

# American Welding Society Literature Update 2010-2012

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# Table of Contents

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	<u>Page</u>
1	Introduction ..... 1
2	Methods..... 1
2.1	Search Strategy ..... 1
2.2	Database Searches ..... 1
2.2.1	PubMed..... 1
2.2.2	TOXLINE..... 2
2.2.3	SCOPUS ..... 2
2.3	Literature Reviews ..... 2
3	Summary of 2010 Literature (Partial) ..... 3
3.1	Exposure..... 3
3.1.1	Summaries ..... 3
3.1.2	Abstracts ..... 4
3.2	Human Health Effects Studies ..... 5
3.2.1	Neurological Effects ..... 6
3.2.2	Cardiovascular Effects..... 6
3.2.3	Cancer ..... 7
3.2.4	Injury ..... 7
3.2.5	Biomarkers ..... 7
3.3	Animal Studies ..... 8
3.4	Mechanistic Studies ..... 9
4	Summary of 2011 Literature..... 9
4.1	Exposure..... 9
4.1.1	Summaries ..... 9
4.1.2	Abstracts ..... 10
4.2	Human Health Effects Studies ..... 13
4.2.1	Neurological Effects ..... 13
4.2.2	Cancer ..... 15
4.2.3	Reproductive Effects..... 16
4.2.4	Respiratory Effects ..... 16
4.2.5	Renal Effects..... 16
4.2.6	Cardiovascular Effects..... 17
4.2.7	Biomarkers ..... 17
4.2.8	Injury ..... 17
4.3	Animal Studies ..... 17
4.4	Mechanistic Studies ..... 19

5	Summary of 2012 Literature .....	19
5.1	Exposure.....	19
5.1.1	Summaries .....	19
5.1.2	Abstracts .....	20
5.2	Human Health Effects Studies .....	23
5.2.1	Neurological Effects .....	23
5.2.2	Respiratory Effects.....	24
5.2.3	Ocular Effects .....	25
5.2.4	Biomarkers .....	25
5.3	Animal Studies .....	26
5.4	Mechanistic Studies .....	27
	References .....	28

# 1 Introduction

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The American Welding Society (AWS) asked Gradient to conduct a comprehensive literature review to identify studies related to the health effects of welding. We conducted a literature search using several large citation databases for 2010-2012. In this report we describe the literature search methods, summarize the results of our searches (*e.g.*, how many articles we identified) and how we identified relevant articles to include in the report (Section 2). We also present a summary the studies by either providing the study abstracts (exposure-related studies only) or article reviews (for relevant health effects studies) for the second half of 2010, 2011, and 2012 (Sections 3-5, respectively).

## 2 Methods

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The PubMed, Toxline, and SCOPUS databases were searched for articles relevant to the health effects of welding. The search methods are described below.

### 2.1 Search Strategy

1. To capture all of 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; occupational lung disease. The details of how these terms were applied are provided in Section 2.2.
3. To narrow the general results and identify specific articles related to "exposure," the 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; sampling. The details of how these terms were applied are provided in Section 2.2.
4. Literature searches were limited to 2010, 2011, and 2012.

### 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 publication dates between 01/01/2010 and 12/31/2012 and this yielded 475 items. The search results were then filtered for citations relevant to health and exposure (as

described in Section 2.1). An citations that were excluded were reviewed to ensure that no relevant articles were missed. An excel file was created with the remaining citations 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 333 articles remained after initial review and were retained in the excel sheet for further review.

### **2.2.2 TOXLINE**

TOXLINE was searched for articles containing "welders" or "welding" published between 2010 and 2012. 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 containing "welders" or "welding" in the title, abstract or key, and published between 2010 and 2012. These results were then filtered to exclude the following subject areas: Engineering; Materials; Physics; Math; Energy; Chemistry; Social Sciences; Agriculture; Business; Dentistry; Biochemistry; Neuroscience. A total of 556 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, and published between 2010 and 2012, but filtered by search terms that included the health and exposure terms described in Section 2.1. This method yielded 379 articles, which were exported to another excel spreadsheet.

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

## **2.3 Literature Reviews**

The results from the various literature searches were sorted by PubMed identification number and duplicates were removed. Case reports, commentaries, conference presentations, and many foreign studies (*e.g.*, exposure studies from China) were also removed. The remaining citations were sorted into separate excel spreadsheets by publication year (2010, 2011, and 2012). For the 2010 search results, articles that were included in the previous review for 2010 were removed.

For each year, the articles' titles and abstracts were reviewed and either removed due to irrelevance or sorted into the following categories:

- Particle characterization and exposure data
- Epidemiology and controlled human studies
- Animal studies
- Cell/*in vitro*/mechanistic studies
- Integrative reports

The breakdown of the articles by year and category is listed in Table 1. We provided full abstracts for exposure-related studies, as was done in previous literature searches for AWS, and we summarized the

abstracts for all health-related studies (Sections 3-5, which correspond to the 2010, 2011, and 2012 health literature, respectively).

**Table 1 Breakdown of Abstracts Reviewed, by Study Category and Publication Year**

Study Category	2010	2011	2012	Total
Particle characterization and exposure	3	6	8	17
Epidemiology and controlled human exposure	10	24	13	47
Animal	6	7	3	16
Cell/ <i>in vitro</i> /mechanistic	1	1	1	3
Integrative reports	0	0	0	0
<b>Total</b>	<b>20</b>	<b>38</b>	<b>25</b>	<b>83</b>

### 3 Summary of 2010 Literature (Partial)

Gradient conducted a literature review of 2010 as outlined in Section 2. We note that several studies were published on-line in 2010 (epub date) but did not appear in the published paper copy of the journal until 2011, the PMID refers to the PubMed reference number. Articles that were not relevant or were included in a prior AWS review were removed. In this section we include a brief summary of exposure studies and study abstracts (Section 3.1) and a summary of health-related studies by health outcome (Section 3.2).

#### 3.1 Exposure

##### 3.1.1 Summaries

We identified three exposure-related papers that were not included in the previous 2010 review. Abstracts are provided below for all relevant studies in lieu of summaries as the focus of our review was on health effects studies. Briefly, the studies reported the following key findings:

- Welders are exposed to significantly higher concentrations of welding fume metals (474  $\mu\text{g}/\text{m}^3$  for welders than non-welders 60  $\mu\text{g}/\text{m}^3$ ). Concentrations of irritant gases, nitrogen dioxide ( $\text{NO}_2$ ) and ozone ( $\text{O}_3$ ) were also higher compared to non-welders, but differences were not statistically significant (Schoonover *et al.*, 2011 [epub: 2010], PMID: 20823632).
- Welding fume metal exposures vary significantly between different types of welding. Gas metal arc welding (GMAW) and shielded metal arc welding (SMAW) yielded higher exposure to welding fume metals than welders performing gas tungsten arc welding (Schoonover *et al.*, 2011 [epub: 2010], PMID: 20823632).
- There are significant differences in the particle number size distributions between different welding aerosols, however, the particle mass size distributions were not significantly different.

For all measure welding techniques, the particle mass was between 0.1 and 1  $\mu\text{m}$  (Berlinger *et al.*, 2011 [epub: 2010], PMID: 20845032).

- Chemical composition of welding particles varies by size: small particles (diameters below 50 nm) contained mostly metal oxides whereas larger particles contained more volatile elements, such as potassium, fluorine and sodium (Berlinger *et al.*, 2011 [epub: 2010], PMID: 20845032).
- After measuring manganese (Mn) exposure from gas metal arc welding using different metal transfer modes and shield gases, exposures to welding fumes include multiple Mn species, both soluble and insoluble. Exposures to Mn species varied with the specific process and shield gas, but the dominant species was acid-soluble  $\text{Mn}^{2+}$  which ranged from 2.6 to 9.3% (Keane *et al.*, 2010, PMID: 21491680).

### 3.1.2 Abstracts

#### **Schoonover *et al.* (2011 [epub: 2010], PMID: 20823632)**

The objective of this study was to characterize personal exposures to welding-related metals and gases for production welders and non-welders in a large manufacturing facility. Welding fume metals and irritant gases, nitrogen dioxide ( $\text{NO}_2$ ) and ozone ( $\text{O}_3$ ), were sampled for thirty-eight workers. Personal exposure air samples for welding fume metals were collected on 37 mm open face cassettes and nitrogen dioxide and ozone exposure samples were collected with diffusive passive samplers. Samples were analyzed for metals using Inductively Coupled Plasma Mass Spectrometry (ICP-MS) and welding fume metal exposure concentrations were defined as the sum of welding-related metals mass per volume of air sampled. Welding fume metal exposures were highly variable among similar types of welding while  $\text{NO}_2$  and  $\text{O}_3$  exposure were less variable. Welding fume metal exposures were significantly higher  $474 \mu\text{g}/\text{m}^3$  for welders than non-welders  $60 \mu\text{g}/\text{m}^3$  ( $p=0.001$ ). Welders were exposed to higher concentrations of  $\text{NO}_2$  and  $\text{O}_3$  than non-welders but the differences were not statistically significant. Welding fume metal exposure concentrations for welders performing gas metal arc welding (GMAW) and shielded metal arc welding (SMAW) were higher than welders performing gas tungsten arc welding (GTAW). Non-welders experienced exposures similar to GTAW welders despite a curtain wall barrier separating welding and non-welding work areas.

#### **Berlinger *et al.* (2011 [epub: 2010], PMID: 20845032)**

Physicochemical properties important in exposure characterisation of four different welding aerosols were investigated. Particle number size distributions were determined by scanning mobility particle sizer (SMPS), mass size distributions by separation and weighing the individual size fractions of an 11-stage cascade impactor. The size distribution of the primary particles of agglomerates, chemical composition and morphology of the particles were examined by TEM. There were significant differences in the particle number size distributions of the different welding aerosols according to the SMPS determinations. The particle mass size distributions determined gravimetrically were, however, not really different. The dominant range with respect to mass was between 0.1 and 1  $\mu\text{m}$ , regardless of the welding technique. Most of the primary particles in all different welding aerosols had diameters between 5 and 40 nm. All types of primary particles had a tendency to form chainlike agglomerates. A clear size dependence of the particle chemical composition was encountered in the case of manual metal arc welding aerosol. Small particles with diameters below 50 nm were mostly metal oxides in contrast to larger particles which also contained more volatile elements (*e.g.*, potassium, fluorine, sodium, sulphur).

**Keane *et al.*, (2010, PMID: 21491680)**

Fumes from a group of gas metal arc welding (GMAW) processes used on stainless steel were generated using three different metal transfer modes and four different shield gases. The objective was to identify and measure manganese (Mn) species in the fumes, and identify processes that are minimal generators of Mn species. The robotic welding system was operated in short-circuit (SC) mode (Ar/CO<sub>2</sub> and He/Ar), axial spray (AXS) mode (Ar/O<sub>2</sub> and Ar/CO<sub>2</sub>), and pulsed axial-spray (PAXS) mode (Ar/O<sub>2</sub>). The fumes were analyzed for Mn by a sequential extraction process followed by inductively coupled plasma-atomic emission spectroscopy (ICP-AES) analysis, and by X-ray diffraction (XRD). Total elemental Mn, iron (Fe), chromium (Cr) and nickel (Ni) were separately measured after aqua regia digestion and ICP-AES analysis. Soluble Mn<sup>2+</sup>, Fe<sup>2+</sup>, Fe<sup>3+</sup>, and Ni<sup>2+</sup> in a simple biological buffer (phosphate-buffered saline) were determined at pH 7.2 and 5.0 after 2 h incubation at 37 °C by ion chromatography. Results indicate that Mn was present in soluble form, acid-soluble form, and acid-soluble form after reduction by hydroxylamine, which represents soluble Mn<sup>0</sup> and Mn<sup>2+</sup> compounds, other Mn<sup>2+</sup> compounds, and (Mn<sup>3+</sup> and Mn<sup>4+</sup>) compounds, respectively. The dominant fraction was the acid-soluble Mn<sup>2+</sup> fraction, but results varied with the process and shield gas. Soluble Mn mass percent in the fume ranged from 0.2 to 0.9%, acid-soluble Mn<sup>2+</sup> compounds ranged from 2.6 to 9.3%, and acid plus reducing agent-soluble (Mn<sup>3+</sup> and Mn<sup>4+</sup>) compounds ranged from 0.6 to 5.1%. Total Mn composition ranged from 7 to 15%. XRD results showed fumes had a crystalline content of 90-99% Fe<sub>3</sub>O<sub>4</sub>, and showed evidence of multiple Mn oxides, but overlaps and weak signals limited identification. Small amounts of the Mn<sup>2+</sup> in the fume (<0.01 to ≈ 1% or <0.1 to ≈ 10 µg/ml and Ni<sup>2+</sup> (<0.01 to ≈ 0.2% or <0.1 to ≈ 2 mg/ml ions were found in biological buffer media, but amounts were highly dependent on pH and the welding process. Mn generation rates for the fractions were tabulated, and the influence of ozone is discussed. The authors concluded that exposures to welding fumes include multiple Mn species, both soluble and insoluble, and that exposures to Mn species vary with specific processes and shield gases.

### **3.2 Human Health Effects Studies**

A prior partial report of the 2010 health effects literature related to welding has been conducted and the key findings from that review are summarized in the bullets below. A summary of relevant studies not covered in the prior review follows.

Summary of findings in prior partial 2010 review:

- Welding was significantly associated with chronic obstructive pulmonary disease in Department of Energy workers' exposure to welding and other agents (Dement *et al.*, 2010, Ref. 7). Welding was also associated with a 20% decline in pulmonary function and increased risk of occupational asthma (Temel *et al.*, 2010, as cited in previous partial review Ref. 20), pneumoconiosis (Molinari, 2010, Ref. 15; Seminario *et al.*, 2010, Ref. 18; Ashizawa *et al.*, 2010, Ref. 1), and invasive pneumococcal disease (Wong *et al.*, 2010, Ref. 22).
- Several cases of metal fume fever were reported (Bydash *et al.*, 2010, Ref. 3; Cain *et al.*, Ref. 4, Yordanov *et al.*, Ref. 24), but the link to welding was not discussed.
- Occupational welders do not have elevated risks of gastrointestinal or testicular cancer (Gatto *et al.*, 2010; Langer *et al.*, 2010) compared with the general population, however, the risk of pleural mesothelioma (Rolland *et al.*, 2010) and non-Hodgkin lymphoid neoplasms (Wong *et al.*, 2010) was higher for welders than for the general population.



- Blue blocking and UV-blocking intraocular lens (IOLs) transmit negligible quantities of ultraviolet-B (UV-B) radiation, which is associated with maculopathy. Also, UV-B radiation passage through crystalline lenses decreases with lens age (Turner, 2010).
- Exposure to noise in the presence of welding fumes may be associated with accelerated hearing loss in welders (Solano *et al.*, 2010).
- Flow cytometry is a useful tool for measurement of cellular oxidative stress and is potentially a viable indicator of disease outcomes. Markers of inflammation and oxidative stress were elevated in blood cells of workers exposed to welding fumes (du Plessis *et al.*, 2010).
- Exhaled breath condensate (EBC) is a viable biomarker of pulmonary exposure, effect and susceptibility (Corradi *et al.*, 2010). Nitrate concentrations in EBC were measured in welders and were significantly higher than controls both before and after shifts, but were lower if personal protective equipment was used (Gube *et al.*, 2010).
- In a study exposing rats to welding fumes, DNA strand breakage increased with exposure duration until day 15 of exposure and then declined to normal levels with continued exposure. Lipid peroxidation, on the other hand, was elevated throughout the entire exposure period (Chuang *et al.*, 2010).

### 3.2.1 Neurological Effects

Chang *et al.* (2010 a,b) conducted two studies to observe the effects of chronic manganese (Mn) exposure on the brain, particularly memory and motor function. In the first study, Chang *et al.* (2010a, PMID: 20620213) evaluated functional MRI (fMRI) tests conducted on subjects during verbal working memory tasks. The results showed that welders with chronic exposure to Mn had higher brain activity while conducting working memory tasks than controls. Authors noted that the findings may indicate that in order to perform memory tasks at the same level as healthy control individuals, welders may require more neural resources in memory networks to compensate for subtle deficits in memory processes, even if they perform tasks at the same level as healthy control individuals..

The second Chang *et al.* (2010b, PMID: 20833761) study used fMRI during finger tapping tests to study how Mn accumulation-induced degeneration in the basal ganglia affects neural processing of motor function. Chang *et al.* (2010b) found that neural activation (specifically in the bilateral primary sensorimotor cortex (SM1), bilateral supplementary motor area (SMA), bilateral dorsolateral premotor cortex, bilateral superior parietal cortex and ipsilateral dentate nucleus) was higher in welders (n = 42) than controls (n = 26), suggesting that increased brain activation results from compensatory activation of ancillary cortical pathways, which ensures adequate motor function.

### 3.2.2 Cardiovascular Effects

Ibfelt *et al.* (2010, PMID: 20581417) conducted a prospective study in Denmark of 5866 male welders and the incidence of cardiovascular disease compared to expected 5-year age and calendar year-specific incidence rates. Observed incidence rates of acute myocardial infarct (AMI), angina pectoris, and cerebral infarct were higher in welders compared to expected rates. Statistical analyses that included adjustment for smoking, alcohol, and hypertension medication resulted in a significantly increasing hazard rate ratio for chronic ischaemic heart disease, but increases for AMI, angina pectoris, and cerebral infarct that were not statistically significant with increasing exposure to particles (evaluated using a job-exposure matrix). The authors concluded that the study results suggest that exposure to welding particles may increase the risk of cardiovascular disease.

Cavallari *et al.* (2010, PMID: 20798005) compared the circadian variation of hourly heart rate variability (HRV) on work and non-workdays among 18 male boilermaker construction workers using 24-hour ECGs over 44 observation days. Decreased HRV and variation in the circadian pattern were observed on workdays. (Note: abstract does not specify how many welders, if any, were amongst the boilermakers.)

Fang *et al.* (2010, PMID: 19736177) assessed the correlation between personal exposures to particulate matter (less than 2.5  $\mu\text{m}$  in diameter or  $\text{PM}_{2.5}$ ) and levels of circulating adhesion molecules involved in leukocyte adhesion (sICAM-1 and sVCAM-1) and coagulation (vWF) in 26 male welders on welding and non-welding days. These biomarkers are important components of vascular function. Welding and  $\text{PM}_{2.5}$  exposure were significantly associated with decreased leukocyte adhesion and increased coagulation following exposure. The authors concluded that  $\text{PM}_{2.5}$  may acutely impact these endothelial components of vascular function.

### 3.2.3 Cancer

Neasham *et al.* (2011 [epub: 2010], PMID: 20884795) studied occupational risks for lymphomas in the European Prospective Investigation into Cancer and Nutrition Study. They used questionnaires on occupational exposures for 52 different occupations. In analyses that adjustment for potential confounders (study center, age, sex, socioeconomic status, smoking, and alcohol) that could explain associations between disease and exposure, the results showed that welding was not associated with risk of non-Hodgkin's lymphoma or Hodgkin's lymphoma.

Sellepa *et al.* (2010, PMID: 20593913) studied the effect of soluble hexavalent chromium (Cr(VI)) exposure from welding on DNA damage and repair. Analysis of blood leucocytes by Micronucleus assay (MN) and the Comet assay were conducted in 93 welders and 60 controls. DNA repair inhibition was analyzed by assessing XPD gene polymorphism. Welders had significantly increased levels of micronucleated cells and significantly larger mean comet length than controls, which suggests that there may be increased DNA damage and repair inhibition.

### 3.2.4 Injury

Lipscomb *et al.* (2010, PMID: 20506461) reviewed tool- and equipment-related injury data for 1998-2005 from the National Institute for Occupational Safety and Health (NIOSH) occupational supplement to the National Electronic Injury Surveillance System (NEISS-Work). The study found that "[a]lthough over 100 different tools or pieces of equipment were responsible for these injuries, seven were responsible for over 65% of the injury burden: ladders, nail guns, power saws, hammers, knives, power drills, and welding tools in decreasing order."

### 3.2.5 Biomarkers

Jonsson *et al.* (2011 [epub: 2010], PMID: 20862590) obtained RNA from induced sputum from 25 male, non-smoking welders to measure change in gene expression in the airways among welders (working in black steel) with and without symptoms. Each welder was sampled twice – before exposure (after vacation) and after one month exposure. There were increased levels (not significant) of expression for 3 of the 7 genes measured in the sputum of asthmatic welders compared to nonsymptomatic subjects, which may suggest some effect from welding exposures on asthmatic welders.

Ohlson *et al.* (2010, PMID: 21029032) measured the association between inflammatory markers in the blood and inhalation of dust from occupational exposures from welding, cutting, grinding, and working in foundries. Total dust was sampled in the breathing zone of 73 subjects, and inflammatory markers (*e.g.*, interleukin-6 (IL-6), C-reactive protein (CRP), fibrinogen, d-dimer, and urate) were analyzed in plasma and serum collected from the 73 workers before and after shifts. The mean level of total dust was 0.93 mg/m<sup>3</sup>; proxies for the mean respiratory fraction, PM<sub>10</sub> and PM<sub>2.5</sub>, were developed based on stationary measurements. Multiple linear regression found only one statistically significant association: a subgroup of 47 subjects had a statistically significant positive relationship between particle exposure and post-shift IL-6, which authors noted may indicate an increased risk of coronary heart disease.

### 3.3 Animal Studies

Heo *et al.* (2010, PMID: 19936710) exposed the lungs of cynomolgus monkeys to welding fumes for 229 days and allowed them to recover for 153 days. After recovery, gene expression profiles were generated using Affymetrix GeneChip Human U133 plus 2.0; 1,116 genes were significantly up or down-regulated. It is anticipated that these profiles will be useful for understanding the changes in lung function following welding fume exposure in future studies.

Sriram *et al.* (2010a, PMID: 20224926) exposed Sprague-Dawley rats to welding fumes from gas metal arc-mild steel and manual metal arc-hard surfacing in order to assess the neurological risk to the dopaminergic system from neurotoxins in welding fumes (*e.g.*, iron (Fe) and Mn). Welding fume exposure had a significant effect on molecular alterations of the dopaminergic system, measured through elemental analysis and various molecular indices of neurotoxicity. Fume exposure was associated with an increase in Mn deposition and a loss of vital proteins in the striatum and midbrain, as well as persistent down-regulation of certain genes in the midbrain. The effect of welding fume exposure on the dopaminergic system in particular is of interest because of its role in Parkinson's disease.

Sriram *et al.* (2010b, PMID: 20798247) conducted a second study chronically exposing Sprague-Dawley rats to manual metal arc-hard surfacing (MMA-HS) or gas metal arc-mild steel (GMA-MS) fumes. Accumulation of Mn in the brain was observed with both types of welding fumes, which caused impairment in mitochondrial function and altered expression of vital proteins in dopaminergic brain areas. The association with change in the PARK gene may be implicated in the pathogenesis of welding fume-mediated dopaminergic dysfunction as the gene is associated with early-onset Parkinson's disease in humans.

Zeidler-Erdely *et al.* (2010, PMID: 20525249) exposed lung tumor susceptible A/J *versus* resistant C57BL/6J (B6) mice to non-carcinogenic, iron abundant gas metal arc-mild steel (GMA-MS) and carcinogenic, Cr and Ni abundant (GMA-SS) fume to observe the differences in regulation and resolution of the lung inflammatory response. Whole lung microarray using Illumina Mouse Ref-8 expression beadchips was conducted on subjects 4 and 16 weeks after exposure. A more marked transcriptional response was observed in the tumor-susceptible rats. GMA-MS fume exposure altered behavioral gene networks, while GMA-SS fume exposure chronically up-regulated chemotactic and immunomodulatory genes. The authors concluded that results suggest that lung tumor susceptibility may lead to a delay in recovery from welding fume-induced lung inflammation and shed light on genetic factors involved in lung response to welding fume.

Antonini *et al.* (2010, PMID: 20560776) exposed rats to gas metal arc-mild steel (GMAW-MS) or manual metal arc-hardsurfacing (MMAW-HS) welding fumes to study the fate of welding fume metals in lung tissue and the associated lung injury and inflammation. GMAW-MS fume appeared to have no effect on toxicity when compared with controls, while MMAW-HS fume induced significant persistent lung

damage early after treatment. Welding fume metals were cleared from the lungs at varying rates and deposited in other organs. Manganese in particular was found to deposit in the brain, including the striatum and midbrain.

Huang *et al.* (2011 [epub: 2010], PMID: 20813406) exposed Sprague-Dawley rats to manganese chloride for 30 days, 90 days, or for 90 days followed by a 30-day post-exposure recovery period to assess the effects of Mn on the liver. A significant positive dose-response effect was observed for liver injury and Mn exposure, however, recovery was observed during the post-exposure period.

### 3.4 Mechanistic Studies

Leonard *et al.* (2010, PMID: 21047424) studied the generation of free radicals and reactive species as a result of exposure to stainless steel and mild steel welding fumes generated by a gas metal arc robotic welder. Both types of welding fumes caused significant oxidative damage. Time since exposure, particle size and chemical composition of the steel also had a significant impact on the level of oxidative damage observed. The authors concluded results suggest that exposure to these welding fumes may be associated with acute lung injury.

## 4 Summary of 2011 Literature

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Gradient conducted a literature review of 2011 as outlined in Section 2. We note that some of the studies were published on-line in 2011 (epub date) but did not appear in the published paper copy of the journal until 2012. Articles that were not relevant were removed. In this section we include a brief summary of exposure studies and study abstracts (Section 4.1) and a summary of health-related human studies by health outcome (Section 4.2), animal studies (Section 4.3), and mechanistic studies (Section 4.4).

### 4.1 Exposure

#### 4.1.1 Summaries

We identified 6 exposure related papers from 2011. Abstracts are provided in Section 4.1.2 below. Briefly, the studies reported the following key findings:

- Hobson *et al.* (2011, PMID: 20870928) attempted to develop a multivariate model to estimate welding fume exposure based on welding particle mass, Mn concentration, and other exposure parameters. The model needed more detailed exposure determinants.
- Total particulate matter and Manganese (Mn) exposure varies significantly by country and industry, however, in most industries, exposure exceeds acceptable concentrations (Liu *et al.*, 2011, PMID: 21355083).
- Richman *et al.* (2011, PMID: 21625364) presents a method using scanning transmission electron microscopy (STEM) to measure the Mn content across the particle size distribution of welding fume particle samples collected on filters for application in exposure and health research.

- The magnetic field associated with grinders, an air hammer, and a drill using electromagnetic anchorage were much lower than the magnetic field associated with welding. All of these magnetic fields were lower than certain guideline thresholds for electrical nerve or muscular stimulation (Yamaguchi-Sekino *et al.*, 2011, PMID: 21670555).
- Two different methods of measuring noise, dosimeter and task-based measurement, yielded significantly different noise exposure measurements for welders. For most other occupations, the two methods reported similar measurements (Li *et al.*, 2011, PMID: 21740746).
- Zugasti *et al.* (2012 [epub: 2011], PMID: 22037834) compared three personal inhalable samplers' efficiencies and found that PGP-GSP 3.5 and Button had similar measurements, while IOM measurements were significantly different.

#### 4.1.2 Abstracts

##### **Hobson *et al.* (2011, PMID: 20870928)**

**Background:** Welders are frequently exposed to Manganese (Mn), which may increase the risk of neurological impairment. Historical exposure estimates for welding-exposed workers are needed for epidemiological studies evaluating the relationship between welding and neurological or other health outcomes. The objective of this study was to develop and validate a multivariate model to estimate quantitative levels of welding fume exposures based on welding particulate mass and Mn concentrations reported in the published literature.

**Methods:** Articles that described welding particulate and Mn exposures during field welding activities were identified through a comprehensive literature search. Summary measures of exposure and related determinants such as year of sampling, welding process performed, type of ventilation used, degree of enclosure, base metal, and location of sampling filter were extracted from each article. The natural log of the reported arithmetic mean exposure level was used as the dependent variable in model building, while the independent variables included the exposure determinants. Cross-validation was performed to aid in model selection and to evaluate the generalizability of the models.

**Results:** A total of 33 particulate and 27 Mn means were included in the regression analysis. The final model explained 76% of the variability in the mean exposures and included welding process and degree of enclosure as predictors. There was very little change in the explained variability and root mean squared error between the final model and its cross-validation model indicating the final model is robust given the available data.

**Conclusions:** This model may be improved with more detailed exposure determinants; however, the relatively large amount of variance explained by the final model along with the positive generalizability results of the cross-validation increases the confidence that the estimates derived from this model can be used for estimating welder exposures in absence of individual measurement data.

##### **Liu *et al.* (2011, PMID: 21355083)**

**Background/Aims:** Exposures to total particulate matter (TP) and manganese (Mn) received by workers during welding and allied hot processes were analyzed to assess the sources and magnitudes of variability.

**Methods:** Compilation of data from several countries identified 2065 TP and 697 Mn measurements for analysis. Linear mixed models were used to determine fixed effects due to different countries, industries

and trades, process characteristics, and the sampling regimen, and to estimate components of variance within workers (both intraday and interday), between workers (within worksites), and across worksites.

**Results:** The fixed effects explained 55 and 49% of variation in TP and Mn exposures, respectively. The country, industry/trade, type of ventilation, and type of work/welding process were the major factors affecting exposures to both agents. Measurements in the USA were generally higher than those in other countries. Exposure to TP was 67% higher in enclosed spaces and 43% lower with local exhaust ventilation (LEV), was higher among boilermakers and was higher when either a mild-steel base metal or a flux cored consumable was used. Exposure to Mn was 750% higher in enclosed spaces and 67% lower when LEV was present. Air concentrations of Mn were significantly affected by the welding consumables but not by the base metal. Resistance welding produced significantly lower TP and Mn exposures compared to other welding processes. Interestingly, exposures to TP had not changed over the 40 years of observation, while those of Mn showed (non-significant) reductions of 3.6% year<sup>-1</sup>. After controlling for fixed effects, variance components between worksites and between-individual workers within a worksite were reduced by 89 and 57% for TP and 75 and 63% for Mn, respectively. The within-worker variation (sum of intraday and interday variance components) of Mn exposure was three times higher than that of TP exposure. The estimated probabilities of exceeding occupational exposure limits were very high (generally much >10%) for both agents.

**Conclusions:** Welding exposures to TP and Mn vary considerably across the world and across occupational groups. Exposures to both contaminants have been and continue to be unacceptably high in most sectors of industry. Because exposures to the two agents have different sources and characteristics, separate control strategies should be considered to reduce welders' exposures to TP and Mn.

#### **Richman *et al.* (2011, PMID: 21625364)**

Increasing evidence suggests that the physicochemical properties of inhaled nanoparticles influence the resulting toxicokinetics and toxicodynamics. This report presents a method using scanning transmission electron microscopy (STEM) to measure the Mn content throughout the primary particle size distribution of welding fume particle samples collected on filters for application in exposure and health research. Dark field images were collected to assess the primary particle size distribution and energy-dispersive X-ray and electron energy loss spectroscopy were performed for measurement of Mn composition as a function of primary particle size. A manual method incorporating imaging software was used to measure the primary particle diameter and to select an integration region for compositional analysis within primary particles throughout the size range. To explore the variation in the developed metric, the method was applied to 10 gas metal arc welding (GMAW) fume particle samples of mild steel that were collected under a variety of conditions. The range of Mn composition by particle size was -0.10 to 0.19 %/nm, where a positive estimate indicates greater relative abundance of Mn increasing with primary particle size and a negative estimate conversely indicates decreasing Mn content with size. However, the estimate was only statistically significant ( $p < 0.05$ ) in half of the samples ( $n=5$ ), which all had a positive estimate. In the remaining samples, no significant trend was measured. Our findings indicate that the method is reproducible and that differences in the abundance of Mn by primary particle size among welding fume samples can be detected.

#### **Yamaguchi-Sekino *et al.* (2011, PMID: 21670555)**

The assessment of the occupational electromagnetic field exposure of welders is of great importance, especially in shielded-arc welding, which uses relatively high electric currents of up to several hundred amperes. In the present study, we measured the magnetic field exposure level of welders in the course of working. A 3-axis Hall magnetometer was attached to a subject's wrist in order to place the sensor probe

at the closest position to the magnetic source (a cable from the current source). Data was acquired every 5 s from the beginning of the work time. The maximum exposed field was 0.35-3.35 mT (Mean  $\pm$  SD:  $1.55 \pm 0.93$  mT, N=17) and the average value per day was 0.04-0.12 mT (Mean  $\pm$  SD:  $0.07 \pm 0.02$  mT, N=17). We also conducted a finite element method-based analysis of human hand tissue for the electromagnetic field dosimetry. In addition, the magnetic field associated with grinders, an air hammer, and a drill using electromagnetic anchorage were measured; however, the magnetic fields were much lower than those generated in the welding process. These results agreed well with the results of the electromagnetic field dosimetry (1.49 mT at the wrist position), and the calculated eddy current (4.28 mA/m<sup>2</sup>) was much lower than the well-known guideline thresholds for electrical nerve or muscular stimulation.

### **Li et al. (2011, PMID: 21740746)**

**Background:** Task-based measurement (TBM) is a method to assess the eight-hour A-weighted equivalent noise exposure level (L(Aeq.8h)) besides dosimeter. TBM can be better used in factories by non-professional workers and staffs. However, it is still not clear if TBM is equal or similar with dosimeter for L(Aeq.8h) measurement in general. This study considered the measurement with dosimeter as real personal noise exposure level (PNEL) and assessed the accuracy of TBM by comparing the consistencies of TBM and dosimeter in L(Aeq.8h) measurement.

**Methods:** The study was conducted in one automobile firm among 387 workers who are exposed to unstable noise. Dosimeters and TBM were used to compare the two strategies and assess the degree of agreement and causes of disagreement. Worker's PNEL was measured *via* TBM for noise; the real PNEL was also recorded. The TBM for noise was computed with task/position noise levels measured *via* sound level meter and workers' exposure information collected *via* working diary forms (WDF) filled by participants themselves. Full-shift noise exposure measurement *via* personal noise dosimeters were taken as the real PNEL. General linear model (GLM) was built to analyze the accuracy of TBM for noise and the source of difference between TBM for noise and real PNEL.

**Results:** The L(Aeq.8h) with TBM were slightly higher than the real PNELs, except the electricians. Differences of the two values had statistical significance in stamping workers ( $P < 0.001$ ), assembly workers ( $P = 0.015$ ) and welding workers ( $P = 0.001$ ). The correlation coefficient of L(Aeq.8h) with TBM and real PNELs was 0.841. Differences of the two results were mainly affected by real PNEL ( $F = 11.27$ ,  $P = 0.001$ ); and work groups ( $F = 3.11$ ,  $P < 0.001$ ) divided by jobs and workshops were also independent factors. PNEL of workers with fixed task/position ( $(86.53 \pm 8.82)$  dB(A)) was higher than those without ( $(75.76 \pm 9.92)$  dB(A)) ( $t = 8.84$ ,  $P < 0.01$ ). Whether workers had fixed task/position was another factor on the accuracy of TBM for noise ( $F = 4.36$ ,  $P = 0.038$ ).

**Conclusion:** TBM for noise has acceptable accuracy on workers' PNEL measurement. The accuracy is affected by job categories, workshops and variability of task/position. TBM for noise can yield a relatively conservative result of worker's PNEL in most cases, so it can be used to measure and assess workers' real PNEL.

### **Zugasti et al. (2012 [epub: 2011], PMID: 22037834)**

Inhalable sampler efficiency depends on the aerodynamic size of the airborne particles to be sampled and the wind speed. The aim of this study was to compare the behaviour of three personal inhalable samplers for welding fumes generated by Manual Metal Arc (MMA) and Metal Active Gas (MAG) processes. The selected samplers were the ones available in Spain when the study began: IOM, PGP-GSP 3.5 (GSP) and Button. Sampling was carried out in a welding training center that provided a homogeneous workplace

environment. The static sampling assembly used allowed the placement of 12 samplers and 2 cascade impactors simultaneously. 183 samples were collected throughout 2009 and 2010. The range of welding fumes' mass concentrations was from 2 mg m<sup>-3</sup> to 5 mg m<sup>-3</sup>. The pooled variation coefficients for the three inhalable samplers were less than or equal to 3.0%. Welding particle size distribution was characterized by a bimodal log-normal distribution, with MMADs of 0.7 µm and 8.2 µm. For these welding aerosols, the Button and the GSP samplers showed a similar performance (P = 0.598). The mean mass concentration ratio was 1.00 ± 0.01. The IOM sampler showed a different performance (P < 0.001). The mean mass concentration ratios were 0.90 ± 0.01 for Button/IOM and 0.92 ± 0.02 for GSP/IOM. This information is useful to consider the measurements accomplished by the IOM, GSP or Button samplers together, in order to assess the exposure at workplaces over time or to study exposure levels in a specific industrial activity, as welding operations.

## 4.2 Human Health Effects Studies

### 4.2.1 Neurological Effects

Kim *et al.* (2011, PMID: 21111757) conducted a study comparing white matter of the human brain in manganese-exposed welders (n=30 males) to gender-matched control subjects (n=19). White matter microstructure indicators [Fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD)] were measured in all subjects. A reduction of FA in the corpus callosum and frontal white matter, as well as increases in RD were observed in welders. Correlation analysis was conducted between these microstructural abnormalities and neurobehavioral performance. The authors concluded that results indicate a possible association with these effects and motor and cognitive effects in welders.

Laohaudomchok *et al.* (2011, PMID: 21192973) conducted a study analyzing the neuropsychological effects of lower level Mn exposure in 46 male welders. Mn exposure was estimated based on air Mn measurement and work history and compared to performance on cognitive, motor control, and psychological tests. Increasing total Mn exposure was significantly associated with slower reaction time on the continuous performance test (CPT), as well as worse mood for several scales on the Profile of Mood States. In addition, 24 subjects who were administered neuropsychology tests before and after work shifts performed worse on the CPT test and significantly worse on fine motor control tests. The authors concluded that the results suggest that even low level Mn exposure that welders experience (median Mn exposures were 12.9 µg/m<sup>3</sup>) may have neuropsychological effects.

Sen *et al.* (2011, PMID: 21307282) assessed the effects of chronic, low-level Mn exposure and relevant areas of accumulation in the brain of seven welders (exposure estimated by occupational questionnaire) and seven controls. MRI tests of the brain and Grooved Pegboard performance of both hands, Trail making, and olfactory function tests were administered to the patients to measure areas of Mn accumulation in the brain and motor and cognitive function. Welders scored significantly worse on the Grooved Pegboard test for both dominant (p=0.06) and non-dominant hands (p=0.03). There were no significant differences between the welders and controls for the Trail-making test or the olfactory test. The authors concluded that results suggest that subclinical exposure to Mn may be associated with deficits in motor function, but not cognitive deficits.

Corbacio *et al.* (2011, PMID: 21544842) conducted a study evaluating the effects of 60 Hz, 3 mT magnetic fields on human cognitive performance. Ninety-nine subjects (double-blind protocol) divided into three groups (sham/sham, MF exposure/sham, or sham/MF exposure) completed psychometric tests under two consecutive magnetic field conditions (MF-exposure groups only). No clear association



between magnetic fields and human cognition was found, but improved performance with practice was not present for both exposure groups, which the authors noted could indicate a possible interference with neuropsychological processes.

Sanchez-Ramos *et al.* (2011, PMID: 21655131) conducted a retrospective study of the utility of quantitative tremor analysis tools in differentiating the symptoms of chronic Mn exposure from welding fumes, Idiopathic Parkinson's Disease (IPD), and Essential Tremor (ET). Welders and ET patients had significantly higher increased postural tremor intensity as well as higher center frequency with extended arms, compared to IPD subjects. Welders, however, had a significantly lower center frequency tremor without arms extended than ET patients. The authors concluded that along with exposure history and neurological examination, tremor analysis may be useful in diagnosing Mn-related symptoms.

Harris *et al.* (2011, PMID: 21724446) evaluated the prevalence of parkinsonism and studied its impact on the quality of life and health status, which have important repercussions for worker safety and performance, in 394 active welders. All subjects completed a Parkinson's disease symptom questionnaire and the PDQ39, a questionnaire used as a measure of health status and quality of life. Welders with parkinsonism consistently scored higher on the PDQ39 (indicating a lower quality of life) than those without parkinsonism, particularly in mobility, emotional well-being, and activities of daily living. Scores in patients with parkinsonism and early Parkinson's disease were not significantly different.

Feldman *et al.* (2011, PMID: 21733735) followed a cohort of 14,169 men for up to 43 years and identified 234 cases of parkinsonism, 204 of which had Parkinson's disease. They analyzed potential occupational risk factors associated with Parkinson's disease and parkinsonism from prospectively collected data in the population-based Swedish Twin Registry. The Job Exposure Matrix was used to assess exposure to 14 chemical and biological compounds the 234 cases. Of the 14 compounds assessed, only exposure to inorganic dust was found to be associated with Parkinson's disease and parkinsonian disorders. No association was found between Parkinson's disease or parkinsonian disorders and occupational exposure to pesticides, welding smoke, metal dust, wood dust, animal handling, stone and concrete dust, chrome and nickel dust, quartz dust, organic dust, oil, asbestos, organic solvents, and irritating gas.

Bowler *et al.* (2011, PMID: 21762725) previously identified dose-effect relationships in a group of 43 confined space welders for adverse neurological/neuropsychological functional effects in relation to Mn in blood or air (cumulative exposure index). The welders' exposure to Mn was unprotected and with poor ventilation, lasting an average of 16.5 months. Three and a half years later after cessation of confined space welding, Bowler *et al.* conducted this follow-up study on 26 welders (mean age of 47 years) who had previously been studied (Bowler *et al.*, 2007) to assess the association between Mn in blood and air and the status of mood, movement/neuromotor, and cognitive functions, and olfaction. Thirteen of the participants were no longer welding. Those still welding had significantly higher blood Mn levels than those who had ceased welding activity ( $p = 0.002$ ). Overall, the mean cognitive functioning, motor dexterity/tactile function and graphomotor tremor improved significantly and emotional disturbance improved slightly. Psychomotor speed and neurological examination findings did not change. Rigidity, dominant postural hand tremor, and body sway worsened. Olfactory scores remained depressed. The authors concluded "[a]s the Mn exposure of the Bay Bridge welders frequently exceeded the Cal-OSHA TLV of 0.2 mg Mn/m<sup>3</sup> at baseline, a more stringent preventative measure is recommended for confined space welding."

Wastensson *et al.* (2012 [epub: 2011], PMID: 22038089) administered quantitative tests of tremor, motor speed, manual dexterity, diadochokinesis (ability to perform rapidly alternating muscular movements), eye-hand coordination and postural stability to 17 retired ship welders (mean age = 69 years, mean exposure = 28 years) in order to evaluate the persistence of neuromotor function impairment after

cessation of Mn exposure, which had ceased on average 18 years before. Cumulative Mn exposure was calculated and compared with 21 controls (mean age = 66 years) working in the same shipyards. The welders had significantly poorer performance on Grooved Pegboard tests than controls, and decreased performance was associated with increased cumulative exposure. Performance on all other neurobehavioral tests was similar between welders and controls, which the authors suggested indicated that previous adverse effects on the neuromotor system may have ceased.

Criswell *et al.* (2011, PMID: 21471467) assessed the effects of welding fume exposure on nigrostriatal neurons in asymptomatic welders. PET scans were administered to 20 asymptomatic welders, 20 non-welder subjects with idiopathic Parkinson's disease, and 20 normal controls. The authors concluded that the results in asymptomatic welders compared to controls suggests that the asymptomatic welders may have dysfunction in the dopamine system. Differences in the scans also indicated that patterns of dysfunction in Mn neurotoxicity are different from those observed in symptomatic Parkinson's disease.

#### 4.2.2 Cancer

Corbin *et al.* (2011, PMID: 20957667) studied the association between occupation and lung cancer using the New Zealand Cancer Registry. They interviewed 457 people in the registry and 792 controls to obtain demographic details, potential confounders, and employment history. Associations were estimated using logistic regression adjusted for gender, age, ethnicity, smoking, and socio-economic status. Welders and flame cutters had an elevated risk, however, the odds ratio was not statistically significant (OR= 2.50; 95% CI: 0.86-7.25).

Halasova *et al.* (2012, [epub: 2011] PMID: 21858514) studied the association of chromosomal damage and chromium exposure in 73 welders exposed 10.2 years  $\pm$  1.67 years and 71 controls without known exposure to chromium. Chromosomal aberrations and polymorphisms in DNA repair genes were measured and chromium concentration in the blood was determined for all subjects. Blood chromium levels were significantly higher in welders than controls. Markers of chromosomal damage measured were similar between both groups. Chromatid aberrations were positively correlated with the concentration of chromium in the blood. Additionally, significantly higher total chromosomal aberrations were associated with the homozygous variant polymorphism in XRCC1 Arg399Gln gene. A similar trend was found for chromatid-type aberrations. The authors concluded that genetic make-up in DNA repair genes may increase susceptibility to the adverse effects of chromium.

Dominici *et al.* (2011, PMID: 21862403) studied the genotoxic risk of occupational exposure to extremely low-frequency magnetic fields (ELF-MF) in 21 workers and 21 controls in Italy. Personal magnetic-field dosimeters were used to assess exposure to ELF-MF, and micronuclei (MN) and sister chromatid exchange (SCE) frequencies in lymphocytes (in blood) were measured. A significantly higher frequency of MN was observed in the welders and correlated with a proportional increase in ELF-MF exposure with a dose-response relationship. Additionally, a significant decrease in SCE frequency was observed in welders compared to controls. The authors concluded that there was some evidence of an association between genotoxicity and ELF-MF exposure, especially with regard to MN.

Guida *et al.* (2011 PMID: 21866050) assessed the association between occupation and lung cancer in a French population-based case-control study. Occupational history was collected for 2923 cases and 3555 controls. For men, excess risks (smoking-adjusted odds ratios) were found for various occupations including welders, plumbers, and several construction crafts.

Sudha *et al.* (2011, PMID: 21790248) compared DNA damage in buccal cells using micronucleus and comet assays in 66 welders exposed to chromium (CrVI) and 60 control subjects with similar mean ages,

smoking prevalence, and alcohol consumption. Welders had significantly more micronucleated cells and larger mean comet tail length, which the authors noted suggests that chronic occupational exposure to CrVI during welding could lead to increased DNA damage.

### 4.2.3 Reproductive Effects

El-Helaly *et al.* (2011, PMID: 21590429) conducted a case-control study to assess the association between paternal occupational exposures during the periconceptional period (the period before conception to early pregnancy) and the risk of congenital malformations. Questionnaires were administered to both parents of 242 congenital malformation cases and 270 controls to collect information on occupational exposures, as well as other potential congenital malformation risk factors (*e.g.*, consanguinity (blood relative), smoking, maternal history of disease). The authors concluded that the results indicated that exposure to welding fumes increased the odds of having a child with congenital malformations (OR: 2.98, 95% CI: 0.99-8.54,  $p < 0.01$ ). Exposure to pesticides and solvents were also found to have significantly increased odds of having a child with congenital malformations.

Riska *et al.* (2012 [epub: 2011], PMID: 21805475) studied the correlation between primary fallopian tube carcinoma (PFTC) and occupational exposures in females aged 30-64 years during the 1960, 1970, 1980/1981 and/or 1990 censuses in Denmark, Finland, Iceland, Norway, and Sweden. Standardized incidence ratios (SIR) were calculated for 53 occupations based on the national population incidence of PFTC. Welders, printers, painters and chemical process workers were associated with an increased risk of PFTC, however, the SIRs were not significant. The authors noted this study did not adjust for possible confounders.

### 4.2.4 Respiratory Effects

Banga *et al.* (2011, PMID: 21407099) studied the characteristics of subjects with work-related asthma through telephone interview questionnaires and lung function tests. Exposure to welding fumes ( $n=142$ ) was the fifth leading cause of work-related asthma. More than a third had FEV<sub>1</sub> less than 80% of predicted. Most of the workers exposed to welding fumes had sought medical treatment for asthma symptoms, required emergency room visits and/or hospitalization.

Omland *et al.* (2011, PMID: 21752438) conducted a prospective cohort study on 1964 farming-school students and 407 non-farming subjects in order to assess exposures in their childhood and adult environment that may increase the risk of asthma onset. For each case, a control subject was selected from the cohort with no asthma. In a multiple regression model, significant odds ratios were reported for welding (OR: 7.0, 95% CI: 1.2-41.6) as well as for smoking and other activities.

### 4.2.5 Renal Effects

Ding *et al.* (2011, PMID: 21511812) measured cadmium in the breathing zone and in urine, and  $\beta(2)$ -microglobulin ( $\beta(2)$ -MG) in urine (as a marker of renal tubular function) in 103 Chinese welders. The concentration of cadmium in the workers' breathing zones ranged from 5 to 86  $\mu\text{g}/\text{m}^3$ , and 17% of the breathing zone samples exceeded the threshold limit value. Six welders had cadmium concentrations in urine exceeding the Chinese recommended reference values.  $\beta(2)$ -microglobulin ( $\beta(2)$ -MG) in urine was positively correlated with urinary cadmium, and in two welders the concentrations were close to levels that indicated chronic cadmium poisoning in China (not provided).

#### 4.2.6 Cardiovascular Effects

Rice *et al.* (2011, PMID: 21187793) conducted a repeated measures panel study on 36 male welders to assess the effects of welding fume particulate matter on circulating lipids. On all welding days, lipid levels were collected before and after welding, and personal exposure to PM<sub>2.5</sub> was measured over 63 exposure and/or control days. A significant decrease in high density lipid (HDL) concentrations was observed 18 hours after welding when adjusted for possible confounders, particularly when welding exposures followed a non-welding day. No other significant effects were observed. The authors noted that the decrease in HDL may be related to the inflammatory and proatherosclerotic effects of PM<sub>2.5</sub> exposure.

#### 4.2.7 Biomarkers

Hoffmeyer *et al.* (2011, PMID: 21103508) studied the effects of different collection devices on the detection of metal concentrations in exhaled breath condensate (EBC). Between two collection devices, ECoScreen and ECoScreen2, ECoScreen2 was preferred because of ECoScreen's potential for contamination of EBC by metallic components. ECoScreen2 was then used to compare iron, nickel, and chromium concentrations in EBC of 36 welders from three different companies and 24 non-exposed controls. Iron concentrations in EBC had the strongest association with exposure to welding fumes. Iron and nickel concentrations differed by working conditions. Chromium was not detected in EBC.

Hoet *et al.* (2012 [epub: 2011], PMID: 21704687) conducted a study to assess potential biomarkers for exposure to Mn in welding fumes in 28 welders. Personal full-shift Mn concentration in air was measured on Monday and Tuesday. On those same days blood and urine samples were collected before and after the shift. Mn in plasma averaged 33% higher in welders than in controls and the after-shift values correlated well with Mn air concentrations above 10 µg/m<sup>3</sup>. Study results indicate that Mn in plasma may be a potential biomarker for Mn exposure and, according to the authors, lends biological plausibility to the intended change for the Mn TLV-TWA of 20 µg/m<sup>3</sup> proposed by ACGIH for respirable Mn particulate.

#### 4.2.8 Injury

Stocks *et al.* (2011, PMID: 21752940) conducted a study comparing standardized incidence ratios (SIR) of work-related ill-health (WRI) in occupations in the UK construction industry. Asthma and musculoskeletal disorders had significantly higher incidence of WRI in welders compared with other workers in the same major Standard Occupational Classifications. Other significantly increased SIRs were identified for other trades.

### 4.3 Animal Studies

Antonini *et al.* (2011a, PMID: 20924559) exposed Sprague-Dawley rats to the two most common welding fumes across US industries, stainless or mild steel welding fumes, to assess their persistence in the lungs and their inflammatory potential. Rats were exposed to either type of fumes or filtered air for 3 hours a day for 3 days. At several points post-exposure, bronchoalveolar lavage was conducted to measure lung injury/inflammation and lung phagocytes. Compared to controls, no effect on lung injury or inflammation was observed for the mild steel fumes, but was significantly elevated at 8 and 21 days post exposure to stainless steel fumes. A higher concentration of metals was found in the lungs of rats exposed to stainless steel fume compared to mild steel fumes. All highly toxic metals cleared from the

lungs more quickly than iron, which could indicate that they are transported more quickly from the respiratory system to other organs. This may have implications for health effects in organs other than the lungs.

Antonini *et al.* (2011b, PMID: 21281223) conducted a study to assess the effects of welding voltage on the physio-chemical properties of fumes and effects on lungs. Rats were exposed *via* inhalation 3 hrs a day for 3 days to 40 mg/m<sup>3</sup> of stainless steel welding fume generated at 25V (normal setting) and 30V. Bronchoalveolar lavage was performed multiple times throughout exposure to assess lung injury and particle size and composition of welding fumes were measured. High voltage (30V) welding fume generated more ultra-fine particles and contained a greater concentration of Mn. Lung injury, however, was more severe and persistence with exposures to welding fumes generated at 25V. The authors concluded that the results suggest that a small increase in voltage impacts particle size of welding fumes, Mn concentration, and lung toxicity.

Zeidler-Erdely *et al.* (2011a, PMID: 21309664) studied exposures to metal arc GMA-SS welding fume in mice to characterize lung inflammation and tumorigenic response. Strains of mice that were susceptible or resistant to tumor formation were exposed to either air (control) or GMA-SS welding fume (40 mg/m<sup>3</sup> for 3 hours a day for 6 and 10 days). Bronchoalveolar lavage was taken repeatedly 10 days after exposure to measure lung cytotoxicity, permeability, inflammatory cytokines, and cell differentials. GMA-SS exposed mice had a significantly elevated inflammatory response in all markers measured, however no increase in tumorigenesis was observed. The elevated levels of markers did not decrease with recovery time. Authors concluded that GMA-SS welding fume causes a sustained inflammatory response in both strains of mice, but was not found to be tumorigenic.

Zeidler-Erdely *et al.* (2011b, PMID: 21480047) conducted a second study to assess the difference in incidence of lung tumors and histopathological alterations in lung-tumor susceptible and resistant rats following exposure to manual metal arc-stainless steel (MMA-SS) welding fume. Mice were exposed once a month for 4 months by pharyngeal aspiration. At 78 weeks post-exposure, histopathological changes in the aorta, heart, kidney, and liver tissue were evaluated. Only in the tumor-susceptible mice, a significant increase in tumors and retention of MMA-SS fume in the lung was observed. Additionally, only the exposed, tumor-susceptible mice had significantly elevated levels of Cr, Cu, Mn, and Zn in kidney and Cr in liver. As the exposed, tumor-resistant mice did not show an increase in tumor incidence, the study results do not suggest significant tumorigenic potential of MMA-SS in the mouse model. However, the authors noted that exposure to MMA-SS may result in other health impacts such as a chronic lung immune response.

Erdely *et al.* (2011a, PMID: 21513782) studied the effects of gas metal arc-stainless steel (GMA-SS) welding fume exposure on systemic inflammation and atherosclerosis lesions in highly susceptible mice (*i.e.*, apolipoprotein E knockout mice). The mice were exposed to GMA-SS for 3 hours a day for 10 days and sacrificed after a 2 week recovery period. Serum chemistry, serum protein profiling and aortic lesion area were measured in all mice following sacrifice. Exposed mice had decreased serum levels of uric acid, potentially reducing their ability to prevent oxidative stress. Serum levels of inflammatory proteins were also increased in exposed mice and they had larger areas of atherosclerotic plaque lesions. The authors concluded that study results suggest increased systemic inflammation and increased plaque progression following GMA-SS exposure.

Erdely *et al.* (2011b, PMID: 21708214) exposed mice to 340 µg of manual metal arc stainless steel (MMA-SS), gas metal arc-SS (GMA-SS) or GMA-mild steel (GMA-MS) by pharyngeal aspiration to assess the effects of exposure to different welding fumes on pulmonary and systemic inflammation. To evaluate inflammation, the mice were sacrificed at 4 and 24 hr after exposure and gene expression profiles were characterized. Minimal differences in inflammation were observed across fume types at 4

hr. At 24 hr, greater changes in gene expression were observed for SS, but not GMA-MS exposure. MMA-SS caused the greatest level of pulmonary cytotoxicity and was the only fume in which exposure increased stress response genes in cardiovascular tissue. The authors concluded that results suggest that a physiological response to welding fume exposure varies by welding fume type.

#### 4.4 Mechanistic Studies

Yu *et al.* (2011, PMID: 21030147) evaluated the effect SiO<sub>2</sub> as a potential additive to shielding gas in reducing biotoxicity of welding fume particles. Analysis of the particles showed that SiO<sub>2</sub> coats the surface of welding fumes particles and promotes particle agglomeration. To assess biotoxicity, *Escherichia coli* (*E. coli*) was exposed to pure SiO<sub>2</sub> generated from the arc welding process. SiO<sub>2</sub> containing welding fumes had significantly less impact on growth rates of *E. coli* than fumes without SiO<sub>2</sub>. Authors concluded that results suggest that SiO<sub>2</sub> may reduce biotoxicity of welding fumes.

## 5 Summary of 2012 Literature

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Gradient conducted a literature review of 2012, as outlined in Section 2. Articles that were not relevant were removed. In this section we include a brief summary of exposure studies and study abstracts (Section 5.1) and a summary of health-related human studies by health outcome (Section 5.2), animal studies (Section 5.3) and mechanistic studies (Section 5.4).

### 5.1 Exposure

#### 5.1.1 Summaries

We identified 8 exposure related papers from 2012. Abstracts are provided below. Briefly, the studies reported the following key findings:

- Cho and Yoon (2012, PMID: 22539557) found that in all respirator models the pressure drop in respirators increased with fume load due to accumulation of particles on the filters.
- In retrospective exposure assessments, the FINJEM (job exposure matrix for asbestos, PAHs and welding fumes designed in Finland) showed a high concordance with expert assessment of welding fume exposure, suggesting that it is an accurate and useful tool in estimating occupational welding fume exposure (Offermans *et al.*, 2012, PMID: 22693270). FINJEM can be used to accurately estimate exposure to metals and welding fumes in Canada and likely other countries (Lavoue *et al.*, 2012, PMID: 22467796)
- Welding process parameters affect the concentration of ultrafine particles present in welding processes metal-active gas (MAG) of carbon steel and friction-stir welding (FSW) of aluminum, though overall FSW results in lower levels of alveolar deposition of particles (Gomes *et al.*, 2012, PMID: 22954401).
- Anderson *et al.* (2012, PMID: 22534696) conducted a qualitative assessment of exposure to thorium, acid mists, asbestos, coal dust, welding fumes, and other chemicals.

- The top three hazards to which American Indian and Alaska natives living in the Southwest U.S. are exposed were pesticides, petroleum, and welding/silver smithing (Redwood *et al.*, 2012, PMID: 22590848).
- Exposure to manganese (Mn) and iron in welding fumes is highly correlated with concentrations of Mn in blood and serum ferritin, respectively (Pesch *et al.*, 2012, PMID: 22377681).
- Exposure to ultrafine particulate matter can be predicted by the welding process. Welding in areas with inefficient local exhaust ventilation and small spaces significantly increase exposure. These factors should be considered to reduce exposure to welding fumes (Lehnert *et al.*, 2012, PMID: 22539559).

### 5.1.2 Abstracts

#### **Cho and Yoon (2012, PMID: 22539557)**

In a previous study, we concluded that respirator testing with a sodium chloride aerosol gave a conservative estimate of filter penetration for welding fume aerosols. A rapid increase in the pressure drop (PD) of some respirators was observed as fumes accumulated on the filters. The present study evaluated particulate respirator PD based on workplace field tests. A field PD tester was designed and validated using the TSI 8130 Automatic Filter Tester, designed in compliance with National Institute for Occupational Safety and Health regulation 42 CFR part 84. Three models (two replaceable dual-type filters and one replaceable single-type filter) were evaluated against CO(2) gas arc welding on mild steel in confined booths in the workplace. Field tests were performed under four airborne concentrations (27.5, 15.4, 7.9, and 2.1 mg m<sup>-3</sup>). The mass concentration was measured by the gravimetric method, and number concentration was monitored using P-Trak (Model 8525, TSI, USA). Additionally, photos and scanning electron microscopy-energy dispersive X-ray spectroscopy were used to visualize and analyze the composition of welding fumes trapped in the filters. The field PD tester showed no significant difference compared with the TSI tester. There was no significant difference in the initial PD between laboratory and field results. The PD increased as a function of fume load on the respirator filters for all tested models. The increasing PD trend differed by models, and PD increased rapidly at high concentrations because greater amount of fumes accumulated on the filters in a given time. The increase in PD as a function of fume load on the filters showed a similar pattern as fume load varied for a particular model, but different patterns were observed for different models. Images and elemental analyses of fumes trapped on the respirator filters showed that most welding fumes were trapped within the first layer, outer web cover, and second layer, in order, while no fumes were observed beneath the fourth layer of the tested respirators. The current findings contribute substantially to our understanding of respirator PD in the presence of welding fumes.

#### **Offermans *et al.* (2012, PMID: 22693270)**

**Objectives:** Reliable retrospective exposure assessment continues to be a challenge in most population-based studies. Several methodologies exist for estimating exposures retrospectively, of which case-by-case expert assessment and job-exposure matrices (JEMs) are commonly used. This study evaluated the reliability of exposure estimates for selected carcinogens obtained through three JEMs by comparing the estimates with case-by-case expert assessment within the Netherlands Cohort Study (NLCS).

**Methods:** The NLCS includes 58,279 men aged 55-69 years at enrolment in 1986. For a subcohort of these men (n=1630), expert assessment is available for exposure to asbestos, polycyclic aromatic hydrocarbons (PAHs) and welding fumes. Reliability of the different JEMs (DOMJEM (asbestos,

PAHs), FINJEM (asbestos, PAHs and welding fumes) and Asbestos JEM (asbestos) was determined by assessing the agreement between these JEMs and the expert assessment.

Results: Expert assessment revealed the lowest prevalence of exposure for all three exposures (asbestos 9.3%; PAHs 5.3%; welding fumes 11.7%). The DOMJEM showed the highest level of agreement with the expert assessment for asbestos and PAHs ( $\kappa$ s=0.29 and 0.42, respectively), closely followed by the FINJEM. For welding fumes, concordance between the expert assessment and FINJEM was high ( $\kappa$ =0.70). The Asbestos JEM showed poor agreement with the expert asbestos assessment ( $\kappa$ =0.10).

Conclusions: This study shows case-by-case expert assessment to result in the lowest prevalence of occupational exposure in the NLCS. Furthermore, the DOMJEM and FINJEM proved to be rather similar in agreement when compared with the expert assessment. The Asbestos JEM appeared to be less appropriate for use in the NLCS.

### **Gomes *et al.* (2012, PMID: 22954401)**

This article describes work performed on the assessment of the levels of airborne ultrafine particles emitted in two welding processes metal-active gas (MAG) of carbon steel and friction-stir welding (FSW) of aluminum in terms of deposited area in alveolar tract of the lung using a nanoparticle surface area monitor analyzer. The obtained results showed the dependence from process parameters on emitted ultrafine particles and clearly demonstrated the presence of ultrafine particles, when compared with background levels. The obtained results showed that the process that results on the lower levels of alveolar-deposited surface area is FSW, unlike MAG. Nevertheless, all the tested processes resulted in important doses of ultrafine particles that are to be deposited in the human lung of exposed workers.

### **Lehnert *et al.* (2012, PMID: 22539559)**

This investigation aims to explore determinants of exposure to particle size-specific welding fume. Area sampling of ultrafine particles (UFP) was performed at 33 worksites in parallel with the collection of respirable particles. Personal sampling of respirable and inhalable particles was carried out in the breathing zone of 241 welders. Median mass concentrations were 2.48 mg m<sup>-3</sup> for inhalable and 1.29 mg m<sup>-3</sup> for respirable particles when excluding 26 users of powered air-purifying respirators (PAPRs). Mass concentrations were highest when flux-cored arc welding (FCAW) with gas was applied (median of inhalable particles: 11.6 mg m<sup>-3</sup>). Measurements of particles were frequently below the limit of detection (LOD), especially inside PAPRs or during tungsten inert gas welding (TIG). However, TIG generated a high number of small particles, including UFP. We imputed measurements <LOD from the regression equation with manganese to estimate determinants of the exposure to welding fume. Concentrations were mainly predicted by the welding process and were significantly higher when local exhaust ventilation (LEV) was inefficient or when welding was performed in confined spaces. Substitution of high-emission techniques like FCAW, efficient LEV, and using PAPRs where applicable can reduce exposure to welding fume. However, harmonizing the different exposure metrics for UFP (as particle counts) and for the respirable or inhalable fraction of the welding fume (expressed as their mass) remains challenging.

### **Anderson *et al.* (2012, PMID: 22534696)**

Exposure was assessed for a cohort of 6409 workers at a former uranium processing facility as part of a mortality study. Workers at the facility had potential for exposure to a wide variety of radiological and chemical agents including uranium, thorium, radon, external ionizing radiation, acid mists, asbestos, and various solvents. Organ dose from internal exposure to uranium was assessed, along with dose from external ionizing radiation and exposure to radon. Qualitative assessment of exposure to thorium, acid mists, asbestos, coal dust, welding fumes, and other chemicals was also performed. Mean cumulative



organ dose from internal uranium exposure ranged from 1.1 mGy (lung) to 6.7  $\mu$ Gy (pancreas). Mean cumulative external ionizing radiation dose was 13.4 mGy. Mean cumulative radon exposure was 26 working level months (WLMs). The chemical agents to which the largest numbers of study subjects were exposed were acid mists, machining fluids, and a tributyl phosphate/kerosene mixture used in the refining process.

**Lavoue *et al.* (2012, PMID: 22467796)**

**Context:** Retrospective exposure assessment in population-based case-control studies poses a major challenge due to the wide range of occupations and industries involved. The FINJEM is a generic job-exposure matrix (JEM) developed in Finland, which represents a potentially cost-effective exposure assessment tool. While FINJEM has been used in several studies outside Finland, little is known of its applicability in other countries.

**Methods:** We compared prevalence and intensity of exposure in FINJEM with a JEM developed from expert assessments of occupational histories obtained in a population-based case-control study in Montreal. Agreement for prevalence of exposure was measured by weighted  $\kappa$  coefficients between prevalence categories. Agreement for exposure intensity was measured by Spearman correlation coefficients between cells with non-null exposure.

**Results:** The comparison involved 27 chemicals, the time period 1945-1995 and included 4743 jobs initially assessed by the Montreal experts. 4293 combinations of agent, occupational title and period were available for comparison of prevalence. Agent-specific prevalence was consistently higher in the Montreal JEM (median difference 1.7%). Agent-specific  $\kappa$  values between prevalence categories varied from 0.89 (welding fumes) to 0.07 (flour dust). The comparison of exposure levels involved 14 agents and 198 cells with non-null exposure in both sources. Agent-specific Spearman correlation varied from 0.89 (flour dust) to -0.35 (benzo(a)pyrene).

**Conclusion:** Our observations suggest that information concerning several agents (*e.g.*, metals, welding fumes) can be successfully transported from Finland to Canada and probably other countries. However, for other agents, there was considerable disagreement, and hence, transportability of FINJEM cannot be assumed by default.

**Redwood *et al.* (2012, PMID: 22590848)**

Most occupational and environmental research describes associations between specific occupational and environmental hazards and health outcomes, with little information available on population-level exposure, especially among unique subpopulations. The authors describe the prevalence of self-reported lifetime exposure to nine occupational and environmental hazards among 11,326 American Indian and Alaska Native (AI/AN) adults enrolled in the Education and Research Towards Health (EARTH) Study in the Southwest U.S. and Alaska. The top three hazards experienced by AI/AN people in Alaska were petroleum products, military chemicals, and asbestos. The top three hazards experienced by AI/AN living in the Southwest U.S. were pesticides, petroleum, and welding/silversmithing. The study described here found that male sex, lower educational attainment, AI/AN language use, and living in the Southwest U.S. (*vs.* Alaska) were all associated with an increased likelihood of hazard exposure. The authors' study provides baseline data to facilitate future exposure-response analyses. Future studies should measure dose and duration as well as environmental hazards that occur in community settings.

**Pesch *et al.* (2012, PMID: 22377681)**

We investigated airborne and internal exposure to manganese (Mn) and iron (Fe) among welders. Personal sampling of welding fumes was carried out in 241 welders during a shift. Metals were determined by inductively coupled plasma mass spectrometry. Mn in blood (MnB) was analyzed by graphite furnace atom absorption spectrometry. Determinants of exposure levels were estimated with multiple regression models. Respirable Mn was measured with a median of 62 (inter-quartile range (IQR) 8.4-320)  $\mu\text{g}/\text{m}^3$  and correlated with Fe ( $r=0.92$ , 95% CI 0.90-0.94). Inhalable Mn was measured with similar concentrations (IQR 10-340  $\mu\text{g}/\text{m}^3$ ). About 70% of the variance of Mn and Fe could be explained, mainly by the welding process. Ventilation decreased exposure to Fe and Mn significantly. Median concentrations of MnB and serum ferritin (SF) were 10.30  $\mu\text{g}/\text{l}$  (IQR 8.33-13.15  $\mu\text{g}/\text{l}$ ) and 131  $\mu\text{g}/\text{l}$  (IQR 76-240  $\mu\text{g}/\text{l}$ ), respectively. Few welders were presented with low iron stores, and MnB and SF were not correlated ( $r=0.07$ , 95% CI -0.05 to 0.20). Regression models revealed a significant association of the parent metal with MnB and SF, but a low fraction of variance was explained by exposure-related factors. Mn is mainly respirable in welding fumes. Airborne Mn and Fe influenced MnB and SF, respectively, in welders. This indicates an effect on the biological regulation of both metals. Mn and Fe were strongly correlated, whereas MnB and SF were not, likely due to higher iron stores among welders.

## **5.2 Human Health Effects Studies**

### **5.2.1 Neurological Effects**

Racette *et al.* (2012, PMID: 22975422) conducted a cross-sectional and nested case-control study on 811 shipyard and fabrication welders to assess the prevalence and symptoms of parkinsonism in the cohort. The prevalence rates were compared to two control groups, 59 non-welder trade workers and 118 newly diagnosed, untreated idiopathic Parkinson's disease patients. The Unified Parkinson's Disease Rating Scale motor subsection 3 (UPDRS3) was used to rate the subjects' symptoms, and exposure was measured as intensity-adjusted, cumulative years of welding. The dose-response relationship for parkinsonism and years of welding exposure was U-shaped, suggesting higher parkinsonism prevalence at low and high exposure. The overall prevalence estimate of parkinsonism was 15.6% in welding-exposed workers compared to 0% in the reference group. The score of the UPDRS3 tests for welders was similar to newly diagnosed idiopathic Parkinson's disease patients. These findings suggest that parkinsonism has a high prevalence in welders compared to non-welders.

Kenborg *et al.* (2012, PMID: 22833432) conducted a follow-up study to a previous cohort study on 5867 Danish welders and 1735 non-welding metal workers exposed to welding fumes. Occupational history and medical records, particularly outpatient data for Parkinson's Disease and other neurological disorders, were obtained for all subjects. Standardized hospitalization ratios (SHRs) were calculated for the entire cohort and for welders, metal workers, and non-responders, as well as for the general Danish population, for 1987-2008. Hospitalization rate ratios (HRRs) for Parkinson's disease associated with exposure to welding fumes were also calculated. Only 45 subjects in the entire cohort, 25 of whom were welders, had a hospital information for Parkinson's disease. No statistically significant difference in hospitalization or Parkinson's disease rate were found across subject groups.

Giorgianni *et al.* (2012, PMID: 22914260) conducted a study on 86 male welders in Messina, Italy to assess the effects of exposure on cognitive ability. Blood levels of aluminum, zinc, Mn, lead and chromium were measured and the Wechsler Memory Scale (WMS), the Colour Word Test or Stroop Test, and the Test of Attention Matrixes were administered to subjects. Compared to controls, exposed

subjects had decreased attention and memory performance, which decreased proportionally with time since exposure and decreased blood metal levels. The authors concluded that findings suggest that metal exposure alters cognitive performance.

### 5.2.2 Respiratory Effects

Thaon *et al.* (2012, PMID: 22281800) conducted a longitudinal cohort study of 503 French blue-collar workers exposed to welding fumes and 709 control subjects to assess the effects of exposure to welding fumes on lung function. Medical data, occupation, sector of activity, and spirometry (FVC and FEV<sub>1</sub>) were measured for all subjects in 1990 and again in 1995. The job exposure matrix was used to calculate weekly exposure duration to welding fumes. Exposure to welding fumes was not significantly associated with a decline in lung function (*i.e.*, reduced FVC and FEV<sub>1</sub>), after adjustment for age, smoking, BMI, and baseline values. However, a significant trend was observed in the decline in FEV<sub>1</sub> with increased exposures to welding fume in never-smokers ( $p=0.046$ ). A similar exposure-response relationship between weekly exposure duration and FEV<sub>1</sub> decline was not observed in smokers. The authors concluded that exposure to welding fumes accelerated the decline in lung function, which in nonsmokers was related to exposure.

Wittczak *et al.* (2012, PMID: 22729494) studied the usefulness of diagnostic methods in assessing metal-induced asthma in 50 welders occupationally exposed to metals and with suspicion of metal-induced asthma (group A), 100 welders occupationally exposed to metals but without suspicion of metal-induced asthma (group B), and two control groups (10 patients with atopic asthma and 10 healthy subjects). All subjects were administered questionnaires to estimate metal fume exposure, clinical examinations, and several tests to assess sensitivity to metal exposure (*e.g.*, skin prick tests, rest spirometry tests, x-rays). Using inhalation challenge tests with metals, 9 cases of metal-induced occupational asthma were observed in group A, compared to only 1 case in group B. Chest x-ray changes were observed in 62% of welders and were significantly associated with having more than 10 years of occupational welding exposure. Positive results of skin prick tests with metal salts were also associated with occupational asthma in welders. The authors noted that results suggest that specific inhalation tests play a key role in diagnosing metal-induced asthma in welders.

t Mannetie *et al.* (2012, PMID: 22343633) studied the effects of confounding by smoking and asbestos exposure on the reported 25-40% increase in lung cancer risk associated with welding as an occupation and the effect of other occupational-welding exposures. Interviews were conducted on 2,197 male lung cancer cases and 2,295 controls from Romania, Hungary, Poland, Russia, Slovakia, the Czech Republic, and the United Kingdom to collect information on exposure to other risk factors. After controlling for smoking and occupational exposures including asbestos, a marginally significant increase in the odds of developing lung cancer from welding/flame cutting was observed (OR= 1.36, 95% CI: 1.00, 1.86). Exposure to welding fumes was associated with an odds ratio of 1.18 (95% CI: 1.01, 1.38), increasing to 1.38 for welders exposed for more than 25 years (95% CI: 1.09, 1.75). In the study population, approximately 4% of the lung cancer cases were attributed to welding-fume exposure. The authors concluded that the results support the hypothesis that occupational exposure to welding fumes is a risk factor for lung cancer.

Holm *et al.* (2012, PMID: 22325166) assessed the prevalence and incidence rates of chronic bronchitis (CB) associated with smoking and welding fume exposure in the Northern Europe. Smoking habits, exposure to welding fumes, CB symptoms, and age at the beginning of symptoms were evaluated by a mail-in questionnaire from 15,909 subjects born in Northern Europe between 1945 and 1971. The overall prevalence rate in the study population was 5.4%, which was positively associated with both smoking and

welding exposure. The welding exposure rate significantly increased CB incidence rate, low exposure hazard ratio 1.4 (95% CI 1.1-1.8) and high exposure hazard ratio 2.0 (95% CI 1.6-2.7).

### 5.2.3 Ocular Effects

Yang *et al.* (2012, PMID: 22333851) conducted a cross-sectional study on 40 welders and 40 age-matched controls to assess the association between welding and occupationally related phototoxicity. Subjects were administered ophthalmologic examinations (*e.g.*, fundus photography, automatic perimeter examination, and high definition optical coherence tomography (OCT) scans) to assess effects on the eyes. No details were given in the abstract on methods used to assess welding exposure. OCT scans revealed a higher prevalence (38%) of maculopathy in welders compared to controls. Authors concluded that these results suggest that exposure to arc-welding is associated with increased risk of phototoxic maculopathy.

### 5.2.4 Biomarkers

Criswell *et al.* (2012, PMID: 22447645) conducted a case-control imaging study on 18 welders and 18 gender and age matched controls to assess the viability of extra-pallidal T1 basal ganglia signal intensity as a biomarker of Mn exposure and basal ganglia diffusion-weighted imaging abnormalities as a potential marker of neurotoxicity. T1-weighted intensity indices and apparent diffusion coefficients were generated for each basal ganglia region of interest. All regional T1 indices were significantly elevated in welders compared to controls. Combined basal ganglia, caudate, and putamen region indices were better correlated with exposure than the pallidal index. Elevated indices were associated with diffusion-weighted abnormalities in the palladium and anterior putamen which authors noted suggests neurotoxicity in these regions.

Wang *et al.* (2012, PMID: 22292500) studied the effects of welding fume exposure on the inflammatory markers and metabolites present in the blood and urine, respectively, of 35 male welders and 16 male office workers at a Taiwanese shipyard. In urine metabolite analysis, higher levels of glycine, taurine, betaine/TMAO, serine, S-sulfocysteine, hippurate, gluconate, creatinine, and acetone, and lower levels of creatinine were found in welders when compared to controls. Among inflammatory markers only tumor necrosis factor-alpha (TNF- $\alpha$ ) in blood samples was significantly associated with welding fume exposure. The association between the urinary metabolites and welding fume exposure was confounded by smoking. Authors noted that these results are consistent with previous studies and suggest that metabolic profiling may be an efficient method for characterizing the effects of welding fume exposure.

Hoffmeyer *et al.* (2012a, PMID: 22622358) measured the association between welding fume exposure and markers of metal toxicity (leukotriene B4 (LTB4), prostaglandin E2 (PGE2) and 8-isoprostane (8-IsoPGF2 $\alpha$ )) as well as the acid-base balance (pH) in exhaled breath condensate (EBC) in 43 gas metal arc welders (20 were smokers). Higher concentrations of 8-isoPGF2 $\alpha$  and LTB4 were associated with high concentrations of iron and nickel in EBC. Chromium was generally undetectable in EBC of subjects with high concentrations of iron and nickel in EBC. The authors suggested that EBC sampling provides a viable matrix for assessing metal exposure and toxicity.

Hassani *et al.* (2012, PMID: 22673643) evaluated the viability of urinary Mn as a biomarker for welding fume exposure and assessed the correlation between respirable Mn and pulmonary function, which was assessed using spirometric measurements done for participants. Personal air samples and urine samples were collected from 118 welders and 37 unexposed controls from two regions in Iran. Maximum exposures to airborne Mn and total fumes were  $0.304 \pm 0.256$  mg/m<sup>3</sup> and  $21.52 \pm 9.40$  mg/m<sup>3</sup>, respectively. The correlation between Mn exposure and Mn in urine was significant, which authors noted

indicates that Mn in urine is a viable biomarker for Mn exposure. The authors also reported there was a significant inverse correlation between urinary Mn and pulmonary function indices, FVC and FEV<sub>1</sub>.

Hoffmeyer *et al.* (2012b, PMID: 22686312) investigated the impact of welding techniques on biological effect markers in exhaled breath condensate (EBC) of 58 healthy welders performing gas metal arc welding with solid wire (GMAW) (n=29) or flux cored wire (FCAW) (n=29). Welding fume particles were collected with personal samplers in the breathing zone inside the helmets. Levels of leukotriene B(4) (LTB(4)), prostaglandin E(2) (PGE(2)), and 8-isoprostane (8-iso-PGF(2 $\alpha$ )) were measured, as well as the EBC pH. Significantly higher 8-iso-PGF(2 $\alpha$ ) concentrations and a less acid pH were detected in the EBC of welders using the FCAW compared to welders using the GMAW technique. The authors concluded that results suggest enhanced irritation of the lower airways of mild steel welders due to the application of FCAW compared to GMAW, most likely associated with a higher emission of welding fumes.

### 5.3 Animal Studies

Antonini *et al.* (2012, PMID: 22369286) conducted a study on Sprague-Dawley rats to assess the effects of welding fumes on the number of circulating total leukocytes and specific leukocyte sub-populations, and the resulting effects on the immune system. Rats were exposed intratracheally to welding fumes either at single 2.00 mg/rat doses or repeated 0.125 or 2.00 mg/rat daily for seven weeks doses. Mn concentrations in the welding fumes varied (no additional details on Mn concentration in the abstract). Following exposure, bronchoalveolar lavage was performed to assess lung inflammation and flow cytometry was conducted on the rat blood to count the number of circulating total leukocytes, as well as specific subsets. Rats exposed to welding fumes with the highest concentration of Mn had significantly higher lung inflammation, injury, and production of inflammatory cytokines and chemokines. Significant decreases in number of circulating immune cells were also observed at this dose group. Low concentration Mn welding fumes had no effects on the number of circulating lymphocytes compared to controls. Authors concluded that these results suggest that both acute and repeated exposure to welding fumes may have impact immune function.

Oh *et al.* (2012, PMID: 21730038) conducted a follow-up study using rat lung samples from an earlier study on inflammatory responses in the lung as a result of welding fume exposure. Gene expression profiles of the lung samples were obtained to identify genes associated with inflammation and subsequent repair. Gene expression profiles were also compared between exposure and recovery groups. Seven genes (Mmp12, Cd51, LOC50101, LOC69183, Spp1, and Slc26a4) were associated with inflammation severity and injury. The gene Trem2 was associated with lung repair. The study provided information on the genes involved in lung inflammation and repair following welding fume exposure.

Erdely *et al.* (2012, PMID: 22776377) conducted a study on mice to assess potential biomarkers and mechanisms associated with systemic effects (*e.g.*, inflammation, immunosuppression and cardiovascular dysfunction) following inhalation exposure to gas metal arc-stainless steel welding fumes. Mice were exposed to the welding fumes at 40 mg/m<sup>3</sup> for 3 hr/day for 10 days and then sacrificed at 4 hrs, 14 days and 28 days post-exposure. Following sacrifice, the mice's serum, blood cells, aorta and lungs were harvested for gene expression analysis. The researchers were able to identify genes that were consistently up-regulated and associated with inflammation in the lungs and systemic effects, such as changes in serum proteins.

Sriram *et al.* (2012, PMID: 22085607) assessed the viability of Mn accumulation in blood and nail clippings as a biomarker of welding fume exposure and neurotoxicity. In order to assess the relationship, the authors exposed rats to fume components collected from gas metal arc-mild steel (GMA-MS) or

manual metal arc-hard surfacing (MMA-HS) welding *via* intratracheal instillation. (Exposure duration, frequency and concentration were not given in abstract). Mn accumulation in the dopaminergic areas of the brain (*e.g.*, striatum and midbrain), as well as Mn concentrations in blood and nail clippings were measured following exposure to welding fumes. Blood Mn concentrations were not detectable, however, Mn concentrations in nails correlated strongly with Mn accumulation in the striatum and midbrain. Similar results were observed with exposure to MnCl<sub>2</sub>. Authors noted that study results indicate that Mn concentrations in nails may be a viable biomarker for long-term Mn exposure.

## 5.4 Mechanistic Studies

Roth *et al.* (2012, PMID: 22543103) assessed the additive effects of Mn and glutamate exposure on neurotoxicity in mouse P19 cells. The authors evaluated various markers of brain cell death, and reported increased markers with exposure to both Mn and glutamate, compared with exposure to only one of them. The anti-glutameric drug, riluzole, had a preventative role on the apoptotic (cell death) effects of Mn and glutamate.

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