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HEALTH EFFECTS FROM WELDING EXPOSURES: 2015 LITERATURE UPDATE

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ACRONYMS AND ABBREVIATIONS

ACGIH	American Conference of Governmental Industrial Hygienists
Al	Aluminium
ALS	Amyotrophic lateral sclerosis
As	Arsenic
CANTAB	Cambridge Neuropsychological Test Automated Battery
Cd	Cadmium
Co	Cobalt
Cr	Chromium
Cr VI	Hexavalent chromium
CT	Computed tomography
Cu	Copper
ELF- MF	Extremely- low- frequency magnetic field
epubs	Electronic publications
F2RL3	Coagulation factor II (thrombin) receptor-like 3
FCAW	Flux- cored arc welding
Fe	Iron
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GMAW	Gas metal arc welding
IL	Interleukin
IPD	Invasive pneumococcal disease
K	Potassium
MCS	Mild carbon steel
MeSH	Medical Subject Headings
MMA- HS	Manual metal arc hard surfacing welding
MMAW	Manual metal arc welding
Mn	Manganese
MnA	Air manganese
MnH	Manganese in hair
MNi	Micronuclei
NA	Nuclear abnormalities
NF	Near- field
Ni	Nickel
NOS2	Nitric oxide synthase
NRD	Nanoparticle respiratory deposition
OA	Occupational asthma
PAFR	Platelet- activating factor receptor
PAHs	Polycyclic aromatic hydrocarbons
Pb	Lead
PI	Pallidal index
PM	Particulate matter

PMID	PubMed identification number
PPEDs	Personal protective eye devices
R1	Relaxation rate
RHINE	Respiratory Health in Northern Europe
ROS	Reactive oxygen species
sCDT	Carbohydrate deficient transferrin in serum
SMAW	Shielded metal arc welding
SS	Stainless steel
TIG	Tungsten inert gas
TLV	Threshold Limit Value
UPDRS3	Unified Parkinson's Disease Rating Scale subsection 3
VEP	Visual evoked potential

1 INTRODUCTION

On behalf of the American Welding Society, Ramboll Environ conducted a comprehensive literature search and summary of studies related to the health effects of welding. In this update, we included literature published in 2015 (including electronic publications or epubs), but excluded any articles that have been included in previous literature updates. 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 summaries of the exposure-related studies in Section 3, and summaries of relevant health effects studies in Section 4.

2 METHODS

We searched the PubMed, Toxline, and SCOPUS databases for articles relevant to welding exposures and health effects 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.
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.
4. Literature searches were limited to documents published in 2015 (either electronically (epubs) 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 2015, yielding 219

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 excluded. 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 48 articles were retained.

2.2.2 TOXLINE

The TOXLINE database was searched for articles containing "welders" or "welding" that were published in 2015, yielding 14 citations. After removing the duplicate studies, no additional relevant studies remained from the TOXLINE query.

2.2.3 SCOPUS

The SCOPUS database was queried for articles containing "welders" or "welding" in the title, abstract, or keywords that were published in 2015, and the results of that query (n=4,374) were filtered using the search terms that included the health and exposure terms described in Section 2.1. Non-relevant articles (*e.g.* engineering/material science, mathematics, physics, astronomy, energy, computer science, dentistry, chemistry, earth/planetary sciences, business management and accounting, nursing) were removed at this stage.

A total of 121 articles remained, however, the results of the PubMed, Toxline and Scopus searches overlapped significantly. After removing the duplicate studies, 3 additional relevant studies 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 and the article titles and abstracts were reviewed for relevance and sorted into the following categories:

- Particle characterization and exposure studies
- Epidemiology and controlled human exposure studies
- Animal studies
- Mechanistic/cell/*in vitro* 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 2015 Totals	SCOPUS 2015 Totals	Total
Particle characterization and exposure	18	0	18
Epidemiology and controlled human exposure	21	1	22
Animal	1	0	1
Mechanistic/cell/ <i>in vitro</i>	5	1	6
Reviews	3	1	4
Overall Total	48	3	51

3 EXPOSURE STUDIES

We identified 18 exposure-related publications from 2015 (*i.e.*, particle characterization and exposure). Several studies were published online in 2015 (*i.e.*, 2015 was the "epub date") but were published in print in 2016; these were included in our summary. Articles that were not relevant or were included in a prior AWS updates (*e.g.*, epub date in 2014) 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.

Andrews *et al.* (2015 PMID: 26345630) evaluated and compared two methods to determine manganese (Mn) levels in air samples. One method involved the sequential extraction of Mn fractions and the more standard acid digestion for determination of total Mn. Air samples were obtained from chamber-generated welding fumes of representative welding processes, such as short circuit gas metal arc welding (GMAW) using both stainless steel (SS) and mild carbon steel (MCS), flux-cored arc welding (FCAW), and shielded metal arc welding (SMAW) using MCS. The sequential extraction procedure was done in four steps to measure various Mn fractions based on selective solubility and this method was compared to the standard hot block acid dissolution method used for total Mn. The authors found statistically significant differences in total Mn concentration using the two extraction methods, but the differences were small enough that there is no practical importance for industrial hygiene purposes. The sequential method, however, provides additional information on the concentration Mn in different oxidation states.

Baker *et al.* (epub 2015 PMID: 26589320) evaluated whether Mn in the blood was a useful biomarkers of Mn inhalation exposure. Blood samples and personal air monitoring information were collected among welder trainees to determine airborne exposures and

associated Mn blood levels by welding type. The authors found little association between blood Mn levels and short-term Mn air exposures, but stronger associations for longer exposure periods and for higher Mn air exposures. This study represents one of the more comprehensive studies of biomarkers of Mn exposure.

Bertram *et al.* (2015 PMID: 25512666) evaluated the uptake and elimination of chromium (Cr), hexavalent chromium (Cr VI), and nickel (Ni) after controlled exposures to welding fumes. Twelve healthy male non-smokers and non-welders were exposed for six hours to welding fumes and urine concentrations of Cr, Cr VI, and Ni were measured. In addition, the authors measured Ni and Cr in particle air samples. The particle concentration averaged 2.5 mg/m³. The authors found significantly elevated Cr concentrations in urine after exposure to welding fumes from high alloyed steel compared to pre-exposure urinary Cr concentration. Cr concentrations exceeded German standards. Ni levels in urine were not significantly elevated following exposure to welding fumes, likely due to the low bioavailability of Ni.

Bertram *et al.* (2015 PMID: 25596709) evaluated biomarkers of aluminium (Al) exposures from welding fumes under controlled conditions to estimate the uptake and elimination of Al. A total of 12 participants with no history of Al exposure were exposed to welding fumes from a metal inert gas welding process for 6 hours. Air filter samples were collected to determine Al concentrations in air and multiple urine and blood plasma samples were also collected. Post-exposure urinary Al concentrations showed a significant increase in Al compared to pre-exposure concentrations, while pre-to-post exposure blood Al concentrations were not statistically significantly increased. German exposure standards were not exceeded and Al levels in the urine returned to normal after seven days.

Cena *et al.* (2015 PMID: 25985454) measured the amount of Cr, Mn, and Ni exposure in 44 welders in two facilities using a nanoparticle respiratory deposition (NRD) sampler during GMAW of mild and stainless steel and FCAW of mild steel. The authors reported a range of concentrations for both processes for Mn, Ni, Cr, and Cr VI of 2.8-199, 10-51, 40-105 and 0.5-1.3 µg/m³, respectively. Respiratory deposition of these metals was estimated based on sampler results. The highest concentrations were observed for the FCAW process in welders working in pairs, likely due to exposures to their own welding fumes as well as those generated from the welding partner. For mild steel welders, the authors reported an estimated 10-56% of the Mn was in the nanosized particle fraction (< 300 nm) and therefore more likely to be deposited in the respiratory system. For stainless-steel welders, the percentage of Cr, Ni and Mn in the nanoparticle size range was 90, 64, and 59%, respectively. These results indicate that most of the Cr and more than 50% of the Ni and Mn in the particles is likely to be deposited in the respiratory system of the stainless steel welders.

Dewald *et al.* (2015 PMID: 26247637) investigated relationship between MMAW fumes, filtered air, and GMAW fumes on inflammation in 12 male subjects exposed for six hours.

Inflammatory markers were measured three times in blood serum pre- and post- exposure (i.e., baseline, 1 and 7 days post-exposure). C-reactive protein, a key marker of inflammation did not increase, however, other inflammatory biomarkers such as neutrophil and endothelin-1 concentrations increased directly after exposure to MMAW fumes, potentially indicating a subclinical inflammatory reaction. In contrast, after exposure to GMAW and filtered air, endothelin concentrations decreased, which may indicate reduced inflammation.

Driscoll *et al.* (2015 PMID: 26324826) examined the prevalence of work-related exposures to polycyclic aromatic hydrocarbons (PAHs) to identify sources of exposure and ways to control exposures. Data for the analysis came from the Australian Workplace Exposures Study, a nationwide telephone survey of the prevalence and sources of exposure to work-related known or suspected carcinogens among Australian workers aged 18-65 years. Of the various occupations, metal workers were found to be exposed to PAHs primarily from welding materials with surface coating. Exposure was estimated based on work-related tasks rather than self-reported exposures. Use of personal protective equipment or other exposure controls was inconsistent.

Driscoll *et al.* (2015 PMID: 26324825) examined the prevalence of work-related exposures to lead based on the Australian Workplace Exposure Study survey as described above. Steel welders were among the occupations identified as having probable lead exposures. Higher lead exposures were associated with soldering and grinding welds.

Eze *et al.* (2015 PMID: 26012516) assessed awareness and use of protective eye devices among 343 male welders in Nigeria between January and March 2011. Participants were aware of ocular hazards associated with welding, but rarely used personal protective eye devices (PPEDs). Barriers to the use of PPEDs were primarily cost, inconvenience, and a "presumed lack of protective benefit." Electric welders and those with lower educational status were significantly more likely to use PPEDs to reduce exposures.

Fethke *et al.* (2015 PMID: 26602453) assessed welding fume exposures among 30 welders during stud welding using conventional methods compared to using a prototype system that allows participants to weld from an upright position. The authors reported that the welding fume concentrations were higher using the conventional methods and exceeded the recommended threshold limit values (TLV) set by the American Conference of Governmental Industrial Hygienists (ACGIH). While welding fume concentrations were lower with the upright system, they still exceeded the ACGIH TLV. The study shows that improvements in the stud welding methods are still needed to lower welding fume exposures.

Graczyk *et al.* (epub 2015 PMID: 26464505) characterized tungsten inert gas (TIG) welding fumes exposures among 20 apprentice welders in a ventilated exposure cabin. Welding fumes were measured inside of the welding helmet, at the "breathing zone," and at a near-field (NF) station at the height of the welding task. Particulate matter, particle number

concentration and particle size, particle morphology, chemical composition, reactive oxygen species (ROS) production potential, and gaseous components were characterized. The average concentrations of particle number in the breathing zone was 1.69×10^6 with 92% of the particle counts below 100 nm and elevated concentrations of tungsten. The mean ROS production potential was higher than typical in-traffic-polluted air and significantly higher for apprentices that burned their metal during welding. The authors indicate that welding performance is a potential exposure modifier for welders with minimal training.

Hanley *et al.* (2015 PMID: 26011602) led the National Institute for Occupational Safety and Health study of occupational exposures to Mn in welding fume in construction workers rebuilding tanks, piping, and process equipment at two oil refineries. The authors evaluated exposures to different Mn fractions using a sequential extraction procedure. Samples were gathered for 72-worker days to monitor either total or respirable Mn during stick welding and associated activities both within and outside confined spaces. The time-weighted average (TWA) of the sum of all Mn fractions in total particulate ranged from 0.52-470 $\mu\text{g}/\text{m}^3$. Total particulate TWA geometric mean concentrations of the Mn(sum) were 99 (geometric standard deviation, GSD = 3.35) and 8.7 (GSD = 3.54) $\mu\text{g}/\text{m}^3$ for workers inside and outside of confined spaces; respirable Mn concentrations were also much higher for welders within confined spaces. The study showed that 25 welders exceeded the recently adopted Mn ACGIH TLV (20 $\mu\text{g}/\text{m}^3$).

Lee *et al.* (2015 PMID: 25953701) examined relaxation rate (R1) as a biomarker of Mn accumulation in the brain using magnetic resonance imaging (MRI) by assessing short- and long-term welding exposures, accounting for potential confounders and co-indicators of welding fume exposure such as blood metal levels [Cr, copper (Cu), Iron (Fe), potassium (K), and lead (Pb)]. Thirty-five welders and 30 controls were studied to determine whether (1) blood levels of these metals are higher in welders compared to controls; (2) both pallidal index (PI), a more traditional marker, and R1 relaxation rate are greater in brain regions of interest in welders compared to controls; and (3) R1 is a more sensitive exposure measure than PI. The authors found that welders with higher exposures showed significantly higher R1 compared with welders who had lower exposures or controls. Furthermore, there was a nonlinear relationship between welding exposure and Mn accumulation in the brain.

Park *et al.* (PMID: 26900208) analysed the collection efficiency of a granular bed as a nanoparticle respiratory deposition sampler. The nanoparticulate matter criterion reflects the total deposition of small particles (<300 nm) in the human respiratory system. One of the five layers of the granular bed, a small beads layer, was tested for various particles, including stainless steel and welding particles, and their collection efficiency was assessed. The authors found that the collection efficiency of the tiny bead layer increased with increasing depth of the small beads layer

Pesch *et al.* (2015 PMID: 25979374) estimated occupational exposure to inhalable hexavalent chromium (Cr VI) among German workers between 1994 and 2009 based on the

MEGA exposure database. Exposures were assigned based on pre-defined occupations. Information about welding jobs, and welding methods comprised the largest cohort (n= 1,898). Mean Cr VI concentrations above 5 $\mu\text{g}/\text{m}^3$ were estimated for shielded metal arc welding (SMAW) and flux-cored arc welding (FCAW) applied to stainless steel. Mean concentrations between 1 and 5 $\mu\text{g}/\text{m}^3$ were estimated for gas metal arc welding (GMAW) of stainless steel. The exposure estimates can be used for epidemiology studies and for informing industrial hygiene studies, however due to large variability in exposure estimates by welding task, exposure-specific information may be necessary to reduce exposure misclassification.

Reiss *et al.* (2015 PMID: 26409267) assessed levels of Mn in hair as an alternative biomarker for welders exposed to Mn. Hair samples (1 cm) and air samples were collected to measure individual levels of Mn in hair (MnH) and air Mn (MnA) concentrations, respectively, for 47 welding school students. After log-transforming 30-day time-weighted average MnA (MnA30d) and hair Mn (MnH), a linear relationship was observed between the two variables. After washing hair, a similar association was found. The authors concluded that hair may be a better alternative to the more commonly used urine and blood biomarkers for assessing inhaled Mn exposure.

Ren *et al.* (epub 2015 PMID: 27122343) evaluated the measurement uncertainty associated with sampling of welding fumes in the air in shipyards to determine the quality of the measurements and provide information regarding quality assurance. Average welding fume concentrations were 3.3 mg/m^3 with an uncertainty of 0.24 mg/m^3 . Duplicate sampling indicated a reproducibility of 1.9%, weighing introduced an uncertainty of 0.3% and additional uncertainty of 3.2% was estimated based on sample quality. The authors determined that to reduce sample quality uncertainty, which was the largest source of uncertainty, quality control should focus on better management of air humidity, sample volume, measurement instruments, and dust sample collection efficiency.

Szewczynska *et al.* (PMID 2015: 26574102) analysed the levels of fluoride in airborne particulate matter emitted during welding processes using the Institute of Occupational Medicine (IOM) sampler, a patented personal inhalable sampler that collects the inhalable and respirable particulate size fractions. Fluoride concentration in the respirable and inhalable fractions were in the range of 0.20 to 1.82 mg/m^3 and 0.23 to 1.96 mg/m^3 , respectively, during an 8-hour shift in the welding room.

4 HEALTH EFFECTS STUDIES

4.1 Studies in Humans

We identified studies in humans that assessed various health effects related to welding fume exposures. These health effects included neurological effects (six studies), respiratory effects (seven studies), cardiovascular effects (five studies), cancer (one study), renal function effects (one study), and multiple health effects (two studies). Summaries of these studies are provided below; links to study abstracts are provided in the reference list.

4.1.1 Neurologic Effects

Banerjee *et al.* (2015 PMID: 25552871) conducted a study in 33 welders and 42 healthy controls (with no welding exposure) to assess the effects of welding fume exposures on optical pathways. The authors measured visual evoked potential (VEP) parameters as a means of evaluating central nervous system effects. The authors found that welding exposures were associated with delays the conduction processes in optical pathways. He authors noted that a limitation of this study was the small sample size, and neuropathy associated with welding exposures should be confirmed in a larger study.

Ellingsen *et al.* (2015 PMID: 25579701) compared 63 welders to 65 controls to assess the possible decline in neurobehavioral function associated with Mn exposure after approximately six years. Compared to baseline measures, welders who had a high concentration of carbohydrate deficient transferrin in serum (sCDT) performed more poorly on the Static Steadiness Test, Finger Tapping Test, and the Grooved Pegboard Test at follow-up than controls. However, no difference in measured neurobehavioral function was observed between welders and controls after excluding subjects with sCDT above 1.7%.

Fischer *et al.* (2015 PMID: 26414853) evaluated the relationship between electric occupations, electric shocks, occupational magnetic fields, and amyotrophic lateral sclerosis (ALS) in a large population-based nested case-control study in Sweden. The authors found no associations between occupational magnetic field (based on three different magnetic job-exposure matrices) or electric shock exposures and ALS. However, the authors found an association between all individuals (and welders specifically) with high electric shock exposure and ALS. The authors concluded that there was limited evidence of an association between ALS and electric shock exposure.

Hassani *et al.* (epub 2015 PMID: 2642330) assessed the relationship between biomarkers of Mn and neuropsychological effects among exposed (27 welders, 31 ferroalloy smelters), and unexposed (30 office workers) workers. Neuropsychological effects were evaluated using the Cambridge Neuropsychological Test Automated Battery (CANTAB) and a questionnaire. Biological samples were collected to determine Mn concentrations in blood, urine, and toenails and authors also measured Mn in air. The mean Mn concentrations in air and in

biological samples of exposed workers were higher among welders than exposed ferroalloy smelters; exposed workers were significantly higher than unexposed controls. The authors reported some statistically significant associations between biomarkers of Mn exposure, air Mn, and some neurocognitive outcome measures.

Searles *et al.* (2015 PMID: 25634431) evaluated blood samples from 201 males exposed to Mn-containing welding fumes. Forty-nine cases, 103 controls, and 49 intermediate workers were classified according to their Unified Parkinson's Disease Rating Scale subsection 3 (UPDRS3) scores. The UPDRS3 assesses the motor skills associated with the longitudinal course of Parkinson's disease. The authors found that the nitric oxide synthase (NOS2) enzyme, which is involved in inflammation is significantly lower in Parkinson cases than in controls. This association was not observed in the intermediate group, which had lower UPDRS3 scores (p-value: 0.59). Overall, this study indicated that there was evidence of inflammation mediated by NOS2 gene expression that may underlie the pathophysiology of Parkinsonism in Mn-exposed welders, however, authors noted that a longitudinal study was needed to help elucidate this relationship.

van der Mark *et al.* (2015 PMID: 25903042) investigated the relationship between occupational exposures to metals and welding fumes and the risk of developing Parkinson's disease. This hospital based case-control study including 444 patients with Parkinson's and 876 age- and sex- matched controls. Participants were interviewed to obtain occupational histories and lifestyle information. Exposures to welding fumes were assessed based on participants self-reported welding activities. The authors found no significant associations between the reported metal/welding fume exposures and Parkinson's disease.

4.1.2 Respiratory Effects

Kauppi *et al.* (2015 PMID: NA) investigated inflammatory and respiratory responses to welding fumes in patients with suspected occupational asthma (OA). Sixteen patients were exposed to mild steel and stainless steel welding fumes and their platelet counts, leucocytes count, hemoglobin, sensitive C-reactive protein, lipids, glucose, fibrinogen, interleukin (IL)-1 β , IL-6, IL-8, TNF- α , endothelin-1, and E-selectin in blood plasma were measured. After exposure to welding fumes, the number of leukocytes, neutrophils, and platelets significantly increased and the hemoglobin levels and number of erythrocytes significantly decreased. The authors concluded that exposure to mild steel and stainless steel welding fumes resulted in a mild systematic inflammatory response based on changes in certain biomarkers.

Kristiansen *et al.* (2015 PMID: 25408460) assessed the relationship between welding fume exposures and bronchial asthma. Data on asthma were based on information on the purchase of asthma medication from 1995 to 2011 obtained from the Danish Medicinal Products Registry. Welding fume exposures were estimated based on data collected the

Danish National Company of a historical cohort of 5303 male ever-welders. Lifetime exposure estimates of stainless steel and mild steel welding fumes were calculated through questionnaires and by application of a welding exposure matrix. The authors reported that cumulative exposures to stainless steel welding were associated with increased risk of asthma in non-smokers.

Lehnert *et al.* (2015 PMID: 25315619) evaluated the association between welding fume exposure and lung function in 219 welders. The authors reported that age- and smoking-adjusted lung function parameters did not significantly decline with increasing exposure duration, or with current or lifetime exposure to welding fumes. For a small fraction of the welders (15%) lung function parameters were lower than normal, but the authors did not attribute these lung function deficits to welding fume exposure.

Patterson *et al.* (2015 PMID: 26062559) reported on an outbreak of invasive pneumococcal disease (IPD; n =4) in workers exposed to welding fumes in a shipyard in Northern Ireland. As a precaution, a subgroup of 679 of the 1500 shipyard workers were given antibiotics because they were identified as being at-risk due to elevated exposures to welding fumes.

Shi *et al.* (epub 2015 PMID: 26887265) evaluated the pathological and other clinical characteristics of 185 welders diagnosed with pneumoconiosis compared to 115 welders with silicosis that were diagnosed between 2008-2013. For a subset of 39 welders, lung function and chest x-rays were obtained 4 to 6 years after diagnosis. The authors reported that welders were diagnosed with pneumoconiosis at a younger age than those diagnosed with silicosis, however, welders with pneumoconiosis were generally rated as having milder stages of pneumoconiosis than those in the silicosis group (stage I vs. stage III). There were also significant differences between the two groups with regards to the amount of particulate deposition in lung tissue and the interstitial fibrosis level. Eighty-three percent of welders with pneumoconiosis compared to 60% of patients with silicosis showed moderate or greater particulate deposition, and almost 100% of patients had no or mild fibrosis in the pneumoconiosis group compared to the majority (78%) of silicosis group showing moderate or higher levels of fibrosis. Overall, the authors found differences in the lung disease characteristics of welders depending on their diagnosis.

Storaas *et al.* (2015 PMID: 26206878) studied the relationship between welding, rhinitis, and asthma among welders and non-welders using the population-based Respiratory Health in Northern Europe (RHINE) study, which included 16,191 responders. Welders were categorized as "ever welding" (n=2181), "welding > 25% of working time" (n=747) and "welding in stainless steel > 6 months" (n=173). Asthma incidence, adult on-set asthma, and rhinitis were significantly higher among male welders compared to non-welders, but authors noted that results should be confirmed with further research.

Wang *et al.* (2015 PMID: 26506774) conducted an industrial hygiene investigation to assess the working conditions in a shipyard in China and develop a plan for improvements. The

authors found that exposures to welding fumes and Mn dioxide exceeded recommended exposure limits. In addition, 2450 workers in the shipyard showed respiratory impairments associated with dust exposures. The authors recommended increasing the use of personal protective equipment to reduce occupational exposures and improve the health of the workers.

4.1.3 Cardiovascular Effects

Hossain *et al.* (2015 PMID: 26395445) investigated the association between welding fume exposure and cardiovascular disease among welders and non-exposed controls (all currently non-smoking) in Sweden by assessing the methylation status of the coagulation factor II (thrombin) receptor-like 3 (F2RL3) gene, a marker for cardiovascular disease prognosis and mortality. The authors reported low-to-moderate exposure to welding fumes (1.2 mg/m³ (standard deviation, 3.3 mg/m³; range, 0.1- 19.3 mg/m³) may have adverse effects on the cardiovascular system.

Kruger *et al.* (2015 PMID: 26323773) studied the effects of strength training as a preventative measure for cardiovascular, metabolic, and muscular strain associated with welding. Two groups were evaluated: 1) an exercise group, that completed a 12-week strength training program, and 2) a control group. Baseline and post training measurements were collected and assessed, including heart rate, blood pressure, lactate, and perceived exertion. The strength training program significantly increased the muscle performance and reduced strain during an experimental welding test. There were no significant differences in the cardiovascular and metabolic health parameters between the two groups, however the exercise group had significantly decreased perceived exertion while welding. The authors concluded that a strength training program could increase tolerance to the physical demands of welding.

Li *et al.* (2015 PMID : 26147298) conducted a cross-sectional study in Sweden to assess the relationship between welding fume exposures and cardiovascular effects using information from structured interviews and biological sampling in non-smoking males (101 welders and 127 controls). The authors collected respirable particulate samples and measured blood pressure and endothelial function (using peripheral arterial tonometry). The authors reported that welders were exposed to 10-fold higher levels of particles than controls, but that there was no clear association between welding and adverse endothelial function. Welders, however, had significantly higher blood pressure compared to controls. Years working as a welder was associated with higher blood pressure, but there was no association between higher blood pressure and respirable particulate matter. The authors concluded that welding fume exposures are likely to be a risk factor for cardiovascular disease, but it was unclear whether this was due to particulate matter exposure.

Umukoro *et al.* (2015 PMID: 26644456) examined the association between heart rate acceleration and deceleration, which are a measure of heart rate variability, and short-term metal fine particulate matter (PM_{2.5}) exposures among 48 male welders between 2010 and 2012. The authors collected continuous recordings of digital electrocardiogram (ECG) readings using a Holter monitor to assess heart rate variability. Significant exposure-response associations were found for increased PM_{2.5} exposures and heart rate variability, adjusting for age, smoking, and season/time of day when ECG reading was obtained. The mean (standard deviation) PM_{2.5} concentration during welding was 0.47(0.43) mg/m³. The authors concluded that exposure to metals in particulate matter from welding may have short-term effects on heart rate variability.

Wong *et al.* (2015 PMID: 25738948) evaluated the relationship between arterial compliance in welders and cumulative exposure to the following metals measured in toenails: nickel (Ni), lead (Pb), cadmium (Cd), manganese (Mn), and arsenic (As) in 25 males. Arterial compliance is an indicator of vascular health; arterial or vascular stiffness is related to decreased cardiovascular health. In this small observational study, the authors reported a statistically significant association between Ni levels in toenails and arterial compliance, but no significant associations for other metals. The authors concluded that welders who are exposed to higher levels of Ni may have an increased risk of adverse cardiovascular events.

4.1.4 Cancer

Ghadimi *et al.* (2015 PMID: 4756483) investigated occupational risk factors associated with bladder cancer. In this case-control study, controls were selected from the specialized clinics in the same city where cases had been registered. The authors found that welding, was a potential risk factors for bladder cancer. In general, the authors reported that working in a metal industry increased the odds of bladder cancer ten times compared to controls. Any exposure characterization or assessment, however, was lacking.

4.1.5 Renal Effects

Chuang *et al.* (2015 PMID: 26673824) assessed the association between metal fumes exposures and renal injury in 66 welders and 12 office workers from a shipyard in southern Taiwan. The authors measured concentrations of biomarkers of renal injury and metals in urine samples at the beginning (baseline) and end of the week (1-week exposure). Personal exposures to fine particulate matter (PM_{2.5}) were also collected. Findings showed: (1) 8-hour mean particulate matter (PM_{2.5}) concentrations were almost twice as high among welders (50.3 ug/m³) than office workers (27.4 ug/m³); (2) post-exposure, some biomarkers of renal injury were significantly elevated in welders; and (3) concentrations of metals in urine (aluminum, chromium, manganese, cobalt, and nickel) were also statistically significantly elevated compared to office workers. The authors concluded that nephrotoxicity in welders may be an emerging health concern.

4.1.6 Multiple Health Effects

Jonsson *et al.* (epub2015 PMID: 25744592) evaluated eye and respiratory symptoms in mild steel welders. Non-smoking welders with (n=74) and without (n=32) work-related symptoms in the last month were enrolled. During three 2-week periods in 1 year, symptoms, work tasks, and exposure to respirable dusts were assessed for each worker. The authors evaluated symptoms associated with 1) days at work, 2) welding time, and 3) respirable dust concentrations. Significant associations were found only for days at work and wheezing (OR: 1.27, 1.03 to 1.56), dry cough (OR: 1.5, 1.23 to 1.82), eye symptoms (OR: 1.79, 1.46 to 2.19), and nasal symptoms (OR: 2.16, 1.81 to 2.58). Only 9% of the samples exceeded the Swedish occupational exposure limit of 5 mg/m³, and the authors concluded that the current limit may not be protective against certain eye and respiratory effects.

Zamanian *et al.* (2015 PMID: 26900437) assessed the association between steel industry welders' exposure to ultraviolet radiation and adverse health events. The study included 200 welders and 200 non-welders who worked in Germany. The authors reported that welders were exposed to higher ultraviolet radiation than permissible contact threshold levels. They also found significantly higher incidence of adverse eye conditions (*e.g.*, cataracts, keratoconjunctivitis), and adverse skin conditions (*e.g.*, dermatitis, erythema) in welders compared to non-welders.

4.2 Animal Studies

We identified one animal study that evaluated the potential health effects of welding fume exposures.

Zheng *et al.* (2015 PMID: 25600139) investigated the effects of welding fume exposure on the cardiovascular system in rats. Three groups of rats were instilled with particles generated from: 1) manual metal arc hard surfacing (MMA-HS, 2mg/rat), 2) gas metal arc mild steel (GMA-MS, 2 mg/rat) welding, or 3) with a saline control once a week for seven weeks. Baseline cardiovascular function and response to increasing doses of adrenoreceptor agonists on cardiovascular function were measured after exposure. The authors found different changes in the cardiovascular response to the adrenoreceptor agonists with exposure to MMA-HS or GMA-MS-generated particles. Neither treatment affected heart rate or blood pressure. The author's concluded that the different type of welding fume exposure might result in different cardiovascular system effects.

4.3 Mechanistic Studies

We identified six mechanistic studies that evaluated the potential health effects of welding fume exposures.

Jara-Ettinger *et al.* (2015 PMID: 26244938) conducted a cross-sectional, matched case-control study of 33 exposed welders and 33 healthy controls to determine if exposures to welding-fumes were associated with an increase in micronuclei (MNI) or other nuclear abnormalities (NA) in oral mucosal cells. These biomarkers of genotoxicity are measured using the micronucleus test and are used to assess the potential for genotoxicity of a chemical, and therefore are markers of an increased risk of cancer. The authors found that exposure to welding-fumes was associated with elevated levels of some, but not all of the genotoxicity biomarkers that were evaluated. The authors cautioned that more research was needed to confirm the findings from this small study.

Mahmood *et al.* (2015 PMID: NA) investigated the association between exposures to welding fumes and markers of oxidative stress. Oxidative stress can result in damage to cells and DNA, and therefore increase risk of cancer. The authors collected blood samples and measured concentrations of cadmium, chromium, lead, and nickel in the blood, as well as malondialdehyde (MDA), a markers of oxidative stress. The authors also collected personal characteristics, lifestyle factors, occupational history, and the use of protective equipment using a questionnaire. Results showed elevated blood levels of all metals in welders and statistically significantly higher levels of MDA.

Parmalee *et al.* (2015 PMID: 26250396) presented a methodology that would help to understand the transcriptional changes associated with elevated exposures to manganese in order to develop better biomarkers of exposure. The method involves RNA sequencing in the *Caenorhabditis elegans* worm to study transcriptional changes that result due to chemical exposures. The results of the differentially expressed genes could aid in the development of studies to further develop better biomarkers of exposure.

Singh *et al.* (2015 PMID: 26088556) assessed the association between welding exposures and DNA damage in blood lymphocytes in 35 welders who worked in iron-based industries. A control group was matched to the welding exposure group based on a number of factors, including sex, smoking, alcohol intake, age, and socio-economic status. The authors reported greater DNA damage in welders compared to controls. Blood lead levels were also correlated with welding duration and with DNA damage. Authors concluded that there was some evidence of DNA damage associated with welding exposures. The study suffered from the lack of exposure measurements and a small sample size.

Suri *et al.* (epub 2015 PMID: 26277596) studied the biological mechanism by which welding fumes could increase risk of developing pneumococcal pneumonia. The authors assessed the relationship between exposures to welding fumes in welders and in animals and the

concentration of platelet-activating factor receptor (PAFR) in cells. PAFR mediates the capacity of pneumococci to infect lower airway cells. The authors found a statistically significant relationship between exposures to mild steel welding fumes and PAFR-dependent pneumococcal pneumonia. In both humans and mice increased exposures resulted in increased pneumococcal adhesion and infection and increased PAFR protein expression in the lung cells. The results suggest increased susceptibility of welders to pneumococcal pneumonia mediated by the increased PAFR due to welding fume exposure.

Villarini *et al.* (2015 PMID: 26152536) evaluated the association between exposure to extremely-low-frequency magnetic fields (ELF-MF) present during arc welding and DNA damage among 42 subjects (21 exposed electric arc welders; 21 healthy blood donors/control subjects). ELF-MF exposure was measured during one complete work-shift and DNA damage was measured from blood samples. Results were mixed with some DNA damage measurements showing significant effects, while others were not significantly different between welders and controls. The authors cautioned that more research was needed to confirm findings due to the small sample size of the study.

4.4 Reviews

We identified four reviews of welding exposure and health effects.

Bahrami *et al.* (2015 PMID: N/A) reviewed the use of biological monitoring to assess exposures and risks associated with exposure to manganese (Mn). Welders are typically exposed to high levels of Mn, which can lead to a Parkinson-like disease called manganism. Studies evaluating workplace exposures to Mn, including the use of biomarkers, published from 1990 to 2014 were identified and reviewed. The authors reported on a large variety of biomarkers that have been evaluated to assess Mn exposure including Mn concentration in biological fluids (blood, urine and saliva) and other parts of the body (hair and nail), as well as variation in Mn to Iron Ratio (MIR), variation in iron and regulatory proteins of iron, serum prolactin, reactive oxygen species (ROS), and magnetic resonance imaging (MRI). In general, the authors concluded that Mn levels measured in the blood or urine were not good biomarkers of inhalation, skin, and ingestion exposures for individuals. Overall, the authors noted that there remains a need for better biomarkers of exposure that would aid in the prevention of Mn-related diseases in exposed workers.

Cosgrove *et al.* (2015 PMID: 26152561) reviewed the literature to assess the relationship between steel welding fume exposures and pulmonary fibrosis. The literature search revealed only case series and case reports of pulmonary fibrosis related to steel welding. The authors concluded that this preliminary review suggested that steel welding fumes may increase the risk of pulmonary injury. However, case studies are less reliable than other types of epidemiological studies.

Greenberg *et al.* (2015 PMID: 25706449) reviewed existing literature on metal fume fever and polymer fume fever, which have similar clinical presentations and require a detailed exposure history to identify the source of exposure. The authors reviewed epidemiology studies to understand the pathophysiology, clinical presentation, diagnosis, treatment, prognosis, and prevention of these fevers. The authors concluded that metal and polymer fume fevers symptoms are generally benign and short-lived following cessation of exposure, although they could potentially be serious especially in workers with preexisting cardiorespiratory disease.

Ould *et al.* (epub 2015 PMID: 26387599) reviewed the literature to identify the main occupational risk factors associated with changes in male sperm parameters. The authors found that welding was one of several occupations associated with altered sperm parameters. The specific exposures associated with changes in sperm parameters included solvents, heat, vibrations, non-ionizing radiation, and heavy metals. The authors reported a large amount of heterogeneity in the methodology used across studies, particularly in the exposure characterization and assessment.

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