4. MECHANISTIC AND OTHER RELEVANT DATA

4.1 Absorption, distribution, and excretion

4.1.1 Humans

All types of welding are associated with siderosis, pulmonary accumulation of iron (Doherty et al., 2004).

(a) Mild steel

In shipyard manual metal arc mild steel (MMA-MS), tungsten inert gas stainless steel (TIG-SS) and manual metal arc stainless steel (MMA-SS) welders, particulates mainly accumulated in the lower parts of the respiratory organs (Kalliomäki et al., 1982). Shipyard arc welders with 2 or 18 years of exposure showed an average of 7 mg and 200–700 mg, respectively, of welding dust in their lungs, compared with less than 4 mg in lungs of unexposed controls (Kalliomäki et al., 1978). [These data suggest time-dependent accumulation of welding dust in lungs of arc welders. The Working Group noted the lack of information on the technique, type of steel used, or on metals in fumes.]

Biological chromium (Cr) was assessed in MS welders (MMA and TIG) compared with SS welders (MMA, metal inert gas (MIG), and TIG) (Edmé et al., 1997). SS welders (MMA, MIG, and TIG techniques) had higher chromium levels in urine, blood, and plasma than MS welders. MMA-SS fumes contained the highest chromium concentrations (mostly hexavalent chromium, Cr(VI), followed by MIG-SS, TIG-SS, MIG-MS, and MMA-MS. Analysis of variance for urinary chromium concentration showed a metal effect, a process effect, and a metal–process interaction. [The Working Group noted that urine levels were not corrected for creatinine levels or osmolarity.]

Using nanoparticle respiratory deposition samplers (worn in the breathing zone, on the lapel), Cena et al. (2015) demonstrated that MS and SS welders using gas metal arc (GMA-SS or GMA-MS) or flux-cored arc (FCA-MS) welding methods are exposed to manganese (Mn), chromium, and nickel (Ni), which can deposit in the respiratory system. Based on the measured size, the estimated percentage of the nanofraction of manganese deposited in an MS welder's respiratory system ranged from 10% to 56%.

Total chromium was elevated in urine, blood plasma, and erythrocytes in MS, high-alloy steel, and SS welders compared with controls (Scheepers et al., 2008). Total chromium in plasma was twofold higher in SS and high-alloy steel welders than in MS welders. Median total content of chromium in erythrocytes was 10 µg/L in all three welder groups. Uptake of total chromium during the shift was confirmed for welders of SS by a median increase of urinary total chromium from before to after the shift of 0.30 µg/g creatinine. Total chromium was not increased for welders of MS and high-alloy steel as a group (Scheepers et al., 2008).

Dufresne et al., (1997) detected quartz was detected in the lungs of four welders. Compared with other subjects working in other occupations, the welders had the highest concentrations of metallic particles (rich in aluminium (Al), Ni, Mn, cadmium (Cd) and Cr). [The Working Group noted the small number of subjects and that the welding technique used was not indicated.]

(b) Stainless steel

A cross-sectional study of 241 welders that included 228 SS welders (GMA, n = 95; FCA, n = 47; TIG, n = 66; and shielded metal arc (SMA) with stick electrodes, n = 20) reported overall urinary levels of chromium and nickel of 1.2 and 2.9 µg/L, respectively (Weiss et al., 2013).

Two cross-sectional studies (Ellingsen et al., 2006, 2014) investigated the levels of manganese, iron (Fe), and other metals in controls, welders (MS or SS base metals; SMA, GMA, or FCA techniques), and former welders (average cessation of welding 5.8 years before, all diagnosed with manganism). Blood manganese levels and urinary chromium and nickel levels were higher in all welders compared with the controls, while cobalt (Co) levels were lower in welders. Blood manganese levels were higher in former welders (8.7 µg/L) than in controls (7.0 µg/L), while urinary concentrations of manganese, cobalt, and iron were lower in the group of former welders. Serum iron levels did not differ significantly between the groups. [The Working Group noted that the welders came from two different facilities: one that produces heavy machinery and the other a shipyard. The results were not reported separately according to material welded or welding technique.]

A 5-year longitudinal study biologically monitored aluminium welders (n = 62) and controls (n = 60 assembly workers) to compare aluminium plasma levels between the two groups (Rossbach et al., 2006). Having a nearly constant dust exposure, welders showed a decrease in median concentrations of aluminium in urine from 40.1 to 19.8 µg/g creatinine, and in plasma aluminium from 8.7 to 4.6 µg/L. Corresponding concentrations in controls ranged from 4.8 to 5.2 µg/g creatinine in urine and from 2.4 to 4.3 µg/L plasma aluminium. No correlation between dust exposure and concentrations of aluminium in either plasma or urine was seen.

In a study of six welders who used three different welding techniques (MMA with alloyed or unalloyed material, or GMA with alloyed material), welding caused an increase in chromium in blood and urine at all time points, an increase in nickel in the blood after 6 and 24 hours, and a decrease in iron after 3 and 6 hours (Brand et al., 2010). [The Working Group noted the small sample size, and that each welder used multiple arc welding methods.] In contrast, no significant elevation of chromium was seen in blood or urine in welders using either TIG-SS or TIG-MS techniques in another study (Bonde & Ernst, 1992).

In MMA-SS shipyard welders (38 men, 2 women) monitored for 1–5 workdays, total chromium and hexavalent chromium in air correlated with total chromium in blood and urine (Stridsklev et al., 1993). Smokers had higher chromium levels than nonsmokers. [The Working Group noted that it was unclear whether analyses were adjusted for differences in the workplace setting, in monitoring (i.e. across or within workweeks), in conditions at the same site, or in materials welded.]

Urinary excretion of aluminium was examined in 23 welders performing mainly MIG, but less frequently TIG welding (Sjögren et al., 1988) after an exposure-free interval of 16–37 days. Air concentrations of aluminium (8-hour time-weighted averages) varied from 0.2 to 5.3 mg/m^3. Urine aluminium concentration depended on the level of current exposure and duration of exposure. The aluminium levels of urine collected before the exposure-free interval varied over the range 6–322 µg/g (creatinine adjusted). After an exposure-free interval, the

urinary aluminium concentrations decreased to 4–285 µg/g (creatinine adjusted). The half-time of urinary aluminium was 9 days for those exposed for less than 1 year, but was 6 months or more for those exposed for longer than 10 years. [The Working Group noted that that the type of steel (SS or MS) was not specified.]

In a study of six welders exposed to aluminium-containing welding fumes from MIG welding, urinary aluminium decreased after cessation (over the weekend) in welders exposed for 2 years or less, but not in welders with more than 15 years of exposure (Sjögren et al., 1985). Urinary aluminium rose rapidly in volunteers exposed to welding fumes containing aluminium for 1 hour, and returned to baseline with an estimated half-life of 8 hours. [The Working Group noted the small number of subjects and that the type of steel (MS or SS) was not specified.]

SS arc welders had elevated chromium concentrations in lungs and urine, and correlated with duration of exposure to welding. Urinary chromium levels were highest in the steel and ferrochromium smelting shops (Huvinen et al., 1997).

An arc welder using galvanized steel showed the highest zinc (Zn) levels reported in the literature, coupled with previously unreported pleural friction rub. The subject was diagnosed with "metal fume fever", which is usually caused by inhalation of zinc oxide, and the subject's elevated urinary zinc excretion markedly decreased after 2 weeks of no welding (Fuortes & Schenck, 2000).

4.1.2 Experimental systems

(a) Mild steel

In male Wistar rats exposed by inhalation to MMA-MS welding fumes (43 mg/m^3; particle size, 0.12 µm average diameter) for 1 hour/workday for up to 4 weeks, a saturation level of 550 µg/g dry lung of the welding fumes was observed. Most of the accumulated particles were excreted from lungs with a half-time of 6 days, and the remainder with a half-time of 35 days. Iron and manganese demonstrated similar patterns of lung retention, but manganese was initially cleared much faster. Some inhaled manganese was quickly absorbed from the lung, whereas the absorption of exogenous iron was slower and was obscured by a simultaneous occurrence of endogenous iron in lung tissue. Following the same protocol but with SS welding fumes, alveolar retention of the MS fumes was much lower and its clearance much faster than the corresponding parameters for SS fumes (Kalliomäki et al., 1983a, b).

Significantly more iron accumulated in the lungs after exposure of male Sprague-Dawley rats to GMA-MS compared with MMA-HS (hard-surfacing) welding fumes by intratracheal instillation (0.5 mg per rat, once per week for 7 weeks), at 1 day and 35, but not 105, days after treatment (Antonini et al., 2010). Manganese increased in lungs at all time points with MMA-HS, and after 1 and 35 days with GMA-MS. Chromium and nickel were similarly elevated in the lungs of the MMA-HS group at all time points compared with other groups. Copper (Cu) levels significantly increased in the lungs of the GMA-MS group at 1 and 35 days compared with the MMA-HS group. At 105 days after treatment, copper and manganese levels in the lungs of the GMA-MS group decreased to levels similar to the control group, while all other metals remained significantly elevated compared with controls. Manganese cleared from the lungs fastest and to the greatest extent, followed by iron, and then chromium and nickel which cleared at similar rates. [The Working Group noted that no data on copper clearance were given.] Manganese and chromium increased in the blood (MMA-HS fumes only) 1 day after the last treatment, but not at 35 and 105 days. Importantly, manganese was elevated in the striatum (1 day) and midbrain (1 and 4 days with MMA-HS fumes). Manganese levels were also elevated 1 day after treatment in the olfactory bulb, frontal cortex, hippocampus, thalamus,

and cerebellum for MMA-HS welding fumes. At 1 day after exposure to MMA-HS welding fumes, manganese was elevated in lung-associated lymph nodes, heart, kidney, and spleen; concentrations were back to that of controls 35 days after treatment in all tissues except lymph nodes. Iron was elevated in lung-associated lymph nodes (both groups) at 1 and 35 days after treatment, but similar to that of controls at 105 days. Chromium was elevated in lymph nodes, liver, kidney, and spleen 1 day after treatment (MMA-HS welding fumes only), and remained elevated in the lymph nodes at 35 days and in the spleen at 105 days after treatment. Copper was elevated in the lungs (GMA-MS welding fumes only) at 35 days after treatment (Antonini et al., 2010).

Significant deposition of manganese in the striatum and midbrain was seen in male Sprague-Dawley rats given dissolved or suspended fumes from GMA-MS or MMA-HS welding by intratracheal instillations at doses related to workplace exposures of welders on 8-hour shifts (5 mg/m^3) (Sriram et al., 2012). The accumulation of manganese, as well as high concentrations of chromium and iron, was also measured in the lung. The group exposed to MMA-HS welding fumes had significant increases in chromium in the liver, manganese and chromium in the heart, and manganese in the kidney. Both welding methods increased manganese in nail clippings, which strongly correlated with concentrations of manganese in the brain and liver.

(b) Stainless steel

A marked dose-dependent increase in lung manganese concentration (change over baseline of 432-fold for the low dose, and 567-fold for the high dose) was reported in a study of six male cynomolgus monkeys (*Macaca fascicularis*) (Park et al., 2007a). Exposure was to MMA-SS welding fumes (low dose, 31 mg/m^3 total suspended particulate, 0.9 mg/m^3 of Mn; high dose, 62 mg/m^3 total suspended particulate, 1.95 mg/m^3 of Mn) for 2 hours per day in an inhalation chamber system equipped with an automatic fume generator for 240 days. Fumes mainly consisted of iron, manganese, chromium, and nickel. Noticeable manganese increases were reported in the liver (twofold), kidneys (twofold), and testes (four- to fivefold). A dose-dependent increase in manganese concentration was seen in the globus pallidus. [The Working Group noted the small sample size (n = 2) for each test group.]

Mice of the A/J strain, but not of the C57BL/6j strain, had elevated hepatic concentrations of chromium, copper, manganese, and zinc in kidney, and chromium after exposure to MMA-SS welding fumes (Zeidler-Erdely et al., 2011a). The mice were exposed monthly for 4 months to MMA-SS fumes (20 mg/kg body weight) by pharyngeal aspiration and assessed 78 weeks after the beginning of the study.

Lung concentrations of chromium, manganese, nickel, and iron increased with duration of exposure in 42 rats exposed via inhalation to MIG-SS welding fumes for 1 hour per day for 1–4 weeks, followed by observation for up to 106 days (Kalliomäki et al., 1983a). Clearance did not occur for iron, was slow for chromium, and was initially rapid for manganese and nickel (2-day and 3-day half-lives, respectively) but then slowed (125-day and 85-day half-lives, respectively). Under comparable exposure conditions, similar results were seen for MMA-SS with half-lives for iron, chromium, manganese, and nickel of 50, 40, 40, and 30 days, respectively (Kalliomäki et al., 1983b).

Male Sprague-Dawley rats showed dose- and time-dependent increases in manganese concentrations in the lungs and liver, and slight but significant increases in the blood (after 60 days), after exposure to MMA-SS welding fumes for 60 days (63.6 and 107.1 mg/m^3, containing 1.6 and 3.5 mg/m^3 Mn, respectively). Marked, significant increases in manganese were seen in the cerebellum (after 60 days), while slight increases were found in the substantia nigra, basal ganglia,

temporal cortex, and frontal cortex (Yu et al., 2003).

The maximum amount of MIG welding fumes retained in the lungs (1100 µg) was somewhat, but not significantly, higher than that for MMA welding fumes (800 µg) in Wistar rats exposed by inhalation to both following the same protocol as in Kalliomäki et al. (1983a, b, 1984). Chromium and nickel were both retained in the lungs. Chromium from exposure to MMA welding fumes was partly cleared, but there was no clearance of chromium from exposure to MIG welding fumes. The half-life of chromium was 40 days from MMA fumes and 240 days from MIG fumes, and the half-life of nickel was 30–85 days from MMA fumes. Chromium found in blood from MMA fumes had a half-life of approximately 6 days. Chromium and nickel were both found in blood from MIG fumes. The amounts of nickel cleared from the lungs during exposure to the MMA and MIG fumes were 0.9 and 8 µg, respectively, and corresponding amounts of chromium were 9.6 and 2 µg. Practically all the lost metals were found in the urine, for which the excretion rates were 0.07 (MMA) and 6.39 µg per day (MIG) for nickel, and 0.23 (MMA) and 0.11 µg per day (MIG) for chromium. [The Working Group noted that metal content in urine was determined by atomic absorption spectroscopy and not corrected for creatinine.]

Tissue distribution of manganese was similar in iron-deficient compared with iron-sufficient male Sprague-Dawley rats exposed to MMA-SS welding fumes (63.5 mg/m^3) for 2 hours per day for up to 30 days (Park et al., 2007b). Fumes consisted mainly of iron (6 mg/m^3), chromium (2.9 mg/m^3), and manganese (2.7 mg/m^3). In both groups of rats, manganese concentrations increased significantly during fume exposure in lungs and livers (on days 15 and 30), in the olfactory bulb (on day 30), and in the cerebellum and frontal and temporal lobe of the cerebrum (on day 15).

4.2 Mechanisms of carcinogenesis

The sections that follow summarize the evidence for key characteristics of carcinogens (Smith et al., 2016). The sections address, in the following order, if welding fumes: induce chronic inflammation; are immunosuppressive; are genotoxic; induce oxidative stress; alter cell proliferation, cell death, and nutrient supply; and modulate receptor-mediated effects. There were insufficient data for the evaluation of the other key characteristics of human carcinogens.

4.2.1 Chronic inflammation and immune suppression

(a) Humans

Numerous studies have reported that the metal content of particles in welding fumes is associated with measures of pulmonary inflammation, oxidative stress, and/or systemic inflammation (e.g. Kim et al., 2005). Several of these studies investigated boilermakers, who perform two major types of activities: the use of oxyacetylene gas torch sets to cut or gouge steel plate and tubes, followed by gas tungsten arc (GTA), SMA, or GMA welding to attach and mend the cut sections of MS tubes and plates. Acute (cross-shift) welding exposure is associated with a blunting of systemic inflammation in acutely exposed boilermakers at the end of work shifts, as measured by biomarkers such as 8-isoprostane (e.g. Nuernberg et al., 2008) whereby chronically exposed workers had a higher value consistent with chronic inflammation at the start of the shift. In contrast, longer-term exposure is related to an increase in markers of tissue damage.

There are also systemic inflammatory effects caused by epithelial damage induced by metal particulate or macrophage activation via cytokine signalling (e.g. Zeidler-Erdely et al., 2012). In a study of 27 welders with regular, long-term exposure to metal fumes (type of welding not specified) and 31 unexposed matched controls,

an increase in blood eosinophil and basophils in welders versus non-welders, with some correlation to exposure level, was observed (Palmer et al., 2006). This study also reported trends for increased blood C-reactive protein (CRP), neutrophil oxidative burst, sputum immunoglobulin-A (IgA), and decreased sputum eosinophils (Palmer et al., 2006). In another study of chronic exposure to manganese fumes (work experience, 6–36 years), significant decreases in blood CD8+ T and CD19+ B lymphocytes were found in welders with high concentrations of manganese in blood compared with workers with lower manganese concentrations (Nakata et al., 2006). In a longitudinal study of mostly healthy, middle-aged, white American men, increased inflammatory markers such as plasma CRP and serum amyloid A (SAA) concentrations were associated with decreased leukocyte telomere length (Wong et al., 2014a). [The Working Group noted that this study provides a window into the relationship between systemic inflammation, immune response, and genomic degeneration.]

Studies using a repeated measures panel design investigated the short-term effects of exposure to welding fumes among boilermakers (Kim et al., 2005; Wang et al., 2005, 2008; Fang et al., 2008, 2009, 2010a; Nuernberg et al., 2008). These studies included assessment of exposure to welding fumes within the personal breathing zone and a self-controlled design to assess biological variability among individuals. Blood samples were collected from welders and non-welding controls before and after their work shift. In nonsmokers, exposure to welding fumes was associated with a significant increase in leukocyte and neutrophil counts immediately after exposure. A significant decrease in fibrinogen levels was observed in nonsmoking welders. No significant changes in leukocyte, neutrophil, and fibrinogen levels were found with exposure to welding fumes in smokers. Sixteen hours after exposure to welding fumes, CRP levels were significantly increased in both nonsmokers and smokers. Concentrations of particulate matter of diameter less than 2.5 μm ($PM_{2.5}$) were significantly associated with absolute neutrophil counts in nonsmokers, and CRP levels in both nonsmokers and smokers (Kim et al., 2005; Fang et al., 2009). [The Working Group noted that exposure to high levels of welding fumes induced acute systemic inflammation in a relatively young and healthy working population, and that smoking may modify the effect of exposure to welding fumes on specific inflammatory markers.]

Reported susceptibility to pneumococcal pneumonia in welders provides evidence of immune suppression as a result of exposure to welding fumes (Coggon et al., 1994; Wergeland & Iversen, 2001; Palmer et al., 2003; Palmer et al., 2009; Wong et al., 2010; Torén et al., 2011; Patterson et al., 2015; Marongiu et al., 2016). A likely mechanism involving platelet-activating factor receptor (PAFR) has been investigated for the observed increase of pneumococcal pneumonia among active welders (Suri et al., 2016; Grigg et al., 2017). Pneumococci co-opt PAFR to infect respiratory epithelial cells, and exposure of respiratory cells to welding fumes upregulates PAFR-dependent pneumococcal infection. Nasal PAFR expression was increased in welders compared with controls. Exposure to welding fumes also significantly increased PAFR expression, and enhanced pneumococcal infection of respiratory cells harvested in vivo.

A toxicogenomic study using whole-blood RNA of welders revealed that welding fumes induced alteration in the expression of genes involved in various aspects of the inflammatory response, including proinflammatory mediators, cytokine receptors, downstream signal transduction genes, and cytotoxic granulysin (Wang et al., 2005). A follow-up study using a similar population extended these observations into a period after exposure. Some acute effects on gene expression profiling induced by welding fumes were transient in nonsmoking welders,

with most diminishing within 19 hours after exposure (Wang et al., 2008).

Wei et al. (2013) performed a two-stage, self-controlled exploratory study including 11 boilermakers from a 2011 discovery panel and 8 boilermaker welders from a 2012 validation panel. Eicosapentaenoic or docosapentaenoic acid metabolic changes after welding were significantly associated with $PM_{2.5}$ exposure ($P < 0.05$). The combined analysis by linear mixed-effects model showed that exposure was associated with a statistically significant decline in eicosapentaenoic acid, docosapentaenoic acid n_3, and docosapentaenoic acid n_6. Pathway analysis identified an association between the unsaturated fatty acid pathway and exposure, indicating that exposure to high concentrations of metal welding fumes decreases unsaturated fatty acids with an exposure–response relationship.

(b) Experimental systems

Numerous studies were available, nearly all of which evaluated males, and examined end-points related to inflammation and immune suppression.

(i) Inflammation in vivo

Despite particle accumulation in the lungs of male cynomolgus monkeys exposed to MMA-SS fumes via inhalation (31.4 or 62.5 mg/m^3, 2 hours per day, 5 days per week, for 229 exposure days), there was no effect on blood leukocyte populations and no significant lung damage ($n = 1$ per group per time point) compared with an unstressed, unexposed control group [control primates were not described as being handled or removed from their housing cages] (Heo et al., 2010).

Exposure to SS welding fumes led to an accumulation of inflammatory cytokines in the bronchoalveolar lavage fluid (BALF) of male rats, along with a cellular influx consisting primarily of alveolar macrophages, neutrophils (polymorphonuclear leukocytes, PMNs), and lymphocytes, effects which were not typically observed after exposure to MS welding fumes (reviewed by Zeidler-Erdely et al., 2012). Exposure to MMA-SS fumes via inhalation (44.1–65.6 or 80.1–116.8 mg/m^3, 2 hours per day, for up to 60 exposure days) did not change BALF tumour necrosis factor alpha (TNFα) or IL-1β levels in Sprague-Dawley rats (Yu et al., 2004). However, after similar exposures, increases in BALF cellularity corresponded to increased reactive pulmonary hyperplasia incidence and severity; this persisted for more than 60 days, and was exacerbated after two cycles of alternating 30-day periods of exposure to high concentration and recovery (Sung et al., 2004; Yang et al., 2009). [The Working Group noted that this indicated incomplete pulmonary recovery and a predisposition to more significant injury upon re-exposure.] Other investigators reported similar changes in Sprague-Dawley rats after exposure to GMA-SS welding fumes via inhalation (40 mg/m^3, 3 hours per day, for 3 days), with increased BALF levels of the PMN chemokine Cxcl2 (Chemokine (C-X-C motif) ligand 2) preceding a transient peak in PMN accumulation, while numbers of alveolar macrophages remained elevated throughout 30 days of recovery (Antonini et al., 2007). A similar influx of BALF leukocytes was also reported in Wistar rats exposed to unspecified welding fumes via inhalation (60 mg/m^3, 6 hours per day, for 5 or 10 days) (Halatek et al., 2017). [The fumes are described as only 10% soluble, consisting primarily iron >> chromium > nickel > aluminium > manganese.] In contrast to SS, short-term exposure to GMA-MS fumes (40 mg/m^3, 3 hours per day, for 3 or 10 days) or resistance spot MS welding fumes (25 mg/m^3, 4 hours per day, for 3, 8, or 13 days) via inhalation in Sprague-Dawley rats had a minimal effect on the cellular composition of the BALF or local lung-associated lymph nodes (LALN) (Antonini et al., 2009a; Zeidler-Erdely et al., 2014).

Immune effector cells in BALF from Sprague-Dawley rats were affected in a route-specific

manner following GMA-SS fume administration; after intratracheal instillation (ITI), there was an immediate PMN influx that was delayed after the inhalation exposure described above [possibly due to inhibition of alveolar macrophages] (Taylor et al., 2003; Antonini et al., 2007, 2009a). Exposure to GMA-SS and MMA-SS fumes by intratracheal instillation increased BALF TNFα and/or IL-6 levels along with increases in pulmonary leukocyte populations and persistently elevated numbers of alveolar macrophages, with MMA-SS welding fumes characterized as the most potent (Antonini et al., 1996, 1997, 2004a, 2013; Taylor et al., 2003). The soluble fraction of SS fumes appeared to elicit the weakest inflammatory response compared with the total fume or insoluble fractions (Taylor et al., 2003); these differed from other reports of relative potency after administration of higher (White et al., 1982) or lower doses (McNeilly et al., 2005).

Similar to rats, exposure to MMA-SS and GMA-SS welding fumes induced persistent pulmonary inflammation in male mice of strains both sensitive (A/J) and resistant C57Bl/6 (B6) to chemically induced lung tumorigenesis (reviewed by Zeidler-Erdely et al., 2012). While lung inflammation was not persistently elevated 78 weeks after short-term exposure of A/J mice to GMA-SS fumes by inhalation (40 mg/m^3, 3 hours per day, for 6 or 10 days; respective cumulative lung burden, approximately 0.071 or 0.120 mg) (Zeidler-Erdely et al., 2011a), subchronic inhalation (40 mg/m^3, 4 hours per day, 4 days per week, for 9 weeks; cumulative lung burden, approximately 0.255 mg), and pharyngeal aspiration (approximately 1.7 or 3.4 mg), the increased severity of pulmonary inflammation was observed after 30 weeks, characterized by infiltrating peribronchial/perivascular-associated lymphocytes, macrophages, and plasma cells (Zeidler-Erdely et al., 2013; Falcone et al., 2017; see Section 3). Similarly, exposure to a high concentration of MMA-SS welding fumes via pharyngeal aspiration (cumulative lung burden, approximately 1.6 mg) increased alveolar macrophage accumulation as well as pulmonary inflammation after 78 weeks in A/J but not B6 mice (Zeidler-Erdely et al., 2011a); this was not observed after exposure to a lower dose (cumulative burden, approximately 0.340 mg; Zeidler-Erdely et al., 2008). After a shorter 28-day recovery period, exposure to GMA-SS fumes via inhalation induced a sustained inflammatory response in A/J and B6 mice (Zeidler-Erdely et al., 2011b); this was consistent with the remaining histiocytic inflammation reported after exposure to MMA-SS fumes via pharyngeal aspiration in A/J mice (cumulative lung burden, approximately 1.0 mg) (Solano-Lopez et al., 2006).

Also similar to rats, BALF cellular content in mice was potently and persistently increased by exposure to SS welding fumes via inhalation (40 mg/m^3 for 3 hours per day, 5 days per week for 2 weeks) or pharyngeal aspiration, whereas exposure to MS fumes (via pharyngeal aspiration) only induced a mild and transient increase in PMNs (Zeidler-Erdely et al., 2008; Erdely et al., 2012). Qualitative differences were also evident between both exposure routes and mouse strains, although the magnitude of the cellular response was not remarkably different between A/J and B6 mice. After exposure to SS fumes by inhalation (as described above), BALF levels of several cytokines increased (IL-6, interferon-gamma or IFNγ) or greatly increased (Cxcl2, Ccl2, and TNFα) in B6 versus A/J mice (Zeidler-Erdely et al., 2011b), while exposures via aspiration elicited responses in similar BALF cytokines that tended to be greater in A/J compared with B6 mice (Zeidler-Erdely et al., 2008).

(ii) Inflammation in vitro

Evidence supporting induction of an inflammatory response in vitro is less consistent [the Working Group noted that studies in vitro may be less informative for chronic inflammation]. Release of β-*N*-acetyl-glucosaminidase (β-NAG)

from primary Sprague-Dawley rat alveolar macrophages was induced by treatment with both MS and SS fumes and, to a greater extent, with the soluble versus insoluble fractions with MMA-SS fumes eliciting the most potent effect (Antonini et al., 1999). Conversely, no effects were reported on β-NAG release from primary bovine AMs [sex not reported] (White et al., 1983) or cytokine production in mouse peritoneal macrophages (RAW 264.7) (Badding et al., 2014) after exposure to MS or SS welding fumes.

(iii) Immunosuppression in vivo

Several studies in male Sprague-Dawley rats have consistently demonstrated a reduced ability to clear bacteria from the lung after exposure to both SS and MS welding fumes by inhalation (reviewed by Zeidler-Erdely et al., 2012). Exposure to GMA-MS and GMA-SS welding fumes via inhalation (40 mg/m^3, 3 hours per day, for 3 days) inhibited pulmonary bacterial clearance of subsequently inoculated *Listeria monocytogenes* in rats (Antonini et al., 2007, 2009a). While prior exposure to GMA-SS and GMA-MS fumes by intratracheal instillation had no effect, prior exposure to MMA-SS welding fumes increased PMN influx and BALF oxidant levels but impaired resolution of infection (Antonini et al., 2004a). Among other effects on BALF cytokines, exposure to MMA-SS fumes via intratracheal instillation decreased IL-2 levels and prevented the *L. monocytogenes* challenge-induced increase in IL-2 and IL-10 content; similarly, soluble chromium also decreased IL-2 levels and inhibited bacterial clearance when given separately (Antonini et al., 2004b; Antonini & Roberts, 2007). [The Working Group noted that this suggests suppression of T-lymphocyte activity, mediated by the soluble chromium component.] GMA-SS fumes had qualitatively similar effects as MMA-SS fumes on rat pulmonary bacterial clearance and cytokine levels, while GMA-MS fumes elicited a weaker response (Antonini et al., 2007, 2009a). Although iron-rich GMA-MS fumes inhibited bacterial clearance in rats, exposure to iron oxide (Fe_2O_3) did not (Antonini and Roberts, 2007). [The Working Group noted that the specific mediator(s) responsible for GMA-MS immunosuppression remains unclear.] Additionally, in uninfected rats, MMA-SS fumes administered via intratracheal instillation increased total peripheral blood mononuclear cell (PBMC) numbers, specifically monocyte and PMN subpopulations, and attenuated leukocyte release of chemokines (e.g. Cxcl10, Ccl4, and Cxcl2) at the post-transcriptional level in response to lipopolysaccharide (LPS) challenge ex vivo (Erdely et al., 2014).

In female mice, two studies reported pulmonary or systemic immunosuppression after exposure to MMA-SS or MMA-MS fumes. MMA-SS fumes increased *Pafr* mRNA expression in the lungs of B6 mice exposed via inhalation (40 mg/m^3, 3 hours per day, for 10 days) (Suri et al., 2016). This induction was associated with increased bacterial colony-forming units (CFUs) in the BALF and lung tissue of female CD-1 mice inoculated with *S. pneumoniae* after exposure to MMA-MS fumes via intranasal instillation. A selective PAFR blocker significantly attenuated BALF CFU concentrations in mice exposed to fumes (Suri et al., 2016). After exposure to total MMA-SS fumes or soluble fractions via pharyngeal aspiration, splenocytes from female B6C3F$_1$ mice exhibited reduced immunoglobulin-M (IgM) activity in response to sheep erythrocyte stimulation in vitro, and a similar reduction in immune function was observed in LALN B-lymphocytes (Anderson et al., 2007). Exposure to the insoluble fraction did not result in this effect.

(iv) Immunosuppression in vitro

Evidence for decreased immune function in rats and mice in vivo is supported by two complementary in vitro studies in rodent cells. GMA welding fumes generated from a consumable of high nickel and copper concentration

(very low levels of Fe, Cr, and Mn) reduced phagocytic activity in RAW 264.7 cells, while no effects were observed after exposure to either MS or SS fumes (Badding et al., 2014). In female $B6C3F_1$ mouse splenocytes, the total and soluble fractions of MMA-SS welding fumes decreased the number of plaque-forming cells in response to sheep erythrocyte challenge, while the insoluble fraction had no significant effect (Anderson et al., 2007).

4.2.2 Genetic and related effects

(a) Humans

The results of the investigations are listed in Table 4.1. Except where noted, the studies generally matched exposed and unexposed subjects on age and sex, and most studies adjusted for smoking.

(i) Cytogenetic end-points

Exposure to welding fumes was without effect on chromosomal aberrations or sister-chromatid exchange in two of the three studies describing cytogenetic effects described in *IARC Monographs* Volume 49 (Husgafvel-Pursiainen et al., 1982; Littorin et al., 1983; IARC, 1990). The third study reported a significant increase in both cytogenetic parameters (Koshi et al., 1984).

Results were also mixed in the additional studies on chromosomal aberrations in welders available to the Working Group. Three studies that controlled for smoking (Elias et al., 1989; Knudsen et al., 1992; Jelmert et al., 1994) and a fourth that did not (Borská et al., 2003) described a positive association between lymphocyte chromosomal aberrations and exposure, while two studies reported negative results (Jelmert et al., 1995; Halasova et al., 2012). The positive results were reported in TIG welders exposed to chromium (Borská et al., 2003), in MMA-SS welders (Jelmert et al., 1994), and in pooled groups of welders involved in different types of welding (TIG, MMA+TIG, and MIG; Knudsen et al., 1992; metal active gas (MAG) with cored wire containing Ni, TIG, and MMA; Elias et al., 1989). It is noteworthy that a significant increase in lymphocyte chromosomal aberrations was only observed in MMA+TIG welders who, unlike other welders, also had increased concentrations of chromium and nickel in blood (Knudsen et al., 1992). Elias et al. reported positive results for MAG with cored wire containing nickel welders group, but not for TIG and MMA groups (Elias et al., 1989).

Negative results for an increase in lymphocyte chromosomal aberrations in welders (type of welding was not specified) were reported by Halasova et al. (2012), and in TIG welders by Jelmert et al. (1995). [The Working Group noted that Jelmert et al. reported a statistically significant decrease of rates of chromosomal breaks and cells with chromosomal aberrations in welders compared with the control subjects.]

Positive findings for micronuclei (MN) in lymphocytes of welders were reported in most available studies, but several had notable deficiencies. In Italian electric arc welders, who were also exposed to extremely low-frequency electromagnetic fields, a significantly higher frequency of MN was found (Dominici et al., 2011). Positive results were obtained in lymphocytes of MMA, TIG, and metal inert/active gas welders in two studies carried out in France (Iarmarcovai et al., 2005, 2006), in one in Turkey (Sener & Eroglu, 2013), and in one in India (Sellappa et al., 2010). A study of 5 MMA-SS welders that did not control for smoking reported negative results compared with 27 control subjects (Medeiros et al., 2003). [The Working Group noted that most of these studies assessed MN in 500 or 1000 binucleated lymphocytes, whereas the recommended number is 2000 OECD (2016).]

Results from studies in exfoliated epithelial cells of welders were mixed. One study (Wultsch et al., 2014) reported increased MN frequencies in nasal cells, but not buccal cells, in TIG welders. In both cell types, significant increases were seen

Table 4.1 Genetic and related effects of welding fumes in exposed humans[a]

End-point	Cell type	Description of exposure and controls	Response	Comments	Reference
Chromosomal aberrations	Lymphocytes	55 welders (group 1, MMA, $n = 22$; group 2, MAG, $n = 18$; group 3, TIG, $n = 15$); 55 control subjects	+	No correlation with Cr, Ni, and Mn in serum, urine; higher CA in smokers; effect of exposure duration	Elias et al. (1989)
Chromosomal aberrations	Lymphocytes	47 TIG, 56 MMA+TIG, and 11 MIG welders; 68 control subjects	+	Higher CA in smoking welders vs smoking controls; higher Cr in serum and urine of welders; urinary Ni increased only in MMA+TIG welders	Knudsen et al. (1992)
Chromosomal aberrations	Lymphocytes	31 MMA welders tested after shift, 20 welders before the start of work and retested 1–4 months after; 40 control subjects	+	No effect of smoking; increased Cr but not Ni in blood and urine of welders	Jelmert et al. (1994)
Chromosomal aberrations	Lymphocytes	23 TIG and 21 MAG or MIG welders on SS; 38 control subjects and 94 reference subjects	–	Decreased CA in welders; no effect of smoking; increased Cr and Ni in urine and blood	Jelmert et al. (1995)
Chromosomal aberrations	Lymphocytes	73 welders (type of welding not specified); 71 control subjects	–	Correlation with blood Cr; no effect of smoking	Halasova et al. (2012)
Chromosomal aberrations	Lymphocytes	20 TIG welders; 20 control subjects	(+)	Did not control for smoking	Borská et al. (2003)
Micronucleus formation	Lymphocytes	21 electric arc welders; 21 control subjects	+	No effect of smoking	Dominici et al. (2011)
Micronucleus formation	Lymphocytes	27 MMA, TIG, and MIG welders working without any protection device; 30 control subjects	(+)	Inadequate number of scored cells (1000, whereas 2000 are recommended)	Iarmarcovai et al. (2005)
Micronucleus formation and FISH with a pancentromeric DNA probe	Lymphocytes	27 MMA, MIG, and TIG welders working in areas without any collective protection device; 30 control subjects	(+)	Inadequate number of scored cells (1000, whereas 2000 are recommended)	Iarmarcovai et al. (2006)
Micronucleus formation	Lymphocytes	23 MAG welders; 25 control subjects	(+)	Inadequate number of scored cells (500, whereas 2000 are recommended)	Sener & Eroglu (2013)
Micronucleus formation	Lymphocytes	93 MMA welders; 60 control subjects	(+)	Effect of smoking, exposure duration, and alcohol consumption; inadequate number of scored cells (500, whereas 2000 are recommended)	Sellappa et al. (2010)
Micronucleus formation	Lymphocytes	5 MMA-SS welders; 27 control subjects	(–)	Did not control for smoking; low number of welders	Medeiros et al. (2003)
Micronucleus formation	Nasal and buccal cells	22 TIG welders; 22 control subjects	+ (nasal cells) – (buccal cells)	Increased Mo, Cr, Mn, Ni, and Cu in blood plasma of welders; no effect of smoking and alcohol consumption	Wultsch et al. (2014)

Table 4.1 (continued)

End-point	Cell type	Description of exposure and controls	Response	Comments	Reference
Micronucleus formation	Buccal cells	58 MMA welders; 52 controls	+		Danadevi et al. (2004)
Micronucleus formation	Buccal cells	66 MMA welders; 60 control subjects	+		Sudha et al. (2011)
Micronucleus formation	Buccal cells	33 MIG welders; 33 control subjects	–	No effect of smoking	Jara-Ettinger et al. (2015)
Micronucleus formation	Buccal cells	11 welders (type of welding not specified); 20 control subjects	(–)	Did not control for smoking; cells were stained with Giemsa (DNA-non-specific stain)	Domínguez Odio et al. (2005)
Sister-chromatid exchange	Lymphocytes	39 MAG and MMA welders; 18 control subjects	–	Increased Cr and Ni in urine of welders; no effect of smoking	Popp et al. (1991)
Sister-chromatid exchange	Lymphocytes	24 MMA-SS welders; 2 matched control groups (24 + 46 subjects) One subgroup of 10 welders tested before the start of work and again 1–4 months after; 10 matched controls	– –	No effect of smoking; increased Cr and Ni in urine and blood	Jelmert et al. (1994)
Sister-chromatid exchange	Lymphocytes	6 TIG and 11 MIG/MAG welders; 7 and 10 controls for each group, respectively	–		Jelmert et al. (1995)
Sister-chromatid exchange	Lymphocytes	39 SS welders; 22 controls	+	Association with blood Cr (increased in welders); no effect of smoking or exposure duration	Myślak & Kośmider (1997)
Sister-chromatid exchange	Lymphocytes	49 TIG, 60 MMA+TIG, and 12 MIG welders; 75 control subjects	–	SCE rates lower in total welders group and in smokers group, but not in nonsmokers	Knudsen et al. (1992)
Sister-chromatid exchange	Lymphocytes	21 electric arc welders; 21 control subjects	–	No effect of smoking; 1.3 times decrease in exposed compared with control subjects	Dominici et al. (2011)
Sister-chromatid exchange	Lymphocytes	39 MMA welders; 39 control subjects	+	Increased Cr in erythrocytes and Ni in whole blood in welders; no effect of smoking	Werfel et al. (1998)
DNA strand breaks (comet assay)	Lymphocytes	26 welders (type of welding not specified); 26 control subjects	+	No effect of smoking or exposure duration	Sardas et al. (2010)
DNA strand breaks (comet assay)	Lymphocytes	30 MMA, TIG, and MIG/MAG welders, 22 control subjects	+	Positive correlation with blood Al, Co, Ni, and Pb; no effect of smoking or alcohol consumption	Botta et al. (2006)
DNA strand breaks (comet assay)	Lymphocytes	102 MMA welders; 102 controls	+	Effect of exposure duration but not smoking, alcohol consumption, or age; positive correlation with Cr and Ni	Danadevi et al. (2004)

Table 4.1 (continued)

End-point	Cell type	Description of exposure and controls	Response	Comments	Reference
DNA strand breaks (comet assay)	Leukocytes	93 MMA welders; 60 control subjects	+	Effect of smoking, alcohol consumption, and exposure duration	Sellappa et al. (2010)
DNA strand breaks (comet assay)	Leukocytes	35 welders (type of welding not specified); 35 control subjects	+	No effect of smoking, exposure duration, or alcohol consumption	Singh & Chadha (2016)
DNA strand breaks (comet assay)	Lymphocytes	26 welders working in areas without any collective protection device, 4 welders working in places equipped with smoke extraction systems; 22 control subjects	+	No effect of smoking or alcohol consumption; association with *XRCC1* gene variant	Iarmarcovai et al. (2005)
DNA strand breaks (comet assay)	Lymphocytes	120 welders (type of welding not specified); 40 controls (managerial workers)	–	No effect of smoking or exposure duration	Zhu et al. (2001)
DNA strand breaks (alkaline elution assay)	Lymphocytes	39 MAG and MMA welders; 18 control subjects	–	Reduced frequency of DNA-strand breaks compared with controls; no effect of smoking	Popp et al. (1991)
DNA strand breaks (alkaline elution assay)	Lymphocytes	39 MMA and other welders; 39 controls	+ with (but not without) proteinase K	Increased Cr in erythrocytes and Ni in blood of welders; no effect of smoking	Werfel et al. (1998)
DNA strand breaks (comet assay)	Buccal cells	66 MMA welders; 60 control subjects	+	Effect of smoking, alcohol consumption, and exposure duration	Sudha et al. (2011)
DNA–protein cross-links	Leukocytes	21 MMA welders; 26 control subjects	+	No effect of smoking	Costa et al. (1993), Toniolo et al. (1993)
DNA–protein cross-links	Lymphocytes	5 male SS welders; 22 control subjects	(+)	Did not control for smoking; small number of exposed subjects	Quievryn et al. (2001)
DNA–protein cross-links	Leukocytes	5 MMA-SS welders; 30 control subjects	(+)	Did not control for smoking; small number of exposed subjects	Medeiros et al. (2003)

[a] Most studies accounted for age, sex and smoking, except where indicated

+, positive; –, negative; (+) or (–), positive or negative in a study with of limited quality; Al, aluminium; CA, chromosomal aberration; Co, cobalt; Cr, chromium; Cu, copper; FISH, fluorescent in situ hybridization; MAG, metal active gas; MIG, metal inert gas; MMA-SS, manual metal arc stainless steel; Mn, manganese; Mo, molybdenum; Ni, nickel; Pb, lead; SCE, sister-chromatid exchange; SS, stainless steel; TIG, tungsten inert gas; vs, versus

in other nuclear anomalies (reflecting genotoxic as well as cytotoxic effects). Of the four studies that used a DNA-non-specific stain, Giemsa [which the Working Group noted can lead to false-positive results (Nersesyan et al., 2006)], two were positive and two were negative. Studies of MMA welders in India reported significantly increased levels of MN in oral mucosa cells (Danadevi et al., 2004; Sudha et al., 2011). MN rates were significantly correlated with the age and smoking status of welders, as well as the duration of exposure. A study of MIG welders in Mexico (Jara-Ettinger et al., 2015), and a study of welders (not otherwise specified) in Cuba that did not control for smoking (Domínguez Odio et al., 2005), gave negative results.

In several studies available on sister-chromatid exchange in lymphocytes of welders, mixed results were obtained. Popp et al. (1991) and Jelmert et al. (1994, 1995) observed no effect in stainless steel (MMA, TIG, MIG, and MAG) welders. Interestingly, a statistically significant negative association was observed between the total chromium in inhaled air and frequency of sister-chromatid exchange (Jelmert et al., 1995). A slight but significant increase in sister-chromatid exchange rates was observed in MMA, MIG, and MMA+MIG welders in the Czech Republic (Myślak & Kośmider, 1997). In TIG, MMA+TIG, MIG, and electric arc welders, the rate of sister-chromatid exchange in lymphocytes was significantly lower in total welders and in nonsmoking welders than in reference groups (Knudsen et al., 1992; Dominici et al., 2011).

Significantly elevated rates of sister-chromatid exchange were observed in MMA welders in Germany. However, no significant difference was found in comparisons between exposed and control smokers, or between exposed and control nonsmokers (Werfel et al., 1998).

(ii) DNA damage

Most studies of DNA damage were positive, but many used an imprecise measure of DNA damage (i.e. Olive tail moment or tail length instead of percentage DNA in tail (%DNA) for the comet assay) (Collins et al., 2008).

A significant increase in the mean %DNA was observed in lymphocytes of welders (type of welding not specified) (Sardas et al., 2010).

Significantly increased levels of DNA damage were seen in lymphocytes of MMA and TIG welders at the end of the working week, but not at the beginning (Botta et al., 2006). Spearman rank correlation analysis indicated positive correlations between blood concentrations of aluminium, cobalt, nickel, and lead and the levels of DNA damage. A significant increase in DNA strand breaks in lymphocytes (Danadevi et al., 2004; Sellappa et al., 2010) or in buccal cells (Sudha et al., 2011) was also found in MMA welders in three studies in India. In another study in India (Singh & Chadha, 2016), significant increases were seen in both damaged cell frequency and mean tail length in welders (type of welding not specified) who were heavily exposed to welding fumes due to poor ventilation and no mask. MMA, TIG, and GMA welders had a significant increase in Olive tail moment distribution at the end of the week when compared with the beginning, and also with controls (Iarmarcovai et al., 2005).

No significant elevation of DNA tail moment was found in the lymphocytes of welders in Guangzhou, China (welding type not specified) compared with controls (Zhu et al., 2001). One study using the alkaline filter elution method reported reduced DNA strand breaks in MAG and MMA welders compared with controls (Popp et al., 1991), whereas another study using the same method and by the same team reported a significantly higher rate of DNA single-strand breaks in the lymphocytes of MMA and other welders (Werfel et al., 1998).

(iii) DNA–protein cross-links

Positive results were reported for DNA–protein cross-links in welders, but most available studies were small and did not control for smoking. In two publications on the same study, higher levels of DNA–protein cross-links were seen in 21 MMA welders (Costa et al., 1993; Toniolo et al., 1993). Two studies evaluated five welders; one reported significantly higher levels of DNA–protein cross-links in peripheral leukocytes of MMA-SS welders (Medeiros et al., 2003), and a study of SS welders in Portugal reported a higher number of DNA–protein cross-links in lymphocytes compared with controls (Quievryn et al., 2001).

(iv) Point mutations and unscheduled DNA synthesis

Exposure to welding fumes was associated with an odds ratio (OR) of 5.65 (95% CI, 1.39–22.93; 6 exposed cases with von Hippel–Lindau (*VHL*) gene mutations) for multiple *VHL* mutations in multivariate analysis restricted to renal cell carcinoma (RCC) patients in Sweden who were smokers (Hemminki et al., 2002). [The Working Group noted that there were only 21 RCC cases exposed to welding fumes; 8 had G-to-A *VHL* mutations, and 6 of the 8 were smokers.]

Knudsen et al. (1992) did not find an increase in unscheduled DNA synthesis and DNA repair capacity in peripheral lymphocytes of TIG, MMA+TIG, and MIG welders.

(v) Oxidative damage to DNA

In a controlled crossover inhalation study of healthy welding apprentices (n = 20), 60 minutes of exposure to TIG welding fumes (Ar shielding gas) on aluminium cubes significantly increased the concentrations of 8-hydroxydeoxyguanosine (8-OHdG) in plasma and urine. The increase in plasma 8-OHdG was related to the exposure level to smaller particles of welding fumes (geometric mean diameter, 44 nm), while no associations were observed with gravimetric mass (Graczyk et al., 2016a, b). Further, in a short-term observational study, 8-OHdG concentrations in urine increased over a full shift in 41 MS stick-welding boilermakers, with a decline back to baseline in samples taken the next morning (Nuernberg et al., 2008). In another study involving 20 boilermakers, all mean concentrations of 8-OHdG in the urine after a work shift were significantly higher than values before the shift; exposure–response was observed with $PM_{2.5}$ (Kim et al., 2004). However, nonsmokers had higher levels of 8-OHdG before the start of the working week, and an interaction between smoking and exposure to welding fumes (varying by metal) was indicated (Mukherjee et al., 2004). In a comparison of 8-OHdG in urine, concentrations at the end of 5 working days were higher than at the start of the first day in both 118 shipyard TIG welders and 45 office worker controls, but the concentrations at the end of the 5 working days were significantly higher in the welders than in controls. Exposure–response was observed with $PM_{2.5}$, and with iron and zinc in urine (Lai et al., 2016).

The effects were less clear in three cross-sectional observational studies. No difference in urinary 8-OHdG was observed in a study of 57 male and female welders and 42 office worker controls (welding technique and material not reported) (Liu et al., 2013), while in another study of MAG welders no significant increase was seen after adjustment for relevant confounders (Li et al., 2015a). Finally, in a study of MIG and TIG welders, and also welders wearing a powered air-purifying respirator (PAPR) in Germany, urinary 8-oxo-guanosine (8-oxoGuo) concentrations did not differ significantly (Pesch et al., 2015). The number of 8-oxo-deoxyguanosine (8-oxodGuo) per 10^6 deoxyguanosine (dGuo) in leukocytes of MIG welders exposed to high concentrations of fumes was significantly higher than in TIG welders and welders wearing a PAPR. For urinary 8-oxoGuo, nonlinear associations were observed with serum Fe.

Table 4.2 Genetic and related effects of welding fumes in non-human mammals in vivo

Species, strain, sex	Tissue	End-point	Test system	Result	Concentration (LEC or HIC)	Route, duration, dosing regimen	Reference
Rat, Sprague-Dawley, M	Lung cells	DNA damage	DNA strand breaks, comet assay; 8-OHdG	+	65.6 mg/m³ of MMA-SS fumes	Inhalation, 2 h/d for 1, 15, 30 d	Yu et al. (2004)
Rat, Sprague-Dawley, M	Blood (leukocytes), kidney, liver	DNA strand breaks	Comet assay	+ (leukocytes, 1–15 d only; liver and kidney, 40 d only)	12.32 mg/kg of MMA fumes	Inhalation for 10 min/d, up to 40 d	Chuang et al. (2010)
Rat, Wistar, M+F	Peripheral blood lymphocytes, bone marrow	Chromosomal damage	Chromosomal aberrations	–	217 mg/m³ of MMA-MS or 144 mg/m³ of MIG-MS	Inhalation for 6 h/day, 5 d/wk, 2 wk	Etienne et al. (1986)
Rats, Wistar, M+F,	Peripheral blood lymphocytes	Chromosomal rearrangement	Sister-chromatid exchanges	–	217 mg/m³ of MMA-MS or 144 mg/m³ of MIG-MS	Inhalation for 6 h/d, 5 d/wk, 2 wk	Etienne et al. (1986)
Mouse, C57BL/6J/BOM9, F	Fur	Gene mutation	Fur spot test	+	100 mg/kg particles of MMA-SS welding fumes	i.p. at 8, 9, 10 d of gestation	Knudsen (1980)

+, positive; –, negative; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; d, day(s); F, female; h, hour(s); HIC, highest ineffective concentration; i.p., intraperitoneally; LEC, lowest effective concentration; M, male; MIG, metal inert gas; min, minute(s); MMA, manual metal arc; MS, mild steel; SS, stainless steel; wk, week(s)

(b) Experimental systems

See Table 4.2, Table 4.3

DNA damage (comet assay) and 8-OHdG increased with exposure duration in a dose-dependent manner in the lung tissue of Sprague-Dawley rats exposed to MMA-SS welding fumes for up to 30 days (Yu et al., 2004). In a study in which Sprague-Dawley rats were exposed to MMA-SS welding fumes for up to 40 days, DNA damage (comet assay, tail moment) increased significantly in leukocytes (1–15 days only) and in liver and kidney cells (40 days only) (Chuang et al., 2010). No increase in chromosomal aberrations in bone marrow cells and in peripheral blood lymphocytes, or in lymphocyte sister-chromatid exchange, was seen in Wistar rats after exposure to welding fumes (MMA-MS, MIG-MS) by inhalation for 60 hours (Etienne et al., 1986).

One study reported positive results in the fur spot test in mice after receiving 100 mg/kg body weight of MMA-SS welding fumes on days 8, 9, and 10 of gestation by intraperitoneal injection (Knudsen, 1980).

SS and MS welding fumes increased DNA damage in a study in vitro in RAW 264.7 mouse peritoneal monocytes, with significantly higher damage from the SS welding fumes (Leonard et al., 2010). [The Working Group noted that DNA damage was assessed by the comet tail length instead of %DNA in comet tail.]

Only a few studies in bacteria were available. MMA-SS and MIG-SS fumes were positive in *S. typhimurium* strain TA100 without metabolic activation (starting from 2.5 µg water-soluble Cr in fume sample) (Pedersen et al., 1983). In the SOS *umu*-test in *S. typhimurium* strain TA1535/pSK1002, exposure to MMA-SS welding fumes

Table 4.3 Genetic and related effects of welding fumes in experimental systems in vitro

Species, strain	End-point	Test system	Results		Concentration (LEC or HIC)	Reference
			Without metabolic activation	With metabolic activation		
Mouse peritoneal monocytes RAW 264.7	DNA damage	DNA strand breaks, comet assay	+	NT	250 µg/mL; SS and MS fumes	Leonard et al. (2010)
Salmonella typhimurium TA 100	Gene mutation	Reverse mutation	+	NT	2.5 µg; MMA-SS and MIG-SS fumes per plate	Pedersen et al. (1983)
Salmonella typhimurium TA1535/pSK1002	DNA damage	SOS *umu* assay	+	NT	NS; MMA–SS welding fumes	Ong et al. (1987)

+, positive; HIC, highest ineffective concentration; LEC, lowest effective concentration; MIG, metal inert gas; MMA, manual metal arc; MS, mild steel; NS, not specified; NT, not tested; SS, stainless steel.

for 4 and 6 hours generated a marked response (Ong et al., 1987).

In a study in an acellular system, DNA damage associated with hydroxyl radical (·OH) formation was demonstrated for MMA welding fumes in plasmid λ *Hind* III (Antonini et al., 2005).

4.2.3 Oxidative stress

(a) Humans

Effects on 8-OHdG are described in Section 4.2.2 (a)(v).

Significant increases in hydrogen peroxide (H_2O_2) were observed in plasma and urine in a controlled crossover experimental inhalation study of TIG aluminium welding (1 hour; particulate matter of diameter < 4 µm or PM_4, 0.72 mg/m³) (Graczyk et al., 2016a). Similarly, an increase of the hydrogen peroxide to tyrosine ratio in exhaled breath condensate was observed during the work shift in a field study of 45 welders using mixed welding techniques (respirable dust, 0.7 mg/m³), but in smokers only (Gube et al., 2010).

No change in urinary 8-isoprostane measured before and after the work shift was observed among 41 boilermaker apprentices and current and retired welders (metal arc welding, MS; $PM_{2.5}$, 0.82 mg/m³) in a controlled experiment of crossover design (Nuernberg et al. 2008). However, the concentrations decreased significantly from the end of the shift to bedtime, and to the next day. Urinary 8-isoprostane increased significantly from the start of day 1 to the end of day 5 in a 5-day observational study of 118 TIG shipyard welders ($PM_{2.5}$, 0.76 mg/m³). Exposure–response relationships were observed with $PM_{2.5}$ in air, and with iron and zinc in urine (Lai et al., 2016). Two cross-sectional studies (concentrations only measured at the end of the work shift) observed higher concentrations of 8-isoprostane in serum and exhaled breath condensate among welders than among unexposed controls; Han et al. (2005) evaluated 197 shipyard (GMA) welders and 150 office controls, while Hoffmeyer et al. (2012a) studied 58 healthy MAG-MS welders. Two other cross-sectional studies found higher 8-isoprostane concentrations in welders at the end of shifts, with high and low concentrations of chromium in exhaled breath condensate and nasal lavage fluid, respectively (Hoffmeyer et al., 2012b; Raulf et al., 2016).

In another cross-sectional study, glutathione (GSH) in blood was lower in welders (44 spot welders and 80 arc welders; material not stated) and in those with bystander (59 assemblers) exposure to welding fumes compared with controls (29 office workers), with no gradient in effect between full-time welders, part-time welders and bystanders, and no effect on plasma malondialdehyde (MDA) (Luo et al., 2009).

Gube et al. (2010) found no overall cross-sectional group difference between 45 welders and 24 controls in the MDA to tyrosine ratio (an indicator of lipid peroxidation), but the ratio was significantly increased in workers without respiratory protection, compared to those with respiratory protection.

Levels of antioxidants in plasma (vitamins C and E) and erythrocytes (superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPX) activity) were all lower in nonsmoking male and female construction welders (n = 70; electric arc welding) as compared with unexposed controls (n = 70), while erythrocyte lipoperoxide concentrations were higher. Antioxidant levels (except catalase) decreased with years working as a welder (adjusted for age), while lipoperoxide concentrations increased. A significant negative association between ozone exposure levels among the welders and each antioxidant was observed, while lipoperoxide concentrations were positively associated with the ozone exposure (Zhu et al., 2004).

No significant differences in plasma MDA and total antioxidant concentrations, or erythrocyte GPX and glutathione *S*-transferase activity, were observed between male and female welders (welding technique and material not stated; n = 57) and office worker controls (n = 42). However, welders had lower erythrocyte GSH concentrations and erythrocyte SOD activities (Liu et al., 2013). [The Working Group noted that these specific comparisons were not adjusted for other factors; sex, smoking, and alcohol intake differed significantly between the exposed group and the control group.] Welders (n = 40) performing MMA welding (material not stated) had significantly lower whole-blood GSH concentrations and higher MDA concentrations when compared with controls (n = 10, Harisa et al., 2014). In another small cross-sectional study including 34 welders (technique and material not reported) and 20 controls, serum thiobarbituric acid reactive substances and protein carbonyl concentrations were higher in welding workers than in controls, while total protein sulfhydryl groups and GSH levels were significantly lower in welders than in controls (Fidan et al., 2005).

No significant difference was observed in total serum antioxidant status, but erythrocyte SOD and GPX activity was lower in male nonsmoking car factory spot welders (n = 46) compared with controls (n = 45) (Sharifian et al., 2009). A negative correlation was observed between the magnetic field intensity from welding, and SOD and GPX activity. No such associations were observed with metal concentrations in air (Pb, Fe, Cu, and Zn). Increasing zinc concentrations in blood were associated with significantly lower total antioxidant concentrations in a cross-sectional study of 94 smoking welders (manual electric arc or gas welding, material not stated) (Kolarzyk et al., 2006), while copper levels in blood were positively associated with total antioxidant status.

Male and female vehicle manufacturer electric arc welders with high exposure to manganese (geometric mean, 1.45 mg/m^3; n = 37) had cross-sectionally higher serum MDA levels and lower erythrocytic SOD activity when compared with controls (n = 50) (Li et al., 2004). In the highly-exposed shipyard welders studied by Han et al. (2005), the total antioxidant status in serum was significantly higher than in 150 controls, as were levels of aconitase and GPX, while no significant difference was observed for manganese SOD (MnSOD). Dose–response associations were observed between the concentrations of manganese or lead in the blood of welders and various

measures of antioxidant status, including GPX and MnSOD (Han et al., 2005).

Haem oxygenase-1 was significantly higher, and associated with particulate matter of diameter < 2 μm, in induced sputum samples from short-term (mean 10 years) aluminium-iron welders (n = 30) compared with non-exposed subjects (n = 27) (Stark et al., 2009). Intermediate levels were seen in long-term (mean, 21 years; n = 16) MS welders.

In a study of 75 male SS and MS shipyard welders using electrodes containing up to 22% chromium, blood levels of Cr(VI) were associated with increased serum apolipoprotein J/Clusterin (ApoJ/CLU) in SS welders (Alexopoulos et al., 2008). The ApoJ/CLU levels decreased in the workers exposed to the highest concentrations after participating in a worker educational programme aimed at reducing exposure levels.

Mitochondrial DNA methylation levels in blood were lower at the end of a work shift compared with before the shift among 48 men, including 35 welding boilermakers (MMA-MS and MIG-MS welding; mean $PM_{2.5}$ concentration, 0.38 mg/m^3), and an exposure–response association indicated that mitochondrial DNA methylation was negatively associated with $PM_{2.5}$ concentrations (Byun et al., 2016). In a cross-sectional approach, Xu et al. (2017) also found less methylation of the mitochondrial regulatory region and higher mitochondrial DNA in 101 welders (mainly GMA-MS; mean respirable dust concentration, 1.2 mg/m^3) compared with 127 controls.

(b) *Experimental systems*

(i) *In vivo*

Several studies reported increases in markers of lung oxidative stress in male Sprague-Dawley rats after exposure to SS fumes via intratracheal instillation. After exposure to MMA-SS welding fumes, increases were observed in lipid peroxidation products in lung tissue homogenate (Taylor et al., 2003), nitric oxide species in the BALF, inducible nitric oxide synthase (iNOS) protein expression in inflammatory infiltrates, and AM or PBMC reactive oxygen species (ROS) production ex vivo (Antonini et al., 2004a; Erdely et al., 2014). Although all fractions of MMA-SS fumes induced lipid peroxidation, the total fraction of fumes was the most potent and the soluble fraction the least potent (Taylor et al., 2003). GMA-SS fumes induced lower levels of lipid peroxidation in rat lungs compared with MMA-SS fumes, and GMA-MS fumes had only a marginal effect (Taylor et al., 2003). Neither GMA-SS nor GMA-MS fumes increased levels of nitric oxide species in the lung BALF, or induced greater alveolar macrophage ROS production ex vivo (Antonini et al., 2004b). No change in serum concentrations of lipid peroxidation products was reported in male Wistar rats exposed to unspecified welding fumes [containing chromium] via inhalation (60 mg/m^3, 6 hours per day, for 5 or 10 days), and lung concentrations were not determined (Halatek et al., 2017).

In male A/J and C57BL/6J mice exposed to SS or MS welding fumes by pharyngeal aspiration, no changes were observed in the lung tissue mRNA expression levels of enzymes involved in oxidative stress (*iNOS*, prostaglandin-endoperoxide synthase 2 (*Ptgs2*) and glutathione *S*-transferase pi-1 (*Gstp1*)) (cumulative lung burden, approximately 0.340 mg) (Zeidler-Erdely et al., 2008). [The Working Group noted that the welding fumes used were not freshly generated, and loss of pro-oxidant activity soon after the generation of SS fumes was hypothesized by Antonini et al. (1998) and Badding et al. (2014) to result from the degradation of a short-lived, reactive chromium species.]

(ii) *In vitro*

Welding fumes have been reported to oxidize biological components in both biochemical assays and cell culture models. MIG-MS welding fumes increased the oxidation of dopamine in a

manner directly related to the generating current and inversely related to the iron:manganese ratio of the fumes (Hudson et al., 2001), while MMA-MS fumes increased the oxidation of both ascorbate and GSH in artificial BALF (Suri et al., 2016). Welding fumes generated ROS as determined by electron spin resonance, with the total fractions eliciting the strongest signals and the soluble fraction the weakest, although CrV was similarly produced (from Cr(VI)) by both fractions (Taylor et al., 2003; Antonini et al., 2005). Initially, neither GMA-SS nor GMA-MS welding fumes produced ROS (Taylor et al., 2003); however, later studies reported ROS generation induced by GMA welding of SS, MS, and a consumable of high nickel and copper content (Leonard et al., 2010; Badding et al., 2014).

MMA-SS, GMA-SS, and GMA-MS fumes increased ROS production in rat BALF lung macrophages (Antonini et al., 1997, 1999; Chang et al., 2013) and in mouse RAW 264.7 macrophages (Leonard et al., 2010).

Iron-chelation did not inhibit the activity of soluble fractions [which suggests that non-ferrous metals were responsible], while total MMA-SS fractions elicited the greatest ROS production in rat lung macrophages (Antonini et al., 1999); ultrafine particle size fractions elicited a greater effect than coarse fractions for both SS and MS fumes (Leonard et al., 2010; Chang et al., 2013).

4.2.4 Altered cell proliferation or death

(a) Humans

As noted previously (see Section 4.2.2 (a) (i)), one study reported nuclear anomalies (reflecting genotoxic as well as cytotoxic effects) in buccal and nasal cells of TIG welders (Wultsch et al., 2014). An in vitro study reported cytotoxicity in human lung A549 cells exposed to SS welding fumes (McNeilly et al., 2004).

(b) Experimental systems

(i) In vivo

Studies in male rats and mice suggest that SS welding fumes induce more lung toxicity when compared with MS fumes, via both inhalation and intratracheal instillation exposure routes (reviewed in Zeidler-Erdely et al., 2012). In Sprague-Dawley rats, BALF albumin concentrations and lactate dehydrogenase (LDH) activity increased within 1 day after inhalation exposure to GMA-SS (40 mg/m^3, 3 hours per day, for 3 days) or MMA-SS (44.1–65.6 or 80.1–116.8 mg/m^3, 2 hours per day, for up to 60 exposure days) welding fumes; levels remained elevated for at least 14 days after exposure cessation, and resolved to baseline after 30 days (Yu et al., 2004; Antonini et al., 2007; Yang et al., 2009). Decreased viability in BALF leukocytes, coupled with increased serum LDH activity, was also induced in Wistar rats exposed to unspecified welding fumes [containing chromium] via inhalation (60 mg/m^3, 6 hours per day, for 5 or 10 days; Halatek et al., 2017). While high metal (HM) fumes (25 mg/m^3, 4 hours per day, for 3, 8, or 13 days) via inhalation induced an initial, transient, increase in albumin levels, there was no corresponding cytotoxicity to the pulmonary epithelium (Zeidler-Erdely et al., 2014). No effects were observed in rats after similar exposures to low metal (LM) MS resistance spot welding fumes (Zeidler-Erdely et al., 2014) or GMA-MS fumes (40 mg/m^3, 3 hours per day, for 3 or 10 days) (Antonini et al., 2009a).

A single intratracheal instillation of MMA-SS welding fumes in Sprague-Dawley rats induced apoptosis in clusters of pulmonary epithelial cells 6–10 days after treatment (Antonini et al., 2005). BALF albumin and LDH activity levels increased after 1 day, remained elevated for up to 6 days (Taylor et al., 2003; Antonini et al., 2004a), and resolved to background levels after 10–35 days (Antonini et al., 1996, 1997, 2004b). MMA-SS fumes were more

potent than GMA-SS and GMA-MS fumes; the total fraction of MMA-SS welding fumes was the most potent compared with the soluble fraction, which induced a lesser lung injury (Taylor et al., 2003).

Several studies from the same group reported increases in proliferative lesions and persistent lung cytotoxicity in male mice after exposure to welding fumes. Short-term exposure to GMA-SS fumes by inhalation (40 mg/m^3, 4 hours per day, 4 days per week, for 9 weeks; cumulative lung burden, approximately 0.255 mg) induced the appearance of hyperplastic foci in 2 A/J mice (vs 0 in control) 30 weeks after exposure initiation (Falcone et al., 2017), consistent with the increased incidence of preneoplastic lesions (hyperplasias and/or adenomas) after a similar duration after pharyngeal exposure (cumulative lung burden, approximately 1.7 or 3.4 mg) (Zeidler-Erdely et al., 2013) (see Section 3). [The Working Group noted that hyperplasia, atypical adenomatous hyperplasia, and early adenoma are difficult to distinguish from each other, so combining the lesions reduces the potential for misclassification.] After a shorter duration of exposure to GMA-SS fumes by inhalation (40 mg/m^3, 3 hours per day, for 6 or 10 days; respective cumulative lung burden, approximately 0.071 or 0.120 mg), BALF LDH activity and albumin levels increased to a similar extent in both A/J and B6 mice and remained elevated during 28 days of recovery (Zeidler-Erdely et al., 2011b; Erdely et al., 2012). Exposure to GMA-MS fumes by pharyngeal aspiration (cumulative lung burden, approximately 0.340 mg) transiently increased BALF LDH activity to a greater extent in A/J compared with B6 mice, with no change in albumin levels. Exposure to MMA-SS and GMA-SS fumes increased both LDH activity and albumin levels, resolving in B6 mice and diminishing in A/J mice after 28 days or more of recovery (Solano-Lopez et al., 2006; Zeidler-Erdely et al., 2008, 2011a; Erdely et al., 2011a). Administration of a mass-equivalent Cr(VI) solution elicited a similar toxicity profile to MMA-SS fumes in B6 mice, but was not as effective in A/J mice (Zeidler-Erdely et al., 2008). [The Working Group noted that this suggests that other mediators contribute to MMA-SS toxicity in the lungs of A/J mice.]

(ii) In vitro

Both SS and MS welding fumes have been consistently reported to induce cytotoxicity and/or alter mitochondrial function in mammalian cells. SS or MS fumes generated from MMA, GMA, and MIG welding induced cytotoxicity in primary rat alveolar macrophages from male rats (Pasanen et al., 1986; Antonini et al., 1997, 1999, 2005), primary bovine alveolar macrophages [sex not reported] (White et al., 1983), and hamster kidney or embryo cells (Hansen & Stern, 1985; Stern et al., 1988). MMA-SS fumes were the most potent, and induced cytotoxicity qualitatively similar to a molar-equivalent Cr(VI) solution (White et al., 1983; Hansen & Stern, 1985; Pasanen et al., 1986). Welding fumes from a consumable of high nickel and copper content were more cytotoxic than GMA-SS or GMA-MS fumes in mouse RAW 264.7 cells (Badding et al., 2014), and preincubation with the antioxidant *N*-acetyl-L-cysteine afforded no protection. All three types of welding fumes attenuated mitochondrial adenosine triphosphate production, maximal respiratory rate, and bioenergenic reserve capacity (Leonard et al., 2010; Badding et al., 2014). SS fumes were the most potently cytotoxic, as were the total or soluble fractions of fumes (Pasanen et al., 1986; Antonini et al., 1999) and the ultrafine particle fractions (Leonard et al., 2010).

4.2.5 Receptor-mediated effects

(a) Humans

Studies available to the Working Group examined the effects of welding and welding fumes on sex hormones such as testosterone, luteinizing

hormone (LH), and follicle-stimulating hormone (FSH). Decreased serum testosterone concentrations were seen in a cross-sectional study of TIG-SS welders (n = 35) compared with non-welding metalworkers (n = 54) (Bonde, 1990), and in male welders exposed to manganese [type of welding not specified] (Tutkun et al., 2014). In contrast, two other studies (Bonde & Ernst, 1992; Hjollund et al., 1998) observed no association between welding (TIG-SS, MMA-SS, MAG-SS) and serum testosterone levels (Bonde & Ernst, 1992). [The Working Group noted that part of the referent group was non-welding metalworkers in the Bonde & Ernst study; a period of only 3 months without welding was considered in the referent group of metal workers in the Hjollund et al. study; and no differences in urine concentrations of chromium, manganese, or nickel were detected between welders and non-welders, or between measurements made at the beginning and end of the work shift.] Serum testosterone levels were higher in welders [type of welding not specified] exposed to manganese [the only metal analysed] for less than 5 years compared with controls and workers exposed for 5 years or more (Wang et al., 2011).

No association was seen between exposure to welding fumes (TIG-SS, MMA-SS, MAG-SS) and levels of FSH and LH (Bonde & Ernst, 1992; Hjollund et al., 1998), or in levels of LH or thyroid-stimulating hormone (TSH) in male welders exposed to manganese [type of welding not specified] (Tutkun et al., 2014). Welders exposed to manganese had significantly higher concentrations of manganese in blood and urine. Long-term exposure to manganese in this group of welders resulted in significantly lower serum levels of LH and FSH (Wang et al., 2011). However, male MMA shipyard welders (CO_2 gas) had significantly higher manganese concentrations in blood and urine, and higher levels of LH, FSH, and TSH-releasing hormone (TRH) compared with control subjects (Kim et al., 2007). [The Working Group noted that hormone levels were not normally distributed, which was not accounted for in the analyses; manganese was the only metal measured.]

Increased serum prolactin levels were observed in a cross-sectional study of male shipyard welders (Ellingsen et al., 2007) and in male welders exposed to manganese (Niu et al., 2004), and a strong positive correlation was seen between whole-blood manganese concentrations and serum prolactin in welders (Tutkun et al., 2014). In contrast, serum prolactin levels decreased in a group of welders exposed to manganese (Wang et al., 2011).

Compared with age-matched controls (turners/fitters from the same shipyard), welders [type of welding not specified] showed increased levels of inhibin B [no differences in geometric mean values], which can downregulate the synthesis and inhibit the secretion of FSH (Ellingsen et al., 2007).

(b) Experimental systems

No data were available to the Working Group.

4.2.6 Other mechanisms

Several studies of exposure to welding fumes in humans reported effects related to epigenetics and telomere length. Using a repeated measure study design, $PM_{2.5}$ was significantly associated with long interspersed nuclear elements-1 (LINE-1) hypermethylation in 66 welders (MMA-MS welding) (Fan et al., 2014). Additionally, $PM_{2.5}$ exposure was associated with increased methylation in the promoter region of the inducible nitric oxide synthase *iNOS* (MMA welding, MS and SS) (Kile et al., 2013). Wong et al. (2014b) found a statistically significant decrease in relative telomere length, and genomic trauma to leukocyte telomeres was more consistent with recent occupational $PM_{2.5}$ exposure, among 48 welders with an 8-year follow-up (MMA welding, mainly MS) (Wong et al., 2014b). Li et al. (2015a) found that telomere

length was significantly shorter in welders, associated with number of years as a welder after controlling for age. Further, a repeated-measures longitudinal study in a panel of 87 MMA (mainly MS) welders with a 29-month follow-up period showed a positive association between both LINE-1 and Alu methylation levels, and telomere length. The interaction between LINE-1 methylation and follow-up time was statistically significant, suggesting that the rate of telomeric change was modified by the degree of LINE-1 methylation (Wong et al., 2014c). Using the same study population as in Li et al. (2015a), Hossain et al. (2015) found that measured exposure to respirable dust as a welder, as well as years worked as a welder, was associated with increased coagulation factor II (thrombin) receptor-like 3 (*F2RL3*) gene hypomethylation.

4.2.7 Gene expression arrays in vivo

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

Lung gene expression studies in rats and mice exposed to welding fumes indicate a dysregulation of cellular signalling and proliferation pathways, and a strong immune response (reviewed in Zeidler-Erdely et al., 2012), also supported by the results of gene expression profiling in non-human primates. Adverse lung pathology was not observed in male cynomolgus monkeys subchronically exposed to MMA-SS fumes via inhalation (31.4 or 62.5 mg/m^3, 2 hours per day, 5 days per week, for 229 days), but gene induction was observed in cancer, immunological disease, inflammatory disease, cellular growth, and proliferation pathways, including activation of pregnane X receptor/retinoid X receptor (*Pxr*/*Rxr*), peroxisome proliferator-activated receptor (*Ppar*), *p53*, nuclear respiratory factor-2 (*Nrf2*), and retinoic acid receptor (*Rar*) (Heo et al., 2010). When compared with the results previously reported in male Sprague-Dawley rats also exposed to MMA-SS fumes via inhalation (51.4 or 84.6 mg/m^3, 2 hours per day, for 30 days), associated with severe lung inflammation and injury (Oh et al., 2009), 7% of the differentially expressed genes were similarly affected between species (Heo et al., 2010). [The Working Group noted that the control and exposed primates were not handled in a similar manner, and statistical analyses in both studies may have inadequately controlled for multiple comparisons.]

In the most comprehensive study from this group, Oh et al. (2012) evaluated the impact of exposure to MMA-SS welding fumes (44.1–51.4 or 80.1–84.6 mg/m^3, 2 hours per day, for 30 days) by inhalation with recovery periods in male Sprague-Dawley rats, including the re-evaluation of tissues from their earlier report (Oh et al., 2009), and compared genetic changes with tissue histopathology and BALF cytology from Yang et al. (2009). Lung immune cell infiltration and inflammation was detectable at both the genetic and cellular level, and pathways related to leukocyte extravasation and activation, antigen presentation, immunosuppression, angiogenesis, and cell cycle, growth, and proliferation were perturbed after repeated exposure and recovery periods (Oh et al., 2012). In PBMCs, approximately three times as many genes were downregulated compared with those induced, including an attenuation of stress response, cell growth, and differentiation pathways, while inflammatory responses were both induced (angiotensinogen, *Agt*, and major histocompatibility complex, *Mhc*) and attenuated (cathepsin E, *Ctse*, and dipeptidase, *Dpep*) (Rim et al., 2004).

Similar changes were reported after exposure to GMA-SS welding fumes in mice as described above after MMA-SS exposure in rats, i.e. responses were largely consistent across rodent species as well as SS welding fume sources (discussed in Zeidler-Erdely et al., 2012). GMA-SS exposure via pharyngeal aspiration

also altered genes involved in inflammatory and immunological disease pathways in both mouse strains, with strain-specificity in the network components and direction of induction affected. Cancer networks were induced primarily in the A/J strain, while haematological disease emerged in the B6 mice (Zeidler-Erdely et al., 2010). Follow-up studies revealed disruption of gene networks related to type I interferon signalling, specifically involving induction of interferon regulatory factor-7 (*Irf7*), and several type I interferon-related genes were upregulated in the blood and lung tissue of B6 mice exposed to GMA-SS but not GMA-MS welding fumes (Erdely et al., 2011a, 2012). [The Working Group noted that this response may be similar to that induced by lung infection.] After exposure to GMA-MS welding fumes via pharyngeal aspiration, Zeidler-Erdely et al. (2010) unexpectedly found differential expression of behavioural genes associated with circadian rhythm signalling, such as increased expression of *Nr1d1* in both A/J and B6 mice. Top networks induced in A/J lungs involved circadian rhythm signalling, stress response, and cell survival involving the *Tp53* and *Myc* pathways. Genes commonly associated with inflammatory lung response and apoptosis were altered in both A/J and B6 mice. The gene induction could not be attributed to a generalized inflammatory response, however, because pulmonary toxicity and lung inflammation were induced by exposure to both SS and MS fumes (Erdely et al., 2012).

While GMA-SS welding fumes were the most potent inducers of inflammation and stress-response pathway activation in the lungs (compared with GMA-MS or MMA-SS fumes), MMA-SS fumes induced stress-response pathway activation in cardiovascular tissues, associated with greater pulmonary cytotoxicity (Erdely et al., 2011a). MMA-SS fumes also transiently activated the inflammation and immune regulation pathways in rat PMBCs (Erdely et al., 2014), although no changes in serum CRP or IL-6 levels were reported after weekly exposure to MMA-HS welding fumes (Popstojanov et al., 2014).

4.3 Cancer susceptibility

No data were available to the Working Group.

4.4 Other adverse effects

4.4.1 Humans

Epidemiological studies show that long-term exposure to welding fumes is associated with respiratory health effects including asthma, bronchitis, lung function changes, neurological disorders and, if cadmium is present, renal tubular dysfunction (Wang et al., 1994; Antonini, 2003; El-Zein et al., 2003; Antonini et al., 2004a; Ding et. al., 2011; Racette et. al., 2012; Szram et al., 2013). Cardiac arrhythmias, myocardial ischaemia, and atherosclerosis have also been reported and epidemiological studies of male welders showed increased risk of cardiovascular disease, including hypertension (Fang et al., 2010b; Ibfelt et al., 2010; Li et. al., 2015b; Mocevic et al., 2015).

The exposure of boilermaker construction workers to $PM_{2.5}$ from metal fumes was associated with alterations in the heart rate variability (HRV) (Cavallari et al., 2007), an effect associated with impaired cardiac health (Kleiger et al., 1987). Long-term metal particulate exposure was shown to decrease cardiac acceleration and deceleration capacities in welding workers (Umukoro et al., 2016). Crossover panel studies of welders showed that HRV was inversely associated with work $PM_{2.5}$ exposures in each of the 14 hours post-work, with a multiphasic cardiovascular autonomic response with immediate (2 hours) and delayed (9–13 hours) responses (Cavallari et al., 2008a), especially at night (Cavallari et al., 2007). Moreover, after analysing workday $PM_{2.5}$ samples, a statistically significant association between HRV and manganese exposure was

observed, but this alone did not account for the observed declines in night-time (non-work) HRV (Cavallari et al., 2008b).

Other well-documented effects are ocular disorders related to welding (both in welders and in nearby workers), including disorders associated with exposure to ultraviolet radiation (cataracts, keratoconjunctivitis) as well as foreign bodies (Lombardi et al., 2005; Zamanian et al., 2015; Slagor et al., 2016).

4.4.2 Experimental systems

Lung function decrements and fibrosis were reported in male Sprague-Dawley rats after exposure to welding fumes by inhalation (reviewed in Zeidler-Erdely et al., 2012). Early perivascular and peribronchiolar fibrosis was induced after treatment for 30 days (44.1–65.6 or 80.1–116.8 mg/m^3, 2 hours per day) (Yu et al., 2004) and was associated with decreased tidal volume, which persisted in the group exposed to the higher concentration after 60 days of recovery (Sung et al., 2004). Fibrosis was not observed in the alveolar spaces after repeated exposure and recovery periods (Yang et al., 2009).

Other pulmonary effects, including pneumonia, pneumonitis, metaplasia, and emphysema were observed in male Syrian Golden hamsters and Sprague-Dawley rats after exposure to SS welding fumes. Hamsters exposed to MMA-SS and MIG-SS fumes via intratracheal instillation for 56 weeks developed moderate interstitial or nonspecific pneumonia, metaplasia, and mild emphysema when evaluated after nearly 2 years (Reuzel et al., 1986). Exposure to MMA-SS welding fumes via intratracheal instillation once per week for 28 weeks induced granulomatous areas associated with inflammatory cell influx and significant pulmonary injury throughout the lungs; the nature and extent of pulmonary injury, as well as the deposition and composition of welding particle agglomerates, were qualitatively similar to that observed in the lung of a human welder (Antonini et al., 2013). Pneumonitis, characterized by a peribronchiolar accumulation of neutrophils and macrophages, was observed in rats exposed once to GMA-SS fumes via intratracheal instillation (Antonini et al., 1996), and in rats infected with *L. monocytogenes* after a single exposure to MMA-SS fumes via intratracheal instillation (Antonini et al., 2004b). Pneumonitis was not reported after exposure to GMA-MS welding fumes.

Decrements in cardiac function and blood flow have been reported in several studies in male rats and mice after exposure to welding fumes. Cardiomyocte contraction was reduced in male Sprague-Dawley rats after exposure to MMA welding fumes by intratracheal instillation once per week for 7 weeks (Popstojanov et al., 2014), while tail artery endothelium relaxation was attenuated in male Sprague-Dawley rats after 3 days of exposure to welding fumes by inhalation (25 mg/m^3, 4 hours per day) (Zeidler-Erdely et al., 2014). Exposure to GMA-SS fumes (40 mg/m^3, 3 hours per day, for 10 days) by inhalation increased markers of systemic inflammation and increased atherosclerotic plaque lesion area development in B6 *ApoE*$^{-/-}$ mice (Erdely et al., 2011a), and a single pharyngeal aspiration of MMA-SS fumes induced stress-response genes in cardiovascular tissues of B6 mice (Erdely et al., 2011b).

Dopaminergic neurotoxicity has been observed in several studies in male Sprague-Dawley rats after exposure to SS and MS welding fumes, with reported effects on *Th* expression (Antonini et al., 2009b; Sriram et al., 2010) and the levels of dopamine, serotonin, and norepinephrine in the olfactory bulb (Sriram et al., 2014).

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