis of smokers *vs*. non-smokers, the authors reported that there was potential confounding by smoking, and that smoking appeared to contribute about 20% of the overall lung cancer risk. There was limited support for a multiplicative effect for welding fumes and smoking. The analysis was limited by the relatively few number of never smokers in the dataset. Although the authors were not able to do an analysis that considered asbestos exposure, based on previous studies they concluded that lung cancer risks from welding could not be fully explained by asbestos exposure. Overall the authors concluded that their analysis supports an increased risk of lung cancer associated with welding fume exposures.

The strengths of the study included a large number of studies that utilized the same study design, allowing for a more statistically powerful analysis. A major limitations is that this evaluation was restricted to case-control studies, which are prone to bias. The authors did not include much discussion of the potential biases in the data, except for a passing mention of exposure misclassification, which they did not believe would impact the findings. The exposure assessment was a major limitation, as the authors were not able to distinguish among the welding processes, the length of time that a person was a welder (other than identifying people for which welding was the longest held profession), or additional occupational exposures. As with all the studies discussed here, the lung cancer risks reported are relatively small, much less than a 2-fold increased risk. In general, epidemiologists do not consider risks that are less that 2-fold to be significant. For example, in a recent report published by the Industrial Injuries Advisory Council of the United Kingdom[2] the Council concluded that the evidence was not strong enough to support a case that welding fumes cause cancer, based on using a 2-fold risk in excess cancer as a threshold for epidemiology evidence.

Overall, these recent studies provide key information on which IARC will rely in the upcoming review of lung cancer risks. However, these studies primarily focus on the epidemiology evidence, which is associated with significant limitations that preclude solid conclusions regarding the causal link between exposures to welding fumes and cancer. Importantly, these studies do not fully resolve the confounding effects of both smoking and asbestos exposure. A more comprehensive review, that incorporates information from other lines of evidence (*e.g.*, animal studies and mode-of-action studies), to support a cancer link is needed to determine if there is biological plausibility for the epidemiology findings.

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[2] https://www.gov.uk/government/publications/lung-cancer-and-welding-iiac-information-note