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HEALTH EFFECTS FROM WELDING EXPOSURES:

2018-2019 LITERATURE UPDATE

RAMBOLL

CONTENTS

ACRONYMS AND ABBREVIATIONS

3-HPMA	S-(3-hydroxypropyl) mercapturic acid
8-oxodG	8-oxo-2′-deoxyguanosine
AAS	Atomic absorption spectrometer
ACGIH	American Conference of Governmental Industrial Hygienists
Al	Aluminium
AM	Additive manufacturing
APDC	pyrrolidine dithiocarbamate
AWS	American Welding Society
ARDS	Acute Respiratory Distress Syndrome
ART	Advanced REACH Tool
BEI	Biological exposure index
BG	Basal ganglia
BMI	Body mass index
CalEPA	California Environmental Protection Agency
CAT	Catalase
CC16	Clara cells secretory protein
Cd	Cadmium
CLIA	Chemiluminescence immunoassay
CI	Confidence interval
CO	Carbon monoxide
Co	Cobalt
Cr	Chromium
Cr (VI)	Hexavalent chromium
CRP	C-reactive protein
Cu	Copper
CVD	Cardiovascular disease
DDR	DNA damage response
DTI	Diffusion tensor imaging
EBC	Exhaled breath condensate
epub	Electronic publication
FAAS	Flame absorption atomic spectrometry
FCW	Flux-cored wire
FDOPA	6-[18F]fluoro-L-DOPA
Fe	Iron
FEF_{25-75}	Forced expiratory flow of 25-75% of the pulmonary volume
FEV_1	Forced expiratory volume in 1 second
FL	Frontal lobe
FR	Formation rate
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
GABA	γ-amminobutyric acid
GP	Globus pallidus
GMA-MS	Gas metal arc- mild steel
GMA-SS	Gas metal arc- stainless steel

GMAW	Gas metal arc welding
GTAW	Gas tungsten arc welding
HBM	Human biomonitoring
HBM4EU	EU human biomonitoring initiative
HC	Hemochromatosis
HRCT	High-resolution computed tomography
ICNIRP	International Commission on Non-Ionizing Radiation Protection
ICP-MS	Inductively coupled plasma mass spectrometry
IFN-γ	Nasal interferon-γ
IMA	Ischemia-modified albumin
JEM	Job-exposure matrix
LH	Luteinizing hormone
IONP	Iron oxide nanoparticles
LOQ	Limit of quantitation
MAG-P	Metal active gas welding - pulsed
MAG-DP	Metal active gas welding – double pulsed
MALDA	Mobile aerosol lung deposition apparatus
MCA	3-methylcholanthrene
MCW	Metal-cored wire
MD	Mean diffusivity
mfERG	Multifocal electroretinogram
Mn	Manganese
Mo	Molybdenum
MRI	Magnetic resonance imaging
mRR	Meta-relative risks
NFkappaB	Nuclear factor kappa B
Ni	Nickel
NIHL	Noise-induced hearing loss
NIOSH	National Institute for Occupational Safety and Health
nm	nanometer
NOCCA	Nordic Occupational Cancer job exposure matrix
Nrf2	Nuclear factor erythroid 2-related factor-2
OEHHA	Office of Environmental Health Hazard Assessment
OEL	Occupational Exposure Limit
OPC	Oral and pharyngeal cancers
OR	Odds ratio
OSHA	Occupational Safety and Health Administration
OX	Oxidizing gases
Pb	Lead
PEFR	Peak expiratory flow rate
PD	Parkinson's disease
PM	Particulate matter
$PM_{2.5}$	Particulate matter less than 2.5 micrometers in diameter
PM_{10}	Particulate matter less than 10 micrometers in diameter
PPE	Personal protective equipment
ppm	Parts per million

ppb	Parts per billion
RSD	Respiratory system diseases
ROS	Reactive oxygen species
SAA	Serum amyloid A
SE	Standard error
SIR	Standardized incidence ratio
SMAW	Shielded metal arc welding
SN	Substantia nigra
SPE	Solid-phase extraction
SS	Stainless steel
SWD	Soluble welding dust
tCr	Total creatine
Ti	Titanium
TLV	Threshold limit value
TIG	Tungsten inert gas welding
UPDRS3	Unified Parkinson's disease rating scale - motor subscore 3
UPF	Ultraviolet protective factor
UVR	Ultraviolet radiation
V	Vanadium
WD	Welding dust
WF	Welding fume
WHO	World Health Organization
WI	Water-insoluble
WRA	Work-related asthma
WS	Water-soluble
wUPF	Welding ultraviolet protection factor
XME	Xenobiotic-metabolizing enzyme
Zn	Zinc

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 2018 and 2019 (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 database 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 years 2018-2019 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.
5. To further limit searches, we used the additional search word "health".

2.2 PubMed and NIOSHTIC-2 Searches

An initial search yielded 708 citations. We further refined the search to include health and this reduced the number of citations to 144. The 144 citations were uploaded to excel for further screening for relevance.

We also searched the NIOSHTIC-2 database using the key words "welding" or "welder" in all fields for the year 2018-2019. Of the citations that resulted only a single reference to a conference abstract was found and this was not retained as it relates to one of the identified citations in PubMed.

2.3 Literature Review

The literature search yielded over 700 references, with 144 relevant to health effects. We reviewed titles to assess the relevance to exposure and health effects from welding, and identified duplicates for exclusion. We also excluded commentaries, conference abstract, 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 82 relevant references were identified after excluding duplicates and other non-relevant references. Some of the references were included in the 2017 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	30
Epidemiology and controlled human exposure	35
Animal	5
Mechanistic/cell/*in vitro*	8
Reviews	4
Overall Total	**82**

3 EXPOSURE STUDIES

We identified 30 exposure-related studies or studies related to regulation or health and safety in welding occupational groups published from 2018-2019 (*i.e.*, particle characterization and exposure). Some studies were published online in 2018-2019 (*i.e.*, 2018-2019 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 2017) were excluded. A brief summary of the exposure abstracts is provided below for all the relevant studies.

The objective of the study by Bailey et al. (2018) was to derive a manganese (Mn) Occupational Exposure Level (OEL) for welders below which neurological effects would not be expected. The OEL was based on a review of studies of exposures to Mn in welding fume and (1) neurological effects in welders; (2) levels of Mn in the brains of welders (via pallidal index [PI] estimated from magnetic resonance imaging [MRI]); (3) levels of Mn in blood and/or urine; and (4) non-human primate studies of Mn brain concentrations, PI, and corresponding neurological effects. The authors reported a large amount of uncertainty in quantifying dose-response associations for Mn from occupational welding studies. Based on the few welding studies with adequate exposure estimates the authors propose an OEL of 100-140 $\mu g/m^3$ for respirable Mn. This range is supported by results reported in other studies, including studies of biomarkers of Mn exposure in welders, and non-human primate studies in non-human primates. The authors, however, noted that future studies were needed to further refine the Mn OEL.

Balkhyour et al. (2019) evaluated self-reported occupational exposures and use of personal protective equipment (PPE) in small-scale industries in Jeddah, Saudi Arabia. The authors recruited 102 workers from 28 small-scale industries (vehicle repair, welding, and paint), and used a survey to collect information on socio-demographic characteristics, self-reported occupational exposures, and frequency of PPEs use. The authors reported occupational exposures as never exposed, sometimes exposed and always exposed. The percentage of workers with occupational exposures in these categories were: noise (19.6, 73.5 and 6.9%); dust/smoke (9.8, 69.6 and 20.6%); vapors/fumes (11.8, 60.8 and 27.5%); and direct sunlight (43.1, 56.9 and 0%), respectively. The results regarding PPE included the use of knee joints mats (50%), welding shields (50%), safety glasses (33.3%), gloves (27.5%), face masks (26.5%), safety shoes (10.8%) and earplugs/ muffs (8.8%). The authors concluded that the study findings suggest the need for more general occupational hygiene (e.g., hand washing) as well as additional occupational health and safety awareness to reduce occupational exposures in small-scale industries.

Bauer 2019 investigated the effectiveness of workwear that was treated for photoprotection against solar ultraviolet radiation (UVR). Photoprotection in clothes relies on the concept of ultraviolet protection factor (UPF) and though much work has been done with regards to natural UVR, little has been done to identify protection of artificial UVR. The authors modified the UPF equation for application to welding arcs and the International Commission on Non-Ionizing Radiation Protection (ICNIRP) action spectrum. The new calculated UPF for welding (wUPF) were established as function of welding power, technique and welded material. The authors found the wUPF was dependent only on the fabric’s transmittance. The authors compared the solar UVR and welding UPFs.

Berlinger et al. (2019a) measured exposures to respirable, inhalable and total PM, as well as concentrations chromium (Cr), iron (Fe), manganese (Mn), molybdenum (Mo), nickel (Ni), copper (Cu), and lead (Pb) during metal active gas and manual metal arc welding, flame and plasma cutting, air carbon arc gouging, and surface grinding in the workers' breathing zone. Gravimetric analysis and plasma-based analytical atomic spectrometry techniques were used to measure PM and metals, respectively. The authors also evaluate the bio-accessibility of the metals using a synthetic lung lining fluid (Hatch´s solution), see Berlinger et al. (2019b). The authors reported (15-75 min) short-term median exposure concentrations of PM across the different hot work processed ranging from 6.0 to 88.7 mg/m^3 for respirable particles and from 15.1 to 193 mg/m^3 for the inhalable fraction. The highest median concentration of metals was found in the inhalable PM fraction for plasma cutting, Fe (107 mg/m^3), and air carbon arc gouging, Mn (28.7 mg/m^3). For all the hot processes evaluated, over 40% of the PM generated was in the respirable fraction.

Berlinger et al. (2019b) investigated the bio-accessibility of 14 elements in welding fume particulate matter obtained from 325 personal air samples in two shipyards and one factory producing heavy machinery. The authors used Hatch's solution (a synthetic lung lining fluid) to determine solubility as a surrogate for bio-accessibility. The solubility in Hatch's solution varied greatly for the different elements, with very low solubility (median < 1%) for aluminium, iron, lead, titanium and between 4 and 6% for cobalt (Co), chromium (Cr), nickel, vanadium (V), and moderate solubility (median between 13 and 27%) for cadmium, copper (Cu), manganese (Mn), zinc and a median of 41% for molybdenum. The range of solubility was quite large for many elements, spanning several tens of percent. The authors also reported that welding techniques and the materials influenced the solubility of several elements including Co, Cr, Cu, Mn and V. To assess the factors that most influenced solubility, the authors conducted a principal component analysis. The results showed that four factors explained about 69% of the variance in the solubility. Two of the factors included elements that occur predominantly as divalent cations and elements forming oxyanions. The authors also noted that the solubility is mainly influenced by the most soluble compounds. The authors concluded that because solubility varied greatly by welding technique and plant, the bio-accessibility of elements in welding fume cannot be determined based solely on the literature, but must be determined experimentally for the location of interest.

Beyene et al. (2013) evaluated the level of awareness of occupational hazards and the adherence to safety measures in welding factory workers. The authors randomly selected 278 workers and collected information using a questionnaire. Data was analysed using logistic regression. The authors reported that 135 (51.9%) of the workers had knowledge of occupational hazards and 225 (86.5%) of the workers used personal protective equipment (PPE). The workers knowledge was significantly associated with work experience, work type, safety training, and work regulations or guidelines. Use of PPE was significantly associated with educational status, work experience, safety training, and work regulations. The authors concluded that health and safety training were essential for increasing occupational hazards knowledge and use of PPE.

Glassford et al. (2018) report on an evaluation of a steel building materials manufacturer requested by the National Institute for Occupational Safety (NIOSH) to address concerns of optical radiation hazards from a plasma arc cutting system. Measurements were taken at several distances from the plasma arc cutter and at different amperages to determine the strength of ultraviolet radiation, visible radiation (light), and infrared radiation. The investigators reported exceedances of safe levels for the ultraviolet-C, ultraviolet-B, and visible light ranges for unprotected eyes, but no exceedances for infrared and ultraviolet-A radiation levels. Even though the highest exposures to non-ionizing radiation were found when no welding curtain was used, the use of the welding curtain did not eliminate optical radiation hazards. The investigators therefore recommended a number of safety measures including the use of a welding curtain, but also posting optical radiation warning signs, use of visual and audible cues, and the use of welding shades to protect the welder’s eyes and face.

Insley et al. (2019) evaluated worker inhalation exposures to particulate matter (PM) and 21 metals in shops where several metalworking tasks were conducted. The authors obtained personal full-shift exposures as well as task-based samples for workers doing flux-cored arc welding or workers performing non-welding metalworking tasks, together with area samples near welders. Of the 21 metals measured, eight were frequently detected. Less than 5% of all metals exceeded occupational limit values, except for manganese in area samples and welder’s personal samples and iron oxide for other metal workers. The measured PM concentrations were similar at distances of about 1 meter from welders to up to 2.7 meters from welders. The authors noted that their study allowed for comparison of worker’s exposure to individual components of welding fume with occupational standards.

Kendzia et al. (2019) conducted a study to estimate exposures to inhalable and respirable welding fumes by welding process. The authors analyzed 15,473 samples of inhalable and 9,161 samples of respirable welding fume concentrations along with sampling and welding-related information compiled in the MEGA German database from 1983 to 2016. Using a statistical model, median and geometric means were estimated by welding process and frequently used welding materials and adjusted for sampling time and calendar year. The authors reported median inhalable concentrations that were about twice the respirable concentrations, 3 mg/m^3 (inter-quartile range: 1.2-7.0 mg/m^3) and 1.5 mg/m^3 (inter-quartile range: < limit of detection -3.8 mg/m^3), respectively. Adjusted geometric means ranged from 0.9 to 2.2 mg/m^3 for respirable welding fumes and from 2.3 to 4.7 mg/m^3 for inhalable fumes for various welding processes including flux-cored arc welding, metal inert and active gas welding, shielded metal arc welding and torch cutting. In contrast, for both particle-sizes, geometric means ranged from 0.1 and 0.9 mg/m^3 for tungsten inert gas, autogenous, resistance, laser, and plasma welding or spraying. The authors concluded that the results from this analysis can be used in exposure and risk assessments for welders.

Kirichenko et al. (2018) evaluated exposures from welding fumes from arc welding operations using 100 and 150 amps of current and various types of electrodes with different covering (e.g., rutile, basic, acidic and rutile-cellulose). The authors sought to characterize PM_{10} and also used dispersion models to assess exposures in workspaces where welding was conducted. They reported high concentrations of the PM_{10} particles at distances 0-3 m from the emission source. The authors also described the particles as a mixture of solid and hollow spheres, 'nucleus-shell' structures, perforated spheres, sharp-edged plates, and agglomerates of the tree-like (coral) shape. They concluded that the study results overall help to provide further understanding of the respiratory hazards associated with welding fume exposures and the need for mitigation of these hazards.

Koh et al. (2018) evaluated the use of occupational grouping schemes to find the optimal grouping for shipyard welders for use in epidemiological studies. The authors collected 2,360 personal welding fume measurements taken between 2002 and 2009 as well as industrial hygiene records from a shipyard. Based on personal welding fume measurements the geometric mean of 1.66 mg/m^3 and a geometric standard deviation of 4.02 was calculated. Eight groups of welding jobs were identified together with nine working areas. Grouping schemes were developed using job, area, and job*area combinations. Based on a group mean ranking method, conducted by ranking geometric means of job*area combinations, the use of 3 groups provided the best exposure contrast and precision, followed by grouping based on job. The authors also explored subsets of data where job*area combinations with less than 10 measurements were excluded. Overall, the authors concluded that both the group mean ranking method or groupings based on job would provide good grouping schemes for use in epidemiological studies.

Ljunggren et al. (2019) assessed metal exposures in an additive manufacturing (AM) facility where they had large-scale metallic component production for two consecutive years and where occupational health and safety actions were implemented in between years. Particulate matter mass concentrations and metal concentrations were obtained, including for particles <300 nm. The authors also conducted biomonitoring, obtaining and analyzing urine and dermal samples of the AM operators, office workers, and welders. The results showed that total and inhalable particulate matter concentrations were mostly below occupational exposure limits, but that AM operators had significant higher cobalt exposure compared with welders. Transient peaks of particle concentrations (<300 nm) were observed in the AM facility, but were lower than in the welding facility. There was a nonsignificant increased concentration of metals in the urine of AM operators. Health and safety actions appeared to work as there was a decrease in dermal cobalt and metals in urine in the second year of sampling. The authors concluded that overall exposure levels to particulate matter were low, with only transient increases in particles <300 nm. Worker's metal exposures were reduced by application of health and safety actions by the company. The authors emphasized the need for careful design and regulation of AM facilities to protect workers.

Mei et al. (2017) assessed the concentrations of manganese (Mn), nickel (Ni), iron (Fe), and chromium (Cr) in welding fume particles as a function of particle size, welding method (manual metal arc welding, metal arc welding using an active shielding gas), different electrodes (solid wires and flux-cored wires) and shielding gases, and a base alloy (austenitic AISI 304L and duplex stainless steel LDX2101). The amount of metal was measured using a phosphate buffered saline solution (pH 7.3, 37°, 24h). Particle characterization was done using microscopic, spectroscopic, and electroanalytical methods. The predominant metal in welding fume released in the saline solution was Cr [3-96% of the total amount of Cr, of which up to 70% was the more toxic form of Cr, hexavalent Cr(VI)], followed by Mn, Ni, and Fe. The highest concentration of Cr(VI) was generated from the base alloy (duplex stainless steel) welded with a flux-cored wire. Ni was present in higher concentrations in nano-sized particles compared to micron-sized particles. Lastly, the authors noted that welding fume contained multi-elemental and highly oxidized metals, rather than single element compounds.

Mohammadyan et al. (2019a) conducted a quantitative and semi-quantitative study to assess risks from exposure to lead in welders (solderers) in the Neyshabur, Iran electronics industry. The study recruited 40 female welders in 2017 and 2018. Risk assessment methods were based on the Singapore Health Department guidelines and the California Environmental Protection (CalEPA) Office of Environmental Health Hazard Assessment (OEHHA) method. The authors reported average exposures to lead in the electronics industry of 93.89 ± 33.40 μg/m^3 and ranging from 9 to 150 μg/m^3. For different occupational workers the authors reported the highest average lead exposure for initial soldering (130.37 ± 40.23 μg/m^3), followed by workers involved in cutting wires, electroplating, and coating bare parts (110.24 ± 30.11 μg/m^3), secondary soldering (90.78 ± 20.22 μg/m^3), and shift supervisors (43.86 ± 10.97 μg/m^3). Based on these exposures, the authors calculate the mean excess lifetime cancer risk was 11 per 100,000 people and the mean non-carcinogenic risk was 7.20, which exceed most guidelines. The authors therefore recommended that managers and employers work to reduce lead exposures using engineering controls (e.g., use of lead-free alloys and increased ventilation) and management controls (e.g., reduced working hours).

Mohammadyan et al. (2019b) assessed occupational exposures and blood lead levels in 40 female welders (solderers) in Neyshabur, Iran in 2017-2018 that worked in two electrical parts manufacturing facility. The authors were particularly interested in lead because of the harmful effects on health, including on fertility outcomes in women. The authors determined lead concentration in air following the Occupational Safety and Health Administration (OSHA) 121 method, and blood lead concentrations following the National Institute for Occupational Safety and Health (NIOSH) 8003 method. Flame atomic absorption spectrometry (FAAS) analysis was used to measure lead in air and blood samples. The female welders had a mean age of 35.42 ± 6.80 years, and average number of year of work was 7.85 ± 5.60 years. The authors reported that the mean air lead concentration was 0.09 ± 0.01 mg/m^3, and the mean blood lead level was 10.59 ± 3.25 μg/dL. All blood parameters including red and white blood cells, haemoglobin and haematocrit were within normal ranges. Air lead concentrations were significantly correlated with blood lead levels ($p = 0.012$, $r = 0.31$). In a multivariate analysis the authors found that lead levels in the workers' respiratory region ($p = 0.033$), body mass index ($p = 0.028$), and season ($p = 0.019$) were the most significant factors influencing blood lead levels. Overall, the authors concluded that to reduce blood lead levels in workers, employers and managers should use lead-free alloys, improve ventilation, and reduce exposure duration.

Odongo et al. (2019) assessed the risks from lead exposures via inhalation and ingestion in spray painters and welders in the automotive industry. They conducted a cross-sectional study of ten automobile repair shops to evaluate the association between air concentrations of lead and blood lead levels and influence of specific occupational tasks. The authors recruited 20 participants and measured air and blood concentrations for five distinct tasks. Inductively coupled plasma atomic emission spectroscopy was used to measure lead concentrations and the authors applied analysis of variance, simple and multiple linear regression analyses. The authors reported significant differences in air lead concentrations by task, with lead-acid battery repairs having the highest air lead concentrations [76.11 ± 10.81 standard error (SE) μg/m^3] and exceeding the World Health Organization (WHO) permissible exposure limit for lead of 50 μg/m^3. Average air lead levels were lower than the WHO limit [22.55 ± 5.05 SE μg/m3], but average blood lead levels were high [25.08 ± (3.48 SE) μg/dl]. There was a significant correlation between air lead concentrations and blood lead concentrations ($r = 0.68$, $p = 0.001$). The authors concluded that occupational tasks were highly correlated with personal exposures to lead, and air lead concentrations determined blood lead concentrations. Therefore, to minimize exposures, they recommended lead exposure assessments, medical screening, and when needed, interventions to reduce lead poisoning risks.

Pesch et al. (2018a) evaluated personal exposures to respirable hexavalent chromium [Cr(VI)] as well as air and urinary concentrations of chromium (Cr) and nickel (Ni) in welders to determine associations between these various measurements of exposure. The authors recruited 50 male welders that used gas metal arc welding (GMAW) (n = 24) or tungsten inert gas welding (TIG) (n = 19), and measured shift concentrations of Cr(VI), Cr, and Ni in respirable welding fumes. Pre- and post-shift urine samples were also collected to determine concentrations of Cr and Ni. The authors imputed any values below the limit of quantification (LOQ) and used spearman correlations (with 95% confidence intervals) to determine associations between exposure measurements. In addition, authors used regression models to estimate the effect of the airborne metal concentrations on urinary metal concentrations. The results showed that 62% of the respirable samples had Cr(VI) concentrations below the LOQ, and in 8 of 50 samples concentrations exceeded 1 μg m^3. The shielded metal arc welding (SMAW) method had the highest shift concentration of 180 μg m^3. The percent of Cr(VI) of total Cr ranged from 4 to 82% (median 20%), but the overall air concentrations correlated with total Cr ($r = 0.55$, 95% CI 0.46; 0.64). Correlations between Cr(VI) and Ni were weaker ($r = 0.42$, 95% CI 0.34; 0.51) compared to correlations between total Cr and Ni in welding fumes ($r = 0.83$, 95% CI 0.74; 0.92). Post-shift urinary Cr was associated with Cr(VI) and total Cr ($p = 0.0008$ and $p \leq 0.0001$, respectively), but not with pre-shift urine samples.

Sadat et al. (2018) evaluate a novel way to determine concentrations of multiple metals in biological samples. This method involved solid-phase extraction (SPE) using a functionalized nano-zeolite Y particles. As described by the authors the SPE was done using ammonium pyrrolidine dithiocarbamate (APDC) surrounded by Triton X-100 micelles, which were loaded into the pores of nano-zeolite Y and optimized for use to determine trace amounts of chromium (Cr), cadmium (Cd), and lead (Pb) in urine samples. Optimization included appropriate pH, APDC concentration, elution conditions, amount of nano-zeolite, and sample volume. The authors reported that the method had a >97% efficiency and an acceptable reproducibility with a coefficient variation of <10%. Urine samples taken from welders were analysed using this optimized method (no further details provided).

Sailabaht et al. (2018) evaluated changes to the Advanced REACH Tool (ART), a tier model used to estimate inhalation exposure to chemicals using a Bayesian approach, to include exposures to welding fumes. The authors noted that the model is currently used to estimate exposure to vapours, mists, and dusts. For application to welding fumes the authors evaluated the model structure to assess how to calibrate it for welding applications. Some of the key modifying factors that were considered included welding process type, input power level, shield gas, and welding electrodes as these have been shown to influence the fume formation rate. The authors also noted that the ART model should incorporate the convective dispersion of the fume away from the weld and the interaction of the welder with the fume plume. In addition, they noted that some aspects of the model don't need modification, such as ventilation considerations. Lastly, because the model does not include impact of use of personal protective equipment, the authors did not include this in their evaluation. Overall, the paper presents recommendations for modifying the ART model for estimating welding fume exposures.

Santonen et al. (2019) presents an example of a study design that applies the EU human biomonitoring initiative, HBM4EU, which aims to advance human biomonitoring (HBM) in Europe. The study involves eight European countries and recruitment of 400 workers involved in electroplating or stainless steel welding activities and are thus potentially exposed to hexavalent Cr [Cr(VI)]. The standard operating procedures for the collection of occupational monitoring data as well as HBM data are presented in order to provide a uniform set of standards across all countries. The authors indicated that data will be collected on occupational exposures to Cr(VI), including personal air samples and wipe samples as well as biomonitoring samples of Cr(VI) exhaled breath condensate, Cr in red blood cells, and total Cr in urine. The overall aim is to use the exposure data to evaluate potential genetic and epigenetic effects of Cr(VI) exposure.

Sauve et al. (2019) evaluated toenail samples of 609 controls from a study of bladder cancer in New England as bioindicators of metals exposure in order to validate surrogate measure of exposure that are estimated retrospectively for use in epidemiological studies. Samples were taken in workers that held a job ≥1 year, 8-24 months prior to toenail collection. Using linear regression, the authors compared associations between toenail metal concentrations (lead and manganese) and exposures that were estimated from five tasks identified from occupational questionnaires (grinding, painting, soldering, welding, working near engines). The authors also evaluated associations between toenail concentrations and exposure estimates from three experts for a subset of the workers (n=139). They reported that painting results in a 1.9-fold increase [95% confidence interval (CI) 1.4 to 2.5] in toenail lead concentrations, and working near engines increased manganese toenail concentrations by 1.4-fold (95% CI 1.1 to 1.7). Estimates from experts were well correlated with lead concentrations, whereas expert estimates for manganese were only weakly associated with toenail concentrations. The authors concluded that experts can generally provide adequate estimates for lead, but they recommend that more refined exposure characterizations be employed when possible.

Sivapirakasam et al. (2017) assessed whether coating electrodes with nanomaterials reduced the emissions of hexavalent chromium [Cr(VI)], which is a suspected human carcinogen that is released during stainless steel welding. The authors coated core welding wires with nano-alumina and nano-titania via a sol-gel coating method and evaluated the Cr(VI) formation rate (Cr(VI) FR) from a shielded metal arc welding process. Atomic absorption spectrometer (AAS) was used to measure Cr(VI). The authors reported that coating electrodes with nano-alumina and nano-titania reduced Cr(VI) FR by 40% and 76%, respectively, and that increasing the fume levels decreased the Cr(VI) FR. The authors concluded that the increased fume levels may be blocking the ultraviolet radiation that likely contributed to formation of Cr(VI).

Stebounova et al. (2018) conducted a study to compare the size, morphology, and manganese (Mn) oxidation states in nanoparticles generated in the laboratory by arc discharge to those from welding collected in heavy vehicle manufacturing facility. The authors collected at the exit of the spark discharge generation chamber and allowed the particles to age and form chain-like aggregates with morphology very similar to welding fumes. Whereas the smaller primary particles were a mixture of hausmannite (Mn3O4), bixbyite (Mn2O3) and manganosite (MnO), the aged samples were more amorphous in structure. X-ray photoelectron spectroscopy showed that both Mn2+ (Mn3O4) and Mn3+ (Mn2O3 and MnOOH) were found on the surface of the laboratory nanoparticles and in welding fume. The authors also conducted dissolution studies in both lysosomal fluid (pH 4.5) and Gamble's solution (pH 7.4), finding differences in dissolution for laboratory nanoparticles and welding fume samples in the lysosomal fluid and limited dissolution in the Gamble's solution. The authors concluded that the method of particle generation affects the crystal structure and oxidation state of Mn; welding fume can consist of Mn in different oxidation states, amorphous or crystalline, and as isolated or agglomerated particles; although dissolution properties vary depending on how the nanoparticles were generated, solubility in the lysosomal solution indicates that Mn ions have the ability to travel to different organs and produce toxic effects distally from the lungs.

Su et al. (2019) developed a mobile aerosol lung deposition apparatus (MALDA) to study the deposition of ultrafine welding fume particles in the respiratory system. To construct the MALDA, the authors used high-resolution 3D printers to make physiologically representative replica of human tracheobronchial airways. In a series of respiratory deposition experiments, a welding fume chamber was used to generate ultrafine fume particles and these were delivered to the MALDA. The authors were able to measure deposition of ultrafine particles (10 to 100 nm in diameter) down to the 9th airway generation of the tracheobronchial airways using the MALDA. They reported that the cumulative respiratory deposition ranged from 9-31%. The authors concluded that their study demonstrated the MALDA is a useful tool for estimating respiratory deposition of ultrafine particles in workplaces.

Szłapa & Marczak (2018) developed a novel method to separate sound pressure levels (total and tA-weighting-filtered) from welding from other background noise in a work environment using the measurements in the 31.5 kHz octave band. This methodology is based on experiments conducted to determine the Acoustic spectra of metal active gas welding. The authors fitted empirical correlation equations of the sound pressure and the welding current were fitted and successfully applied. This method was able to separate welding process noise from the total noise, which included grinding and hammering noises. The authors note that an advantage of their method compared to other more conventional methods is that it does not require a stable background noise level.

In a follow-up study, Szlapa & Marczak (2020) verified the application of a method that is used to measure sound pressure levels (total and A-weighting-filtered) using selected bands of ultrasonic frequencies. The authors conducted a study of pulsed and double pulsed metal active gas welding (MAG-P and MAG-DP) taking 226 sets of acoustic measurement during welding. Using an empirical equation the authors successfully assessed total sound pressure levels in the octave band with center frequency of 31.5 kHz, with an uncertainty of ±1 dB (equivalent to uncertainty using direct measurement). The estimates of A-weighting-filtered sound pressure levels were done using 1/3 octave frequency bands centered at 40 kHz and 20 kHz for MAG-P and MAG-DP, respectively. Uncertainty was higher, but still in an acceptable range. The authors concluded with refined recommendations for the appropriate frequency band selection for use based on the author's methodology.

Takahashi et al. (2019) investigated the risks associated with ultraviolet radiation (UVR) during gas tungsten arc welding (GTAW), shielded metal arc welding (SMAW), and gas metal arc welding (GMAW) of cast iron. They measure UVR using the approach recommended by American Conference of Governmental Industrial Hygienists (ACGIH). The authors reported effective irradiances ranging from 0.045 to 2.2 mW/cm^2 at 500 mm from the welding arc, which corresponds to an allowable exposure time of only 1.4-67 s/day. They also found higher exposures with higher welding currents, radiation hazards that were dependent on the welding process (GMAW > SMAW > GTAW), and radiation hazards that were also dependent on the filler material used (iron > nickel or chromium).

Yang et al. (2018) evaluated exposures to welding fume metals during construction of pipeline. The authors used cascade impactors to obtain size-fractioned personal samples of welders engaged in shielded metal and gas tungsten arc welding outdoors. They used inductively coupled plasma mass spectrometry to determine the concentrations of iron (Fe), aluminium (Al), zinc (Zn), chromium (Cr), manganese (Mn), copper (Cu), nickel (Ni), and lead (Pb) in both water-soluble (WS) and water-insoluble (WI) particle fractions. The authors reported that the mass distribution of the welding fumes was bimodal. The ranking for the metal concentration was Fe>Al>Zn>Cr>Mn>Ni>Cu>Pb. With regards to solubility, the capacity for metals to dissolve were greater for Zn, Mn, and Pb compared to Cu, Cr, Al, Fe, and Ni, and appeared related more to size that metal species. Considering deposition in the lungs by particle size, and the composition and water solubility of the metals the authors estimated that 4.9% to 34.6% of the WS metals would be deposited in the alveolar (gas-exchange) region of the lungs.

Zuidema et al. (2019a) describe the development and use of low-cost sensors to measure concentrations of particulate matter (PM), carbon monoxide (CO), oxidizing gases (OX), and noise in a heavy-vehicle manufacturing facility. Low-cost sensors are increasingly popular because of their small size, low cost, low power usage, and customizability, and have been used to date primarily in ambient environments. For this study, the authors developed a 40-node multi-hazard network with low-cost sensors for PM (SHARP GP2Y1010AU0F), CO (Alphasense CO-B4), OX (Alphasense OX-B421), and noise (custom made). Measurements were obtained at 5-min intervals and collected at a central database connected to the low-cost sensor network wirelessly for 8 months. The authors reported 1-hr mean ± standard deviation) concentrations of 0.62 ± 0.2 mg/m^3, 7 ± 2 parts per million (ppm), 155 ± 58 part per billion (ppb), and 82 ± 1 dBA, for PM, CO, OX, and noise, respectively for typical production periods. The authors reported diurnal and weekly temporal patterns for all measured hazards as well as spatial patterns for different manufacturing processes. The highest concentrations were observed for machining and welding (PM and noise), staging (CO), and manual and robotic welding (OX). The different sensors had differing precision and bias, assessed by collocating sensors and using direct-reading monitors, respectively. The precision was 0.21 mg/m^3 for PM, 0.4 ppm for CO, 9 ppb for OX, and 1 dBA for noise, and median percent bias was 27%, 11%, 45%, and 1%, for PM, CO, OX, and noise, respectively. The authors conclude that the study demonstrates successful deployment of low-cost sensor network in a manufacturing facility that allows for a high degree of temporal and spatial resolution. The results offer a rich database for comprehensively assessing occupational exposures and associated risks.

In a follow-up paper, Zuidema et al. (2019b) evaluated the quality of particulate matter mass concentrations derived from low-cost sensor, which rely on a calibration procedure for the accurate conversion of the sensor output (voltage) to the mass concentration. The authors describe two primary sources of variability, including temporal changes in sensor calibration and spatial and temporal variability in gravimetric correction factors. The authors analysed results from their 40-node sensor network installed in a heavy vehicle manufacturing facility. To calibrate the low-cost sensors particulate matter was continuously measured with three sensors of the network and a traditional photometer in order to obtain the calibration slope and intercept. In addition, the authors conducted three sampling campaigns, in which particulate matter measurements were obtained from gravimetric samplers and photometers to obtain correction factors for the low-cost sensors. The authors found that the calibration measurements obtained in the field were statistically significantly different from those obtained in the laboratory. They also reported that weekly field calibration values increased over time, likely due to the deterioration of the low-cost sensors. Correction factors for PM also varied by task and location in the facility, with mean correction factors of 2.9 for the cutting and shot blasting area and 4.6 in the machining and welding area. Therefore, different correction factors should be determined near different occupational processes to accurately estimate particle mass concentrations.

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 (8 studies), respiratory effects (8 studies), cardiovascular effects (2 studies), cancer (3 studies), reproductive effects (1 study), eye effects (3 studies), and multiple or other health effects (9 studies). Summaries of these studies are provided below.

4.1.1 Neurological Effects

Casjens et al. (2018) examined the relationship between manganese (Mn) and iron (Fe) exposure with γ-aminobutyric acid (GABA) and additional neurometabolites in the striatum and thalamus. A total of 154 men, representing 47 active welders, 20 former welders, 36 men with Parkinson's disease (PD), 12 men with hemochromatosis (HC), and 39 male controls, from the WELDOX II study participated in the study. GABA, glutamate, total creatine (tCr) and other neurometabolites levels were determined from GABA-edited and short echo-time Magnetic Resonance Spectroscopy at 3T. Volumes of interest were put into the striatum and thalamus of the participants. Mn and Fe exposures were evaluated by participant group, concentrations in the blood, R1 and R2 relaxation rates, and airborne exposures for active welders. Associations were examined using linear mixed models adjusted for age and cerebrospinal fluid content as well as other items. The authors reported that active welders were exposed to a median of 23 $\mu g/m^3$ of Mn and 110 $\mu g/m^3$ of Fe during a shift. No other neurometabolite concentration was related to airborne Fe and Mn exposures. Active and former welders had the highest levels of blood Mn and serum ferritin. Exposure to Mn or Fe was not related to GABA concentrations, but tCr was lower in welders and PD patients compared to the controls. Increasing R1 values in the globus pallidus (GP) were inversely associated with tCr ($\exp(\beta)=0.87$, $p<0.01$) and choline ($\exp(\beta)=0.84$, $p=0.04$). A negative association with myo-inositol and a positive association with glutamate-glutamine was observed for R2*. The authors concluded that the evidence provided no support of a difference in striatal and thalamic GABA in the different groups examined, however, greater metal levels in the GP as determined by R1 were associated with lower concentrations of neurometabolites.

The mechanism by which occupational manganese (Mn) exposure may lead to neurotoxicity and parkinsonism is unclear. Criswell et al. (2017) sought to understand this relationship by exploring Mn exposure, 6-[18F]fluoro-L-DOPA (FDOPA) striatal uptake, and clinical parkinsonism. The authors included a total of 72 participants, which consisted of 27 welders exposed to Mn, 14 other workers exposed to Mn, and 31 non-exposed individuals. Work histories were used to determine cumulative welding exposure. Participants took the Unified Parkinson Disease Rating Scale motor subscore 3 (UPDRS3) to evaluate parkinsonism and were examined by a movement disorders expert. In addition, participants underwent PET scans and aligned magnetic resonance imaging (MRI) to determine striatal volumes. Graphical analyses were used to determine FDOPA uptake. Average caudate FDOPA uptake was lower by $0.0014 min^{-1}$ in welders exposed to Mn and by $0.0012 min^{-1}$ in other workers exposed to Mn compared to the non-exposed group ($p\leq0.001$). A dose-response relationship was not detected between caudate FDOPA uptake, UPDRS3 scores, and Mn exposure. The authors concluded that the decreased caudate FDOPA uptake observed in those exposed to Mn suggested a "pre-synaptic dopaminergic dysfunction" that was not associated with clinical parkinsonism.

Lee et al. (2018) reviewed studies focused on cohorts of symptom free welders with lower manganese (Mn) exposure, compared to earlier work, in order to better understand the effects of long-term exposure to low levels of Mn on brain and functional changes. They found that Mn may non-linearly concentrate in the brain as evidenced by magnetic resonance imaging (MRI) R1 (1/T1) signals that became significantly elevated only after reaching a certain level of exposure. In addition, they reported that R1 may be better than the palladial index at identifying short term changes in the accumulation of Mn. Secondly, they reported that microstructural changes (defined as "lower diffusion tensor fractional anisotropy values in the basal ganglia (BG)") may result from chronic exposure to Mn; these changes may be particularly evident after 30 or more years of welding. Synergy metrics (indices of motor stability) may be better at identifying hard to detect motor dysfunctions related to Mn than measurement of the fine motor tasks that are traditionally used. Higher R2* values in the basal ganglia provide evidence that Fe may be involved in neurotoxicity from welding. The authors concluded that future studies and policies related to Mn exposure may benefit from their findings.

Lee et al. (2019) sought to understand the association between chronic manganese (Mn) exposure and alterations in the hippocampus. A total of 42 welders and 31 non-welder controls participated. Occupational questionnaires, whole blood manganese, and R1 imaging were used to determine Mn exposure. The outcomes measured were hippocampal volume and diffusion tensor imaging (DTI), which provides information on changes to the brain microstructure. The authors reported statistically significantly greater DTI hippocampal mean diffusivity (MD) values in the welders compared to the controls ($p = .035$); the difference was even greater in welders over 50 years of age ($p = .002$). In welders only, hippocampal MD was statistically significantly associated with age ($p<0.001$). Adjusting for age, hippocampal MD values and chronic Mn exposure were positively associated ($p=0.021$). No statistically significant differences were detected in volume between the welders and controls. The authors concluded that Mn exposure and aging may increase the risk of Alzheimer's disease in welders, as the MD brain changes observed in the welders is in line with what is seen in individuals at higher risk for Alzheimer's.

Ma et al. (2017) examined the effects of chronic occupational exposure to manganese (Mn) on the thalamic GABAergic system. The study population consisted of 26 welders with low manganese exposure (mean air Mn=0.13 ± 0.1 mg/m^3), 13 welders with high exposure (mean air Mn=0.23 ± 0.18 mg/m^3) and 22 controls (mean air Mn=0.002 ± 0.001 mg/m^3); Mn fumes were a typical part of the occupational environment of the welders. Edited Magnetic Resonance Spectroscopy was used to measure γ-amminobutyric acid (GABA) and other neurometabolites in vivo non-invasively. Mn's use as a Magnetic Resonance Imaging (MRI) contrast agent offered the opportunity to examine how Mn is deposited in the brain. Personal air sampling at the working place, work history questionnaires, and neurological assessment, using the Unified Parkinson's Disease Rating Scale (UPDRS3) were also used to gather data. The authors reported that welders with high Mn exposure had thalamic GABA levels that were increased by 45% ($p<0.01$, $F(1,33)=9.55$), and poorer general motor function performance ($p<0.01$, $F(1,33)=11.35$). No differences were detected between the low exposure welders and controls. Exposure levels in the previous 12 months were the best predictors of thalamic GABA levels and were impacted by Mn deposition in the substantia nigra and globus pallidus. The authors suggest that there may be a threshold effect as thalamic GABA levels and motor function responded in a non-linear fashion to Mn exposure.

Ou et al. (2018) studied the relationship between occupational manganese (Mn) exposure at high levels and neural endocrine hormones using a cross-sectional study design. Participants were 52 welders, 48 smelters, and 43 office workers matched on age from a factory in China. Endocrine hormone levels were assessed in the serum. Airborne concentrations of Mn were measured. Mn levels in erythrocytes and urine were determined via inductively-coupled plasma atomic emission spectroscopy. The authors reported geometric mean air concentration of Mn was 19.7 μg/m^3 in welders and 273.1 μg/m^3 in smelters. Higher concentrations of Mn were detected in the erythrocytes of smelters compared to welders and controls; no differences were detected between the welders compared to controls. In addition, urinary Mn levels were higher in welders and smelters compared to controls and in the smelters compared to welders. Furthermore, neurobehavioral symptoms self-reported by the participants were increased in the welders and smelters compared to the controls. Lastly, thyroid-stimulating hormone levels were lower in welders compared to controls, and prolactin, testosterone and follicle-stimulating hormone were lower in smelters compared to controls and welders. The authors concluded that their results suggest that occupational Mn exposure at high levels may lead to negative neurobehavioral effects and endocrine disruption.

Park and Berg (2018) performed a risk assessment of manganese (Mn) exposure and neurobehavioral impairments using studies from the literature to build on prior work and to determine exposure and excess risk estimates. A benchmark dose approach was conducted using results from studies in a chemical manufacturer, two smelter and two welder populations. Larger dust particles (>1.0 μm) appeared to be less potent than smaller particles and condensation fume aggregates. The focus was on the effects of continuous, long-term, low exposures that lead to a steady state condition. Neurobehavioral impairments are generally considered to be any departures greater than the 5th percentile observed in a general population. For the populations of interest, however, the authors calculated the Mn and particle concentrations anticipated to lead to a 1% excess prevalence of impairment over different time periods. The authors found that approximately 10 μg/m^3 for Mn fume and 25 μg/m^3 for particle dusts led to a 1% excess of impairment over a five-year period. For Mn, the levels are below the United States recommended occupational limits.

Pesch et al. (2018b) sought to examine the relationship between airborne and systematic exposure to manganese (Mn) and iron (Fe) and brain deposition. A total of 161 men, including 48 active welders, 20 former welders, 41 individuals with Parkinson's disease (PD), 13 with hemochromatosis (HC), and 39 controls, who were part of the WELDOX II study participated. R1 and R2* relaxation rates served as biomarkers of metal accumulation in different brain areas [globus pallidus (GP), substantia nigra (SN), and frontal lobe white matter (FL)] in both hemispheres. Measures of Mn in the whole blood and serum ferritin were also collected. During a welding shift, respirable Mn and Fe were measured. Mixed regression models were used in the analysis. The authors reported that

Mn in the whole blood and serum ferritin were associated with R1, but not R2*in the GP and weakly associated with R1 in the SN and FL. No group effects on R1 or R2* were observed in the welders or in those with Parkinson's disease or hemochromatosis outside of whole blood Mn and serum ferritin. Stronger associations with R1 signals in the GP were observed in active welders with respirable Mn levels >100 μg/m^3 during a shift. No additional relationships were found for welding technique. These results suggest metal accumulation in the GP in particular. Higher R1 signals in the GP were also observed with greater airborne Mn concentrations. The authors hypothesize that effects of Mn exposure are more likely linked to concentrations of Mn in the blood than to airborne levels.

Racette et al. (2018) developed a linear regression model to help non-neurologist identify workers with potential manganese (Mn)-related neurotoxicity, which often presents with the signs and symptoms of Parkinson disease (i.e., parkinsonism). The authors collected data from a cohort of Mn-exposed welders for which clinical data were available. This included 596 workers age≤65years. The data were used in the regression model to predict the Unified Parkinson Disease Rating Scale motor subsection part 3 (UPDRS3) score. The authors focused primarily on easily collected data that are also common factors that are associated with parkinsonism (e.g., age, timed motor task results, and selected symptoms/conditions). Other factors that were also considered included demographics and welding exposure. The authors selected a final model based on its simplicity, biological plausibility, and the statistical significance of the variables in the model. The variables in the model included age, timed motor task scores for each hand, and indicators of action tremor, speech difficulty, anxiety, depression, loneliness, pain and current cigarette smoking. The authors found that the model performed very well and was able to identify workers with clinically significant parkinsonism (UPDRS3≥15) with 80% sensitivity, and 52% specificity. The authors concluded that the model would be useful in many different setting as welding exposure data was not part of the final model. They note that this would be useful as a first step in an occupational screening program.

4.1.2 Respiratory Effects

Ithnin et al. (2019) examined the relationship between welding fumes and lung function. A total of 30 welders and 31 non-welders from the Lumut shipyard in Perak were included. A questionnaire based on the 1987 American Thoracic Society was used to collect demographic and smoking information as well as respiratory symptoms. Lung function (forced expiratory volume in 1 second [FEV_1], forced vital capacity [FVC], FEV_1/FVC, Peak expiratory flow rate [PEFR]) was measured by spirometry and metal concentrations in welding fume (cadmium, iron, lead, and zinc) were measured according to the Occupational Safety and Health Administration (OSHA) ID-121. The mean concentration of 2.75 mg/m^3 for lead was above the PEL-TWA of 0.5 mg/m^3. Welders reported more symptoms related to cough and phlegm than non-welders ($p = 0.001$). FEV_1 and FVC were lower in the welders compared to the non-welders ($p = 0.001$). Welders were also more likely to smoke than non-welders; smoking and having symptoms of a chest illness were associated ($p = 0.01$). The authors concluded that their findings suggest that welding fumes, in addition to smoking, may have a detrimental effect on respiratory health. However, it should be noted that it is difficult to determine whether either alone is a causal factor from this study.

Karatas et al. (2019) used levels of thiol-disulfide homeostasis and ischemia-modified albumin (IMA) levels to better understand oxidative status in patients with welders' lung. The study included male welders with welder's lung disease as well as a healthy comparison group who participated in lung function tests and provided plasma to measure levels of disulfide, disulfide/native thiol ratio, disulfide/total thiol ratio, IMA, and catalase (CAT). The thiol-disulfide homeostasis parameters of disulfide, disulfide/native thiol, and disulfide/total thiol and IMA levels were statistically significantly higher in the welders with lung disease compared to the healthy individuals. CAT results were statistically significantly higher in the control group compared to the welders. The authors concluded that plasma thiol-disulfide homeostasis and IMA levels may serve as signs of oxidative stress, and this may play a role in the development of welders' lung disease.

Koksal et al. (2020) reported on a case of a 56-year-old man with an abnormal chest X-ray but no symptoms. For the previous 25 years, the man had worked as a welder both indoors and outdoors. Laboratory, exercise capacity and lung function tests were conducted and determined to be normal as were collagen tissue markers. Bronchial lavage, stained with Prussian blue, confirmed welding-related pulmonary fibrosis. Hemosiderin-laden macrophages (25%) also provided evidence of this association and helped clarify the diagnosis. The man elected to stop working as a welder following his diagnosis.

Mehrifar et al. (2019) examined the relationship between different welding processes (in flux cored arc, shielded metal arc, gas metal arc) and lung function and respiratory symptoms in a cross-sectional study. In 2018, 60 welders from an Iranian shipbuilding factory and 45 controls from the factory's administrative unit were recruited. Questionnaires were used to collect demographic information and respiratory symptoms. Lung function tests were also performed. Samples were taken from each welder's respiratory tract and analyzed for fumes and gases as recommended by the National Institute of Occupational Safety and Health (NIOSH)[NOTE: unclear if these are breathing zone/personal air samples?]. Welders (all types) reported more respiratory symptoms than the controls ($p<0.05$). In addition, mean FVC, forced expiratory volume in 1 second [FEV_1] and FEV_1/FVC were lower in all three welding groups compared to the controls. An obstructive spirometry pattern was observed in the in flux cored arc and shielded metal arc welders. A mixed obstructive ad restrictive pattern was found in the gas metal arc welders. The authors concluded that the study results indicate poorer lung function in welders and that gas metal arc welders may be experiencing more lung function deficits than other types of welders. However, the cross-sectional design of the study limits the conclusions that can be drawn from the study results. Comments raised about this paper also indicated several concerns with the study design and results (Jalilian 2019).

> *In a letter to the editor Jalilian (2019) expresses several concerns about the paper written by Mehrifar et al. (2019) including its small size, lack of control confounders such as alcohol intake, and an unclear reporting of how past or secondhand smokers were handled. The author's biggest concerns are related to the measurements of gases and fumes, specifically unclear detail on the measurement of magnesium, describing air samples as being collected from the "respiratory tract" (assumes they mean breathing zone), and no detail on the number of samples collected from each welder or for how long the samples were collected.*

Özmen et al. (2018) described radiological findings in the lungs of welders. Sixteen male welders who had been hospitalized with respiratory symptoms and who had clinical and radiological results between January of 2010 and January of 2017 were included. Thirteen of the welders worked in shipyards; the remaining three worked in construction or elsewhere. The mean age of the welders was 37 (± 8) years and the mean duration of employment as a welder was 12 (± 7) years. Coughing, sputum, and dyspnea were reported by 87, 63 and 63 percent of the welders, respectively. A physical examination revealed rhonchi in three of the welders; these same three welders also had forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) below 70%. Thorax high resolution computed tomography revealed centrilobular micronodules that were ill-defined and not clearly identified during chest radiographs. Seven patients had bronchoscopy, which revealed iron-positive pigment granules and ferruginous bodies in the bronchoalveolar lavage. The authors concluded that physicians should more closely examine the chest X-rays of welders and opt for high-resolution computed tomography (HRCT) in the event of uncertain findings.

Roach (2018) conducted a retrospective chart review in an effort to better understand exposure to occupational welding fumes and lung function. The charts included lung function tests and questionnaires starting with the preplacement exam to the most current exams. A multiple regression model adjusted for age and portion of time using a respirator was used to compare smokers and nonsmokers. The author reported that years of welding was statistically significant ($p=0.04$) in the model and concluded that the findings provided evidence of smoking and welding operating synergistically on lung function declines. However, the study has limitations as noted by the comment below (Dunbar 2018). Based on the abstract it does not appear that exposures were assessed. In addition, it would be difficult to disentangle the impacts of welding exposures and smoking, as well as other factors that could contribute to lung function changes (e.g., other air pollution exposures or lifestyle factors). Lastly, the authors did not report the magnitude of lung function decline and whether a dose-response was observed. Observance of dose-response strengthens a causality assumption.

> *A letter to the editor written by Dunbar (2018) expresses concerns about inaccurate statements made in the Roach (2018) paper and highlights areas where clarification is needed in the purpose, problem statement, and significance of the problem sections of the paper. For example, he cautions about the use of the phrase "exposure to welding fume" and explains that poor health effects tend to result from "overexposure" (levels of welding fume that exceed health-based occupational standards). He also notes that the authors are inaccurate in their explanation of Cr(VI) exposure and welding, noting that Cr(VI) risks are primarily from welding stainless-steel, and not the more common welding of mild steel. Importantly, that Cr(VI) is not directly emitted from welding, but forms depending on the welding conditions.*

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 like that of healthy controls.

Taghiakbari et al. (2018) examined the relationship between welding fume exposure and prevalence of nasal symptoms and nasal patency in 85 welders who were part of a larger inception cohort of welding apprentices. The welders were followed for 7 to 17 years after their apprenticeship (2013-2017). Welders with at least two of the three symptoms of sneezing, runny nose, and/or nasal congestion during a study visit were defined as having rhinitis. Welders were tested with a peak nasal inspiratory flow (PNIF) meter to determine nasal patency and spirometers and a methacholine challenge test to evaluate lower airway function. Welding fume exposure was determined three ways: 1) self-report, 2) industrial hygienist determination, and 3) job exposure matrix (JEM) Univariate logistic regression models were used to examine the association between various factors (age, sex, smoking, body mass index [BMI], wheezing, Forced expiratory volume in 1 second [FEV_1] % predicted, nonspecific bronchial hyperresponsiveness, elevated total IgE, duration of current employment, and welding fume exposure at current job according to each of the three methods) and having both rhinitis and low nasal patency. The odds ratio for rhinitis and low nasal patency was statistically significantly elevated when welding fume exposure was determined by industrial hygienist (odds ratio [OR] 6.50 95% 1.37–30.95); odds ratios were elevated, but not statistically significant for the other two methods of exposure determination (self-report: OR 2.54, 95% CI 0.81–7.95; JEM: OR 2.75, 95% CI 0.79–9.47). No other statistically significant findings were identified. The authors concluded that current welding fume exposure may increase risk of having both rhinitis and low nasal patency but assert that larger studies are necessary.

4.1.3 Cardiovascular Effects

Baumann et al. (2018) conducted a human exposure study to assess whether exposures to ultrafine welding fume particles containing zinc and copper elicited an inflammatory response involving several biomarkers associated with cardiovascular disease including IL-6, C-reactive protein (CRP) and serum amyloid A (SAA). The authors recruited 15 non-smoking males to participate. The participants were exposed to controlled welding fume exposures containing zinc and copper (2.5 mg/m^3) or ambient air (randomized order), and nasal secretions were obtained 1, 3, 6, 10, and 29 hours after exposure. Electrochemiluminescent assays were used to measure selected biomarkers. The authors reported significantly elevated nasal interferon-γ (IFN-γ) 1 hr after exposure to welding fumes compared to controls and statistically significantly elevated CRP and SAA at 10 and 29 hours after exposure compared to controls. The authors concluded that there were significantly elevated levels of important cardiovascular biomarkers in nasal samples after exposures to welding fumes and that measurement of these biomarkers may be a good way to survey welders potentially exposed to ultrafine particles in the workplace. It is important to note, however, that small and transient changes in biomarkers such as the ones included in this study may not necessarily be clinically significant and if a surveillance approach based on measurement of biomarkers is conducted, clinically significant changes in these biomarkers should be defined.

Ellingsen et al. (2019) conducted a study to assess whether there was an association between increased mortality from cardiovascular disease (CVD) in welders and exposures to particulate matter. The authors recruited 70 welders and 74 non-welders for comparison. Welders had worked an average of 15 years. Blood samples were obtained to measure biomarkers associated with cardiovascular disease, including of TNF-α, P-selectin, CD40L, prothrombin fragment 1 + 2 and D-dimer. For two days prior to blood sample collection, air in the work room was measured by personal sampling over the full shift. Mean PM exposures were 8.1 mg/m^3. Concentrations of TNF-α, P-selectin, CD40L, prothrombin fragment 1 + 2 and D-dimer were statistically significantly higher in the welders than in the non-welders. Furthermore, PM exposure was positively associated with D-dimer and CD40L concentrations. The authors concluded that the changes in biomarkers observed were consistent with elevated CVD mortality. The study has several limitations, however, including no reference to lifestyle factors, including diet and smoking, that could impact the biomarker findings. A causal association with PM exposures cannot be shown without proper control for these confounding factors.

4.1.4 Cancer

Honaryar et al. (2019) performed a meta-analysis on welding and welding fume exposure and lung cancer risk based on cohort and case control studies. Studies were identified using PubMed, other databases and a search of reference lists, and any duplicate publications were excluded. The analysis included the use of random effects models to determine meta-relative risks (mRR) adjusted for smoking and asbestos exposure and funnel plots, Egger's and Begg's test to determine publication bias. The analysis included 37 studies (22 cohort, 15 case-control). Meta-relative risks for ever welders or welding exposure were statistically significantly elevated compared to never welders of no welding exposure in both cohort (mRR 1.29, 95% CI 1.20 to 1.39; I2=26.4%; 22 studies) and case-controls studies (mRR

1.87, 95% CI 1.53 to 2.29; I2=44.1%; 15 studies) and risks remained statistically significant, although lower, following adjustment for smoking and asbestos exposure (mRR 1.17, 95% CI 1.04 to 1.38; I2=41.2%, 8 case-control studies). Meta-relative risks were statistically significantly elevated in shipyard welders (mRR 1.32, 95% CI 1.20 to 1.45; I2=6.3%; 15 studies) and mild steel welders (mRR 1.44, 95% CI 1.07 to 1.95; I2=35.8%; 3 studies) and elevated, but not statistically significant in stainless steel welders (mRR 1.38, 95% CI 0.89 to 2.13; I2=68.1%; 5 studies). Similar findings were observed when examined by occupation type, method of assessing exposure, lung cancer subtype, geography, time period, and study design. The authors concluded the findings supported an association between increased lung cancer risk and welding exposures regardless of welding method and independent of smoking and asbestos exposure. Although associations are significant for many of the analyses, there remain significant uncertainties with the underlying occupational studies primarily because of issues with 1) exposure assessment and 2) control for confounding. Even for known confounders, such as asbestos and smoking, incomplete or inaccurate data could still contribute to residual confounding.

Michalek et al. (2019) assessed the incidence of cancer in the renal pelvis in occupational groups in Denmark, Iceland, Finland, Norway and Sweden. The study included 14.9 million workers and individual data on working history was obtain from the national census in each country. The authors reported the highest standardized incidence ratios (SIRs) of 1.51 (95% confidence interval [CI] 1.23-1.82) for seamen, 1.39 (95% CI 1.11-1.71) for printers, 1.37 (95% CI 1.03-1.78) for welders, and 1.35 (95% CI 1.12-1.62) for public safety workers. The lowest SIRs (<1.0) were observed for forestry workers, gardeners and woodworkers. The authors suggest that there is a potential association between occupation and risk of cancer of the renal pelvis.

Michalek et al. (2019) examined the relationship between kidney cancer and occupational exposure to welding fumes and the heavy metals (chromium (VI), iron, nickel, and lead) in a nested case control study. Between 1960 and 1990, 59,778 kidney cancer cases were identified in the Finnish, Swedish, and Icelandic population censuses and matched on sex, age, and country to 298,890 census controls. The Nordic Occupational Cancer (NOCCA) job exposure matrix was used tp estimate exposure to welding fumes, four heavy metals, and 24 additional work-related exposures. Exposures were lagged by 0, 10, ad 20 years. In those below 59 years of age, the odds ratio (OR) for kidney cancer was statistically significantly increased in those with high nickel exposure (OR 1.49, 95%CI 1.03-2.17). In those 59 to 74 years of age, the odds ratio for kidney cancer was statistically significantly increased in those with high iron or welding fume exposure (iron: OR 1.41, 95%CI 1.07-1.85; welding: OR 1.43, 95%CI 1.09-1.89). High asbestos exposure was positively and statistically significantly associated with kidney cancer, while high ultraviolet exposure, high wood dust exposure or high perceived workload were negatively and statistically significantly associated with kidney cancer. No other associations were detected for the exposures of primary interest. The authors concluded that there was potentially age - specific elevations in kidney cancer risk for workers exposed to high levels of nickel, iron, or welding fumes. Based on the study summary, however, it is unclear if confounding was a significant issue in the studies (i.e., whether both asbestos and metals/welding exposures occurred simultaneously). It is also unclear if cases and controls were matched for other potential confounders such as alcohol consumption or smoking.

4.1.5 Reproductive Health Effects

Dehghan et al. (2019) examined the association between lead fume concentration and reproductive hormone levels. The study population consisted of 85 exposed welders and 80 non-exposed employees working in administrative positions who were part of water pipeline construction. Lead fumes were sampled and analysed using the National Institute for Occupational Safety and Health (NIOSH) 7300 method and blood lead levels were measured using the NIOSH 8003 method. Chemiluminescence immunoassay tests were employed to determine luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone levels. Mean lead fume concentrations (breathing zone: 0.57 ± 0.12 mg/m^3, blood: 460.28 ± 93.65 μg/L) were statistically significantly greater than American Conference of Governmental Industrial Hygienist's (ACGIH) threshold limit values (TLV) and biological exposure index (BEI) ($P < 0.05$). The exposed group had higher mean levels of LH and FSH and lower mean levels of testosterone than the non-exposed group ($P < 0.05$). Blood lead levels were positively correlated with lead fume concentrations ($r = 0.82$; $P = 0.003$). Furthermore, blood lead levels were positively correlated with LH ($r = 0.72$; $P = 0.004$) and FSH ($r = 0.78$; $P = 0.001$) levels and inversely correlated with testosterone levels. The results provide some suggestion that lead fumes from welding may affect reproductive hormones. However, it is unclear if the study controlled for potential confounding factors.

4.1.6 Eye Effects

Asharlous et al. (2018) examined tear film and evaluated dry eye in welders using both subjective and objective measures. A total of 140 welders who had worked for five or more years and 172 controls were identified from a historical cohort. Each participant underwent an ocular health exam, which included two objective assessments, the Schirmer test and Invasive Tear Break-Up Time, and one subjective test, the Ocular Surface Disease Index. Values from all three tests were statistically significantly lower in welders compared to controls. The authors reported that 81.2% of welders had dry eye compared to 35.5% of controls. Dry eye was severe in 46.2% of welders. The authors suggest that aqueous deficiency may be the primary cause of the welders' dry eyes.

Atukunda et al. (2019) conducted a cross-sectional study of small-scale welders from Katwe, Kampala and described the patterns and prevalence of eye disorders as well as related factors. Simple random sampling was used to select 343 welders. The welders completed a questionnaire on demographics, welding, and health history when they were given an eye examination. Sixty percent of the welders (average age: 36 ± 12 years) were found to have eye disorders, defined as an abnormal finding of any type during the examinations. Conjunctiva disorders and presbyopia led the list of disorders identified, affecting 32% and 27% of welders, respectively. In a logistic regression model, eye disorders were statistically significantly associated with being 35 or more years of age (odds ratio [OR] 4.2, p value < 0.001), being female (OR 4.3, p value 0.007), and having had a foreign body removed from the eye (OR 1.7, p value 0.041). Eye disorders were high in this group of small-scale welders, with an overall prevalence of 59.9%. The authors recommended eye health education, regular eye examinations, and policies requiring the use of personal protective equipment. The cross-sectional study design, however, limits any conclusions regarding a causal association between welding and ocular disorders.

Kim et al. (2019) described a case report of a 47-year-old man with binocular maculopathy. For a period of 10 to 15 minutes, the individual conducted electric arc welding while not outfitted with personal protective equipment and developed eye discomfort and diminished visual sharpness. During a clinical visit his corrected visual acuity was 0.5. Optical coherence tomography revealed ellipsoid zone disruption and multifocal electroretinogram (mfERG) indicated a reduction in mfERG amplitudes in the central 10° in both eyes. His visual acuity has remained an issue for one and a half years. The authors stress the importance of using the proper personal protective equipment regardless of the length of welding work to reduce any potential for photic retinal injury.

4.1.7 Multiple or Other Health Effects

Chen et al. (2019) evaluated the prevalence and factors that contribute to noise-induced hearing loss (NIHL) in the automotive industry in China, as these data are scarce. The authors conducted a cross-sectional study of 6557 workers in the industry, collecting information via a questionnaire, measuring noise levels in the workplace, and evaluating hearing loss. The authors reported that 96.4% of the workers were male (median age 27 years old) and 28.8% had NIHL. The measured noise levels exceeded 85 dB(A) in 62.5% of the samples, primarily in jobs that included metal cutting, surface treatment, stamping, welding, grinding, assembly, plastic molding, and forging. However, the source of noise all different in the temporal waveform that it generated. Personal protective equipment (PPE) was used regularly by 53.2% of the workers to protect against noise. Trend analysis showed that the prevalence of NIHL increased with increased noise level <94 dB(A) and also with cumulative noise exposure. Overall, the authors concluded that important determinant of NIHL included the frequency of use of PPE and cumulative noise exposure. They also stressed that more surveys were needed to better understand hearing loss in workers in the automotive industry.

Cherry et al. (2018) evaluated differences in welding work tasks and exposures between men and women. The authors stressed that this information was important for setting occupational standards that would be protective to both men and women. The authors established four different Canadian cohorts of 1001 welders and 885 workers in the electrical trade, two of women working in welding (N= 447) and electrical trades (N= 438) apprenticeships starting in 2005, and two of men in the same trades (N = 554 welders; N= 447 in the electrical trade) working during the same period. The authors collected information via a questionnaire during recruitment, with a follow up every 6 months to collect information on work tasks and health, including mental health and harassment. The last questionnaire was administered after 5 years and 3 years, for women and men, respectively. The authors reported that they obtained follow-up information for 89% of the cohorts. The authors found that women were more educated than men before starting their trade and were less likely to be married with children. A greater percentage of welders smoked, and a higher percentage of men were heavy drinkers. Welders also reported more prevalence of sneezing and runny nose, depression, and anxiety then those in the electrical field. Depression was more prevalent in female workers (38%, compared to 30% in males and 24% in those in the electrical trades). Men reported more shoulder pain, and welders had a higher percentage of new-onset asthma. Overall, women reported less variety in the trade tasks, they were less likely to be in construction, and also less likely to be industrial electricians. With regards to personal protective equipment, more women welders (54%) than men (46%) reported never using respiratory protection. A total of 49% of the workers reported harassment issues during their apprenticeship, with a higher percentage for welders and women. Higher percentage of harassment correlated with higher anxiety and depression. The authors concluded that while in general men and women appeared to be doing the same work, there were observed differences and the detailed information provided by the study could be useful for estimating exposures and health among men and women in the welding and electrical trades.

Chuang et al. (2018) examined the relationship between fine particulate matter from welding fumes ($PM_{2.5}$) and sleep quality. The authors measured lung function, urinary biomarkers (serotonin and cortisol), and sleep quality using a device for determining hours awake. The authors included 96 shipyard welders ($PM_{2.5}$ exposure: 82.1 ± 94.1 μg/m^3) and 54 office workers ($PM_{2.5}$ exposure: 82.1 ± 94.1 μg/m^3) for comparison. For lung function, the forced expiratory flow at 25-75% of lung volume (FEF_{25-75}) was lower in welders than office workers ($p < 0.05$). For a subset of 16 welders and 16 office workers, randomly selected, that wore a device to assess sleep quality; the welders spent more time awake than the office workers ($p < 0.05$). For urinary serotonin, a 1 μg/m^3 increase in FEF_{25-75} was associated with a 0.003 ng/mL decrease in urinary serotonin in all workers ($p < 0.05$) and a 0.001 ng/mL decrease in welders only ($p < 0.05$). Urinary cortisol and $PM_{2.5}$ were not associated with each other in any workers. Urinary serotonin and cortisol were both associated with copper, manganese, cobolt, nickel, cadmium, and lead. The authors concluded that welders may experience disturbed sleep due to exposure to heavy metals in $PM_{2.5}$ welding fumes. The study had a small sample size and it is unclear if confounding factors were considered in the analysis.

Ghimire et al. (2018) conducted a cross-sectional study of 86 welders in Dharan in eastern Nepal with the aim of understanding injury prevalence and identifying injury risk factors in welders. A semi structured questionnaire was used to gather demographic and occupational information. Injuries that had taken place in the last two weeks or in the last 12 months were noted. The welders were male, approximately half were younger than 25 years of age and approximately 20 percent had received welding training. Slightly more than 20% of the welders had experienced a work-related injury in the last year. Nearly all, 95%, had used one or more forms of personal protective equipment (PPE). The authors reported that working for 5+ years, being 35+ years of age, lacking training, and not using PPE was associated with more injuries, but also reported that these associations were not statistically significant. The authors noted that a high percentage of welders in this study experienced work-related injuries; more research is necessary to understand risk factors.

Hassan et al. (2017) evaluated health complaints and level of awareness of occupational hazards in 70 welders in Lahore, Pakistan. In this cross-sectional survey, the authors applied a questionnaire to collect information on demographics, health complaints, and use of protective personal equipment (PPE). The authors reported that all the welders were male (mean age 25.7 years old) and 54% were aware of welding risks. Almost all, 99%, had PPE. The most prevalent reported occupational hazards included cuts and injuries (50%), burns (49%), foreign body in the eye (47%), and arc eye injury (46%). The authors concluded that there was generally poor awareness of welding risks and a large degree of reported health hazards. They recommended that preventive measures be implemented to reduce welding health hazards.

Piernicki et al. (2019) reported on three welders who may have developed skin diseases or whose skin diseases may have been aggravated by the high bursts of ultraviolet light radiation (UVR) exposure common in welding. The skin diseases included refractory subacute cutaneous lupus erythematosus, diffuse actinic damage and squamous cell carcinoma. In the latter two cases, the disease occurred outside the skin area shielded by personal protective equipment. The authors also provided a review of UVR exposures in welders, dermal effects, and recommendations for safety measures.

Saeed et al. (2019) described a case report of a 39-year-old male welder of thirteen years who arrived at the emergency room with a cough, including blood, and shortness of breath. At the time his symptoms began, he had been welding a steel tank while in a closed area. His medical history was unremarkable. He experienced oxygen impairment as evidenced by his arterial blood gas and required intubation and assisted ventilation. Radiography showed interstitial shadowing throughout both sides of his lungs. Cardiogenic pulmonary oedemic was not suspected after his heart was shown to be normal on an echocardiogram. Nothing was found from microbiological tests. He was ultimately determined to be experiencing Acute Respiratory Distress Syndrome (ARDS), a diagnosis of exclusion, resulting from welding fumes. He was treated with ventilation for 12 days. The authors believe that welding fume resulted in injury from direct inhalation and/or issues with the immune system that lead to the ARDS. They recommend safety measures to prevent similar occupational hazards.

Shen et al. (2018) evaluated metabolomics changes in a group of 52 boilermakers before and after exposure to welding fumes during a work shift to better understand whether welding fume contributes to systemic inflammation. Plasma samples were gathered pre- and post- shift and ultra performance liquid chromatography - tandem mass spectrometer method was used to determine metabolite concentrations in order to assess metabolic changes. The authors reported changes primarily in the metabolites involved in the lipid pathway [glucocorticoid class (cortisol, corticosterone, and cortisone), acylcarnitine class, and DiHOME species (9,10-DiHOME and 12,13-DiHOME)], in how amino acids are used (isoleucine, proline and phenylalanine), and in S-(3-hydroxypropyl) mercapturic acid (3-HPMA) after the work shift. The authors noted that the compounds where changes occurred are all related to inflammation based on prior research. The analysis also revealed an interaction between smoking and 3-HPMA. The authors also conducted an analysis of the disease related to the metabolites identified in the plasma samples and found that the metabolite pathways were associated most strongly with diseases involving systemic inflammation like lupus erythematosus and rheumatoid arthritis. The authors concluded that exposure to welding fumes may lead to systemic inflammation and that metabolites identified may be used as biomarkers for health monitoring.

Zhang et al. (2019) conducted a study to evaluate how to improve the ergonomics of welders in China. The authors created six digital humans and a welding torch model and used Jack software to assess three welding actions: walking, raising arm, and contracting arm. The authors applied the Lower Back Analysis, Ovako Working Posture Analysis, Comfort Assessment, and Rapid Upper Limb Assessment to determine the optimal range of the weight of the welding torch, the upper limb posture, and the welder's neck posture. The results showed that the welding torch should not weigh more than 6 kg when the welder is standing. Also, they determined that the best operating distances are 321 mm, 371 mm, and 421 mm, for men in the 5th, 50th, 95th percentile of body weight, respectively, and the best operating heights are 1050 mm, 1100 mm, and 1150 mm, respectively; for females in the same size ranges, the corresponding distances are 271 mm, 321 mm, and 371 mm, and the heights are 1000 mm, 1050 mm, and 1100 mm, respectively. To avoid neck strain the horizontal and vertical rotation angle of the neck should not be greater than 15° and 8.7°, respectively. The authors concluded that these results would help to prevent fatigue and injury.

4.2 Animal Studies

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

Falcone et al. (2018a) investigated whether inhalation of gas metal arc-mild steel (GMA-MS) welding fume, which lacks known carcinogens (chromium and nickel) 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-MS welding fumes (target concentration 34.5 mg/m^3) for 4 hours per day, 4 days a week for 8 weeks, one week after receiving injections of 10 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 tumors from exposures to GMA-MS fumes that were also given MCA (21.86 ± 1.50) compared to MCA/air-exposed mice (8.34 ± 0.59). The authors also noted an absence of lung inflammation. The authors concluded that exposures to GMA-MS promote lung tumorigenesis and these findings are consistent with epidemiological findings of potential increased risk of lung cancer in welders.

Falcone et al. (2018b) sought to better understand the relative toxicity of various different metals typically found in welding fumes. The authors conducted a study in which male lung tumor susceptible A/J mice were exposed to chromium (as Cr(III) oxide [Cr2O3] and Cr (VI) calcium chromate [CaCrO4]), nickel [II] oxide (NiO), iron [III] oxide (Fe2O3), and gas metal arc welding-SS (GMAW-SS) fume. The mice were exposed by oropharyngeal aspiration to either vehicle (control), GMAW-SS fume (1.7 mg), or a low or high dose of each metal oxide: Cr2O3 + CaCrO4 (366 + 5 µg and 731 + 11 µg), NiO (141 and 281 µg), or Fe2O3 (1 and 2 mg). The authors evaluated the mice by bronchoalveolar lavage, histopathology, and lung/liver qPCR 1, 7, 28, and 84 days post-exposure. Some of the mice received injections of 10 ug/g of chemical initiator 3-methylcholanthrene (MCA) or corn oil intraperitoneally before exposures to the control or the metals (1 time per week for 5 weeks) and were evaluated 30 weeks after exposure. The authors reported that inflammation potential of the metals was greatest and most persistent for Fe2O3, acute but not persistent for Cr2O3 + CaCrO4, and negligible for NiO. In addition, Fe2O3 significantly promoted lung tumors, but not the other metal oxides. The authors concluded that iron oxides rather than chromium or nickel oxides may be the key mediator for welding fume toxicity and support epidemiological findings.

Halatek et al. (2018) studied the pulmonary toxicity of welding dust (WD) in Winstar rats, specifically the role of inflammatory and anti-inflammatory markers. The authors exposed the rats to 60 mg/m^3 of respirable WD (mean diameter 1.17 µm) or soluble welding dust (SWD) for 1 and 2 weeks (6 hours per day, 5 days per week) using a nose-only chamber. They measured the concentration of several inflammation biomarkers in bronchoalveolar lavage fluid including clara cells secretory protein (CC16), differential cell counts, total protein concentrations and the cellular enzyme lactate dehydrogenase. In addition, the authors measured corticosterone and thiobarbituric acid reactive substances and prolactin concentrations in serum. They also examined the histopathology of lung, brain, liver, kidney, spleen, and obtained slices of the brain and lung for further analysis. The authors reported that histopathology showed a significant inflammatory response after exposure to WD and SWD, and that anti-inflammatory potential was overall decreased, based on decreases in CC16. The authors concluded that WD and SWD exposure impacted the levels of CC16 and that this provides support for an impact on pulmonary inflammation. The authors also reported association between CC16 and prolactin as potential pathways that are involved in the inflammatory response.

Krishnaraj et al. (2017) evaluated the effects of welding fume exposures via inhalation on the expression of molecules involved in the DNA damage response (DDR). The authors exposed male Sprague-Dawley rats to 50 mg/m^3 stainless steel (SS) welding fumes for 1 hour per day for 4, 8 and 12 weeks. A histopathology evaluation was conducted as well as measurement of DDR markers and signalling of nuclear factor erythroid 2-related factor-2 (Nrf2) and expression of noncoding RNAs (ncRNAs) as well as other impacts on respiratory cells. The authors reported that for exposed rats' lungs, there was evidence of preneoplastic changes, elevated level of DDR markers (e.g., 8-oxo-2'-deoxyguanosine), ATM phosphorylation, cell cycle arrest, apoptosis induction, activation of homologous recombination, activation of Nrf2 signalling, and changes in ncRNA. The authors also noted that after 12 weeks DDR appeared to be compromised because of resumption of the cell cycle, inhibition or DNA repair mechanisms, and no evidence of apoptosis. The authors concluded that exposure to SS welding fumes appears to impact DDR mechanisms via phosphorylation of key proteins, effects on ncRNAs, which modulate the DDR, and these effects can lead to neoplastic changes in the lungs.

Shoeb et al. (2019) evaluated the effects of welding fume (WF) on changes in telomere length as a possible marker of neurodegeneration. The authors used male Fischer-344. Rats were exposed by inhalation to stainless steel WF (20 mg/m^3; 3 hours per day; 4 days a week for 5 weeks) or filtered air (control). Twelve weeks after exposure ended, the authors assessed telomere length, DNA-methylation, gene expression of Trf1, Trf2, ATM, and APP, protein expression of p-Tau, α-synuclein, and presenilin 1 and 2 in the rats' whole brain tissue. They reported that WF exposures increased telomere length and that the components, Trf1 and Trf2, which protect telomere length may be involved. In exposed rats, they also found that increased expression of several neurodegeneration markers (e.g., p-Tau, presenilin 1-2 and α-synuclein proteins) compared to controls. The authors conclude that the study results suggest an effect of WF exposures on telomere length and related neurodegeneration markers. They recommend future studies that specifically focus on the brain and on the timing of the response after exposure to WF.

4.3 Mechanistic/cell/*In vitro*

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

Aksu et al. (2019) evaluated the genotoxic effects of exposures to welding fumes in 48 welders and 48 control subjects. To assess DNA damage, the authors used the comet assay for whole blood and lymphocyte samples, and the micronucleus assay for buccal epithelial cells collected for each subject. In addition, the authors measured blood levels of chromium (Cr), manganese (Mn), nickel (Ni), copper (Cu), arsenic (As), cadmium (Cd), and lead (Pb) using Inductively Coupled Plasma-Mass Spectrometer (ICP-MS). The authors reported that compared to controls, welders had significantly higher DNA damage in all collected samples (i.e., blood, lymphocytes, and buccal cells). They also found higher blood levels of Cr, Cu, Cd, Ni and Pb levels in welders compared to controls. The authors concluded that welding fumes had the potential to cause genotoxicity and recommended more extensive epidemiological studies to assess health risks of welders.

Amrani et al. (2019) conducted a cross-sectional study in a group of Algerian welders to assess whether there were correlations between exposures to metals in welding fume and three circulating miRNAs (miR-21, miR-146a and miR-155), which are markers of renal function injury. The authors surveyed workers to obtain demographic and work history. Blood and urine levels of metals were determined using Inductively coupled plasma mass spectrometry (ICP-MS), and miRNAs studied were quantified using PCR. Simple and multiple regression analyses were conducted to determine associations between miRNAs and internal metals concentrations. The authors reported that results from analyses that adjusted for age, body mass index, smoking status and length of employment as a welder showed significantly lower miR-21 in welders ($p = 0.017$) compared to controls. They also found significant associations between urinary chromium (Cr) and miR-21 and miR-155 ($p = 0.005$ and $p = 0.041$, respectively), and miR-146a and urinary nickel (Ni, $p = 0.019$) in adjusted regression models. Based on a multivariate analysis, duration of employment was the primary variable associated with the variation of miRNAs among welders. The authors concluded that metals in welding fume (primarily Cr and Ni) were associated with decreased expression of miRNAs and recommended further studies to confirm these findings.

Audureau et al. (2018) evaluated the potential toxicity of metal oxide nanoparticles (NP) that the authors identified from a previous study in welder's lungs. The authors used human macrophages exposed to these metal oxide NP (Fe2O3, Fe3O4, MnFe2O4 and CrOOH NP) to conduct an in-depth gene analysis. The authors reported expression of 2,164 genes in the exposed macrophages, using the analysis criteria |fold change| ≥1.5, $p \leq 0.001$. The authors then used Gene Ontology enrichment analysis to assess cellular content, biological processes and Swiss-Prot/Protein Information. The analysis results suggest that there are significant changes in the differential gene expression of the macrophages, and MnFe2O4 was associated with the largest induction of macrophage activation. The authors concluded that this novel analysis provides important insight for elucidating the mechanisms potentially associated with adverse effects of welding-related metal oxide NP and can be used to supplement known evidence of the processes underlying the toxicity of NPs.

Kornberg et al. (2019) evaluated the genotoxicity of iron oxide nanoparticles (IONP) and whether modifications to the particles such as an amorphous silica coating would reduce toxicity (i.e., the coating reduces solubility and prevents direct contact with cells). The authors exposed human bronchial epithelial cells (Beas-2B) to 0.6 μg/cm^2 of the IONP (nFe2O3) and the coated IONP (SiO2-nFe2O3) or gas metal arc mild steel welding fumes (GMA-MS, ~0.58 μg/cm^2, composed of about 80% iron/iron oxide) for 6.5 months. They observed time-dependent neoplastic-like cell transformation (e.g., cell proliferation and attachment-independent colony formation) in the nFe2O3 and GMA-MS exposed cells along with decreases in intracellular iron, insignificant changes in reactive oxygen species (ROS) production, and DNA damage. In contrast, there were no neoplastic or other changes observed in cells exposed to the silica-coated iron oxide particles (SiO2-nFe2O3). The authors concluded that the study results indicate the potential for nFe2O3-containg particles toxicity after prolonged exposures and that the use of an amorphous silica coating would be an option to reduce toxicity.

McCarrick et al. (2019) evaluated the toxicity of welding fume particles generated by active gas shielded metal arc welding (GMAW) of chromium-containing stainless steel to determine how different welding conditions influence the particle characteristics and any associated toxicity. The authors assessed the following toxicity endpoints: generation of reactive oxygen species (ROS);cytotoxicity; genotoxicity and activation of ToxTracker reporter cell lines. The authors reported that the primary determinant of toxicity was the filler material. They observed that particles from welding with a tested flux-cored wire (FCW) were more cytotoxic, generated more ROS, produced more DNA damage, and activated reporter cell lines, compared to welding with solid wire or metal-cored wire (MCW). Furthermore, the FCW welding fume was found to be the most soluble and generated more hexavalent chromium and manganese compared to welding fumes from other wires. The authors concluded that solubility may play a key role in determining the toxicity of welding fume particles.

Rana et al. (2019) used a quantitative framework to determine how welding fume affects gene expression, which in turn may play a role in the development of respiratory system diseases (RSD). Datasets containing tissues exposed to welding fume and tissues affected by chronic bronchitis, asthma, pulmonary edema, and lung cancer were identified and used to analyze gene expression microarray data. Disease-gene association networks were used to determine whether the tissues had genes in common related to signalling abnormalities or different pathways that lead to disease. The authors reported that there were 34, 27, 50 and 26 genes from the chronic bronchitis, asthma, pulmonary edema, and lung cancer tissues that also had altered gene expression in the welding fume tissue. They concluded that the differentially expressed genes analysis indicated notable relationships between welding fume and the development of several respiratory system diseases, and that these relationships could offer key insight into the causes of RSD in welders.

Sarkar et al. (2019) assessed whether exposure to divalent manganese (Mn2+) can produce neurotoxicity via increased inflammation. The authors exposed activated mouse microglial cells to Mn2+ and measured various inflammatory markers associated with the multiprotein, NLRP3 which is responsible for mediating neuroinflammation. They reported cells exposed to Mn2+ had significantly increased NLRP3 as well as other inflammation-related effects such as caspase-1 cleavage and presence of the inflammatory cytokine interleukin-1β (IL-1β). The authors found that these effects were consistent with findings in mice exposed to Mn^{2+} as well as welders exposed to manganese-containing fumes. The authors concluded that all together, the data may indicate that Mn^{2+} exposure could produce neurotoxicity by amplifying the NLRP3 inflammasome signalling.

Su et al. (2019) evaluated the role of oxidative stress induced by heavy metal exposures in welders. In 174 nonsmoking male welders in a shipyard , the authors collected urine samples to obtain internal doses of chromium (Cr), nickel (Ni), cadmium (Cd), and lead (Pb) as well as 8-hydroxy-2'-deoxyguanosine (8-OHdG), a marker of oxidative damage. Multiple regression was used to assess the relationship between the multiple heavy metals and oxidative damage. The authors reported welders had higher geometric mean urinary concentrations of Cr, Ni, Cd, and Pb than controls. In adjusted models, both urinary Cr and Ni were significantly associated with urinary 8-OHdG levels (Ln Cr: $\beta = 0.33$, 95%C.I. = 0.16-0.49; Ln Ni: $\beta = 0.27$, 95%C.I. = 0.12-0.43). The authors concluded that there was evidence of potential oxidative DNA damage in shipyard welders exposed to fumes containing Cr and Ni, and noted that respirators did not reduce metals exposures or potential oxidative damage. They recommended a further hazard evaluation be conducted.

4.4 Reviews

We identified four reviews of welding exposure and health effects.

Awan et al. (2018) conducted a systematic review of the occupational exposure risks associated with oral and pharyngeal cancers (OPC), which represent the seventh most common and leading cause of cancer worldwide. The authors conducted a search of various databases including PubMed, MEDLINE, EMBASE, and ISI Web of Science between January 1995 and July 2016 using topic-related keywords. After exclusion of Letters to the Editor, reviews, case reports, and unpublished articles, fourteen relevant published articles were included. The authors found that most of the studies were based in Europe and used a case-control study design. They reported that study results identified significant associations between OPC and exposures to formaldehyde, wood dust, coal dust, asbestos, and welding fumes. The authors concluded that there is suggestive evidence that several potential occupational carcinogens may be associated with development OPC, particularly cancer of the pharynx. However, the confidence in the limited evidence would be increased with more well-designed studies.

Leso et al. (2019) conducted a systematic review of possible epigenetic changes (heritable genetic changes) associated with welding fume exposures. The authors did a search of various databased Pubmed, Scopus, and ISI Web of Knowledge databases. The outcomes that were reported for epigenetic changes included DNA methylation in genes responsible for cardiac function and coagulation, regulation of energy-generation/redox-signalling, and inflammation. They noted, however, that the evidence was limited, and results were uncertain because most studies were cross-sectional, lacked quantitative exposure measurements, and there was a large number of outcomes investigated. Thus, the authors concluded that there was not enough evidence to conclude that there is a causal relationship between welding fume exposures and epigenetic changes. More studies are needed to identify possible markers, assess dose-response, and elucidate molecular mechanisms.

Yatera et al. (2018) evaluated studies of inhalation to hexavalent chromium (Cr VI)-containing particles and fumes and cancers of the lung, nose and nasal sinuses, especially in certain occupational environments. Occupations where workers can be exposed to Cr(VI)-containing particles and fumes include chromium production, plating, welding, electroplating, jobs involving contact with certain pigments and paints. The authors also summarized epidemiological studies that evaluated associations between lung, nose, and nasal cavity cancer mortality and exposure to Cr(VI), noting positive associations. In addition, the authors reported on studies that nasal symptoms, such as nasal irritation, ulceration and perforation of the nasal septum, nasal turbinate engorgement and hypertrophy, as key indicators for early diagnosis of these cancers in workers exposed to Cr(VI). The authors stressed that occupational exposure to Cr(VI) remains a concern and urged appropriate protection for workers in the relevant occupations.

The review by Falcone et al. (2019) focused on skin cancer risk in welders. The authors noted that ultraviolet radiation from welding was classified as a carcinogen in humans by IARC based on evidence of ocular melanoma from exposure to UVR. The authors also reviewed the associations between full spectrum UVR from the welding arc and an increased risk of developing skin cancer.

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