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HEALTH EFFECTS FROM WELDING EXPOSURES:
2017 LITERATURE UPDATE

RAMBOLL

CONTENTS

ACRONYMS AND ABBREVIATIONS

8-oxodG	8-oxo-2'-deoxyguanosine
AC	Acceleration capacity
ACGIH	American Conference of Governmental Industrial Hygienists
AD	Alzheimer's disease
AK	Actinic keratosis
ANOVA	Analysis of variance
Ar	Argon
ATLL	Adult T-cell leukemia/lymphoma
AWS	American Welding Society
BAL	Bronchoalveolar lavage
BCC	Basal cell carcinoma
BnMn	Bone manganese
CEI	Cumulative exposure index
CI	Confidence interval
cm	centimetre
CMM	Cutaneous malignant melanoma
CO_2	Carbon dioxide
Cr	Chromium
Cr +6	Hexavalent chromium
Cr +3	Trivalent chromium
CT	Computed tomography
DA	Dopamine
DC	Deceleration capacity
DHE	Dihydroethidium
DIP	Desquamative interstitial pneumonia
EBC	Exhaled breath condensate
ECG	Electrocardiogram
EEG	Electroencephalogram
ELF-MF	Extremely low frequency magnetic field
EMF	Electromagnetic field
epub	Electronic publication
ERP	Event-related potential
FAAS	Flame absorption atomic spectrometry
FCA-HS	Flux core arc- hard surfacing
Fe	Iron
FEF_{25-75}	Forced expiratory flow at 25% to 75% lung volume
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GMA-MS	Gas metal arc- mild steel
GMA-SS	Gas metal arc- stainless steel
HPG	Hypothalamic-pituitary-gonadal
HO-1	Heme oxygenase-1
HR	Hazard ratio

ICP-MS	Inductively coupled plasma mass spectrometry
IgG	Immunoglobulin G
IgE	Immunoglobulin E
INTEROCC	International Occupational Case-Control Study
IL	Interleukin
IONP	Iron oxide nanoparticles
ITI	Intratracheal instillation
LASSO	Least absolute shrinkage and selection operator
LT-B4	Leukotriene B4
MCA	Methylcholanthrene
MDA	Malondialdehyde
MDI	Methylene diphenyl diisocyanate
MeSH	Medical Subject Headings
Micro-PIXE	micro-proton-induced X-ray emission
MMA-HS	Manual metal arc- hard surfacing
Mn	Manganese
MnCl2	Manganese chloride
mtDNA	Mitochondrial DNA
MRI	Magnetic resonance imaging
NHBE	Normal human bronchial epithelium
Ni	Nickel
NIOSH	National Institute for Occupational Safety and Health
nm	nanometer
NFkappaB	nuclear factor kappa B
NPC	Nasopharyngeal carcinoma
NPPB	5-nitro-2-[(3-phenylpropyl)amino]benzoic acid
Nrf2	nuclear factor erythroid 2-related factor-2
OR	Odds ratio
OSHA	Occupational Safety and Health Administration
PAFR	Platelet activating factor
PEF	peak expiratory flow or the maximum flow after exhalation
PEFR	Peak expiratory flow rate
P-HNE	4-hydroxylnonenal protein adduct
$PM_{2.5}$	Particulate matter less than 2.5 micrometers in diameter
PMID	PubMed identification number
PPE	Personal protective equipment
ppm	Parts per million
ppb	Parts per billion
PPV23	Pneumococcal polysaccharide vaccine
ROS	Reactive oxygen species
SCC	Squamous cell carcinoma
SCD	Stop-change delay
SCT	Stop-change task
SMAW	Shielded metal arc welding
SSc	Systemic sclerosis
TH	Tyrosine hydroxylase

TIG	Tungsten inert gas
UFP	Ultrafine particles
UM	Uveal melanoma
UV	Ultraviolet
UVR	Ultraviolet radiation
VOC	Volatile organic compound
WF	Welding fume
WRA	Work-related asthma
XME	Xenobiotic-metabolizing enzyme

1 INTRODUCTION

On behalf of the American Welding Society (AWS), Ramboll conducted a comprehensive literature search and summary of studies related to the health effects of welding. In this update, we included literature published in 2017 (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 of relevant health effects studies in Section 4.

2 METHODS

We searched the PubMed, TOXNET, SCOPUS, and NIOSHTIC-2 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" or simply weld* (where the "*" is wild).
2. Searches were restricted to the year 2017 either electronically (epubs) or in print. Articles included in previous reviews were excluded from this review.
3. Where possible search terms were limited to searches of the titles and abstracts.
4. Searches were also limited to full text publications and English language.

2.2 Database Searches

2.2.1 PubMed

An initial search for weld* in the Title or Abstract, filtered for full text and year 2017, yielded 251 citations. All citations were uploaded to Mendeley reference manager for further screening.

2.2.2 SCOPUS

The SCOPUS database was queried for articles containing "welders" or "welding" in the title, abstract, or keywords that were published in 2017 and were English language only. Irrelevant subject areas (*e.g.* engineering/material science, mathematics, physics, astronomy, energy, computer science, dentistry, chemistry, earth/planetary sciences, business management and accounting, nursing) were excluded. The search identified 254 publications that were uploaded to Mendeley for further screening.

2.2.3 TOXNET

We searched TOXNET using the search term "weld*" for the year 2017 and filtered by English language. This yielded 104 citations that were uploaded to Mendeley.

2.2.3 NIOSHTIC-2

We searched the NIOSHTIC-2 database using the key words "welding" or "welder" in all fields for the year 2017. The 25 publications that resulted from the search were uploaded to Mendeley.

2.3 Literature Review

The literature search yielded a total of 634 references. We reviewed titles to assess the relevance to exposure and health effects from welding, and identified all the duplicates for exclusion. We also excluded 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

A total of 78 relevant references were identified after excluding duplicates and other non-relevant references. Several of the references were included in the 2016 review and thus not summarized in this report. The breakdown of the remaining references by category is listed in Table 2.1.

Table 2.1. Breakdown of Abstracts Reviewed by Study Category

Study Category	**Totals from all databases**
Particle characterization and exposure	18
Epidemiology and controlled human exposure	23
Animal	8
Mechanistic/cell/*in vitro*	2
Reviews	12
Overall Total	**63**

3 EXPOSURE STUDIES

We identified 18 exposure-related publications from 2017 (*i.e.*, particle characterization and exposure). Some studies were published online in 2017 (*i.e.*, 2017 was the "epub date") and these were included in our summary. Articles that were not relevant or were included in prior AWS updates (*e.g.*, epub date in 2016) were excluded. A brief summary of the exposure abstracts is provided below for all the relevant studies.

Welders as well as workers nearby can be exposed to detrimental optical radiation emissions from arc welding. Bauer et al. (2017) designed three mathematical models that can be used to assess optical radiation emission as a function of welding amplitude (range 70 to 350 A, similar to industry values) and to calculate the limits of exposure duration that would be protective of welders from adverse optical radiation emissions. The optical radiation emissions ranged from 200 to 2700 nm for metal active gas, metal inert gas, and cold metal transfer welding, as measured by spectro- or radiometric measurements. The model for metal active gas emission was validated with manual arc welding. Depending on the welding material and welding process (standard or pulsed), the maximum permissible exposure durations ranged from <1 second (ultraviolet spectrum), 1-10 seconds (visible light range), minutes to hours (infrared).

The bioaccessability of metalic elemets, which is important for uptake, has not been well-studied and welders are at risk from exposures to these metalic elements. Therefore, Ellingsen et al. (2017) investigated the bioaccessability of chromium (Cr), molybdenum (Mo), vanadium (V), and tungsten (W) in welders working in a shipyard workroom. Using a lung lining fluid simulant called Hatch solution that quantified the soluble (Hatchsol) and non-soluble (Hatchnon-sol) elements in workroom air and analysing whole blood, serum, blood cells and urine from 70 welders and 74 controls, the authors evaluated the associations between air concentrations and the bioavailability of the elements. In air samples, only a small fraction of Cr, V, and W were found to be soluble (Hatchsol); Mo was found in equal fractions in Hatchsol and Hatchno-sol. Welders had significantly higher urine and serum concentrations of the four elements compared to controls. When considering only the soluble fraction in the air, significant associations between Hatchsol elements and the corresponding biological concentrations were observed for W (urine) and V (serum). Furthermore, timing of air sampling influenced the strength of the associations, i.e. the closer in time of biological and air sampling, the stronger the association.

Gomes and Miranda (2017) measured nanoparticle (NP) emissions in different locations of a welding facility during metal active gas welding of carbon steel, taking into account different processes and varying levels of argon (Ar) and carbon dioxide (CO_2). Based on the measurements taken at different distances from the welding source, the authors generated a graphical representation of the data to identify "safe" and "critical" regions of exposure. This methodology can be used to categorize sites where regulatory measures may be needed to reduce exposures, including operation contaiment or use of dedicted exhaust ventilation.

The National Institute for Occupational Safety and Health (NIOSH) conducted an evaluation of exposure to manganese (Mn) fractions in welding fumes at three factories manufacturing heavy equipment (Hanley et al., 2017). Total or respirable Mn samples from 109 worker-days were measured during gas metal arc-welding and samples were separated into fractions based on selective chemical solubility (using a sequential extraction procedure). Full shift particle size Mn time-weighted average (TWA) concentrations at the worker breathing zone ranged from 0.38-26 μg/m^3 for soluble Mn; 3.2-170 μg/m^3 for $Mn^{0,2+}$, 3.1-290 μg/m^3 for Mn $^{3+,4+}$, and non-detectable (ND)-130 μg/m^3 for insoluble Mn fractions. The total particulate Mn TWA concentrations ranged from 6.9 to 610 μg/m^3. The range of respirable size Mn TWA concentrations were 0.33-21 μg/m^3 for soluble Mn; 15-140 μg/m^3 for $Mn^{0,2+}$; 14-170 μg/m^3 for $Mn^{3+,4+}$; 5.3-230 μg/m^3 for insoluble Mn; and 36-530 μg/m^3 for Mn (sum of fractions). Total particulate TWA GM concentrations of the Mn (sum) were 53 μg/m^3 (GSD = 2.5), 150 μg/m^3 (GSD = 1.7), and 120 μg/m^3 (GSD = 1.8) for the three separate factories. All exposures measurements were below the Occupational Safety and Health Administration's (OSHA's) regulatory permissible exposure limit and NIOSH's recommended exposure limit for Mn, but the exposures of 70 welders were over the American Conference of Governmental Industrial Hygienists's (ACGIH's) Threshold Limit Value (TLV) for total Mn (100 μg/m^3) and 29 welders' exposure exceeded the TLV for respirable Mn (20 μg/m^3). The authors concluded that a welding fume exposure control and management program was warranted to reduce exposures to Mn including improved ventilation or use of respiratory protection.

Kendzia et al. (2017a) used over 8,000 individual measurements of nickel (Ni) collected from 1990-2009 in workplaces across Germany and stored in a German exposure database (MEGA) to estimate the average occupational exposure to inhaled Ni. The median for all measured Ni concentrations was 9 μg/m^3, with a 95th percentile of 460 μg/m^3. The predicted geometric mean (GM) for welders centered around 1999 was influenced by welding process and the Ni content of the materials. Gas metal and shielded metal arc welders using tools containing Ni, metal sprays, grinders, forging-press operators, or workers involved in battery and accumulator manufacturing were in the highest-exposure groups: GM ≥20 μg/m^3 Ni. The estimated exposure profiles are useful for exposure assessment in epidemiological studies and industrial hygiene evaluations.

Kendzia et al. (2017b) analyzed 5,771 personal exposure measurements of manganese (Mn) from 1989-2015 from a German exposure database (MEGA), which also contains information regarding occupation, job tasks, and sampling conditions, to estimate the average occupational exposure to inhaled Mn. Mn is of particular concern because exposure to low concentration of Mn have been linked to neurotoxicity. The authors calculated the geometric means (GMs) and medians adjusted for a 2-hr sampling duration and analytical method and centered around 2009. The median Mn exposure concentration for welders was estimated to be 74 μg/m^3 (interquartile range (IQR) 14-260 μg/m^3) compared to 8 μg/m^3 (IQR < limit of quantification – 30 μg/m^3). A third of the GMs of the measurements in welders were >100 μg/m^3, 20% exceeded 200 μg/m^3, and 5% of measurements were >1000 μg/m^3 in shielded metal arc welders using consumables with high Mn content (>5%). Other welding tasks such as Tungsten inert gas welding or laser welding, and other occupations such as foundry worker, electroplater, or grinder generally had GM Mn exposure

< 10 μg/m^3. Higher measured Mn concentrations were associated with shorter length of sampling. The results showed that job tasks, materials used, and occupations influenced overall inhaled Mn exposure.

Welders in the US (over 300,000) are at risk of occupational exposures to manganese (Mn), which can result in neurological disorders similar to Parkinson's disease. To date, a biomarker for long-term Mn exposure has not been identified. Liu et al. (2017) describes the development and testing of a tool to quantify Mn concentrations in bone as a biomarker for long-term cumulative exposure to Mn. The detector system uses deuterium-deuterium-based neutron generator technology, which is based on a hand irradiation assembly and a high purity germanium detector system. The authors reported that a detection limit of 0.64 ug Mn/g bone and acceptable hand dose of 36 mSv has been achieved.

Mettakoonpitak et al. (2017) described testing of a Nafion/Bi-modified electrochemical sensor that uses adsorptive stripping voltammetry as a low-cost method of measuring cobalt (Co) and nickel (Ni) in air and welding fume samples. Using carbon stencil-printed electrodes (CSPEs) on PET films and a Co(II) and Ni(II) chelator (dimethylglyoxime) with selective chemical precipitation for trace electrochemical analysis, the Nafion/Bi-modified sensor quantified Co and Ni with a diffusion-controlled redox reaction. The electrode has a high standard of repeatability for upto 15 runs (<15% RSD) and low detection limits: 1 ug/L (Co) and 5 ug/L (Ni). Testing also indicated that no other metal species interfered with the Co and Ni measurements under test conditions. The sensor has a working range for Co and Ni of 1-250 and 5-175 ug/L, respectively. The authors concluded that this low-cost tool can be used reliably to measure Co and Ni, and validation with ICP-MS showed no statistically significantly different results between the sensor and the ICP methods when tested using reference materials.

Pacheco et al. (2017) evaluated the impact on fume formation rates and emissions of nanoparticles with potential for deposition in the lung alveolar region using different gas mixtures with varying heat inputs during the process of metal inert gas/metal active gas stainless steel welding. The authors found that the spray transfer mode showed higher values of nanoparticle generation. The authors also reported that among the gas mixtures tested, the gas mixture with 82% argon and 18% carbon dioxide had higher nanoparticle emissions and fume formation rates.

Sajedifar et al. (2017) examined the impact of operational parameters (current intensity, travel speed, heat input) on fume emissions during the process of shielded metal arc welding (SMAW). The number concentration (NC) and mass concentration (MC) of particles generated during the SMAW process was measured using a dust monitor at a distance of 23 cm (hood inlet) and 41 cm (welder's breathing zone) from the weld point. The authors reported that the NC of particles decreased with increased particle size, with the highest mass concentration (MC) in MC_1 (0.35 μm-0.5 μm) and MC_8 (>6.5 μm). The authors concluded that for maximal exposure reduction, the lowest voltage and amperage and highest travel speed possible should be used to the extent possible without compromising the quality of the weld. The authors recommended considering both MC and NC in the assessment of welding fume exposures.

Sani et al. (2017) conducted a study to collect baseline data on concentrations of metals in urine and blood in residents of Kano, Nigeria, many of which are occupationally exposed to metals. The participants reported having a wide range of health problems including metal fume fever, eye and skin irritation, dizziness, respiratory problems and respondents also noted inadequate use of personal protective equipment. The authors measured urine and blood levels of metals by atomic absorption spectrophotometry. Elevated levels of manganese, lead, and nickel were found in the urine and blood of the sampled population; high levels of chromium were also found in blood. The authors concluded that workers in Kano may be exposed to dangerous levels of metals, and in particular manganese and lead, and emphasize the necessity of improved surveillance of occupational metal exposures.

Sousan et al. (2017) assessed the accuracy, bias, and precision of mass concentration measurements in the workplace using three low-cost (<$300) consumer aerosol monitors (CAMs): Foobot (Airoxlab), Speck (Carnegie Mellon University), AirBeam (HabitatMap). CAMs were used to measure $PM_{2.5}$ in salt, welding fume, and Arizone road dust and the results were compared to those of reference instruments and a medium-cost aerosol photometer (personal DataRAM 1500, Thermo Scientific). All three had a bias for welding fume (<-82%). The Foobot had the strongest correlation with the reference instruments (r-value=0.99) compared to the Speck (r-value range=0.91-0.99) and the AirBeam (r-value range=0.7-0.96) and had an optimal precision (coefficient of variation range=5-8%). Therefore, the authors conculded that because of a better linear response to different aerosol types and good precision, the Foobot could provide good estimates of $PM_{2.5}$ in the workplace with appropriate site-specific calibration to account for particle size and composition.

Stanislawska et al. (2017) measured concentrations of metals in fine and ultrafine particles in two metal industry plants during stainless steel and mild steel welding. Stationary welding fume samples were taken to assess morphology and structure using scanning electron microscope (SEM) and energy dispersive spectrometry (EDS). Personal exposure samples from welders' breathing zones were also collected to evaluate iron, manganese, nickel, and chromium (Cr^{+6} and Cr^{+3}) in inhalable and respirable fractions (using flame absorption atomic spectrometry and inductively coupled plasma mass spectrometry). The authors resported that results showed concentrations of potentially carcinogenic and neurotoxic metals that exceeded regulatory limit values from stainless steel welding.

Tompkins (2017) tested the performance of a low-cost, high-flow (10 L/min) inhalable prototype sampler against a traditional inhalable air sampler (IOM, 2 L/min) during welding, grinding, soldering, pouring, sawing, tending, and shooting gun processes in metal working facilities. The sampling time ranged from 4.2 to 8.3 hours and the most common metals detected were iron, manganese, zinc, copper, and lead. Linear regression equations yielded significant differences between the two samples: the prototype collected 71% of the measure concentrations of the IOM, and performed better in area sampling compared to personal sampling. The prototype also performed better in collecting smaller, heat generated particles compared with the collection of larger, mechanically generated particles and may be superior in sampling lower concentrations depending on the metal composition.

The flow rate of 10 L/min was difficult to maintain for an entire work shift for the high-flow prototype. Overall, slight differences were found between prototype and traditional sampler measurements, but further testing is needed to assess the sensitivity of the prototype sampler to detect lower concentrations of metals.

As part of the INTEROCC study, Vila et al. (2017) created a source-exposure matrix (SEM) to estimate occupational exposures to electromagnetic fields (EMFs). Source-based measurements from a database of published and unpublished resources were used taking into account the quality and relevance of the data. The authors used a novel methodology for combining available measurements and calculated arithmetic and geometric means, estimates of variability and maximum exposures by EMF source, frequency band and dosimetry type. Weighting of mean estimates was done based on the confidence in the pooled estimates. The final SEM included weighted means and maximum exposure estimates for 312 EMF exposure sources ranging from 0 Hz to 300 GHz. The authors reported that magnetic fields ranged from 0.14 muT in visual display terminals to 17 muT for tungsten inert gas welding. The methodology described by the authors could be used for development of SEMs for other physical or chemical agents.

Fume exposures from plasma cutting in metal fabrication can cause pulmonary toxicity and other health effects. Wang et al. (2017) conducted an assessment of how operation parameters (arc current and arc time) in stainless steel plasma cutting affected the rates of fume formation, release of carcinogenic hexavalent chromium and other toxicants, particle size distribution (PSD) and particle morphology. The study was conducted in a fume chamber and a high-volume pump was used to collect fume samples using a glass fiber filter. Plasma cutting of stainless steel plates was conducted with arc currents between 20 and 50 A. Fume generation increased with increases in arc current, ranging from 16.5 mg/min at 20 A to 119.0 mg/min at 50 A arc current. The authors determined that the fumes had a multimodal size distribution, and a large proportion of particles were between 96 and 235 nm. The higher the arc current, the more particles generated. Wang et al. (2017) concluded that arc current was the principal factor associated with fume emissions from plasma cutting and recommended that workers use personal protective equipment and work in well ventilated areas to reduce exposures.

Welding fume is a source of occupational exposure to manganese (Mn), and exposure to Mn has been associated with neurological health impacts. However, there is no universally accepted biomarker of exposure to Mn. Ward et al. (2017) evaluated the utility of using toenail manganese (Mn) concentrations as a biomarker for exposure in a cohort of 45 male welders and 35 age-matched unexposed factory worker controls. Toenail Mn was significantly higher ($p<0.001$) in welders compared with controls (6.87 +/- 2.56 versus 2.70 +/- 1.70 μg/g). The authors found that using a cutoff of 4.14 μg/g allowed for distinguishing between controls and welders with 91% specificy and 94% sensitivity (area under curve = 0.98). A cutoff of 4.66 μg/g helped to categorize people with mean exposure above or below the Threshold Limit Value (0.02 mg/m^3) set by the American Conference of Governmental Industrial Hygienists for an exposure window of 7-12 months before nail clipping. The authors also found the dietary intake, body mass index, smoking status, and ethnicity had no significant effect on toenail Mn. The authors concluded that toenail Mn concentrations are an sensitive, specific, and easily obtained biomarker of Mn exposure.

Following Poland's labor safety regulations in 2016 regarding electromagnetic field (EMF) emission levels, Zubrzak et al. (2017) measured EMF exposure in high frequency welding facilities during normal operations and presented examples of elevated EMF exposure in areas with dielectric welding. Solutions were presented ranging from simple low-cost controls to more complex electromagnetic shielding systems that could reduce EMF exposure by 80% or more and decrease exposure to non-hazardous levels. The authors stated that excess EMF exposure is likely due to poor design, installation, or operation of welding machines.

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 (4 studies), respiratory effects (10 studies), cardiovascular effects (4 studies), cancer (3 studies), and multiple health effects (2 studies). Summaries of these studies are provided below.

4.1.1 Neurological Effects

Bowler et al. (2017) compared neuropsychological testing results with shortened MRI T1 relaxation time, a biomarker of manganese (Mn) accumulation in the brain, in 26 active welders exposed to manganese for a mean duration of 12.25 years at an average level of 0.11 +/- 0.05 mg/m^3 Mn in air. Compared with controls, welders had worse scores in verbal fluency (Fruit Naming) and the Parallel Lines test of graphomotor tremor in addition to shorter MRI T1 relaxation times in the globus pallidus, substantia nigra, caudate nucleus, and anterior prefrontal lobe. The lower caudate nucleus and substantia nigra relaxation times were associated with lower performance on verbal fluency, verbal learning, memory, and perseveration tests (WHO-UCLA AVLT) in welders. The authors noted that verbal function may be one of the first cognitive domains affected by Mn deposition in the brain.

Nie et al. (2017) investigated the relationship between bone manganese (BnMn) and estimated cumulative manganese exposure in 30 ferroalloy factory workers and 30 manufacturing workers. Those working in welding, smelting, mining, and battery production are at risk for high exposures to manganese (Mn), which can cause a neurological disease, manganism that resembles Parkinson’s disease. The disease is progressive and irreversible. To test the value of a long-term cumulative Mn biomarker, the authors measured BnMn noninvasively in vivo, conducted neurocognitive and neurobehavioral tests, and estimated cumulative exposure index (CEI) of manganese. Ferroalloy factory workers had significantly higher BnMn than manufacturing factory workers and there was a significant association between BnMn, years of employment, and 15 years of Mn CEI. Furthermore, BnMn was significantly correlated with decreased cognitive and motor function. The authors concluded that this new in vivo BnMn biomarker may be important for understanding and preventing neurological disease due to occupational Mn exposure.

Parent et al. (2017) used 1,800 incident glioma cases and 5,160 controls between the ages of 30 and 69 years in seven-country INTEROCC study to examine the association between risk of glioma and occupational exposure to welding fumes as well as lead, cadmium, nickel, chromium, and iron. The authors estimated lifetime occupational exposure to welding fumes and metals using the INTEROCC job-exposure matrix (JEM), a modified version of a Finnish JEM. A slightly increased prevalence of glioma was associated with exposure to some metals compared to controls. Glioma prevalence was 1.7 and 2.2% for cadmium exposure and 10.2 and 13.6% for iron exposure in controls and cases, respectively. With multivariable logistic regression analysis, the authors found no association between ever-exposure to the metals or welding fumes and glioma risk: odds ratios (95% confidence interval) 0.8 (0.7-1.0) for lead and 1.1 (0.7-1.6) for cadmium. Similar results were obtained for other models using cumulative exposures or duration. The authors concluded that based on findings from this large-scale international study, there is no evidence of glioma risk from exposures to metals in welding fumes.

Van Thriel et al. (2017) conducted a cross-sectional study of 50 male welders and 28 age-matched controls to assess potential neurochemical effects of manganese (Mn) exposure. Mn is initially neurotoxic by disrupting striatal γ-aminobutyric acid levels, therefore the welders and controls were tested for cognitive function involving the frontal-striatal loops using the stop-change task (SCT), which is used to determine multi-component behavior control and action cascading. The authors collected information on reaction times, accuracy of responses, and event-related potentials (ERP) from electroencephalogram (EEG) recordings. The welders were divided into groups by level of exposure to respirable Mn with the low-exposed group including 23 welders (median 4.7 $\mu g/m^3$ Mn exposure) and the high-exposed group including 27 welders (median 86.0 $\mu g/m^3$ Mn exposure). The authors reported no differences between welders and controls based on the stop-change task results or from the ERP readings. In addition, the authors observed no correlation between measured Mn and ERP results. The authors concluded that multitasking performance and cognitive flexibility are not influenced by exposure to welding fumes.

4.1.2 Respiratory Effects

Abrahamsen et al. (2017) conducted a cross-sectional study to investigate the prevalence of respiratory symptoms and physician-diagnosed asthma and its association with occupational exposures. The authors used a questionnaire sent out to randomly selected residents of Telemark, Norway (aged 16-50). The authors calculated the odds ratio (OR) for respiratory symptoms and asthma for each occupational group based on self-reported exposures and an asthma-specific job-exposure matrix (JEM). The response rate was 33% resulting in 16,099 responses. The overall prevalence of asthma was 11.5%. Overall, the odds ratio of having wheezing or asthma attacks in agriculture/fishery workers was 1.3 (95% CI 1.1-1.6) and in craft/related trade workers was 1.9 (95% CI 1.2-2.8). Exposure to flour was associated with dyspnea, as were exposures to diisocyanates, welding/soldering fumes, and vehicle/motor exhaust (OR 3.2 (1.4-7.3), 2.9 (1.5-5.7), 3.2 (1.6-6.4), and 1.4 (1.0-1.8), respectively). The authors concluded that occupational exposure to flour, diisocyanates, welding/soldering fumes and vehicle/motor exhaust are associated with respiratory symptoms in the past 12 months and asthma medication use.

Cetintepe et al. (2017) investigated the association between blood cadmium (Cd) and blood lead (Pb) levels and lung function in 207 non-smoking male welders at the Occupational Disease Hospital in Ankara, Turkey. The workers were divided into three groups: non-smoking, unexposed office workers (reference group), and exposed workers divided into workers exposed > 4 hours/day and those exposed < 4 hours/day. Cd and Pb levels were significantly elevated in both exposed welder groups ($p<0.0001$). In the exposed group less than 4 hours per day, the forced vital capacity (FVC) % and forced expiratory volume in 1 second (FEV_1) % increased, and the FEV_1/FVC ratio decreased ($p<0.0001$). All lung function test results including peak expiratory flow (PEF) values were significantly decreased in welders exposed for more than 4 hours per day and in subjects with high blood cadmium ($p<0.0001$). The authors concluded that welders with prolonged exposures or elevated exposure to metals were at increased risk of lung function decline.

Dierschke et al. (2017) conducted a double-blind chamber exposure study in which welders were exposed to levels of gas metal arc-mild steel (GMA-MS) particles expected on a normal workday (i.e., 1 mg/m^3) and evaluated effects on eyes, upper and lower respiratory system, lung function, exhaled breath condensate (EBC) leukotriene B4 (LT-B4), and blood and nasal lavage (NL) inflammation markers (Interleukin-8, IL-8, IL-6, and neutrophils). The authors recruited 21 welders with or without work-related symptoms in the lower airways and 11 symptom-free non-welder controls. Welders and controls were exposed to welding fumes or filtered air. The authors found no effects on respiratory symptoms and lung function from welding fume exposures. EBC LT-B4, however, was decreased significantly in all groups following welding fume exposure compared to filtered air, and some inflammatory markers were increased (NL IL-6 in non-symptomatic welders and controls, and neutrophils in the symptomatic group). Results from samples collected the morning after exposure showed decreased serum IL-8 and neutrophils in all groups exposed to welding fumes. The authors also reported that symptomatic welders had ten times the level of EBC LT-B4 compared with the non-symptomatic groups. The authors concluded that study results suggest that welding fume exposures can produce changes in inflammatory markers that are indicative of subclinical effects, even without any observed clinical effects, at level below the Swedish occupational standards for respirable dust.

Ewing et al. (2017) described an outbreak of pneumococcal disease between April and June 2015 that included four confirmed and five probable cases among multinational workers exposed to metal fumes during refurbishment of an oil rig in a Belfast shipyard. The working conditions included proper environmental control measures and respiratory protective equipment were available. The pneumococcal strains of serotypes 3 and 4 were identified via genomic sequencing in the confirmed cases, which are both vaccine-preventable strains. The pneumococcal polysaccharide vaccine (PPV23) and antibiotics were offered to 680 people potentially exposed to metal fume to provide protection and stem the outbreak. The authors concluded that the use of a pneumococcal vaccine may be an appropriate preventative measure for metal fume-exposed workers to reduce the risk of developing pneumococcal disease even when other appropriate control measures are used.

Ghani et al. (2017) conducted a cross-sectional study of Pakistani welders to assess the association between lung function and respiratory symptoms and welding exposures. The authors collected information using a questionnaire and measured lung function by spirometer. The results were evaluated using analysis of variance. The authors reported statistically significant declines in forced vital capacity (FVC), % and forced expiratory volume in 1 second (FEV_1), forced expiratory flow (FEF 25-75%), peak expiratory flow rate (PEFR), and FEV1/FVC ratio among different types of welders. The authors concluded that preventive measures should be implemented to reduce the health-related impacts from welding fume exposures.

Gobba et al. (2017) evaluated the effects of iron/welding fumes on makers of inflammation and allergic response and lung function. The authors recruited 40 nonsmoking and 40 smoking Egyptian welders and 40 healthy, nonsmoking, never-exposed controls. Smoking welders had the lowest peak expiratory flow rates (PEFR) at the end of a work shift compared with the nonsmoking groups. Lung inflammatory/allergic response markers including serum iron and immunoglobulin E, as well as plasma thiobarbaturic acid reactive substances, C-reactive protein, tumor necrosis factor-alpha, haptoglobin, interleukin-2, interleukin-6 and interleukin-23 histamine, lactate dehydrogenase isoenzyme-3, and calcitonin were significantly increased. Antioxidant enzymes in the blood including catalase, superoxide dismutase, glutathione peroxidase, and glutathione reductase, among others, were significantly decreased in welders compared with the control group. Other markers were not significantly changed (e.g., arginase and alpha-L-fucosidase) in the welders compared to controls. The authors concluded that exposure to welding fumes can increase the risk of lung inflammation, especially in smokers.

Hariri et al. (2017) assessed heavy metal exposure during welding in an air-conditioned Malaysian facility by analysing the concentration of chromium (Cr) and manganese (Mn) in the welders' breathing zones as well as in toenail samples using inductively coupled plasma mass spectrometry. The authors also conducted lung function tests. The heavy metal concentrations in the breathing zone trended with the toenail concentrations. The concentrations of Cr and Mn in the breathing zone air samples exceeded the Malaysian permissible exposure limits, but there was no statistically significant decrease in lung function among the welders. Despite the negative findings on health effects, the authors recommend implementation of exposure control measures.

He et al. (2017) described the application of a novel method, micro-proton-induced X-ray emission (micro-PIXE) analysis, as a useful tool for the development of risk index for welder's and coal miner's pneumoconiosis, an occupational disease that is associated with long-term lung function decline. Micro-PIXE is a highly sensitive method that allows for the identification of the elemental composition of particles in the lungs. The authors used this method to evaluate the lungs of Chinese welders and coal miners, along with results from chest radiographs and lung function tests. The lung function test results, including percent vital capacity (%VC) and forced expiratory volume in the 1st second over forced vital capacity (FEV_1/FVC), indicated that some welders had improved symptoms after 5 years, whereas the majority of coal miners had worse symptoms. The elemental make-up of the pneumoconiosis differed across welders and miners: particles in the welder's lungs were primarily made up of iron, manganese, and titanium (metallic oxide) and lesser amounts of silica, aluminum, calcium (aluminum silicate); whereas particles in the coal miner's lungs consisted primarily of carbon, silica, aluminum, potassium, and titanium particles and lesser amounts of calcium or iron. Fibrosis severity was correlated with particles containing aluminum, silica, sulfur, potassium, calcium, and titanium (orthoclase and anorthite). Particles containing silica and smoking were independently associated with a decrease in FEV_1/FVC and a decrease in %VC was correlated with particles containing silica and titanium. Based on these results the authors developed a risk index to predict the development of pneumoconiosis. They concluded that Micro-PIXE analysis is a good method for the evaluation of the elemental composition of dust exposures.

High levels of eosinophils, an inflammatory marker, are often found in the respiratory tract of welders with occupational inhalation exposure to metal fumes. Janwadkar et al. (2017) describe a case of a 19-year-old male welder with upper respiratory tract infection, persistent moderate eosinophilia, and increased eosinophilic precursors upon bone marrow exam. The authors conclude that welding is a risk factor for persistent respiratory tract inflammation with eosinophilia. Although short-term steroid treatment for the condition can provide symptomatic relief, the authors recommend reducing or eliminating inhalation of welding fumes as a more effective preventive measure.

Suojalehto et al. (2017) aimed to identify the nasal protein expression components of work-related asthma (WRA), as the mechanism of WRA has not been fully identified. The authors collected nasal brush samples from 82 nonsmoking volunteers, including both healthy controls and WRA patients after exposure to either protein allergens, isocyanates, or welding fumes. The authors analyzed the samples using two-dimensional gel electrophoresis, and the individual proteins were identified by mass spectrometry. Immunological analyses were conducted using a Western blot. The authors reported that protein allergens had the greatest effect on the proteome, after analysis of 228 out of 2500 spots chosen for identification compared to control results. Overall, the increased expression of proteins during WRA included proteins involved in defense response, protease inhibitor activity, inflammatory and calcium signaling, complement activation, and cellular response to oxidative stress. Welding fume-related asthma had a distinct nasal proteome profile from those of protein allergen- and isocyanate-related asthma. The authors concluded that unlike protein allergen and isocyanate induced asthma, the protein profile of welders was similar to that of healthy controls.

4.1.3 Cardiovascular Effects

Ko et al. (2017) evaluated the associations between occupational exposures to metals and biomarkers of oxidative and DNA damage in 117 workers in fitness equipment manufacturing plants. Blood concentrations of chromium (Cr) and manganese (Mn) were measured and malondialdehyde (MDA) levels and telomere length (via the alkaline Comet assay) were assessed. MDA levels varied depending on the workers' roles with the highest MDA levels in workers involved in cutting and painting, followed by welders and the lowest levels in administrative workers. Welders had significantly ($p=0.058$) shorter telomere lengths on average, and higher Cr and Mn levels in the blood. Metal blood concentrations were correlated with increased MDA levels compared with administrative workers. These findings suggest that telomere length and MDA levels could be useful biomarkers for cardiovascular disease in welders exposed to metal fumes.

Mitochondrial DNA (mtDNA) is a target for particle-induced oxidative stress, therefore, Xu et al. (2017) investigated the relationship between occupational exposure to welding fumes on biomarkers of mtDNA function. The second aim was to investigate whether the biomarkers influenced the association between particle exposure and blood pressure as a proxy for cardiovascular health, as particle exposure is a known risk factor for cardiovascular diseases. The authors measured respirable dust via personal sampling of 101 welders (compared with 127 controls) during work hours (average sampling time: 6.8 hrs; range 2.4-8.6 hrs), and blood pressure once for each worker. The authors measured mtDNA copy number by quantitative PCR and methylation of the mitochondrial regulatory region D-loop and the tRNA encoding gene MT-TF by bisulfite-pyrosequencing. The relative number of unmethylated D-loop and MT-TF were used as markers of mtDNA function and indicators of oxidative stress. Statistical analyses were done using general linear models. A higher mtDNA copy number ($beta = 0.11$, $p = 0.003$) and lower DNA methylation of D-loop (beta

= -1.4, p = 0.002) and MT-TF (beta = -1.5, p = 0.004) was observed for welders compared to controls. The authors reported a weak association between increased mtDNA copy number and welders exposed to levels of fume greater than 0.7 mg/m^3 ((beta = 0.037, p = 0.054). Low mtDNA function was associated with higher blood pressure in welders compared to controls, whereas no difference was observed in the group with high mtDNA function. The authors concluded that results are indicative of exposure-related oxidative stress and that the modifying effects of mtDNA function on exposure-related increases in blood pressure suggest a mitochondria-environment interaction.

Zhang et al. (2017a) aimed to identify the hazardous metal components in environmental and occupational metal mixtures that are associated with changes in autonomic cardiac function. The authors analysed the concentration of 16 types of metals in urine and quantified cardiac autonomic effect indicators, acceleration capacity (AC) and deceleration capacity (DC) from the electrocardiogram (ECG) recordings of 54 welders. The authors used a linear mixed-effect model with least absolute shrinkage and selection operator (LASSO) to identify metals associated with changes in cardiac autonomic function. The authors evaluated the effects of mercury and chromium on DC and mercury, chromium and manganese on AC. Only the effects of mercury remained significant after applying the linear mixed-effects model. The authors reported that 1 ug/L increase in urinary mercury was associated with -0.58 ms (-1.03, -0.13) change in DC and 0.67 ms (0.25, 1.10) change in AC. The authors noted that the results should be verified with a larger sample size.

In a follow-up study, Zhang et al. (2017b) investigated the association between epigenetic alterations (i.e., changes that affect gene expression or gene activity and that can be hereditary) and changes in cardiac autonomic function measured by acceleration capacity (AC) and deceleration capacity (DC). In the same group of 54 welders as in Zhang et al. (2017a), the authors examined DNA methylation as a measure of epigenetic changes at over 472,506 CpG (5′-cystine-phosphate-guanine-3′) sites using the Illumina Infinium HumanMethylation450 BeadChip assay. The authors applied linear mixed models to assess associations between DNA methylation and AC and DC. One CpG site (cg26829071) in the GPR133 gene was found to be negatively associated with DC measurements. The authors noted that results should be verified in future studies with a larger sample size.

4.1.4 Cancer

Arc welding generates ultraviolet radiation that may contribute to skin cancer, but there is limited research in this area. Heltoft et al. (2017) evaluated the risk of developing malignant melanoma and/or basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) on exposed skin (neck, head, and upper extremities) from metal arc welding. The authors used a Danish national company-based historic cohort of 4,333 male metal arc welders that were followed from 1987 to 2012 to assess skin cancer risk. The reference comparison group consisted of Danish skilled and unskilled male workers of similar ages; the Danish Cancer Registry and the Danish Pathology Register supplied information about skin cancer diagnoses (BCC, SCC; cutaneous malignant melanoma, CMM; precancerous conditions; and actinic keratosis, AK) of the neck, head, upper extremities. The authors reported no significant risk of skin cancer in welders when analysing all skin cancer types, but the adjusted hazard ratios and 95% confidence intervals (CI) for AK and BCC in the neck area were 2.49 (95% CI 1.03-5.99) in welders exposed for over 20 years and 2.46 (95% CI

1.02-5.94) in those exposed for over 30 years, respectively (adjusted for age and social group information collected at baseline). The authors concluded that exposure to metal arc welding in the long-term could lead to increased risk of BCC and AK in the neck area, though analyses were based on a small number of exposed cases.

Although foundry work has been linked with development of lung cancer, the relationship between welding and lung cancer is less clear because of potential confounding effects of smoking. Wong et al. (2017) examined the risk of incident lung cancer (n=2,034) in a prospective randomised trial of 53,454 heavy smokers (>30 pack-years) in the US that were part of the National Lung Screening Trial, and the potential relationship to welding and foundry work exposures. The cohort was followed from 2002-2009 and the history and duration of welding and foundry work were assessed via questionnaire. Cox regression models were used to estimate hazard ratios and 95% confidence intervals (CI) and results were adjusted for screening arm, component study, sex, age, race/ethnicity, education, smoking status and pack-years, body mass index and personal/family medical history. A total of 2,034 incident lung cancers were observed during follow-up. The length of time employed in welding and foundry work was associated with elevated lung cancer risk (p= 0.039 and p=0.005, respectively). Ever-employment as a welder or foundry worker yielded increased, but nonsignificant risks of lung cancer (HR=1.12 (95% CI 0.91 to 1.37) and HR=1.09 (95% CI 0.85 to 1.39), respectively), and ever-employment in both jobs was associated with a significantly increased risk (HR=1.48 (95% CI 1.08 to 2.04). The authors concluded that exposures to welding or metal fumes may be associated with elevated risk of lung cancer.

In order to assess the occupational risk factors associated with nasopharyngeal carcinoma (NPC), Xie et al. (2017) conducted a case-referent study collecting occupational histories via face to face interviews from 352 incident NPC cases and 410 controls (referents) between 2010 and 2012 in Hong Kong. The authors used unconditional logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CI), adjusting for potential confounders. Compared with clerical support workers (referents), workers in craft-related trades and elementary occupations had increased risk of NPC (OR 2.09, 95% CI 1.09-4.01 and OR 2.14, 95 CI 1.04-4.41, respectively). In addition, occupational exposures to cotton dust, chemical fumes and welding fumes were significantly associated with risk of NPC: adjusted OR (95%CI): 93 (1.13, 3.28), 13.11 (1.53, 112.17), and 9.18 (1.05, 80.35), respectively. The authors concluded that although results suggest increased risks of NPC from these various occupational exposures, further research is warranted to clarify the role of specific occupational exposures.

4.1.5 Multiple Health Effects

As part of a Health Hazard Evaluation Program, Methner et al. (2017) measured exposure to airborne crystalline silica, welding fume, and methylene diphenyl diisocyanate (MDI) in workers involved in tank finishing operations, tank fabrication, and application of spray foam insulation, respectively, in addition to collecting medical information and blood samples for biomarkers of isocyanate exposure and sensitization. Crystalline silica levels were reported to be high, but MDI and welding fume concentrations were below occupational exposure limits. Employees reported work-related asthma, confirmed by MDI-specific IgE in two employees' blood, and MDI-specific IgG in five employees' blood suggested exposure to MDI despite workplace preventative measures. The authors concluded that improvements in ventilation, medical surveillance, and hazard training are necessary.

Zhang et al. (2017c) administered an anonymous questionnaire to 505 welders at three facilities in Qingdao City, China to investigate health effects of manganese in welding fumes, including neurological symptoms. The results showed that 43% of respondents reported difficulty with eyes, 30% reported a sore throat, and over 18% reported tremors. Longer work hours and facility cleanliness correlated with symptoms of tremor, but smoking did not. The authors concluded that welders exposed to manganese reported a variety of symptoms, including neurological symptoms that were associated with the level of exposure (i.e., longer work periods).

4.2 Animal Studies

We identified eight animal studies that evaluated the potential health effects of welding fume exposures.

Resistance spot welding in the automotive industry involves adhesives and anti-spatter compounds, and the process produces complex aerosols containing metal and volatile organic compounds (VOCs). Exposures to these aerosols can potentially cause lung disease in welders. Antonini et al. (2017) conducted a study in male Sprague-Dawley rats exposed via inhalation to 25 mg/m^3 of aerosol from spot welding of galvanized zinc-coated steel with or without a glue or anti-spatter spray for 4 hours/day for 8 days. Control animals were exposed to filtered air. The fumes were analyzed and found to be composed of 72.5% iron and 26.3% zinc. Particle size distribution changed and VOCs (methyl methacrylate, acetaldehyde, ethanol, acetone, benzene, xylene) were present with the addition of anti-spatter spray and glue during welding, but metal composition remained the same. Bronchoalveolar lavage (BAL) on day 1 resulted in significantly increased lung injury and inflammation, but returned to control levels on day 7. The authors concluded that the observed acute lung toxicity was likely due to exposure to zinc-containing particles.

Falcone et al. (2017) investigated whether inhalation of gas metal arc-stainless steel (GMA-SS) welding fume was a lung tumor promotor using lung tumor-susceptible mice. A/J mice were exposed by whole-body inhalation to air or freshly generated GMA-SS welding fumes (target concentration 40 mg/m^3) for 4 hours per day, 4 days a week for 9 weeks, one week after receiving injections of 1 ug/g of chemical initiator 3-methylcholanthrene (MCA) or corn oil intraperitoneally. Thirty weeks post-initiation the lung tumor counts were assessed. The authors reported an increase in lung nodules from exposures to GMA-SS fumes that were also given MCA (16.11 +/- 1.18) compared to MCA/air-exposed mice (7.93 +/- 0.82). The type of lung nodules was consistent with development of lung tumors. The authors concluded that exposures to GMA-SS promote lung tumorigenesis and these findings are consistent with epidemiological findings of potential increased risk of lung cancer in welders.

A neurological disorder with symptoms similar to Parkinson's disease is sometimes seen in welders, and studies suggest this may be due to exposures to welding fumes that alter circulating prolactin concentrations. Changes in prolactin levels are an early marker of injury to the dopamine (DA) neurons in the substantia nigra region of the brain. Reproductive dysfunction has also been linked with welding fume exposure. Krajnak et al. (2017) measured prolactin (a marker of DA neuron injury), hypothalamic tyrosine hydroxylase (TH) levels (a marker of DA synthesis) and other hypothalamic-pituitary-gonadal (HPG) function markers in rats that were repeatedly exposed to welding fumes from flux core arc-hard surfacing (FCA-HS), manual metal arc-hard surfacing (MMA-HS), gas metal arc-mild steel welding (GMA-MS), or manganese chloride ($MnCl_2$). The authors also measured levels of metals in rat tissues. Excess accumulation of metals was found in the pituitary and testes, and changes in hypothalamic TH and serum prolactin levels were observed. High concentrations of soluble manganese (Mn) appeared to have the greatest effect on hypothalamic TH and prolactin levels. Testosterone and other reproductive measures were also collected as biomarkers for reproductive dysfunction. The authors concluded that prolactin may be a useful biomarker for neurotoxicity and reproductive dysfunction associated with welding fume/Mn exposure.

Krishnaraj et al. (2017) evaluated the effects of welding fume exposures via inhalation to the lung tissue of male Sprague-Dawley rats by measuring oxidative stress, DNA damage response, and signalling of nuclear factor erythroid 2-related factor-2 (Nrf2) and nuclear factor kappa B (NFkappaB). Animals were exposed to 50 mg/m^3 stainless steel (SS) welding fumes for 1 hour per day for 1 day, 1 week, 2 weeks, and 4 weeks. In exposed rats' lungs, the authors found increased chromium levels and reactive oxygen species (ROS) associated with 8-oxo-2'-deoxyguanosine (8-oxodG) accumulation, greater xenobiotic-metabolizing enzymes (XME), and antioxidant expression. In addition, the authors found upregulation of DNA damage sensors, G1/S phase cell cycle arrest, overexpression of DNA repair enzymes and apoptosis mediated by caspase enzyme and activation of Nrf2 and NFkappaB signalling. The authors concluded that exposure to SS welding fumes changes the expression of 37 genes involved in oxidative stress, detoxification, inflammation, DNA repair, cell cycle progression, and apoptosis in rats. There was also evidence that activation of the DNA damage response and oxidative stress Nrf2 and NFkappaB pathways may be the main molecular events mediating the adaptive cell response associated with welding fume exposure.

Máté *et al.* (2017) examined the effects of common metal oxide components of welding fumes including manganese (Mn) on young adult Wistar rats. The rats were exposed to oxide nanoparticles of Mn, Mn and iron (Fe), Mn and chromium (Cr), and all three metal oxides combined in an aqueous suspension via the trachea for 4 weeks. Blood and brain metal levels were measured, and general toxicity and functional neurotoxicity (by measuring evoked cortical activity) were assess. The authors found that the decrease in body weight gain from Mn exposures was counteracted by Fe, but not Cr. Mn alone also caused increased frequencies in cortical electrical activity and evoked potential latency, which were also counteracted by Fe, but not Cr. The authors concluded that iron may have a protective antioxidant effect in this animal model.

In order to assess potential epigenetic changes (i.e., changes that affect gene expression or gene activity and that can be hereditary) due to welding fume, Shoeb et al. (2017a) exposed male Sprague-Dawley rats via intratracheal instillation (ITI) to 2.0 mg/rat of gas metal arc-mild steel (GMA-MS; composed of 85% Fe, 14% Mn) or manual metal arc-stainless steel (MMA-SS; composed of 41% Fe, 29% Cr, 17% Mn, 3% Ni). Sterile saline via ITI was given to control animals. Peripheral blood mononuclear cells (PBMCs) from whole blood were collected and tested for DNA methylation and telomere length to assess potential epigenetic changes. Lung inflammation was also assessed by bronchoalveolar lavage (BAL) at 4 hours, 14 hours, 1, 3, 10, and 30 days. Reactive oxygen species (ROS) were measured by levels of dihydroethidium (DHE) fluorescence and 4-hydroxylnonenal protein adduct (P-HNE) formation. Exposure to MMA-SS, which is more soluble and chemically complex, resulted in a more persistent and greater inflammatory response and produced an increase in oxidative stress markers measured at 24 hours compared to those seen in the control and GMA-SS groups. DNA methylation did not vary between groups, but those exposed to MMA-SS had significantly longer telomeres (indicative of genotoxicity) at 1 and 30 days after a single exposure compared to the other two groups. The authors concluded that because MMA-SS contains potential genotoxic (e.g., chromium and nickel) and soluble (e.g., chromium and manganese) metals compared to GMA-SS, MMA-SS exposure results in enhanced lung toxicity, including a greater inflammatory and genotoxic response.

To examine the effect of welding fumes containing nanoparticles and several cytotoxic metals such as chromium, manganese, nickel, and iron, Shoeb et al. (2017b) used a rat model to assess lung toxicity in vivo and also tested effects on RAW264.7 cells in vitro. Sprague-Dawley rats were exposed intratracheally to 2.0 mg of gas metal arc-mild steel (GMA-MS), manual metal arc-stainless steel (MMA-SS), or saline (vehicle control). MMA-SS was composed of 41% Fe, 29% Cr, 17% Mn, 3% Ni and GMA-MS consisted of 85% Fe and 14% Mn. Lung toxicity was measured at 1, 3, and 10 days via bronchoalveolar lavage. Both groups exposed to welding fumes had increases in lung injury and inflammation, but the MMA-SS group showed increased lung toxicity at all measured time points post-exposure. Homogenized lung tissue collected one day after exposure yielded evidence of an elevated inflammatory response with increased expression of cyclooxygenase-2, Nrf2, and heme oxygenase-1 (HO-1). In the in vitro investigation of the molecular mechanisms of cytotoxicity, RAW264.7 cells were exposed to MMA-SS and GMA-MS (both 0-100 mug/mL) for 24 hours. Compared to cells exposed to GMA-MS and the control group, the cells exposed to MMA-SS showed an increased inflammatory response related to the activation of reactive oxygen species/protein-HNE/ERK1/2/Nrf2 signaling pathways. The authors concluded that both in vivo and in vitro results support evidence of increased lung toxicity associated with MMA-SS exposures.

Zeidler-Erdely et al. (2017) used a lung tumor susceptible strain of mice (A/J) to compare the lung toxicity of the gas metal arc-stainless steel welding fume (GMA-SS WF) to the toxicity from individual metal oxide components including chromium (III) oxide, nickel (II) oxide, and iron(III) oxide. Exposed, male A/J mice were given suspensions of GMA-SS WF (1.7 mg) or equivalent doses (weight percent) found in the total fume of the metal oxide components (chromium (III) oxide/calcium chromate (366 ug/11 ug), nickel (II) oxide (141 ug), or iron (III) oxide (1 mg)) via oropharyngeal aspiration and were euthanized at one, seven, 28, and 84 days post-aspiration. Controls were given 50 ul PBS vehicle. To assess lung toxicity, whole lung bronchoalveolar lavage (BAL) fluid was assessed and macrophages were challenged with E. coli for 2 hours at 1:25 infection multiplicity. An adverse effect on macrophage function was seen after 1 day of exposure for all welding fume components, but in mice sacrificed at 28 days there was no difference in macrophage function compared with controls. The authors reported differences in lung toxicity between individual components and total metal fume particles. For example, lactate dehydrogenase levels in BAL fluid (a proxy for lung toxicity), peaked at 7 days in the total GMA-SS welding fume group but peaked at 1 day followed by a decline in the individual component groups. The total GMA-SS also caused more lung inflammation compared to the metal components individually suggesting a synergistic effect of the metal oxide components. Furthermore, the persistent markers of inflammation in the animals exposed to total GMA-SS fume may indicate chronic toxicity. The authors concluded that GMA-SS welding appeared to be more toxic than the sum of the individual component.

4.3 Mechanistic/cell/*In vitro*

We identified two mechanistic/cell/*in vitro* study that evaluated the potential health effects of welding fume exposures.

Fedan et al. (2017) examined the effects of fume particulates from manual metal arc-stainless steel (MMA-SS) and gas metal arc-mild steel (GMA-MS) on cultured normal human bronchial epithelium (NHBE). The authors hypothesized that fume particles target airway epithelial ion transport and therefore make the cells more susceptible to infection. The MMA-SS particles, which are more soluble and composed of chromium (Cr), nickel (Ni), iron (Fe) and manganese (Mn) and GMA-MS particles, which are less soluble and made up of Fe and Mn, were applied to the NHBE at a concentration ranging from 0.0167-166.7 $\mu g/cm^2$. The authors conducted a number of tests to assess ion transport after 18 hours, including measuring transepithelial potential difference (Vt), resistance (Rt), and short circuit current (Isc). The effects on Na(+) and Cl channels and the Na(+),K(+),2Cl -cotransporter were evaluated using amiloride (apical), 5-nitro-2-[(3-phenylpropyl)amino]benzoic acid (NPPB, apical), and bumetanide (basolateral), respectively. The authors reported increased basal Vt from MMA-SS concentrations ranging from 0.0167-16.7 $\mu g/cm^2$, but only for GMA-MS at 16.7 $\mu g/cm^2$. MMA-SS, and to a lesser extent GMA-MS decreased the Isc response to amiloride and bumetanide, but did not affect response to NPPB. Similarly, the impacts of MMA-SS on ion transport were greater than for MMA-SS than GMA-MS, including observed hyperpolarization in the absence of LDH, and decreases of Vt, Rt, and Isc with higher particulate dose accompanied by LDH release. The authors concluded that MMA-SS is more potent than GMA-MS in enhancing Na(+) absorption and decreasing surface liquid, which could compromise cellular defenses against infection.

Based on a previous study showing that exposure to welding fumes upregulates platelet activating factor (PAFR)-dependent pneumococcal infection, Grigg et al. (2017) investigated the role of oxidative stress in promoting pneumococcal infection by affecting PAFR and the effectiveness of using nasal epithelial PAFR expression as a biomarker of infection susceptibility in welders. Using flow cytometry analysis, nasal PAFR expression was significantly higher in welders compared with controls. Furthermore, exposure to welding fumes significantly increased reactive oxygen species production, HIF-1alpha (a mediator of PAFR-dependent infection), and pneumococcal infection of respiratory cells. In tests with unexposed respiratory cells, knockdown of HIF-1alpha decreased PAFR expression and overexpression of HIF-1alpha led to an increase in expression of PAFR, thus inhibiting basal pneumococcal infection in mechanisms independent from PAFR. The authors concluded that nasal epithelial PAFR expression was a useful biomarker for identifying individuals at high-risk of pneumococcal disease that would benefit from a pneumococcal vaccine.

4.4 Reviews

We identified 13 reviews of welding exposure and health effects.

An adverse side effect of arc welding (due to exposure to ultraviolet (UV) light) is outer retinal damage (retinopathy) as the photoreceptors and retinal pigment epithelium in the posterior pole are particularly vulnerable to UV light radiation. Begaj et al. (2017) reviews the causes, diagnostic methods, treatment, and prevention of UV-induced retinopathy. Optical coherence tomography, fluorescein angiography, and fundus autofluorescence together are most effective in identifying UV retinopathy. Most acute UV retinopathy patients recover completely, but some have chronic reduced acuity and lifelong central/paracentral scotomas. The authors concluded that education about the dangers of UV radiation, prevention and protection are necessary for those potentially exposed to UV radiation for prolonged periods, including welders.

Guha et al. (2017) summarized the results from the International Agency for Research of Cancer (IARC) meeting in March 2017 to evaluate the carcinogenicity of welding, molybdenum trioxide, and indium tin oxide. The complete assessments were published in volume 118 of the IARC Monographs in July 2018.[1] The authors noted that 11 million workers list their job title as welder and that 110 million additional workers are potentially exposed to welding-related fumes, gases, or radiation [ultraviolet (UV) and electromagnetic fields]. Welding is also associated with a number of co-exposures including asbestos and solvents. There are also different welding process (e.g., gas, arc, resistance) and materials (mild and stainless steel), and exposure depends on these processes and materials as well as any workplace and personal protections used. The carcinogenicity of welding was last evaluated in 1989, and IARC at the time determined that welding was "possibly carcinogenic to humans (Group 2B)" based on limited evidence in humans and inadequate evidence in animals. Based on new evidence since this last review, IARC has determined that welding is "carcinogenic to humans (Group 1)." UV radiation generated from arc welding is a risk factor for developing a rare type of ocular melanoma and is also associated with various eye disorders such as cataracts and keratoconjunctivis. Evidence for the carcinogenicity from UV radiation came from epidemiological studies that found positive associations between ocular melanoma and UV exposures. Lung cancer risks from welding fume exposures were reported in more than 20 case-control studies and over 30 occupational or population-based studies that mostly reported positive associations. Large, high-quality studies also reported exposure-response associations. IARC noted that potential confounding exposures to asbestos or smoking could not explain the observed increases in lung cancer among welders as studies that controlled for these factors showed that positive association persisted. There was also evidence of increased risk of kidney cancer among welders, although few studies adjusted for exposures to solvents as a potential confounder. For this cancer outcome chance, bias and confounding could not be ruled out. Similarly, for other cancers there was insufficient evidence because of inconsistent findings, small number of studies, or studies in which confounding or bias could not be ruled out. Therefore, IARC concluded that there was sufficient evidence that welding fumes cause lung cancer in humans, and limited evidence for kidney cancer. Evidence from animal studies was limited, but mechanistic

[1] Available at : http://publications.iarc.fr/569

studies support the hypothesis that welding fumes induce chronic inflammation and can be immunosuppressive.

Welders are exposed to extremely low frequency magnetic fields (ELF-MF), which may be a risk factor for developing Alzheimer's disease (AD). Jalilian et al. (2017) conducted a systematic review on the literature on occupational exposure to ELF-MF and risk of AD. The authors searched a number of databases including PubMed, EMBASE, Cochrane Library, and Web of Science in November 2017. Risk of bias analysis was done for all the included studies. A total of 20 articles met inclusion criteria. The authors performed a random-effects meta-analysis on the included publications and found an increased risk of AD with exposure to ELF-MF: metaRR: 1.63; 95% CI: 1.35-1.96. Higher risk estimates were found for case-control studies (OR: 1.80; 95% CI: 1.40, 2.32) compared to cohort studies (RR: 1.42; 95% CI: 1.08, 1.87). The authors reported moderate to high heterogeneity (I(2)=61.0%) and the likelihood of publication bias as evidenced by Egger test results $p<0.001$. Therefore, the authors concluded that results should be interpreted with caution.

Keane et al. (2017) reviews the controls available for reducing welder's exposures to hazardous air pollutants. Welders comprise over 200,000 US workers and 1.8 million workers worldwide. The occupational hazards of welding include exposure to intense light, heat, and toxic components in welding fumes, including manganese, iron, carbon monoxide, ozone, hexavalent chromium (a known carcinogen), and nickel (a possible carcinogen). While there are many available approaches to controlling welder's exposures including engineering controls, personal protective equipment and other measures, achieving the OSHA Permissible Exposure Limit for hexavalent chromium (5 $\mu g/m^3$) and the NIOSH Recommended Exposure Limit (0.2 $\mu g/m^3$) is difficult. The author concluded that the best strategy for reducing exposures is at the source, most efficiently done by substituting a lower-emission welding process for a higher emission process together with more traditional engineering approaches.

Klotz et al. (2017) conducted a review of literature on the potential harmful effects of aluminum and the threshold values associated with adverse effects. The authors conducted a selective search of the literature in PubMed and SCOPUS related to aluminum and neurotoxicity, Alzheimer's disease (AD), breast cancer and supplemented by the author's knowledge and experience in the field of occupational and environmental medicine. Occupational exposures often result in an exceedance of the reference value for internal aluminum load (<15 μg /L in urine, <5 μg /L in serum). A decline in neuropsychological test performance (attention, learning, and memory) was associated with aluminum concentrations in excess of 100 μg/g creatinine in urine. Excess aluminum levels are found in AD patients' brains, although it is not known whether this is a cause or an effect of the disease. The evidence for carcinogenicity is conflicting. The authors concluded that keeping levels of aluminum below the occupational tolerance level of 50 μg per gram of creatinine in the urine would likely help prevent subclinical signs of aluminum toxicity, and more research is needed regarding the potential health impacts from other sources of aluminum.

Kornberg et al. (2017) reviewed human, in vivo, and in vitro studies of the health effects from exposure to iron oxide nanoparticles (IONPs). Occupational exposure to IONPs can occur during iron ore mining, steel processing, and welding and these exposures have been linked to adverse respiratory health impacts. However, the evidence is inconsistent, with some studies showing an effect and others showing no effect. In addition, IONPs are increasingly being used in drug delivery systems, in unique imaging protocols, as environmental catalysts, and for incorporation into thermoplastics. The authors reported that in vivo studies, supported by in vitro findings, suggest that inhalation on IONPs can produce inflammation, pulmonary fibrosis, genotoxicity, and extra-pulmonary effects. Adverse outcomes appear to be mostly related to oxidative stress that may be related to release of free iron ions upon particle internalization and disruption of iron homeostasis. The biological mechanism of action, however, remains unknown making it challenging to set safe exposure limits for occupational exposures.

Nayman et al. (2017) conducted a systematic review of meta-analyses of uveal melanoma (UM) risk factors with the aim to develop a clinical risk assessment tool to identify patients at risk for UM who would benefit from regular screening. Literature searches were conducted in Pubmed, Medline, Embase, and Web of Science until July 2016 using keywords and MeSH terms, and identified studies were screened by two people. Eligible studies supplied odds ratios (ORs) or sufficient information for calculating ORs. The authors included four meta-analyses with an average methodological quality score of 65.9% (min 54.5%, max 72.7%). The results indicated that welding was among the highest risk factors (OR 2.05, 95% CI 1.20-3.51) for developing UM, other significant risk factors included atypical cutaneous nevi (OR 2.82, 95% CI 1.10-7.26), occupational cooking (OR 1.81, 95% CI 1.33-2.46), fair skin color (OR 1.80, 95% CI 1.31-2.47), light eye color (OR 1.75, 95% CI 1.31-2.34), common cutaneous nevi (OR 1.74, 95% CI 1.27-2.39), propensity to sunburn (OR 1.64, 95% CI 1.29-2.09), iris nevi (OR 1.53, 95% CI 1.03-2.27), and cutaneous freckles (OR 1.27, 95% CI 1.09-1.49). Additional risk factors were not statistically significantly associated with UM, including outdoor leisure activity, occupational sunlight exposure, birthplace latitude, and hair color. The authors concluded that the identified risk factors can be used to develop formal risk assessment tools and allow clinicians to identify individuals that may be at increased risk and may need regular screening.

Rubio-Rivas et al. (2017) conducted meta-analyses of studies published from 1960 to 2014 investigating the association between systemic sclerosis (SSc) and occupational and environmental exposures. The authors did a literature search in MEDLINE and SCOPUS using the terms: "systemic," "scleroderma," or "systemic sclerosis/chemically induced" [MesH] and employed the Newcastle-Ottawa Scale was for the qualifying assessment. They used the inverse variance-weighted meta-analysis method. Welding fume exposure was among the occupational exposures with studies linking exposure to SSc. The authors reported a small, but not statistically significant increased risk from welding based on 4 studies (OR 1.29, 95% CI: 0.44-3.74). Among the various other occupational and environmental exposures, the authors reported that evidence is strongest for exposures to silica (based on 15 case-control studies and 4 cohort studies) and solvents (based on 13 case-control studies). The authors noted that silica exposure is associated with only certain jobs, whereas solvent exposures are more widespread and therefore more people may be at risk of developing SSc from these exposures.

Song et al. (2017) reviewed nickel (Ni)-associated neurotoxicity, including underlying mechanisms, and potential chemicals with neuroprotective effects for use in treating Ni-induced neurotoxicity. Ni is used in alloy, welding, printing inks, electrical and electronic industrial sectors and occupational exposures have been linked to adverse health effects including damage to the nervous system.

Swarnkar et al. (2017) reviews a new more environmentally friendly welding process called Friction Stir Welding (FSW) of aluminum alloys and the impact on mechanical, thermal and microstructural properties of different input parameters such as the tool's rotational speed, feed rate, and tool geometry. Traditional welding techniques including arc welding, tungsten inert gas welding, and metal inert gas welding have been associated with harmful health effects including bronchitis, airway irritation, lung function changes, asthma, and possibly lung cancer. Therefore, The Welding Institute in the UK had developed a less harmful FSW technique. This method uses a non-consumable tool with a specialized shoulder and pin. The pin is inserted into the plates to be joined and then is rotated to cause severe plastic deformation in the nugget zone and generate a permanent weld joint.

The Swedish Council on Health Technology Assessment (2017) conducted a systematic review of the occupational epidemiological literature of associations between occupational exposures to a wide range of chemicals and heart disease, pulmonary heart disease, stroke, and high blood pressure. The authors reported positive associations between silica dust, engine exhaust or welding fumes and heart disease. Other chemicals linked to heart disease included arsenic, benzopyrenes, lead, dynamite, carbon disulfide, carbon monoxide, metalworking fluids, and tobacco smoke in the workplace. In addition, heart disease was associated with electrolytic production of aluminum, paper production involving sulfate pulping, and now-prohibited chemicals like dioxin and asbestos. Pulmonary heart disease was linked to silica dust and asbestos exposures. Stroke was also associated with electrolytic production of aluminum, lead, carbon disulfide, and dioxin. High blood pressure was associated with asbestos or lead exposures. The review noted the lack of evidence on sex-specific vulnerability to occupational exposures to these chemicals.

Viitanen et al. (2017) conducted a literature search on occupational exposures to ultrafine particles (UFP) to summarize the current literature (excluding engineered nanoparticles) for use in epidemiological studies. They identified 72 publications and over 314 measurement results and UFP concentrations reported. The authors compared the mean UFP concentration from occupational exposures to mean concentrations in a typical urban environment (a non-occupational background measurement). They found that the mean of 240 workplace measurements was higher than typical urban concentrations and mean concentrations from the welding and metal industry were over 100 times the urban background concentrations. However, the authors found that in general the measurements of UFP in workplaces are too limited and heterogenous to be able to draw conclusions regarding worker's exposures. The authors concluded that a more standardized system of UFP measurement in work environments is needed.

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