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HEALTH EFFECTS FROM WELDING EXPOSURES:
2016 LITERATURE UPDATE

RAMBOLL ENVIRON

CONTENTS

ACRONYMS AND ABBREVIATIONS

8-iso-PGF2α	8-isoprostane
8-OHdG	8-hydroxy-2'-deoxyguanosine
AC	Acceleration capacity
ACGIH	American Conference of Governmental Industrial Hygienists
AOR	Artificial optic radiation
Ar	Argon
AWS	American Welding Society
BG	Basal ganglia
CFQ	Cognitive failures questionnaire
CI	Confidence interval
cm	centimetre
CN	Caudate nucleus
CO_2	Carbon dioxide
Cr	Chromium
CRP	C-reactive protein
Cr VI	Hexavalent chromium
CT	Computed tomography
Cu	Copper
DC	Deceleration capacity
EBC	Exhaled breath condensate
EMFs	Electromagnetic fields
ENMs	Engineered nanomaterials
epub	Electronic publication
FCAW	Flux-cored arc welding
Fe	Iron
FEF_{50}	Forced expiratory flow at 50% lung volume
FEF_{75}	Forced expiratory flow at 75% lung volume
FEV_1	Forced expiratory volume in 1 second
fMRI	functional magnetic resonance imaging
fpm	feet per minute
FVC	Forced vital capacity
GMAW	Gas metal arc welding
GMD	Geometric mean diameter
GTAW	Gas tungsten arc welding
HLB	High level baseline
HR	Hazard ratio
HRV	Heart rate variability
ICARE	Investigation of occupational and environmental causes of respiratory cancers
IL	Interleukin
LSDA	Lung deposited surface area
LT	Leukotriene
MDG-ICP-MS	Microdroplet generation inductively coupled plasma mass spectrometry
MeSH	Medical Subject Headings
mm	millimetre

MMP-9	Immunoreactive matrix metalloproteinase
Mn	Manganese
MnB	Manganese concentrations in blood
MS-WF	Mild steel welding fumes
mtDNA	Mitochondrial DNA
NALF	Nasal lavage fluid
Ni	Nickel
NIOSH	National Institute for Occupational Safety and Health
nm	nanometer
NO	Nitric oxide
OR	Odds ratio
PD	Parkinson's disease
PEF	peak expiratory flow or the maximum flow after exhalation
PI	Pallidal index
PM	Particulate matter
$PM_{2.5}$	Particulate matter less than 2.5 micrometers in diameter
PMID	PubMed identification number
PPE	Personal protective equipment
PVC	Polyvinyl chloride
R1	Relaxation rate
R2	Transverse relaxation rate
RBD	Rapid eye movement sleep behavior disorder
SAA	Serum amyloid A (SAA)
Scfm	standard cubic feet per minute
SF-36	36-item short-form health survey
SMAW	Shielded metal arc welding
SVE	Supra ventricular ectopy
T1WI	T1-weighted intensity
TE	Transposable elements
TGCT	Testicular germ cell tumor
TIG	Tungsten inert gas
TIMP-1	Tissue inhibitor of metalloproteinase-1
UFP	Ultrafine particles
UPDRS	Unified Parkinson's Disease Rating Scale
UPDRS3	Unified Parkinson's Disease Rating Scale subsection 3
UV	Ultraviolet
UVR	Ultraviolet radiation
VA	Visual acuity
VE	Ventricular ectopy
WCST	Wisconsin Card Sorting Task

1 INTRODUCTION

On behalf of the American Welding Society (AWS), Ramboll Environ conducted a comprehensive literature search and summary of studies related to the health effects of welding. In this update, we included literature published in 2016 (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, Toxline, and SCOPUS databases for articles relevant to welding exposures and health effects as described below.

2.1 Search Strategy

1. To capture all the potentially relevant literature, the initial keyword searches included the word "welding" or "welders."
2. To narrow the search and identify specific articles related to "health," specific terms and their variants were applied, as necessary, in conjunction with the general terms welding and welders. Search terms included: toxicology, risk, epidemiology, morbidity, mortality, inhalation, cancer, lung(s), lung inflammation, respiratory, cardiovascular, bronchitis, Parkinson's, asthma, neurological/neurotoxicity, metal fume fever, and occupational lung disease.
3. To narrow the general results and identify specific articles related to "exposure," specific terms and their variants were applied, as appropriate, in conjunction with the general terms welding and welders. The search terms included: exposure monitoring, exposure characterization, occupation, workers, workplace, laborers, cohort, dose, particle characterization, inhalable, respirable, and sampling.
4. Literature searches were limited to documents published in 2016 (either electronically (epubs) or in print. Articles included in previous reviews were excluded from this review.

2.2 Database Searches

2.2.1 PubMed

An initial search for "welders" or "welding" in all fields or in Medical Subject Headings (MeSH) terms was conducted. Results were filtered for the year 2016, yielding 527 citations. The search results were then filtered for citations relevant to health and exposure (as described in Section 2.1). Any citations that were excluded were reviewed to ensure that no relevant articles were excluded. Any additional non-relevant articles (*e.g.*, materials processing, nano-synthesis, prosthetics, and chemical structure or analysis) were removed at this stage.

2.2.2 SCOPUS

The SCOPUS database was queried for articles containing "welders" or "welding" in the title, abstract, or keywords that were published in 2016, and the results of that query (n=279) were filtered using the search terms that included the health and exposure terms described in Section 2.1. Non-relevant articles (*e.g.* engineering/material science, mathematics, physics, astronomy, energy, computer science, dentistry, chemistry, earth/planetary sciences, business management and accounting, nursing) were removed at this stage.

The results of the PubMed and Scopus searches overlapped significantly. We identified 108 duplicates that were removed.

2.3 Literature Review

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

- Particle characterization and exposure studies
- Epidemiology and controlled human exposure studies
- Animal studies
- Mechanistic/cell/*in vitro* studies
- Reviews

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

Table 2.1. Breakdown of Abstracts Reviewed by Study Category

Study Category	**Totals from PubMed and SCOPUS**
Particle characterization and exposure	15
Epidemiology and controlled human exposure	42
Animal	2
Mechanistic/cell/*in vitro*	1
Reviews	9
Overall Total	**69**

3 EXPOSURE STUDIES

We identified 15 exposure-related publications from 2016 (*i.e.*, particle characterization and exposure). Several studies were published online in 2016 (*i.e.*, 2016 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 2015) were excluded. A brief summary of the exposure abstracts is provided below for all the relevant studies.

Ali *et al.* (2016 PMID: 26186033) evaluated the interaction between proteins in the nasal mucosa and particles and how these interactions are influenced by particle size. The particles studied included particles generated from welding because these particles include agglomerated particles that form from nanoparticles. The authors added nasal mucosa to particles and determined the size of the agglomerates that were formed. They found that the size of the agglomerates (i.e., the protein bound particles) differed depending on the type of particle and hypothesized that surface area was related to the binding capacity of the particles. The authors also reported that the protein content of the agglomerates also differed and they noted the importance of understanding protein function after particle binding to understand the potential for particle toxicity. The authors concluded that their findings underscore the need to use particles generated from real working environments when studying the potential toxicity of particles.

Cena *et al.* (2016 PMID: 27559198) measured first-hand (30 cm from the source) and second-hand (200 cm from the source) exposures to gas metal arc welding fumes generated from mild steel plates during 1-minute welding runs and at 5-minute intervals following cessation of the welding process. Number size distributions, particle mass distributions, and total mass concentrations were also measured. A micro-orifice uniform deposition impactor was used to measure particle size distributions and total mass concentrations were collected using polytetrafluoroethylene filters. In addition, membrane filters were used for samples to assess morphology using an electron microscopy. The average mass concentrations measured near the arc and at a distance were 45 mg/m^3 and 9 mg/m^3, respectively. In addition, mass concentrations of second-hand exposure samples decreased by 31% after 5 minutes and an additional 13% after 10 minutes. Exposure measurements taken during the welding process suggested particle number and mass distributions were similar at both distances. However, particles smaller than 50 nm and larger than 3 μm were found at higher concentrations near the arc. With regard to number size concentrations, the authors reported that during active welding second-hand exposures may be as high as exposers experienced first-hand.

Dahal *et al.* (2016 PMID: NA) highlighted the health implications from exposure to welding fumes and discussed the importance of ventilation in the workplace. The authors noted that exposure controls require an accurate estimation of fume exposure concentrations in the welder's breathing zone, which is often difficult to measure. Dahal *et al.* (2016) proposed using predicted carbon dioxide concentrations to indirectly predict concentrations of welding fumes. This methods is based on the idea that particles of sufficiently small size follow the same diffusion pattern as gases. The authors concluded this method has the potential to aid in predicting welding fume concentrations in the breathing zone of welders.

Geiss *et al.* (2016 PMID: NA) measured lung deposited surface area (LSDA) concentrations of ultrafine particles (UFP) in various settings including a welding workshop. A handheld online-monitor was used to evaluate concentrations. Depending on the type of micro-environment, the ongoing activities or the material investigated in the chamber tests, large differences were observed in terms of measured LDSA concentrations, some exceeding up to 1,000 times that of the baseline concentration detected before activities initiated. In some of the investigated environments LDSA concentrations were measured for the first time. The data might therefore serve as reference for future studies. The handheld instrument used to measure this data worked well both for stationary measurements as well as for personal monitoring and proved to be a good alternative to bulkier benchtop instruments.

Gschwind *et al.* (2016 PMID: NA) evaluated methodologies for preserving the integrity of exhaled breath condensate (EBC) samples obtained from welders to measure inhaled nanoparticles. Two preservation strategies were evaluated, a flash-freezing method and a method where the EBC is kept at room temperature. The samples were tested using microdroplet generation inductively coupled plasma mass spectrometry (MDG-ICP-MS) and electron microscopy. The authors found that because welding fume nanoparticles can degrade quickly the freezing method, which is easy, effective and inexpensive, should be used to preserve EBC for future characterization.

Jeong *et al.* (2016 PMID: 27340603) measured total and size-fractionated manganese concentrations from welding operations in shipbuilding work areas. The authors took 86 samples using closed-face cassette samplers (total mass) and 8-stage cascade impactors (size-selective mass) to obtain mass and size distributions. The results showed that about 67% of the samples had measured levels that exceed current American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit of 100 $\mu g/m^3$ for inhalable mass and about 91% of samples exceeded the ACGIH threshold limit of 20 $\mu g/m^3$ for respirable manganese. The total concentration measured using the cassette sampler was lower than that obtained using the impactor samplers.

Jorgensen *et al.* (2016 PMID: 27016529) investigated inhalation exposures in workers during rehabilitation of a subsea tunnel. Personal exposure sampling of the workers' breathing zone was conducted to determine the exposure, to ultrafine particles (concentration and particle size distribution). Background air sampling was also performed. Participants included workers who were involved in: the operation of the slipforming machine, operations related to finishing the verge, and welding the PVC membrane. Authors reported average values of ultrafine particles ranged from 6.26×10^5 - 3.34×10^6 particles/cm^3, with workers involved in vertical PVC welding experienced the highest particle exposures. In addition, horizontal welding produced the highest maximum peak exposure, 8.1×10^7 particles/cm^3. Particles were present in the tunnel, as a background exposure, at concentrations of 4.0×10^4 - 3.1×10^5 particles/cm^3. At peak particle concentrations, the diameter of the particles ranged from 10.8 nm during horizontal PVC welding and breaks to 60.4 nm while finishing the verge. The authors concluded exposure to ultrafine particles was very high for workers performing vertical PVC welding compared to workers involved in other work tasks. Furthermore, they note the importance of measuring particle concentrations in the breathing zone of the worker compared to at a stationary work area. In addition, more data on particle size distributions in working environments is needed.

Keane *et al.* (2016 PMID: 26267301) investigated various welding processes in order to identify the best process to reduce workplace exposures and costs. The authors assessed the fume generation rates, fume generation rates per gram of electrode consumed, and emission rates for hexavalent chromium (Cr VI) of 9 gas metal arc welding (GMAW) processes for stainless steel. Shielded metal arc (SMAW) welding, the most commonly used welding process, was also studied. Additionally, emissions per unit length of weld, and costs (labor plus consumables) were estimated for manganese, nickel, chromium and iron.

The welding processes evaluated included Surface Tension Transfer, Regulated Metal Deposition, Cold Metal Transfer, short-circuit, axial spray, and pulsed spray modes. The authors report a range of fume emission factors for the processes evaluated. GMAW pulsed-spray mode produced the lowest fume emission rate (0.2 mg/g), while SMAW produced the highest fume emission rate (8 mg fume/g electrode). Emission rates for Cr VI, manganese, and nickel, ranged from 50-7800 μg/min, 50-300 μg/g, and 4-140 μg/g, respectively. Generation rates per gram electrode ranged from 1-270 μg/g for Cr VI, and 13-330 μg/g for elemental Cr, respectively. Furthermore, GMAW processes (pulsed spray) cost less than SMAW, while equipment costs for some GMAW processes appear to be considerably higher than for SMAW. The authors concluded that all GMAW processes significantly reduced exposure to fume, Cr VI, manganese and costs compared to SMAW.

Miettinen *et al.* (2016 PMID: 27390355) investigated the physicochemical properties of airborne particles in a workshop with gas tungsten arc welding (GTAW) as the primary welding method. Air samples were collected from welders' breathing zone (personal sample), as well as in the middle of the workshop (area sample), and analyzed for particle number concentration, number size distribution, particle morphology, and chemical composition. Condensation particle counters and electrical mobility particle sizers, were used to measure particle number concentration and size distributions, respectively. Particle morphology and chemical composition were assessed using scanning and transmission electron microscopy and energy-dispersive X-ray spectroscopy. The number particle distribution was unimodal in area workshop samples (geometric mean diameter (GMD = 46 nm), while the distribution was multimodal in the personal breathing zone samples (GMD = 10-30 nm). The breathing zone samples consisted of two different types of agglomerates. The first type was made up of primary particles of iron oxide (size up to 40 nm) and variable amounts of chromium (Cr), manganese (Mn), and nickel (Ni) replacing iron in the structure. The second type was made up of very small primary particles and was composed of a higher proportion of Ni compared to the proportion of (Cr + Mn) in the first type of particle. Overall, the authors presented a unique characterization of different welding particles (area and personal) with a distinct distribution of Ni.

Nakashima *et al.* (2016 PMID: 26632121) assessed the hazards presented by ultraviolet radiation (UVR) emitted in gas tungsten arc welding (GTAW) of aluminum alloys. The authors determined hazard by comparing their findings with the effective irradiance levels as defined by the American Conference of Governmental Industrial Hygienists (ACGIH) guidelines. The authors found that the effective irradiances, measured 500 mm from the welding arc, were in the range of 0.10-0.91 mW/cm^2, which corresponds to a maximum allowable exposure time of 3.3-33 seconds/day. These data suggest unprotected exposure to UVR emitted from GTAW of aluminium alloys could be hazardous. Additionally, UVR exposures exceeded guidelines at higher welding currents, when magnesium was included in the welding materials, or depending on the direction of emission from the arc.

Nakashima *et al.* (2016 PMID: 27488036) evaluated the level of ultraviolet radiation (UVR) emitted during gas metal arc welding (GMAW) of mild steel. This study assessed pulsed welding currents and a non-pulsed welding currents, and shielding gases containing either 80% argon (Ar) + 20% carbon dioxide (CO_2) or 100% CO_2. UVR hazard was determined based on the effective irradiance limits as defined in the American Conference of Governmental Industrial Hygienists (ACGIH) guidelines. Analyses of measurements taken 500 mm from the arc revealed that the effective irradiance was in the range of 0.51-12.9 mW/cm^2, for which the maximum allowable exposure times was 0.23-5.9 s/day. The authors concluded that UVR exposure exceeds the ACGIH guidelines during the GMAW of mild steel at higher welding currents, when 80% Ar + 20% CO_2 is used as a shielding gas at higher welding currents, for pulsed welding currents, or when metal transfer is the spray type. Overall, the authors concluded that unprotected exposure to UVR emitted by the GMAW of mild steel could be hazardous.

Rahmani *et al.* (2016 PMID: 27621798) examined the efficacy of four types of protective eyewear (used for welding) in meeting the allowable transmission values of harmful rays set by the American National Standard Institute. The protectors tested included Type 1- Uvex futura (Shade No. 4; Germany), Type 2- Parsoptic (Shade No. 5; Iran), Type 3 (Shade No. 7; no identified company and country), and Type 4-unnamed (Shade No. 8; China). All protectors tested provided good blocking properties for near and far UV and blue light, but only Type 1 (Uvex) eyewear could sufficiently protect from infrared spectra. The authors suggest further research to identify which eyewear can provide the best protection against hazards.

Sousan *et al.* (2016 PMID: NA) assessed the effectiveness of low-cost sensors for measuring mass concentrations of aerosols in occupation settings. One of four tested aerosols was welding fume and three types of sensors were used (a DC1700 from Dylos and two commodity sensors from Sharp) together with an aerosol photometer, reference instruments, and testing concentrations up to 6,500 $\mu g/m^3$. The authors reported differences in the precision of the sensors with higher precision for the DC1700 (CV = 7.4%) than the two sharp devices (CV = 25% and 17%) likely due to differences in manufacturer calibration. Of note the authors reported that aerosol type strongly influenced sensor response. Overall, the authors concluded that the low-cost sensors were useful for estimating aerosol concentrations in occupational settings, but on-site calibration was needed to convert the sensor output to mass concentration.

Yarahmadi *et al.* (2016 PMID: NA) tested the effectiveness of an exhaust system for reducing exposures to particles in welders. The proto-type exhaust system was tested using ACGIH standard methodology, and the NIOSH 7200 method was used to measure the total particle concentrations. The duct velocity averaged 6,296.1 ± 92.50 fpm and flow rate averaged 34.06 ± 0/50 scfm. Total particle concentrations in the off and on positions of the vent were 75 ± 7 mg/m^3 and 16.7 ± 4 mg/m^3, respectively. The authors concluded that local exhaust ventilation as reported significantly reduced total particle concentrations.

Yarmohammadi *et al.* (2016 PMID: NA) evaluated welding technicians' exposure to welding fumes and gases in workshops within the Nahav and Hamadan City of Iran. Authors measured the density of welding fumes found in the respiratory system of welders using NIOSH methods. Results indicated that 12 out of 15 samples taken exceeded applicable NIOSH and ACGIH standards. The authors note that these results highlight the importance of ventilation systems, routine check-ups, alternative processes, and personal protective equipment to reduce exposures to welding fumes.

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 (12 studies), respiratory effects (7 studies), cardiovascular effects (7 studies), cancer (3 studies), ocular (4 studies), reproductive (2 studies), systemic (3 studies), and multiple health effects (4 studies). Summaries of these studies are provided below.

4.1.1 Neurological Effects

Al-Lozi *et al.* (2017 PMID: 27862095) examined the relationship between cognitive control and chronic occupational exposure to manganese (Mn). Cognitive control refers to the ability to monitor and regulate continuous cognitive demands. In a group of 95 welders with varying levels of welding fume-related Mn exposure (median of 15.5 years), the authors found a significant inverse relationship between exposure to welding fume and overall performance on cognitive control tasks ($p = 0.009$) that was more significant in the Two-Back and Letter Number Sequencing tests used to assess working memory ($p = 0.02$). The authors concluded that long-term exposures to Mn could contribute to reduced working memory performance.

Casjens *et al.* (2017 PMID: 27865828) evaluated the effect of former occupational manganese (Mn) exposure on sense of smell in an elderly German population. Data were collected on participants' occupational history involving job tasks with Mn exposure. Their ability to identify odors was determined using Sniffin' sticks, as a part of the Heinz Nixdorf Recall Study. Data were collected on 354 men that had reported working in jobs with potential Mn exposure. A variety of exposure metrics were used to evaluate the effect of Mn on sense of smell, including job tasks, cumulative Mn exposure, and Mn measured in archived blood samples (MnB). Authors reported an association between having ever worked as a welder, and better sense of smell, when compared to unexposed blue-collar workers. Impaired odor detection was not associated with Mn exposure concentrations above 185 mug/m^3 years or greater than/equal to 15 mug/L blood Mn. Based on their findings, the authors concluded that there was no evidence of an association between former occupational Mn exposure, at relatively low levels, and impaired sense of smell.

Jacobs *et al.* (2016 PMID: 26889635) identified risk factors for Parkinson's disease (PD) in cases with or without rapid eye movement sleep behavior disorder (RBD), which is a strong indicator of the disease. Risk factors for PD including demographic, medical, environmental, and lifestyle variables were assessed *via* questionnaire for 189 PD patients with or without associated confirmed RBD. A risk profile was calculated for patients with or without RBD, adjusting for potentially confounding variables. The authors reported that PD patients with RBD were more likely to have been a welder (OR = 3.11, 95% CI: 1.05-9.223), and a regular smoker (OR = 1.96, 95% CI: 1.04-3.68). No differences were observed for use of caffeine or alcohol, other occupations, pesticide exposure, rural living, or well water use. The authors concluded that the RBD subtype of PD may have a specific set of associated risk factors.

Lee *et al.* (2016 PMID: 27466214) investigated the association between exposures to manganese (Mn), iron (Fe), and copper (Cu) in welders [including blood metal levels and estimates of metals in the basal ganglia (BG)] and the microstructural integrity of the BG in asymptomatic welders. Subjects included 43 welders and 31 (age and gender-matched) controls with no welding history. Welder occupational exposures were determined using a questionnaire to estimate short-term (welding hours and cumulative exposures in the past 90 days) and long-term (total years of welding and cumulative lifetime exposures). Whole blood metal levels were measured and brain MRIs were used to estimate Mn and Fe accumulation in the BG (using pallidal index and RI and R2). Diffusion tensor imaging was used to assess BG microstructural changes associated with exposures measurements. The authors reported microstructural changes in one region of the BG (the globus pallidus) associated with long-term Mn exposures, but not short-term exposures. No associations were observed for Cu or Fe exposures. The authors concluded that these microstructural changes could be used as a biomarker for neurotoxicity associated with low-level Mn exposures in asymptomatic welders.

Lee *et al.* (2017 PMID: 27871916) examined the relationship between occupational exposure to manganese (Mn) and iron (Fe), and neurobehavioral and brain imaging changes in participants with or without a history of welding exposure. Questionnaires were administered to 46 welders and 31 controls to obtain information on recent and life-time welding exposures. Brain MRI indices were assessed to estimate Mn and Fe concentrations in portions of the brain including the basal ganglia [caudate nucleus (CN), putamen, and globus pallidus], amygdala, and hippocampus. Behavioral differences between welders and controls were examined though various neuropsychological tests. The authors reported welders had significantly higher R2 (estimate of Mn and Fe levels) in the CN and lower performance on the Phonemic Fluency test compared to controls. The authors concluded that neurobehavioral performance in asymptomatic welders was worse than for controls with no welding exposures, which may be associated with higher Fe accumulation in the CN.

Lee *et al.* (2016 PMID: 26769335) examined the differences in iron (Fe) accumulation in the basal ganglia of 42 welders and 29 controls using transverse relaxation rates [R2* (1/T2*)] to estimate Fe accumulation. Occupational exposures to Fe were estimated from data collected *via* questionnaire. In addition, blood samples were collected and brain imaging was performed. Results showed that welders had significantly higher Fe exposures and higher blood Fe levels, compared to controls. After controlling for various confounders including age and respirator use, welders had significantly higher R2* levels in the caudate nucleus, which was also positively associated with Fe concentration in the blood. The authors concluded that the higher R2* levels in the caudate nucleus of welders indicated Fe accumulation in this area and recommended further research to determine if there are any related neurobehavioral effects.

Lewis *et al.* (2016 PMID: NA) investigated the association between relaxation rate (R1) and short-term manganese (Mn) exposures in 29 welders at baseline and after 12 months. R1 is increasingly being used as a biological marker of Mn accumulation in the brain and may be a useful indicator of potential neurotoxicity. The authors used questionnaires to estimate short-term exposures (welding hours 90 day prior to the study visit). The authors also measured blood Mn levels, the pallidal index (PI; globus pallidus T1-weighted intensity (T1WI)/frontal white matter T1WI), and R1 values in brain regions of interest at each visit. The authors reported that short-term welding exposures were associated with R1 values in various regions of the brain including the putamen ($r = 0.541$, $p = 0.005$), caudate ($R = 0.453$, $p = 0.023$), globus pallidus ($R = 0.430$, $p = 0.032$), amygdala ($R = 0.461$, $p = 0.020$), and hippocampus ($R = 0.447$, $p = 0.025$), but not the PI. The authors concluded that R1 may be a useful indicator of short-term Mn exposures compared to more traditional blood lead Mn levels or PI.

Lewis *et al.* (2016 PMID: 27373673) evaluated basal ganglia (BG) dysfunction in 20 asymptomatic right-handed welders and 13 matched controls. They used a newly developed method called multi-digit synergies that quantifies the stability of motor action as an indicator of BG dysfunction. The BG is most susceptible to toxicity from exposure to metals such as manganese (Mn) and iron (Fe). The welders performed single- and multi-finger pressing tasks with right and left hands and the synergy index stabilizing force and anticipatory synergy adjustment were computed. Authors also used the Unified Parkinson's Disease Rating Scale (UPDRS) and Grooved Pegboard scores to assess gross and fine motor dysfunction, respectively. In addition, high-resolution (3T) T1-weighted, T2-weighted, T1 mapping MRIs were conducted to determine Mn accumulation [pallidal index (PI), R1(1/T1)], Fe accumulation [R2*(1/T2*)], and structural changes in the BG [fractional anisotropy and mean diffusivity], and these estimates were compared between welders and controls and correlated with testing scores. The authors reported no differences in the UPDRS and Grooved Pegboard test scores between controls and welders. The synergy index was significantly different in welders compared to controls with the left hand but not the right hand. Anticipatory synergy adjustment was not different between the groups. In welders, higher synergy indices were correlated with more structural changes in the left globus pallidus of the BG, but were not correlated with PI, R1, or R2*. The authors concluded that the multi-digit synergy methodology could serve as an adequate preclinical marker for BG dysfunction in asymptomatic welders that could be at risk for neurodegenerative diseases.

Racette *et al.* (2017 PMID: 28031394) examined whether the phenotype for Parkinsonism is progressive and whether this progression is associated with the level of exposure to manganese (Mn)-containing welding fume. Parkinsonism is any condition that causes a combination of the movement abnormalities seen in Parkinson's disease. A total of 886 American welding-exposed workers were examined by a movement disorders specialist, including 398 workers with a follow-up examination up to 9.9 years later. Progression of Parkinsonism was defined based on annual change in Unified Parkinson Disease Rating Scale motor subsection part 3 (UPDRS3). Cumulative exposure to Mn was estimated using detailed work histories. A positive association was found for progression of Parkinsonism and cumulative Mn exposure. Data analyses revealed an annual change in UPDRS3 of 0.24 for each mg Mn/m^3-year of exposure. Progression of symptoms including upper limb bradykinesia, upper and lower limb rigidity, and impairment of speech and facial expression, were strongly associated with exposure. The association between exposure and effect was greater in welders who participated in flux core arc welding in a confined space or workers whose baseline examination was within 5 years of their first welding exposure. Overall, the authors presented evidence of a dose-response relationship between exposure to Mn-containing welding fume and the progression of Parkinsonism, particularly noting upper limb bradykinesia, limb rigidity, and impairment of speech and facial expression.

Rahmani *et al.* (2016 PMID: 27093360) assessed whether exposure to welding fumes could affect cognitive health and health-related quality of life. Sixty five participants were examined, with 40 welders and 25 welding assistants representing the exposed group, and 44 office workers representing the unexposed group. Air monitoring was conducted in all participants' workplaces. Cognitive and overall health were assessed via questionnaires including the Cognitive Failures Questionnaire (CFQ) and the 36-item Short Form Health Survey (SF-36). Results showed that welders were exposed to higher concentrations of airborne metals than office workers, except for aluminum and chromium. On average, welders scored higher on the CFQ (26.42) compared to welding assistants (22.68) and the unexposed group (21.38), but results were not statistically significantly different. Additionally, welders scored significantly lower on the SF-36 than the other groups. Furthermore, a significant association was found for CFQ scores and peak nickel concentrations for welders. In conclusion, the authors noted that cognitive and overall health was not strongly associated with measures of welding fume exposure, and suggested more research should be done to identify other influencing factors.

Seo *et al.* (2016 PMID: 27208889) investigated the motor and cognitive health effects associated with chronic exposure to manganese (Mn) by comparing the executive functioning in welders to healthy controls. Executive functioning refers to cognitive skills involving mental control and self-regulation. Participants were assessed following various cognitive tests, including two versions of the Wisconsin Card Sorting Task (WCST) and a task that established a high-level baseline (HLB) condition. Card Sorting Test and Word-Color Test were also employed to assess executive performance. Functional magnetic resonance imaging (fMRI) scans were also performed. In healthy controls, there was greater neural activation of the bilateral superior-frontal cortex, right-inferior parietal cortex, and bilateral insula cortex compared to welders based on results from administration of the difficult version of the WCST and HLB task. The authors also found associations between brain activation and executive functioning using the Card Sorting Test and Word-Color Test. The authors concluded that under conditions of high cognitive demand, welders had altered processing related to executive function in the prefrontal cortex, and that welders also had less activation of the insula cortex compared to controls.

Sriopas *et al.* (2017 PMID: 27885242) investigated occupational noise-induced hearing loss in welders in an auto factory in Thailand. A total of 60 welders were randomly sampled from 180 workers in three factories. Data were collected using a face-to-face questionnaire and noise exposure levels were measured. The authors reported noise exposure levels of 86-90 dB (A) and a higher significantly increased risk of hearing loss in either ear. Prevalence of hearing loss in both ears was significantly increased by noise exposure levels higher than 90 dB (A). In addition, smoking history (10-pack-year) and employment duration exceeding 10 years significantly increased the prevalence of hearing loss in either ear. Overall, the authors recommended engineering or personal controls should be used to decrease noise exposure levels to 85 dB (A) or lower for 8 hours.

4.1.2 Respiratory Effects

Fell *et al.* (2016 PMID: 27365181) identified occupations and exposures associated with respiratory work disability. A self-administered questionnaire was used to gather data on a random sample of the general population in Telemark County, Norway. Participants, aged 16-50, answered questions regarding occupational exposure and respiratory work disability, such as 'have you ever had to change or leave your job because it affected your breathing?' Risks were calculated for cases and controls (approximately 50 per case). The authors reported that 247 respondents experienced respiratory symptoms that resulted in a change of their job, representing 1.7% of the sample. Welders were among the occupations with the highest proportion of people that had to change their job due to respiratory issues (OR = 5.2, 95% CI: 2.0-14). Other jobs included cooks, sheet metal workers, cleaners, hairdressers and agricultural laborers. The authors concluded that preventative measure should be implemented in occupations that resulted in a high rate of job change due to respiratory issues.

Khoor *et al.* (2016 PMID: 26997453) examined the correlation between exposures to hard metal and giant cell interstitial pneumonia, a rare lung disease that is thought to be an indicator of hard metal exposure. Researchers evaluated surgical pathology files of 3 lung transplants with diagnosed giant cell interstitial pneumonia, and reviewed the associated medical histories. In addition, mass spectrometry, energy-dispersive x-ray analysis, and human leukocyte antigen typing data were evaluated. One patient was a 58-year-old welder that received a double lung transplant, and had no reported exposure to hard metals or cobalt dust. Lung sample analyses revealed elevated levels of cobalt only in the welder, and no evidence of hard metals in the other patients. The authors concluded that giant cell interstitial pneumonia may not be limited to individuals with hard metal exposure.

Marongiu *et al.* (2016 PMID: 27030577) assessed the risk of pneumococcal infection in welders. Data were collected from January 2013 to December 2013 on 529 male workers exposed to welding fume in a large shipyard in the Middle East. The authors assessed the risk of respiratory symptoms including cough, phlegm, wheezing, shortness of breath and 'chest illness' associated with welding exposures. In addition, the authors reviewed 103,840 consultation records during 2000-2011 for 15,954 workers who were evaluated for respiratory infections. The authors reported that 13% of participants had respiratory symptoms during the winter. Overall, data showed that welders have 1.72 times the odds of experiencing respiratory symptoms compared to manual workers, with the odds increasing to 2.3 during winter months. Additionally, welders experienced 45% greater risk of consultation for respiratory infection than manual laborers. The authors concluded that welders may be more vulnerable to respiratory infection particularly in the winter months.

Raulf *et al.* (2016 PMID: 27924706) examined the relationship between exposures to welding fumes and upper respiratory tract inflammation. Exposure to inhalable welding fumes was measured from the breathing zones of 190 male welders (median age 40 years, 54.7% smokers and 32.9% atopic) that were part of the WELDOX study during a single workday. Air samples were analyzed for levels of chromium (Cr), nickel (Ni), manganese (Mn), and iron (Fe). Nasal lavage fluid (NALF) samples were also taken *via* nasal irrigation following the welders' workday and analyzed for metals of interest, the numbers of particles and various inflammatory biomarkers including total and differential cell counts, interleukin (IL)-8, leukotriene (LT) B4, 8-isoprostane (8-iso-PGF2α), tissue inhibitor of metalloproteinase-1 (TIMP-1), and immunoreactive matrix metalloproteinase (MMP)-9. The authors reported that metal concentrations in NALF samples were associated with concentrations of these metals in air samples. Moreover, increasing metal concentrations in NALF were associated with an increase in concentrations of total protein and other inflammatory biomarkers (IL-8, MMP-9, and TIMP-1). Although there was no significant association between metal concentrations in air and biomarkers of inflammation in nasal fluid samples, LTB4 and 8-iso PGF2α were elevated at higher concentrations of Cr or Ni in NALF, and to a lesser extent Fe in NALF. The authors concluded that metal concentrations in NALF were associated with inflammatory biomarkers noting that NALF sampling offers a non-invasive way to assess biomarkers of exposure and preclinical effects such as inflammation.

Skoczyńska *et al.* (2016 PMID: 27274987) retrospectively evaluated changes in lung function in copper miners based on their job. Participants included 225 operators, 188 welders, and 475 representatives of other jobs. Spirometry, a test used to assess lung function (the amount and speed of air inhaled or exhaled), was conducted at the beginning of employment and after 10, 20, and 25 years of work. Lung function testing included forced vital capacity (FVC), the amount of air which can be forcibly exhaled after a deep breath, and forced expiratory volume in 1 second (FEV_1), the amount of air exhaled in one second, and FEF_{75}, FEF_{50}, forced expiratory flow at 75% and 50% lung volume, respectively, and PEF, peak expiratory flow or the maximum flow after exhalation. Lung function decline as measured using FEV_1 or FVC was similar across all groups. Multiple linear regression analyses, however, showed an association between workplace and some lung function measurements. Specifically, welders had lower FEF_{75} compared to operators and miners as early as after 10 years of work. Additionally, results showed that smoking habits contributed to lower lung function in welders. The authors concluded that among underground copper miners, smoking welders are at increased risk of impaired lung function.

Sun *et al.* (2016 PMID: 25619320) reported a rare case of tracheobronchial foreign body in a welder without a history of allotriophagy (eating things that are not food) and foreign body aspiration. A chest computed tomography (CT) and mineralogical analysis, was used in the diagnosis and a flexible fiberoptic bronchoscope was used for removal of the foreign body. Chemical analyses showed that the composition of the foreign body was similar to residue collected in the garage where the patient worked. The authors concluded that this is an unusual case of the welding-related respiratory disease that is distinct from more common diseases for welders such as Welder's siderosis and broncholith.

Svanes *et al.* (2016 PMID: 27565179) investigated the relationship between paternal smoking and welding exposures prior to conception and their children's risk of asthma. A total of 24,168 parents provided information on smoking habits, occupations exposure to welding and metal fume and their offspring's asthma and hay fever before and after 10 years old. Non-allergic early-onset asthma was more common in children whose fathers smoked before conception, and the highest risk was observed for fathers that started smoking before 15 years old. The authors reported that paternal smoking and welding exposure were independently correlated with non-allergic asthma in the children. No association was found between asthma risk and paternal welding or smoking exposures after birth. The authors concluded that there was a correlation between paternal welding exposure and smoking and the risk of asthma in children, recommending further research.

4.1.3 Cardiovascular Effects

Byun *et al.* (2016 PMID: 27107129) assessed the association between exposures to metal-rich particulate matter (particles less than 2.5 micrometers in diameter [$PM_{2.5}$]) and mitochondrial DNA (mtDNA) methylation related to heart rate variability in 48 healthy male welders that were part of a boilermaker union (Boilermaker Union Local 29 in Quincy, Massachusetts). Damage to mtDNA *via* oxidative stress can cause mitochondrial dysfunction that has been implicated in human diseases including cardiovascular diseases. The authors measured blood mtDNA methylation in the mtDNA promoter (D-loop) and genes involved in ATP synthesis (MT-TF and MT-RNR1) by bisulfite pyrosequencing and collected personal and ambient $PM_{2.5}$ samples in the work environment. Personal mean $PM_{2.5}$ concentrations (0.38 mg/m^3) were higher than ambient (area) measurements (0.15 mg/m^3) ($P<0.001$). After adjusting for demographics, type of job, season, welding-work day, and experimental batch effect, the results showed that blood mtDNA methylation in the D-loop promoter was negatively associated with $PM_{2.5}$ levels, but not MT-TF and MT-RNR1 methylation. The interaction between $PM_{2.5}$ concentrations and mtDNA methylation in the D-loop promoter was also associated with markers of heart rate variability. The authors concluded that there was an inverse association between $PM_{2.5}$ exposure and mtDNA methylation and that this association we related to the adverse effects of $PM_{2.5}$ on heart rate variability.

Cavallari *et al.* (2016 PMID: 27052768) investigated the relationship between personal exposure to fine particulate matter ($PM_{2.5}$) and cardiac arrhythmias among 72 healthy male welders (mean age 38 years old). Welders underwent simultaneous ambulatory electrocardiographic (ECG) test and personal exposure monitoring of $PM_{2.5}$ (using a DustTrak Aerosol Monitor) during work and non-work periods for 5-90 hours. Generalized linear fixed-effects analyses were performed to assess the relationship between $PM_{2.5}$ exposure (averaged hourly and with lags of 0-7 hours) and ECG results [hourly supraventricular ectopy (SVE) and ventricular ectopy (VE)] that are indicative of cardiac events, and whether associations differed between work and non-work periods or based on smoking status. The authors reported highly skewed data for the number of hourly cardiac events with a mean of 14 VE and 1 SVE. A marginally significant increase in VE events was observed with increased $PM_{2.5}$ exposure with a six and seven hour lag, with odds of a VE event increasing by 3% for every 100 ug/m^3 increase in six hour lagged $PM_{2.5}$ concentration. The authors concluded that there was a small increased risk of VE events with short-term $PM_{2.5}$ exposure among the healthy male welders in this group.

Han *et al.* (2016 PMID: 27677526) investigated heart rate variability (HRV) in welders who used a respirator, compared to welders who did not use a respirator. Various heart rate indices were assessed using an ambulatory ECG test and personal exposure to $PM_{2.5}$ were collected. The authors found an association between exposure to $PM_{2.5}$ (5-minute mean) and a reduction in various HRV metrics. Exposure-related HRV effects were greater in welders who did not wear a respirator, although, workers that used a respirator also experienced small reductions in various HRV indices. The authors concluded that wearing a respirator could reduce the effects particulate matter exposures on HRV in welders.

Lai *et al.* (2016 PMID: 27641436) assessed exposure to metal fumes in the welding and office areas of a shipyard in Taiwan. The authors aimed to identify cardiovascular toxicity related to $PM_{2.5}$ exposure among welders and office workers. Air monitoring of the shipyard revealed significant amounts of bimodal metal fume particles with count median diameters of 14.1~15.1 and 126.3~135.8 nm were produced. Exposure to metal fume $PM_{2.5}$ resulted in decreased cell viability and increased 8-hydroxy-2'-deoxyguanosine (8-OHdG), interleukin (IL)-6, and nitric oxide in human coronary artery epithelial cells. Following personal exposure monitoring and biomonitoring, the authors observed that a 10-mug/m^3 increase in mean $PM_{2.5}$ concentration was associated with a 2.15% increase in 8-OHdG and an 8.43% increase in 8-iso-PGF2α in welders. In addition, 8-OHdG and 8-iso-PGF2α were associated with urinary iron and zinc. The authors concluded that inhalation of $PM_{2.5}$ metal fume could increase the risk of cardiovascular toxicity.

Lucas *et al.* (2016 PMID: NA) investigated noise exposure and cardiac health among five welders working on a ship repairing yard. A questionnaire was administered at the beginning and end of the work day to collect data on participants' lifestyle, feeling at work, and work tasks. Additionally, participants underwent a cardiac health assessment, and noise assessment of their workplace. Authors reported high noise levels for arc-air welding (118 dB [A] and peak at 143 dB [C]), but no correlation between the noise levels and the cardiac measurements Authors concluded that despite the negative findings, they recommended that appropriate assessments should be conducted for these workers due to the potential cardiovascular risks.

Umukoro *et al.* (2016 PMID: 26949871) investigated whether chronic exposure to metal particulates affect cardiac acceleration capacity (AC), deceleration capacity (DC), or both. The authors examined this relationship in 50 boilermakers. Participants' chronic exposure index (CEI) for $PM_{2.5}$ was calculated, and their resting AC and DC were obtained. Age, acute effects of welding exposure, and diurnal variation were controlled for in the analyses. A mean CEI for $PM_{2.5}$ exposure was reported to be 1.6 (2.4) mg/m^3-work years and ranged from 0.001 to 14.6 mg/m^3-work years. In addition, results indicate a positive association for long-term $PM_{2.5}$ exposure, and AC and DC, respectively. Specifically, a 1 mg/m^3-work year increase in $PM_{2.5}$ CEI was associated with a decrease of 1.03 ms resting AC, and a decrease of 0.67 ms resting DC. The authors concluded chronic exposure to metal particulate decreased cardiac accelerations and decelerations.

Umukoro *et al*. (2016 PMID: 26949872) investigated whether associations of acceleration capacity (AC) and deceleration capacity (DC) with metal-$PM_{2.5}$ are mediated by inflammation. The authors obtained $PM_{2.5}$, inflammatory markers (C-reactive protein, and interleukin (IL)-6, 8, and 10), and electrocardiograms to compute AC and DC, from 45 male welders. They used linear mixed models to calculate associations between $PM_{2.5}$ exposure, inflammatory mediator, and AC or DC, controlling for covariates. The authors reported that about 4% of the total $PM_{2.5}$ effect on AC or DC (indirect effect) was mediated through IL-6. In addition, when controlling for IL-6 (direct effect), a 1 mg/m^3 increase of $PM_{2.5}$ was associated with a decrease of 2.16 (95% confidence interval -0.36 to 4.69) ms in AC and a decrease of 2.51 (95% confidence interval -0.90 to 5.93) ms in DC. The authors concluded that IL-6 may be mediating the effect of metal particulates on AC.

4.1.4 Cancer

MacLeod *et al.* (2017 PMID: NA) investigated the association between exposure to welding fumes and cancer risk in a Canadian population of 12,845 male welders that were part of the population-based Canadian Census Health and Environmental Cohort. The authors estimated the risks of developing lung cancer, mesothelioma, ocular melanoma, nasal, brain, stomach, kidney, and bladder cancer for the study population using Cox proportional hazards analysis. The authors reported that welders had elevated risks of lung cancer [hazard ratio (HR): 1.16, 95% confidence interval (CI): 1.03-1.31], mesothelioma (HR: 1.78, 95% CI: 1.01-3.18), bladder cancer (HR: 1.40, 95% CI: 1.15-1.70), and kidney cancer (HR: 1.30, 95% CI: 1.01-1.67) compared to non-welders and controlling for age group, region, and education level. When comparing to blue-collar workers only, lung cancer and mesothelioma risks were reduced, while bladder and kidney cancer risk were increased. The authors concluded that welding-specific exposures may increase the risks for bladder and kidney cancers, and suggested that more research is needed to separate effects specific to welding exposures from those related to smoking and asbestos exposures.

Matrat *et al.* (2016 PMID: 26865654) evaluated the relationship between occupational exposure to welding and lung cancer among 2276 men (and 2780 male controls) that were part of the Investigation of occupational and environmental causes of respiratory cancers (ICARE) study, a population-based case-control study. Occupational history was assessed *via* questionnaire. Risk of lung cancer was calculated using unconditional logistic regression and controlling for occupational exposure to asbestos and smoking history. The authors reported that among welders, there was an increased risk of lung cancer (OR=1.7, 95% CI: 1.1 to 2.5), which was increased with duration of exposure (OR=2.0, 95% CI 1.0 to 3.9 when duration >10 years). Lung cancer risk was increased for exposures associated with gas welding (OR=2.0, 95% CI: 1.2 to 3.3), when the workpiece was covering with substances like paint or grease (OR=2.0, 95% CI: 1.2 to 3.4), and when the workspace was cleaned with chemicals before welding. Occasional welders did not experience a significant increased risk of lung cancer. In conclusion, the authors highlighted the potential for increased risks of lung cancer in welders and the potential influence of the type of welding and the welding environment on risk.

Sadetzki *et al.* (2016 PMID: 27664150) investigated the relationship between occupational exposure to metals and risk of developing meningioma (a brain tumor that is usually benign), as a part of the international INTEROCC study, a seven country population-based case-control study. The authors collected data from 1,906 adult meningioma cases (2000-2004) and 5,565 population controls and estimated metal and welding fume exposure using a job-exposure-matrix developed from extensive occupational histories that were collected. The authors reported higher cumulative exposures to metals and welding fume in cases *vs*. controls. Using conditional logistic regression, the authors found that the odds ratio (OR) for ever metal-exposed adults compared to never metal-exposed adults was greater than 1 (suggesting an increased risk of meningioma), with the strongest association found for exposure to iron (OR 1.26, 95 % CI 1.0–1.58), and an increased risk in ever exposed women (1.70, 95 % CI 1.0–2.89). In addition, the authors reported positive trends for risk of meningioma and both cumulative exposure and duration of exposure for women. The authors concluded that there may be an increased risk of meningioma associated with occupational exposures to metals, particularly in women. They propose an iron-estrogen metabolic interaction as a potential mechanism for carcinogenicity, and recommend further research in this area.

4.1.5 Ocular

Abu *et al.* (2016 PMID: 27195090) assessed the ocular health and safety among 500 mechanics in the Cape Coast Metropolis, Ghana. The authors collected data on the population's demographics, occupational history, and ocular health history *via* a structured questionnaire. In addition, various ocular health assessments were performed including determination of visual acuity (VA) using LogMAR chart, external eye examination with a handheld slit lamp biomicroscope, dilated fundus examination, applanation tonometry and refraction. Of the 500 mechanics, 433 were examined, 408 (94.2%) male and 25 (5.8%) female subjects. The authors reported that the visual impairment prevalence (VA < 6/18) was 2.1%, and eye injuries were sustained in 171 (39.5%) mechanics, likely because of the large number of workers that did not use eye protective devices (314 or 72.5% of the workers). Workers with the highest risk of sustaining an eye injury were mechanics in the auto welding category (odds ratio [OR], 13.4; P < 0.001). The authors concluded that eye safety needed to be a crucial part of the public health agenda in the Cape Coast Metropolis.

Heydarian *et al.* (2016 PMID: NA) examined the occurrence of occupationally-related color vision deficiency. Participants included 50 randomly selected male welders (welding for at least 4 years), and 50 age-matched non-welder males. Color vision was evaluated using the Lanthony desatured panel D-15 test. Results indicated that 15% of welders experienced an inability to perceive colors normally, which was significantly higher than controls (2%). Among the 15% who experienced non-normal color vision, 72.7% of color vision deficiency effected only one eye. The authors found a statistically significant association between color vision loss and both length of employment as a welder and average hours worked per day. The authors concluded that welding increases the risk of color vision deficiency, and the damage depends on the t length of welding employment and hours worked per day.

Shirzadeh *et al.* (2016 PMID: NA) investigated the use of anesthetic tetracaine eye drops, how the drug was obtaining and ocular complications in 162 patients with ocular pain, foreign body sensation, red eye or lid edema admitted to an eye clinic in Sabzevar, Iran. The authors collected patient information including age, sex, chief compliant, job, site of foreign bodies, diagnosis of problem, use of tetracaine drops, drug provision, times patients referred to the eye clinic, and kinds of treatment. Abnormal and/or excessive production of tears was the most common complaint, followed by eye pain and foreign body sensitization.

Welders comprised a significant proportion of patients who inappropriately used topical tetracaine eye drops, which has been shown to be hazardous. The most common foreign body reported was of metallic origin. The authors concluded that inappropriate topical tetracaine use was common among welders because it is simple to use and provides quick pain relief, but that this could be harmful. Therefore, increased supervision is needed to prevent purchasing drugs without a prescription as well as increased public awareness of potential harm

Slagor *et al.* (2016 PMID: 27243234) examined whether metal welding increases the risk of developing cataracts. Risk of cataract diagnosis from 1987-2012 was assessed in a cohort of 4,288 male metal arc welders and was compared to a Danish group of workers with a similar age distribution. Information on welding was collected from the group of welders *via* questionnaire. Danish national registers were used to gather medical history information on cataract diagnosis and operation. The authors found that 266 welders and 29,007 controls were diagnosed with and/or operated on for cataracts, and that the risks were similar across the two groups. The authors concluded that Danish metal arc welders did not have an increased risk of developing cataracts and that this may be due to the use of personal protective equipment.

4.1.6 Reproductive

Togawa *et al.* (2016 PMID: 27439405) investigated the association between parental occupational exposure to heavy metals and welding fumes and the occurrence of testicular germ cell tumor (TGCT) in offspring. A total of 8,112 TGCT cases, diagnosed at ages 14-49 years, were identified through nationwide cancer registries in Finland (1988-2012), Norway (1978-2010), and Sweden (1979-2011), and matched by country and birth year to controls (26,264 controls). Prenatal/preconception exposures to chromium, iron, nickel, lead, and welding fumes (all three countries), and cadmium (Finland only) were estimated using parental occupation information from census data and job-exposure matrices. Exposures were categorized based on a product of prevalence and mean exposure levels. A non-statistically significant elevated risk of TGCT was found for those whose exposure indices were greater than zero (*i.e.*, those who had some exposure). A statistically significant increase in risk of TGCT was observed for offspring whose parental exposures to chromium were high. The authors concluded further research is needed to assess the potential effects of parental exposure to chromium on offspring.

Xu *et al.* (2016 PMID: 26849258) investigated the health effects associated with electromagnetic fields (EMFs) emitted from plastic welding machines. The authors assessed the prevalence of neurovegatative symptoms (associated with depression) and menstrual disorders in 180 female workers in a shoe factory compared to an unexposed group of 349 female workers in a supermarket. The average radiation emitted from welding machines ranged from 51.3 to 368.9 V/m. Results showed a significant positive association between EMF exposures and prevalence of neurovegetative symptoms and menstrual disorder. In addition, the exposed group experienced significantly lower levels of an important female hormone, progesterone, compared to unexposed group. The authors concluded that EMF exposures may be associated with adverse effects in female workers.

4.1.7 Systemic

Baumann *et al.* (2016 PMID: 27816692) evaluated systemic biomarkers of welding fumes containing zinc and traces of aluminium, with or without copper because studies have found that C-reactive protein (CRP), which is a biomarker of inflammation, is increased after exposures to welding fumes. A total of 15 non-smoking males, with no history of exposure to occupational metal fumes, were exposed under controlled conditions to ambient air or three different welding fumes for 6 hours on four different days. Lung function tests were performed and blood samples were taken before exposure and after 6, 10 and 29 hours after exposure. The concentrations of biomarkers in blood samples were evaluated. Results show that IL-6, a protein responsible for inflammatory response, was significantly increased at 10 hours after exposure for all three welding fume metal combinations, compared to baseline measurements. Additional markers of inflammation, CRP and serum amyloid A (SAA), were also increased at 29 hours after exposure in welding fume groups. Other inflammatory marker levels evaluated did not differ from baseline levels. Baumann *et al*. (2016) concluded IL-6 may represent a sensitive and early biomarker for exposure to zinc and copper-containing welding fumes, and that activation of these biomarkers (IL-6, CRP and SAA) may present important information regarding cardiovascular disease risk in long-term welders.

Graczyk *et al.* (2016 PMID: 27286820) examined the time course changes of particle-associated oxidative stress in welders exposed to tungsten inert gas (TIG) under controlled conditions. Oxidative stress refers to the imbalance between the production of harmful free radicals and our body's ability to detoxify them, and is often characterized by the production of reactive oxygen species. Twenty non-smoking welders were exposed for TIG for 60 minutes in well-ventilated settings. Exhaled breathe condensate (EBC), blood and urine samples were measured before exposure, immediately after exposure, 1 and 3 hours following exposure. Various biological indices were assessed in the samples collected from participants. Results showed significant increases in the measured biomarkers at 3 hours post exposure, including plasma- and urinary-hydrogen peroxide, and 8-hydroxy-2'-deoxyguanosine (8-OHdG). Moreover, an association was found between a doubling of particle number concentration (PNC) and an increase of plasma-8-OHdG at 3 hours post exposure. The authors concluded that 60-minute controlled exposure to TIG welding fume, in a well-ventilated setting, induced acute oxidative stress in exposed non-smoking apprentice welders. Furthermore, the results suggested additional exposure metrics should be included in occupational risk assessments, and challenged the belief that TIG represents a safer welding process.

Markert *et al.* (2016 PMID: 26849256) investigated the inflammatory response associated with exposure to welding fumes containing either zinc, copper, or zinc and copper. Controlled exposure conditions were used to evaluate asymptomatic systemic inflammation in 15 health male participants exposed to the three various welding fumes. Findings showed that all welding fume exposures caused blood C-reactive protein to increase. The authors concluded that zinc- and copper-containing welding fumes stimulates a systemic inflammatory response in humans.

4.1.8 Multiple Health Effects

Alexander *et al.* (2016 PMID: 27682579) investigated health problems and the usage of personal protective equipment (PPE) among welders in unorganized welding units in Vellore, India. One hundred fifty welders were surveyed to assess the number of skin, ear, eye, and respiratory injury and PPE usage. Results showed significant differences in the number of skin complications (burns, redness, hyper pigmentation and itching), eye injuries, and sensorineural deafness seen in welders, compared to non-welders. Additionally, hypertension was notably higher among welders. None of the welders used appropriate PPE. A significant association was found between low educational attainment and an increased risk of eye injury. The authors conclude the use of PPE could considerably reduce skin, eye and ear injuries.

Budhathoki *et al.* (2016 PMID: 27891236) examined the patterns of injury and illness among a group of welders working in eastern Nepal. Three hundred welders were administered a questionnaire to gather their occupational and medical history, including symptoms experienced in the past 6 months (prior to the study). Results showed all welders did not receive formal health and safety training, and the most common health problems were injuries, skin problems and eye symptoms. In addition, the authors found a relationship between sustained injuries or illnesses and welder's age, duration of employment and number of hours worked per day.

Volberg *et al.* (2017 PMID: 28160819) investigated injury rates among workers in the Electric Power Research Institute's Occupational Health and Safety Database, which contains data from 18 participating electric power companies from 1995 to 2013. The authors calculated injury rates by age, sex, occupational group, and injury type. Authors reported an overall injury rate of 3.2 injuries per 100 years of employment during the study period. The authors noted injury rates steadily decreased from 1995 to 2000, spiked in 2001, and decreased to the lowest rate in 2013. Results showed that welders experienced the highest injury rates out of the occupations considered, with an injury rate of 13.56 injuries per 100 years on employment during the study period. Additionally, welders who were male, and/or 65+ years of age had higher injury rates. In conclusion, the authors identified specific groups that experience high risk of injury, which include older welders, and recommended protective measures and targeted safety programs to ensure the health and safety of electric power workers.

Zare *et al.* (2016 PMID: NA) assessed the relationship between mental workload and prevalence of musculoskeletal disorders among 100 welders working at Tehran Heavy Metal Structures Company. Mental workload refers to the amount of metal effort involved in completing a task and their capacity to process information in order to make appropriate decisions or take appropriate action. A series of questionnaires were administered to gather data on the participants' demographics, evaluate their mental workload, and musculoskeletal symptoms. The results indicated that 84% of participating welders experienced musculoskeletal disorders during the past 12 months (before the study), of which 65% involved the waist. The authors report significant associations between the prevalence of disorders in the legs and physical demand, and between disorders in the wrist/hand and overall mental workload. The authors concluded that mental workload and the prevalence of musculoskeletal disorders was high among welders. They stressed the importance of evaluating risk factors for such disorders and ways to reduce or prevent them.

4.2 Animal Studies

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

Halatek *et al.* (2017 PMID: 27901646) used a rat model to assess the pulmonary toxicity of inhaling welding dust. Rats were exposed (nose-only) to 60.0 mg/m^3 of respirable-size welding dust for 2 weeks (6 hours/day, 5 days/week). Halatek *et al.* (2017) also investigated the effect of betaine supplementation (250 mg/kg/day) on lung deterioration. Cellular parameters were measured in fluid samples collected from the lungs, and corticosterone and thiobarbituric acid reactive substances were assessed in blood samples. The authors reported that the level of induced toxicity largely depends on the solubility of the metal compound. Effects were seen in total cell, number of white blood cells, total protein concentrations, and cellular enzyme activity during 2 weeks exposure to either welding dust or water-soluble dust form. Supplementation of betaine attenuated stress indices and corticosterone and TBARS serum levels, and simultaneously stimulated increase of polymorphonuclear cells (white blood cells) in lung fluid in all rat study groups. The authors concluded exposure to welding dusts produces deleterious effects in the rat's lungs and brain.

Présumé *et al.* (2016 PMID: 27680323) examined the pulmonary effects of repeated exposure to occupationally relevant doses of nanoparticles (NP) in rodents. Mice were exposed once a week for 3 months at two different doses; one dose to represent an exposure relevant to welding activity, and one dose to represent an exposure relevant to a NP-manufacturing facility. The authors reported that 3 months of repeated NP exposures, relevant to welding activities, produced limited pulmonary effects including mild lung fibrosis. The mice dosed with a concentration relevant to a NP-manufacturing facility, however, developed lung fibrosis and experienced inflammation. The authors concluded that there was a potential risk for respiratory effects from occupationally-relevant doses of NP. They also proposed that occupational exposure limits to NPs be addressed.

4.3 Mechanistic/cell/*In vitro*

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

Lu, X. *et al.* (2016. PMID: 25938281) determined whether engineered nanomaterials (ENMs) that are currently used in industrial and biomedical applications target the cellular epigenome at low cytotoxic doses. The authors evaluated cells relevant to inhalation exposures such as human and murine macrophages (THP-1 and RAW264.7, respectively) and human small airway epithelial cells and these were exposed to a variety of ENMs including mild steel welding fumes (MS-WF). The authors examined a number of toxicological effects, including cytotoxicity, oxidative stress and inflammatory responses, and effects of ENMs on cellular epigenome were evaluated using global and transposable elements (TEs)-associated DNA methylation and expression of DNA methylation machinery and TEs. Cytotoxicity for all cell lines ranged from 0-15%. Oxidative stress was not evident for welding. The author's, however, did find that exposure to ENMs resulted in modest alterations in DNA methylation and decreased expression of DNA methylation machinery in a cell-, dose- and ENM-dependent manner. The authors concluded that exposure to ENMs at environmentally relevant concentrations can affect the epigenome of target cells as well as have cytotoxic effects.

4.4 Reviews

We identified nine reviews of welding exposure and health effects.

Aasen TB. (2016 PMID: NA) highlighted the role of workplace exposures and vulnerability to lung infections. The authors noted that exposure to welding fumes might reduce resistance to infection, and could explain the increased mortality from pneumonia seen in welders

Alici *et al.* (2016 PMID: NA) conducted a review of risk factors for pneumoconiosis, an occupational and restrictive lung disease often caused by the build-up of inhaled dust. Medical records of patients diagnosed with pneumoconiosis at a single center from 2013 to 2015 were reviewed. Out of the 60 male participants, 2 cases were welders. Other occupations included dental technicians, sandblasters, and ceramic workers. The authors concluded that institutional preventative measures, personal protection, and surveillance examinations are critical in preventing occupational hazard-related deaths.

Coggon *et al.* (2016 PMID: 27103350) reviewed welders risk of respiratory infection. The authors cited epidemiological evidence that welders are at increased risk of infectious, lobular pneumonia, and experience a higher rate of upper respiratory infection. Additionally, studies suggest this increased risk is associated with recent exposure, which may be indicative of the reversibility of the effects. Authors also noted that these effects extend to other occupations that involve metal fume exposures, suggesting these effects are not specifically related to welding fumes. Furthermore, the authors mentioned various mechanisms that could be responsible for these effects; 1) inhaled iron promoting the growth of bacteria; 2) metal fume-related impairment of immune responses in the lung; 3) enhanced binding of pneumococcus to lung tissue related to metal fume exposure. The authors concluded that more research is needed to confirm whether welder's experience a significantly increased risk of developing respiratory infections.

Geier *et al.* (2016 PMID: NA) reviewed whether chromate sensitization is associated with occupational contact to chromium (VI)-compounds (chromates) in German workers. The authors noted that since occupational exposure to chromates has been significantly reduced in the past 15 years (prior to publishing), occupational contact sensitization to chromate is not as widespread a problem in terms of occupational skin diseases. However, in cases of strong sensitization due to exposure of low concentrations of chromate (which is very prevalent) the impact could be greater. The authors reported relevant occupational exposures related to sensitization can occur during welding, handling chromated metal parts, electroplating and other jobs. In addition, wearing glove and shoes made from chromium-tanned leather may also be a relevant exposure route.

Gourzoulidis *et al.* (2016 PMID: 27422373) reviewed the occupational health and safety area of artificial optical radiation (AOR), which includes visible light, ultraviolet (UV) light and infrared light emitted during various activities covered under the European Directive 2006/25/EC. The authors reported that arcs created during metal welding are the most important source of AOR to consider for health effects. Additionally, the authors assessed the exposure limits of AOR in a welding laboratory. UV and blue light produced during typical welding procedures were measured. Results supported the need for evaluating personal protective equipment (PPE) integrity and conducting integrated risk assessment of welding environments. The authors concluded that their review of radiation hazards is useful for workers and employers.

Hiller *et al.* (2016 PMID: NA) evaluated the literature regarding the association between welding and the risk of uveal melanoma, and whether welding-related melanoma could be classified as an occupational disease under German legislation. A literature search was conducted and the authors found multiple studies that have investigated this relationship. Most studies found a positive, though non-statistically significant, association between melanoma and welding exposures, but authors could not draw a clear causal conclusions. The authors reported that there is insufficient evidence to determine whether welders have a substantially higher risk of uveal melanoma, and therefore this does not meet the scientific requirements of German occupational disease legislation. They also recommend further research to determine the mechanism of action, dose-response relationship, and the role occupation plays in uveal melanoma.

Muruganandam *et al.* (2016 PMID: NA) reviewed the health effects associated with different welding processes and the characteristics, focusing on issues related to arc and gas welding methods. The authors note that some hazards can be reduced with the use of local exhaust ventilation and the use of personal protective equipment, but recommend alternative "eco" welding processes that could be implemented to reduce health hazards as well as reduce energy consumption and greenhouse gas emissions.

Tian *et al.* (2016 PMID: 27074799) reviewed the transport and deposition of welding fume particles in the nasal cavity of humans. The authors noted the ability for manganese (Mn), commonly contained in welding fume, to be deposited in the human respiratory system and be transported to an area of the brain that is the target of Mn neurotoxic effects.

Parmalee *et al. (2016* PMID: 27293182) reviewed the effects of manganese (Mn) exposure and how Mn may play a role in mechanisms of aging such as neurogenesis, oxidative stress, and microglial activation and inflammation. The authors noted that welding can serve as proxy for exposures to Mn.

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