Welding fumes

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Current evaluation
Conclusion from the previous Monograph
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> There is *limited evidence* in humans for the carcinogenicity of welding fumes and gases. There is *inadequate evidence* in experimental animals for the carcinogenicity of welding fumes.

Exposure and biomonitoring

The number of workers worldwide whose work involves some welding is estimated to be about three million. Most welding is performed using electric arc processes - manual metal arc, metal inert gas and tungsten inert gas welding – and most welding is on mild steel.

Welders are exposed to a range of fumes and gases (evaporated metal, metal oxides, hydrocarbons, nanoparticles, ozone, oxides of nitrogen (NOx)) depending on the electrodes, filler wire and flux materials used in the process, but also physical exposures such as electric and magnetic fields (EMF) and ultraviolet (UV) radiation. Fume particles contain a wide variety of oxides and salts of metals and other compounds, which are produced mainly from electrodes, filler wire and flux materials. Fumes from the welding of stainless-steel and other alloys contain nickel compounds and chromium[VI] and [III]. Ozone is formed during most electric arc welding, and exposures can be high in comparison to the exposure limit, particularly during metal inert gas welding of aluminium. Oxides of nitrogen are found during manual metal arc welding and particularly during gas welding. Welders who weld painted mild steel can also be exposed to a range of organic compounds produced by pyrolysis. Welders, especially in shipyards, may also be exposed to asbestos dust. Physical exposures such as electric and magnetic fields (EMF) and ultraviolet (UV) radiation are also common.

Biomarkers of exposure or effect

There are several biomarkers of exposure and effect for various exposures in welding: saliva Mn, serum Mn, urine Mn, Centromere-positive micronuclei in periphery blood lymphocytes, DNA protein-crosslinks in peripheral white blood cells, oxidative stress as urinary 8OHdG, and long-term oxidative damage measured as erythrocytic superoxide dismutase (SOD) activity (measure of systemic oxidative stress) and serum malondialdehyde (MDA) (product of lipid peroxidation and reflect tissue injuries).

Occupational exposure

Different welding environments may present different and complex profiles of exposures. In a Swedish study to characterize welding fume aerosol (Isaxon et al., 2008), nanoparticles in mild steel metal active gas welding showed a mass median diameter (MMMD) of 200-300 nm.

Particle elemental composition was mainly iron and manganese. Ni and Cr exposures were very low in the vicinity of mild steel welders, but much higher in the background in the workshop where there presumably was some SS welding.

In Canadian welders, personal exposures to manganese ranged from 0.01–4.93 mg/m^3 and to iron ranged from 0.04–16.29 mg/m^3 in eight Canadian welding companies in Manitoba. Types of welding identified were mostly (90%) MIG mild steel, MIG stainless steel, and TIG aluminum. Carbon monoxide levels were less than 5.0 ppm (at source) and ozone levels varied from 0.4–0.6 ppm (at source). Ventilation was poor in many companies, and only 7 percent of the welders wore respiratory protection. These Canadian Mn and Fe air concentrations are 300-2600 times *lower* than what was measured in Russian welders: 97 mg/m3 (range 3–4620 mg/m^3; n = 188) and 894 mg/m3 (range 106–20 300 mg/m^3; n = 188), respectively (Ellingsen et al., 2006). No substantial difference was observed in the air Mn concentrations when welding mild steel as compared to welding stainless steel. Three welding methods were included in this study: Shielded-metal arc welding (manual welding), gas metal-arc welding shields (semi-automatic), and fluxed-core arc welding (automated). Welding in a confined space, as expected, created higher ambient Mn breathing zone levels of 1.5 - 0.7 mg/m^3, and lowest in the workshop 0.2 - 0.05 mg/m3 (Lu et al., 2005).

Biological monitoring was also performed in this Russian study, where Mn in whole blood was 25% higher in welders compared to controls. A significant difference was not found comparing urinary Mn. A significant correlation (0.31, p= 0.01) was found between blood Mn and Mn in the workroom air that was collected the day before blood sampling. Former welders had blood Mn concentration higher than controls of similar age (8.7 mg/l vs. 7.0 mg/l), while their urinary concentrations of cobalt, iron and Mn were all statistically significantly lower.

Cancer in humans
(*limited evidence*, vol. 49, 1990)
There has been considerable evidence over the past 3 decades regarding cancer risks in relation to welding activities. Some of the research has focused on the job title of "welders" or the exposure of "welding fumes" as the only descriptor of exposure, while some of the research has focused on more finely discriminated subsets defined by such characteristics as the industry in which the welding occurred (e.g., shipyards), the material welded (e.g., stainless steel, mild steel), or specific chemicals released by the welding activities (e.g., chromium VI, nickel compounds). In 1990 an IARC Monograph Working Group considered that there was limited epidemiologic evidence carcinogenicity of welding fumes, where the main concern was with lung cancer as the outcome. Since then, a large number of additional studies have been published. Some of the accumulated evidence has been used by IARC Monograph Working Groups in assessing the evidence regarding some agents which can be found in welding fumes, notably chromium VI and nickel compounds. But there has not been a formal reevaluation of welding since 1990. The only exception to this statement is a recent evaluation of overexposure of the eyes to UVR, common among electric arc welders. Several case-control studies reported excess risks of ocular melanoma in welders (Guenel et al., 2001; Lutz et al., 2005, Shah et al., 2005). This association may be due to the presence in some

welding environments of fumes of thorium-232, which is used in tungsten welding rods (NCRP, 1988 ; Nuclear Regulatory commission, 2001).

While there has not been such a formal reevaluation recently regarding risks of lung cancer, a widespread consensus seems to have formed to the effect that some welding environments, notably in stainless steel welding, do carry risks of lung cancer. This widespread consensus is in part based on empirical evidence regarding risks among stainless steel welders and in part on the fact that stainless steel welding entails moderately high exposure to nickel and chromium VI compounds, which are recognized lung carcinogens. In this line of reasoning, the presence of nickel and chromium VI compounds would explain the excess lung cancer risk among stainless-steel welders. The corollary is that welding without the presence of nickel and chromium VI compounds, namely mild-steel welding, should not carry risk. But it appears that this line of reasoning in not supported by the accumulated body of epidemiologic evidence.

As reviewed by Ambroise et al. (2006), there have been around 60 studies published that are informative about lung cancer risks in welders. While there remained some uncertainty about possible confounding by smoking and by asbestos, and some possible publication bias, the overwhelming evidence is that there has been an excess risk of lung cancer among welders as a whole in the order of 20%-40%. Further, there was no evidence from the 11 studies of stainless steel welders, the 8 studies of mild steel welders, the 16 studies of shipyard welders, and the 24 studies of unspecified welders that the risks differed by type of welder. Indeed, the meta-estimates of relative risk were very similar among these four categories of welders. In the absence of reliable data on levels of average levels of exposure in these groups it is difficult to conclude that the risks were actually similar, but it can be claimed that there is no evidence that the risks were different. This finding was not only true overall, but also in the largest and arguably best conducted study, the IARC-coordinated multi-center European cohort study (Simonato et al., 1991), and in two large and recently published Danish (Sorensen et al., 2007) and Finnish (Siew et al., 2008) studies.

Cancer in experimental animals
(inadequate evidence, vol 49, 1990)
Recently, lung tumorigenicity of welding fumes was investigated in lung tumour susceptible (A/J) strain of mice (Zeidler-Erdely et al., 2008). Male mice were exposed by pharyngeal aspiration four times (once every 3 days) to 85 μg of gas metal arc-mild steel (GMA-MS), GMA-SS, or manual metal arc-SS (MMA-SS) fume. At 48 weeks post-exposure, GMA-SS caused the greatest increase in tumour multiplicity and incidence, but did not differ from sham exposure. Tumour incidence in the GMA-SS group versus sham control was close to significance at 78 weeks post exposure (p = 0.057) (Zeidler-Erdely et al., 2008). Histopathological analysis of the lungs of these mice showed the GMA-SS group having an increase in preneoplasia/tumour multiplicity and incidence compared to the GMA-MS and sham groups at 48 weeks. The increase in incidence in the GMA-SS exposed mice was significant compared to the GMA-MS group but not to the sham-exposed animals, and the difference in incidence between the GMA-SS and MMA-SS groups was of border-line significance (p = 0.06). At 78 weeks post-exposure, no statistically significant differences

were observed between the groups. The study concluded that the data are supportive but not conclusive for tumorigenicity of GMA-SS welding fumes in the lung tumor susceptible A/J mouse. The *in vivo* data obtained in the study did not, however, suggest tumorigenicity of MMA-SS or GMA-MS fumes (Zeidler-Erdely et al., 2008).

Mechanisms of carcinogenicity

Genotoxicity in experimental systems in vitro and in vivo

Oxidative DNA damage to lung tissue assessed by immunohistochemical staining of 8-OH-dG was shown in rats exposed to MMA-SS welding fumes at low-dose ($\sim$ 65 mg/m^3) and high-dose ($\sim$ 116 mg/m^3) concentrations in whole body exposure. Higher 8-OH-dG levels were detected after high-dose exposure (Yu et al., 2004). Genotoxicity in individual lung cells determined by alkaline Comet assay was increased in a dose-dependent manner. It was concluded that a variety of major welding fume components were associated with ROS production, including Fe, Mn, Cr, Cr^{VI}, gaseous ozone, NO$_2$, nitrous fumes and SO$_2$ (Yu et al., 2004).

MMA-SS welding fumes induced DNA damage, likely via generation of reactive oxygen species, in an *in vitro* DNA strand breakage assay (Antonini et al., 2005). The study concluded, as many other studies by the same research group, that the DNA damage was attributable to the soluble components present in MMA-SS welding fumes, suggested to be predominantly chromium well known for its capacity to generate radical oxygen species and to induce diverse forms of genotoxicity (Antonini et al., 2003b; Antonini et al., 2005; Salnikow and Zhitkovich 2008).

Toxic effects in lungs in vivo and in lung cells in vitro

In all, the *in vivo* studies suggest that different welding fumes cause varied responses in rat lungs *in vivo*, and the toxic effects typically correlate with the metal composition of the fumes and their ability to produce free radicals. In many studies both soluble and insoluble fractions of the stainless steel welding fumes were required to produce most types of effects, indicating that the responses are not dependent exclusively on the soluble metals (Antonini 2003, Antonini et al., 2003a, b; Antonini et al., 2004).

In human A549 lung cells *in vitro*, three types of welding fumes (NIMROD 182, NIMROD c276, COBSTEL 6), all high in Cr content, and their soluble fractions induced cytotoxicity, generation of ROS, and significant increase in pro-inflammatory cytokine expression (McNeilly et al., 2004). The two nickel-based fumes were found to significantly increase intracellular ROS production, but not the cobalt-based fume. These pro-inflammatory responses were proposed to be attributable to soluble transition metal components and ultrafine particulate composition (mean diameter <0.1 um) of welding fumes, likely effective via oxidative stress mechanisms (McNeilly et al., 2004).

Histological analysis of nasal respiratory mucosa in rats exposed to MMA-SS welding fumes indicated various types of histopathological changes, suggesting diminished protection and defence mechanisms in nasal respiratory (Jeong et al., 2006).

Genotoxicity in humans

The latest IARC evaluation recognised only one study out of three indicating increased chromosome aberrations and sister chromatid exchanges in stainless steel welders (IARC 1990). Since then, a number of studies have investigated a variety of genotoxicity endpoints in subjects exposed to welding fumes, as summarised briefly in the following.

Urinary 8-OH-dG, DNA-protein crosslinks, and single strand DNA breaks in welders

Statistically significant pre- to post-shift changes in urinary 8-OH-dG of boilermakers have been found (Nuernberg et al., 2008). Significant increases in DNA-protein crosslinks have been observed in welders in several studies (Costa et al., 1993; Zhitkovich et al., 1998). Levels of Cr and Ni in blood of MMA welders in India correlated positively with the DNA damage using the Comet assay. Smoking did not to have a significant effect on DNA damage in these welders (Danadevi et al., 2004). A statistically significant association between polymorphism for *XRCC*, one of the DNA repair genes, and DNA damage (Iarmarcovai et al., 2005) have also been found. These two studies agree with earlier studies showing significantly increased DNA single strand breaks in welders (Werfel et al., 1998).

Cytogenetic effects in welders

Some cytogenetic studies have shown significant increases in chromosomal aberrations (Elias et al., 1989, Knudsen et al., 1992, Jelmert et al., 1994), while others did not (Jelmert et. al., 1995, Halasova et al., 2008). A recent study reported some suggestive influence of *XRCC1* polymorphism on the total chromosome aberration frequency (Halasova et al., 2008).

SCE frequency studies also show inconsistencies (Werfel et al., 1998, Knudsen et al., 1992).

Micronuclei from welders

A significantly higher frequency of micronuclei in peripheral blood lymphocytes (binucleated cell assay) and higher mean levels of both centromere-positive and centromere-negative micronuclei was observed in welders (n=27) who worked without protective device compared to controls (n=30).The rate of micronucleated cells did not correlate with the duration of exposure (Iarmarcovai et al., 2005, Iarmarcovai et al., 2006). Polymorphisms, smoking, or drinking did not affect the outcome.

Induction of micronuclei in buccal epithelial cells were found, and the frequency was associated with increasing duration of welding work as well as blood chromium levels; however increase in micronuclei showed age dependence (Danadevi et al., 2004).

Research needs and recommendations

Research needs based on current epidemiological data

Thus it seems that the reasons for excess risk among welders, whether stainless steel or mild steel, remains unknown. It may still be the case that excess risks are due to nickel and

chromium VI compounds among stainless steel welders and other factors among mild steel welders, but this seems unlikely. The most parsimonious explanation is that there is an as-yet unexplained common reason for excess lung cancer risks that applies to all types of welders. Siew et al. (2008) have proposed that iron fumes may play such a role, and their Finnish data appear to support this hypothesis, though not conclusively. This hypothesis would also imply that excess lung cancer risks among welders are not unique to welders, but rather may be shared among many types of metal working occupations.

Further evidence needs to be systematically assembled to compare and synthesize lung cancer risks among metal working occupations, including welders. Further, to the extent possible, existing cohorts of welders should be re-examined to try to describe risks according to various dimensions of exposure, including the type of welding process, the type of metal being welded, the types of rods and fluxes used, and other characteristics of the welding environment such as abrasives, cleaners and degreasers used. It would be justified to initiate new studies (industry-based cohorts or community-based case-control) if information on these various dimensions could reliably be collected. If biomarkers of exposure to Mn or Fe could be integrated into such studies, that could be helpful. But this is hampered by the difficulty of obtaining biospecimens in retrospective cohort studies, and the questionable historic relevance of biospecimens collected at time of disease diagnosis in case-control studies.

Research needs based on current experimental and mechanistic data

Welding fumes are complex particulate mixtures containing multiple hazardous metals, metal oxides and gases; also radiation hazards and heat are involved in welding. Given such huge variation, just a fraction of the types of fumes and processes of welding has been studied. Research needs include experimental animal studies using inhalation as the route of exposure. Employment of transgenic mouse models, e.g. the heterozygous p53 deficient ($p53^{+/-}$) mouse assay, may offer one option for future studies. It would also be useful if experimental carcinogenicity assays were carried out on different components of welding fumes.

Studies to characterize the generation of radical oxygen species and oxidative DNA damage in human and animals for each of the numerous types and processes of welding would be informative. Some of the genotoxicity studies suggest somewhat differential effects of welding fumes containing Cr or Ni as the predominant metal component; such questions may deserve more attention.

Large proportion of ultrafine or nanosized welding fume particles (mean diameter of ~ 0.1 μm and range of 0.01 - < 1.0 μm) (McNeilly et al., 2004; Ayers et al., 2008), together with the high content of metals and metal oxides, further points to a efficient capacity of welding fumes to generate oxidative stress, both direct generation of reactive oxygen species and indirectly through inflammatory responses in the lungs. Inhaled ultrafine welding particles easily reach the lower respiratory tract, including bronchioles, alveolar ducts, alveolar sacs, and alveoli (Zeidler-Erdely et al., 2008) and may also be translocated in a facilitated way elsewhere in the body. Studies on welding fumes in this area of particle research may aid in understanding cellular and molecular mechanisms involved in welding-related lung carcinogenesis.

Finally, research using the current powerful technologies to study epigenetic mechanisms, such as DNA methylation and histone modification, gene expression pathways, and functional level changes following welding fume exposure may provide further insight into molecular mechanisms of welding fume carcinogenesis.

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