American Welding Society
Literature Update 2013

Prepared for

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1 Introduction

The American Welding Society (AWS) asked Gradient to conduct a comprehensive literature review to identify studies related to the health effects of welding for 2013. The present document is an extension of this work conducted previously of literature published between 2010 and 2012. In this report, we describe the literature search methods and provide a summary of the results of our searches (*e.g.*, how many articles we identified) and how we identified relevant articles for inclusion (Section 2). We also present summaries of the exposure-related studies (Section 3) and relevant health effects studies (Section 4).

2 Methods

We searched the PubMed, TOXLINE, NIOSHTIC-2, and SCOPUS databases for articles relevant to exposure during welding and the health effects of welding, as described below.

2.1 Search Strategy

1. To capture all of the potentially relevant literature, the initial keyword searches included the words "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." Section 2.2 provides details on how we applied these terms.
3. To narrow the general results and identify specific articles related to exposure, specific terms and their variants were applied, as appropriate, in conjunction with the general terms welding and welders. The search terms included "exposure monitoring," "exposure characterization," "occupation(al)," "workers," "workplace," "laborers," "cohort," "dose," "particle characterization," "inhalable," "respirable," and "sampling." Section 2.2 provides details on how we applied these terms.
4. We limited our literature searches to 2013. We deleted any articles we reviewed previously (including with epub in 2012 but hard copy in 2013) 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 2013; this yielded 167 items. The search results were then filtered for citations relevant to health and exposure (as described in Section 2.1). Any citations that were excluded were reviewed to ensure that no relevant articles were missed. A Microsoft Excel file with the remaining citations was created and reviewed. Any additional non-relevant articles (*e.g.*, materials processing, nano-synthesis, prosthetics, and chemical structure or analysis) were removed at this stage. A total of 41 articles remained after initial review and were retained in the Excel spreadsheet for further review.

2.2.2 TOXLINE

TOXLINE was searched for articles containing "welders" or "welding" published in 2013. No relevant items were found.

2.2.3 SCOPUS

Two separate search methods were conducted in SCOPUS, one filtering by inclusion and one by exclusion. The first search approach searched for articles published in 2013 containing "welders" or "welding" in the title, abstract, or key word. These results were then filtered to exclude the following subject areas: engineering, materials, physics, math, energy, chemistry, social sciences, agriculture, business, dentistry, biochemistry, and neuroscience. A total of 98 articles were found and exported into an Excel spreadsheet. The second search approach also included articles containing "welders" or "welding" in the title, abstract, or key word, and published in 2013, but it was filtered by search terms that included the health and exposure terms described in Section 2.1. This method yielded 35 articles, which were exported to another Excel spreadsheet.

The results of the two searches overlapped significantly, and they also overlapped significantly with the PubMed search results.

2.2.4 NIOSHTIC-2

The NIOSHTIC-2 database was queried for articles published in 2013 containing "welders" or "welding" in the title, abstract, or key word, yielding 15 results. Four of these articles were not relevant to our review, and the remaining articles were found in the PubMed search.

2.3 Literature Reviews

We sorted the results from the various literature searches by PubMed identification number and removed duplicates. We also removed case reports, commentaries, conference presentations, and many foreign studies (of little or no relevance). We copied the remaining citations into an Excel spreadsheet and then reviewed the articles' titles and abstracts, which we either removed due to irrelevance or sorted into the following categories:

- Particle characterization and exposure data;
- Epidemiology and controlled human study;
- Animal study;
- Cell/*in vitro*/mechanistic study; or
- Integrative/review articles.

Table 1 lists the breakdown of articles by category.

Table 1 Breakdown of 2013 Abstracts Reviewed by Study Category

Study Category	Total
Particle characterization and exposure	**9**
Epidemiology and controlled human exposure	**22**
Animal	**4**
Cell/*in vitro*/mechanistic	**1**
Integrative or review articles	**4**
Overall Total	**40**

3 Exposure Studies

We identified nine exposure-related papers published in 2013 from the literature search outlined in Section 2. We note that several studies were published on-line in 2013 (epub date); we included these articles in our review. We did not review articles that were not relevant or were included in a prior AWS review. In this section, we summarize the exposure studies we reviewed and provide their PubMed ID (PMID) numbers.

Brand *et al*. (2013a; PMID: 23028013) compared the distributions of ultrafine (< 100 nm in diameter) and larger particles in welding fumes across different kinds of welding. Welding processes with high mass emission rates, such as manual metal arc welding, metal active gas welding, metal inert gas welding, metal inert gas soldering, and laser welding, produced welding fumes primarily comprised of particles that were greater than 100 nm in diameter. Only 10-15% of the particles were 50 nm or smaller. Welding processes with low mass emission rates, such as tungsten inert gas welding and resistance spot welding, produce welding fumes comprised primarily of ultrafine particles.

Chen *et al*. (2013; PMID: 23428060) found that four different respiratory protective devices removed over 98% of particulates and 83.5-94.1% of particulate-phase reactive oxygen species particulates in welding fumes; however, removal efficiency of gas-phase reactive oxygen species were only 1.3-21.1%.

Grashow *et al*. (2014; epub 2013, PMID: 24372360) compared concentrations of manganese (Mn), lead (Pb), and cadmium (Cd) in toenails with the prior 12 months of exposure to metal-rich welding fumes in occupational welders. Mn, Pb, and Cd concentrations in toenails were statistically significantly associated with hours welding 7-12 months prior to testing, depending on the metal. Nickel (Ni) and arsenic (As) were also analyzed in toenails but were not statistically significantly associated with exposure ($p = 0.06$ for Ni, p-value for As not reported). Toenail metal concentrations were not associated with the number of years as a welder.

Gube *et al*. (2013; PMID: 22311006) compared the blood and urine biomarkers of chromium (Cr) and nickel (Ni) in 12 healthy, non-smoking males who had never worked as welders. Biomarkers were collected before and after 6 hours of exposure to ambient air (0 mg/m^3) and 1 mg/m^3 and 2.5 mg/m^3 welding fumes generated by metal active gas welding. Subjects' biomarkers showed a dose-dependent increase in concentrations of Cr and Ni following exposure.

Iavicoli *et al*. (2013; PMID: 23348430) measured fine and ultrafine particle emission rates in a mechanical engineering factory as a result of grinding, welding, and brazing. The highest concentrations of fine and ultrafine particles were in the welding booth area, suggesting that welding generates the largest emissions of these particulates.

Lehnert *et al*. (2014; epub 2013 PMID: 23719851) measured exposure to airborne metals before and after increasing exhaust ventilation and respiratory protection. Air, blood, and urine samples were collected before and after intervention. Respirable particles were reduced from 4.1 mg/m^3 to 0.5 mg/m^3. Metal specific reductions were 399 *vs*. 6.8 $\mu g/m^3$ for manganese (Mn), 187 *vs*. 6.3 $\mu g/m^3$ for chromium (Cr), and 76 *vs*. 2.8 $\mu g/m^3$ for nickel (Ni). Reductions in urine biomarkers were 14.8 *vs*. 4.5 μg/L for Cr, 7.9 *vs*. 3.1 μg/L for Ni, and 12.8 to 8.9 μg/L for Mn (significance not reported in abstract). Improving exhaust ventilation and respiratory protection significantly reduced exposure to airborne metals.

Ojima (2013; PMID: 23183022) conducted a study to measure the generation of carbon monoxide (CO) from carbon dioxide arc welding and determine ventilation rates required to prevent CO poisoning. The measured generation rate of CO was 386-883 ml/min for solid wire welding and 331-1,293 ml/min for flux cored welding. Given these rates of CO generation, the ventilation rate required to maintain CO levels at the Occupational Safety and Health Association permissible exposure limit of 50 parts per million CO are 6.6- 25.9 m^3/min.

Weiss *et al*. (2013; PMID: 22926021) compared the concentrations of inhalable and respirable nickel (Ni) and chromium (Cr) in the breathing zone to their concentration in urine for 241 welders. Inhalable metal particles are small enough in diameter to be inhaled, however, may not reach the alveoli of the lungs. Respirable particles are small enough to infiltrate the alveolar region of the lungs if inhaled. Urine concentrations of respirable Ni and Cr were approximately half of their respective total inhalable concentrations and based on regression analyses, urine concentrations of the metals were predicted by concentrations of respirable Ni and Cr. Air concentrations of Ni and Cr were predicted by base material, welding technique, size of surrounding work space, ventilation system, and respirator use.

Wolska (2013; PMID: 23650770) measured welders' exposure to "blue light" and ultraviolet radiation during tungsten inert gas and Manual Metal Arc welding with different parameters and materials. In all cases, exposure exceeded the maximum permissible exposure limit for photochemical hazards for eyes. Use of eye and face protective equipment was strongly recommended based on the study results.

4 Health Effects Studies

4.1 Studies in Humans

We identified 22 studies in humans that assessed various health effects related to welding fume exposures. These health effects included neurological effects (seven studies), respiratory effects (seven studies), cancer (three studies), effects on the eyes (one study), and other effects (four studies). We also identified four animal studies, one mechanistic study, and four reviews. As with the exposure studies, several studies were published on-line in 2013 (epub date); we included these in our review. We did not review articles that were not relevant or were included in a prior AWS review. In this section, we summarize the health effect studies we reviewed and provide their PMID numbers.

4.1.1 Neurological Effects

Ellingsen *et al*. (2014; epub 2013, PMID: 24263125) compared biomarkers of manganese (Mn) exposure and neurobehavioral outcomes in 137 welders and 137 referents (turners and fitters) working at the same plants. Self-reported alcohol consumption and carbohydrate deficient transferrin in serum (sCDT), a biomarker of alcohol consumption, were also collected. Air sampling was conducted for two days. The geometric mean air concentration of Mn was 214 $\mu g/m^3$, ranging from 1-3,230 $\mu g/m^3$. In welders, the average concentrations of Mn were 12.8 µg/L in blood and 0.36 µg/g creatinine in urine. The average biomarker concentrations of Mn in the referent group were significantly lower (8.0 µg/L in blood and 0.07 µg/g creatinine in urine). Welders scored lower on neurobehavioral tests, including Grooved Pegboard, Finger Tapping, Simple Reaction Time (SRT), and Maximum Frequency tests. Also, welders with sCDT above the upper reference limit had substantially poorer performances on the Grooved Pegboard, Finger Tapping, and SRT tests than those with sCDT levels in a normal range. The authors concluded that sCDT should be measured in studies of Mn-exposed workers for a more accurate estimation of high alcohol consumption.

Tutkun *et al*. (2013; PMID: 24337778) compared the prolactin levels between 95 non-exposed control subjects and 179 Mn-exposed male welders. Prolactin is a hormone that acts as a mediator in multiple processes in multiple organs, including the central nervous system and the reproductive system. Some studies have demonstrated that Mn exposure affects dopamine neurotransmission, which can inhibit prolactin release. A significantly positive correlation was found between whole blood Mn levels and serum prolactin ($r = 0.860$, $p < 0.001$). Serum aspartate transaminase (also referred to as aspartate aminotransferase) and potassium levels were significantly higher in the control group than in the Mn-exposed group ($p = 0.002$ and $p = 0.048$, respectively), and body-mass index was significantly lower in the control group than in the Mn-exposed group ($p = 0.033$). The authors concluded that serum prolactin is a diagnostic marker for determining the effect of Mn exposure.

Teschke *et al*. (2014; epub 2013, PMID: 24166740) reviewed a population-based sample of 403 Parkinson's disease (PD) cases and 405 controls to determine potential increases in risk by occupation. The authors found that welders had three times higher odds of developing PD than controls (odds ratio [OR] = 3.0).

Marie *et al*. (2013; PMID: 24129037) conducted a similar study for systemic sclerosis in which they reviewed the occupational exposures of 100 patients with a definite diagnosis of systemic sclerosis and three controls per patient matched for age, gender, and smoking habits. Significantly higher ORs for developing systemic sclerosis were found with occupational exposures to crystalline silica ($p < 0.0001$), white spirits ($p < 0.0001$), aromatic solvents ($p = 0.0002$), chlorinated solvents ($p = 0.014$), trichloroethylene ($p = 0.044$), ketones ($p = 0.002$), and welding fumes ($p = 0.021$).

Lundin *et al*. (2013; PMID: 24035927) conducted a study to determine the accuracy with which a health status questionnaire (PDQ39) and a Parkinson disease (PD) Symptoms Questionnaire could predict parkinsonism in manganese-exposed workers, when the results of the questionnaires were compared to the results of examination by a movement specialist for signs of parkinsonism. A total of 490 occupational welders completed both questionnaires and were examined by a movement specialist. At 70% sensitivity, the specificity for PDQ39 score and PD Symptoms Questionnaire score for the prediction of parkinsonism was 73.1% and 80.1%, respectively. The authors concluded that the questionnaires could be a valuable first step in a tiered screening approach for manganese-exposed workers.

Chang *et al*. (2013; PMID: 23685157) compared the brain morphologies in 40 welders with chronic manganese (Mn) exposure and 26 age-matched control subjects. Voxel-based morphometry tests were used to observe differences in brain volume between welders and controls, and neurobehavioral tests were administered to measure correlation between brain size and cognitive performance. Chronically exposed welders had significantly smaller globus pallidus and cerebullar region volumes ($p < 0.05$), and these decreases in brain volume were negatively correlated with cognitive performance and grooved pegboard scores. The authors concluded that these results suggest that brain morphology could be useful in assessing potential manganism (*i.e.*, health effects resulting from exposure to Mn) in welders.

Ross *et al*. (2013; PMID: 22767555) conducted a study to determine if the high prevalence of severe cognitive symptoms observed in professional divers who have welded is associated with welding fume exposure or diving. They administered the Short Form 12 questionnaire (SF12) to assess quality of life and the Cognitive Failures Questionnaire (CFQ) to three age-matched groups: 153 professional divers who had worked as a welders, 108 professional welders who had not dived, and 252 offshore oil field workers who had neither dived nor welded. CFQ scores were highest in professional divers who had worked as welders; however, scores were not outside of the normal range for any group. Using regression analysis and controlling for age, alcohol consumption, and somatization, no significant association was found between the CFQ score and either welding fume exposure ($p = 0.79$, $n = 152$) or diving ($p = 0.84$, $n = 74$).

4.1.2 Respiratory Effects

Hedmer *et al*. (2013; PMID: 23979145) evaluated the prevalence of work-related symptoms among mild steel welders in Sweden and quantified the exposure to welding fumes by repeatedly measuring respirable dust (RD), respirable Mn, and ozone. They administered a questionnaire concerning airway symptoms and occupational history. Over 50% of the Mn concentrations and 2% of the ozone concentrations exceeded their respective Swedish occupational exposure limits. Of the work-related airway symptoms, 33% of welders reported stuffy nose, 28% reported ocular symptoms, and 24% reported dry cough.

Golbabaei *et al.* (2013; PMID: 24321643) conducted spirometry tests on 91 welders and 25 unexposed clerks in Iran to assess the effects of welding exposure on pulmonary function (*e.g.*, changes in forced vital capacity [FVC], forced expiratory volume in 1 second [FEV_1] and the FEV_1/FVC ratio) before and after work shifts. Welders had significantly lower FVC and FEV_1/FVC ratios than clerks ($p < 0.001$). Smoking habits, work history, and fume concentrations had no significant effects on the majority of spirometric indices. Most welding subjects reported at least one respiratory symptom. In addition, there were significant differences between pre- and post-shift indices (as a percentage of predicted values calculated) and between welders engaged in some welding tasks and the control group.

Haluza *et al*. (2014; epub 2013, PMID: 24217987) conducted a longitudinal study over 9 years to measure annual changes in pulmonary function in welders in Austria. Spirometry tests were conducted and anthropometric measures and smoking history were collected at annual routine occupational health checkups of 1,982 workers. Welders who were heavy smokers (but not moderate smokers) and had long-term exposure to welding fumes had significantly lower spirometry indices (FVC -70.7 ml, $p = 0.07$; FEV_1 -167.4 ml, $p < 0.001$; maximum expiratory flow after 50% of expired FVC [MEF_{50}] -356.2 ml/s, $p < 0.001$). There were also decreases in pulmonary function indices based on duration of exposure to welding fumes per year; two were significant (FEV_1 -2.91 ml, $p< 0.001$; MEF_{50} -4.7 ml/s, $p = 0.047$). The authors concluded that smoking cessation was highly recommended for all workers with long-term exposure to welding fumes.

Ryu *et al*. (2013; PMID: 24131874) used data from records of public health exams and identified spirometry test results for 448 male Korean workers who were exposed to organic solvents, iron oxide, or welding fumes. Logistical regression analysis was conducted to evaluate the association between exposures and pulmonary function. The prevalence of airway obstruction was significantly higher in workers exposed to iron oxide dust as compared to workers exposed to organic solvents (OR = 9.61; 95% confidence interval [CI]: 2.20 to 41.97). There was no significant difference between workers exposed to organic solvents and workers exposed to welding fumes (OR = 2.83, 95% CI: 0.74 to 10.8).

Kendzia *et al*. (2013; PMID: 24052544) used data from the SYNERGY project database to study the effect of welding on the risk of developing lung cancer in welders. Data from 15,483 male lung cancer cases and 18,388 male controls from 16 studies conducted between 1985 and 2010 in Europe, Canada, China, and New Zealand were used to calculate ORs based on welding frequency and lung cancer with adjustment for smoking, age, study center, and employment in other occupations associated with lung cancer risk. Overall, 568 cases and 427 controls had ever worked as welders. They had an OR for developing lung cancer of 1.44 (95% CI: 1.25 to 1.67); the OR increased with longer duration of welding. Occupations with occasional exposure to welding also had elevated ORs for developing lung cancer, though not as much as those regularly engaged in welding. The authors concluded that their results support the association between welding and an increased risk of lung cancer.

Subhashree *et al*. (2013; PMID: 23449620) conducted a cross-sectional study comparing the red cell distribution width (RDW) and spirometry indices of 50 welders and 50 non-welding office workers in Chennai, India, to assess the use of RDW as a biomarker of pulmonary function. The demographic data, smoking habits, work history, and respiratory symptoms were gathered using a standard self–administered questionnaire. A complete haemogram study was done together with pulmonary function tests for both the cases and the controls. A statistically significant inverse correlation was found between RDW and spirometry measures, indicating a relationship between RDW and pulmonary function and the potential for using RDW as a biomarker of pulmonary effects.

Brand *et al*. (2013b; PMID: 22311008) conducted a cross-over study in which 12 young men were exposed to fume concentrations of 0, 1, and 2.5 mg/m^3 for six hours in the "Aachen Workplace Simulation Laboratory." To evaluate effects on inflammatory markers and other effects, spirometry, and impulse oscillometry were conducted and breath condensate samples were collected before and after exposures. No significant differences were found for any endpoint.

4.1.3 Cancer

Wultsch *et al*. (2014; epub 2013, PMID: 24698449) studied the genotoxic potential of welding fumes by assessing chromosomal alterations and acute cytotoxicity in epithelial cells of the respiratory tract in 22 welders and 22 controls. In addition, concentrations of metals and biochemical parameters were measured in both groups. Using multivariate regression analyses, they found that micronuclei damage in nasal cells was associated with exposure to molybdenum (Mo), nickel (Ni), and manganese (Mn); Ni exposure was associated with cytotoxicity in nasal and buccal cells. The authors concluded that these results suggest that metal concentrations in the epithelial cells of the respiratory tract can be used as biomarkers of DNA-damage and cytotoxic effects of welding fume exposure.

Paget-Bailly *et al*. (2013; PMID: 23969505) used data from ICARE, a French population-based case-control study on head and neck cancer. Complete occupational histories were collected for 1,833 cases and 2,747 controls. The authors found an elevated risk of head and neck cancer for welders (OR = 1.9; 95% CI: 1.3 to 2.8), with risk increasing with duration of employment.

d'Errico *et al*. (2013; PMID: 23739491) reviewed data on cases of sinonasal inverted papilloma (IP), a benign tumor, to assess possible risk factors. Exposure to 17 occupational hazards was determined based on a occupational history questionnaire that was completed by 127 cases and 337 hospital controls. The relationship between IP and cumulative exposure to these hazards was evaluated using regression and adjusting for age, sex, area of residence, smoking and co-exposures. The risk of developing sinonasal IP increased with exposure to welding fumes (OR = 2.14, no CI provided). However, the authors noted that the lack of a dose-response relationship for welding fumes suggested that the observed association with ever exposure should be interpreted with caution.

4.1.4 Effects on the Eye

Serinken *et al*. (2013; PMID: 24104708) conducted a prospective study on workers admitted to an emergency department in Turkey with work-related eye injuries. Exposure to "welding light" was the most commonly reported cause of work-related eye injury (26.9%, 219 cases out of a total of 778 cases).

4.1.5 Other Health Effects

Liu *et al*. (2013; PMID: 24106453) compared the vitamin B6 status and plasma homocysteine of 57 welders and 42 controls to assess the degree of oxidative stress and the antioxidant capacities in welders. No significant differences in vitamin B6 or plasma homocysteine were found. Significantly higher levels of oxidized low-density lipoprotein cholesterol and lower erythrocyte glutathione concentration and superoxide dismutase (SOD) were found in welders as compared to controls. There was no correlation between plasma pyridoxal 5'-phosphate concentration and either oxidative stress indicators or antioxidant capacities in either group. However, plasma homocysteine was significantly correlated with total antioxidant capacity (TAC) (partial r(s) = 0.34, $P < 0.05$) and erythrocyte SOD activities (partial r(s) = 0.29, $p < 0.05$) after adjusting for potential confounders. The authors concluded that elevated plasma homocysteine seemed to be a major contributing factor to TAC and erythrocyte SOD activities in welders.

Kile *et al*. (2013; PMID: 23758843) followed 38 male boilermaker welders for 54 days to assess the effects of fine particulate matter ($PM_{2.5}$) on DNA methylation. Personal $PM_{2.5}$ was measured, whole blood samples were collected, and questionnaires were completed to assess job history and job duration as a boilermaker. Linear mixed model regression analysis showed that $PM_{2.5}$ exposure was associated with increased methylation in the promoter region of the inducible nitric oxide synthase gene; methylation increased with years worked as a boilermaker.

Järvelä *et al*. (2013; PMID: 23690265) evaluated the inflammatory response to acute exposure to welding fumes during the working day by measuring pulmonary function and exhaled nitric oxide, as well as blood leukocytes and their differential counts, platelet count, hemoglobin, sensitive C-reactive protein, fibrinogen, E-selectin, interleukin- (IL-) 1β, IL-6, IL-8, tumor necrosis factor alpha, and endothelin-1 in blood from 20 workers exposed to welding fumes and airborne particles before and after their shift. The total blood leukocytes and neutrophils increased after the work shift, whereas IL-1β and E-selectin decreased significantly. No significant changes were seen in spirometry indices or heart rate; however, a slight, acute inflammatory effect was estimated based on the increased values of leukocytes and neutrophils in blood and a decrease in IL-1β and E-selectin values.

Hambach *et al*. (2013; PMID: 23104735) conducted a cross-sectional study in 36 solderers to assess the viability of cadmium concentrations in blood and urine as a biomarker of exposure to Cd and resulting oxidative stress. Using multiple linear regression analysis, a significant association between Cd in blood and urine and biomarkers of renal stress was found (p value not provided). In addition, a significant association between Cd in blood and biomarkers of oxidative stress was found. While an association between Cd in urine and biomarkers of oxidative stress was observed, it was of borderline statistical significance. Results suggest that Cd in blood and urine may be used as a biomarker of renal damage and oxidative stress.

4.2 Animal Studies

Ngwa *et al*. (2013; PMID: 24362016) exposed C57 black mice to vanadium pentoxide (which can be formed from elemental vanadium during welding) intranasally three times a week for a month to assess its relationship with early symptoms of neurological diseases. Following the month of exposure, behavioral, neurochemical, and biochemical studies were performed. When compared to control animals, the animals exposed to vanadium pentoxide had impaired olfaction and locomotion, as well as significantly smaller olfactory bulb weights, tyrosine hydroxylase levels, and levels of dopamine (and its metabolite, 3,4-dihydroxyphenylacetic acid), as well as increases in astroglia of the glomerular layer of the olfactory bulb. The authors noted that their results suggest that nasal exposure to vanadium pentoxide may lead to adverse effects in the olfactory bulb, which may result in neurobehavioral and neurochemical impairment.

Kim *et al*. (2013; PMID: 24304306) conducted a study of the effects of long-term welding fume exposure on the activity levels of cynomolgus monkeys. Following a one-month acclimation, the monkeys were divided into three exposure groups and exposed to manual metal-arc stainless steel welding fumes for 2 hours per day for 8 months at either low or high concentrations, in addition to controls. The low concentration corresponded to 31 mg/m^3 total suspended particulate (TSP) and 0.9 mg/m^3 of Mn, while the high concentration corresponded to 62 mg/m^3 TSP and 1.95 mg/m^3 of Mn. Cage locomotor activity was monitored by a camera system for 2-4 days. Activity was five to six times higher in the high concentration group compared to the no exposure group, starting at 25 weeks of exposure and continuing until 7 weeks recovery. By 13 weeks after exposure, the high concentration group's activity levels were only three times higher than the control group. The authors noted that these findings, along with previous studies they conducted, suggest that prolonged welding fume exposure may case neurobehavioral changes.

Zeidler-Erdely *et al*. (2013; PMID: 24107379) measured the incidence of lung tumors in lung tumor susceptible A/J mice exposed weekly to chromium-containing gas metal arc (GMA)-SS welding particulate matter. Male mice (n = 28-30/group) were treated either with the initiator 3-

methylcholanthrene (MCA) or vehicle (corn oil) followed by five weekly pharyngeal aspirations of either low or high concentrations of GMA-SS (340 or 680 μg/exposure) or the control (phosphate-buffered saline) once a week for 5 weeks. At 30 weeks post-initiation, no lung tumors were found in the corn oil groups. In the MCA-initiated groups, both the low and high GMA-SS exposure groups had significantly higher lung tumor multiplicity (average number of tumors/mouse lung) than the MCA-initiated control group ($p < 0.0001$). Multiplicity was also highly significant ($p < 0.004$) across all individual lung regions of GMA-SS-exposed mice. The authors noted that these results provide evidence in animals to support the epidemiology data showing that welders have an increased lung cancer risk.

Antonini *et al*. (2013; PMID: 23798603) compared the effects of chronic exposure to welding fumes on human and rat lung tissue. Human lung tissue was donated post-mortem from a career welder. Sprague-Dawley rats were exposed once a week for 28 weeks to 2 mg of a stainless steel, hard-surfacing welding fume *via* intratracheal instillation. The lung conditions were similar in both the human and rat models following exposure. Welding particles, particularly metals including iron, chromium, and nickel accumulated and persisted in the lung tissue of both humans and rats. The authors conclude that chronic exposure to welding fumes can lead to serious chronic lung disease. The lung responses were similar between human and rat lungs, as evidenced by inflammatory cell influx and pulmonary disease, as well as the composition of the individual welding particles and *in situ* agglomerations.

4.3 Mechanistic Studies

Stephenson *et al*. (2013; PMID: 23296100) studied the effects of manganese (Mn^{2+}) on human neuroblastoma SH-SY5Y cells to assess potential mechanisms of toxicity of Mn^{2+}. Cells were exposed to 2 µM, 62 µM, or 125 µM for 24 hours and cell viability was measured at 24, 48, and 72 hours after exposure. The median lethal dose (LD_{50}) was 12.98 ($p < 0.001$ for control *vs*. 24-hour Mn treatment). Apoptosis assays confirmed the induction of apoptosis in the cells (*i.e.*, cell death) following exposure to Mn^{2+} at all three doses tested. In addition, Mn^{2+} induced both the formation and accumulation of DNA single strand breaks and oxidatively modified thymine bases. Pre-incubation of the cells with characteristic antioxidants, either 1mM N-acetylcysteine or 1mM glutathione, reduced the level of DNA strand breaks and the formation of thymine base lesions, suggesting protection against oxidative cellular damage. The authors concluded that (1) exposure of SH-SY5Y cells to Mn promotes both the formation and accumulation of oxidative DNA damage, (2) SH-SY5Y cells with accumulated DNA damage are more likely to die *via* an apoptotic pathway and (3) the accumulated levels of DNA damage can be reduced by the addition of exogenous chemical antioxidants.

4.4 Reviews

Szram *et al*. (2013; PMID: 23258779) conducted a systematic review of published longitudinal studies on pulmonary function decline (specifically FEV_1) in welders, followed by a meta-analysis on suitable data. The authors considered seven studies to be of good quality, although all studies had limited exposure assessment and there was significant heterogeneity across study findings; only five of these studies were deemed suitable for meta-analysis. Based on a pooled estimate, the difference in FEV_1 between welders and non-welders was -9.0 mL/year (95% CI: -22.5 to 4.5; $p = 0.193$); for welders and referents who smoked, the difference in FEV_1 was larger (-13.7 mL/year, 95% CI: -33.6 to 6.3; $p = 0.179$). The difference in FEV_1 between welders and referents who did not smoke was smaller (-3.8 mL /year, 95% CI: -20.2 to 12.6; $p = 0.650$). The authors concluded that, overall, the available longitudinal data on the decline in pulmonary function in welders and effects on respiratory symptoms suggest a greater effect in those who smoke, supporting a focus on smoking cessation as well as control of fume exposure in the workplace.

Baur (2013; PMID: 23706060) conducted a review of the literature on agents associated with occupational asthma and found "moderate evidence" that welding fumes are a worksite irritant that may cause occupational asthma.

Taube (2013; PMID: 22997412) reviewed published studies regarding the physicochemical properties (*e.g.*, particle sizes, composition, and solubility of welding fumes) of gas metal arc welding, shielded metal arc welding, and flux-cored arc welding fumes. The review focused on the solubility of welding fumes as this factor is strongly associated with bioaccessibility and, therefore, the potential health effects associated with welding fumes.

Fortoul *et al*. (2014; epub 2013, PMID: 23659523) reviewed the history of vanadium use in workplace settings, including welding. The authors assessed increases in environmental concentrations of vanadium and epidemiological data relating to health risks of vanadium. The health risks that were considered included hypertension, dysrhythmia, systemic inflammation, hyper-coagulation, cancers, and bronchial hyper-reactivity. Detailed findings and conclusions were not reported in the abstract.

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