

Carcinogenicity of welding, molybdenum trioxide, and indium tin oxide

In March 2017, 17 scientists from ten countries met at the International Agency for Research on Cancer (IARC; Lyon, France) to evaluate the carcinogenicity of welding, molybdenum trioxide, and indium tin oxide. These assessments will be published in volume 118 of the IARC Monographs.¹

Worldwide, an estimated 11 million workers have a job title of welder, and around 110 million additional workers probably incur welding-related exposures. Welding can involve exposures to fumes, gases, radiation (ultraviolet [UV] radiation and electromagnetic fields) and co-exposures to asbestos and solvents. Welding involves several processes (eg, oxyfuel [gas], arc, and resistance welding) and materials (eg, mild and stainless steel). Exposure determinants include the process, material welded, ventilation, degree of enclosure, and use of personal protection.

The carcinogenicity of welding fumes was assessed by IARC in 1989² and classified as “possibly carcinogenic to humans” (Group 2B), based on “limited evidence in human beings” and “inadequate evidence” in experimental animals.³ UV radiation was classified in Group 1 in volume 100D of the IARC Monographs. Substantial new evidence has since accumulated from observational and experimental studies. In the present evaluation, welding fumes and UV radiation from welding were classified as “carcinogenic to humans” (Group 1).

Arc welding generates UV radiation, a risk factor for the rare cancer ocular melanoma. Various ocular disorders (eg, cataracts or keratoconjunctivitis) occur in both welders and nearby workers. Sufficient evidence for the carcinogenicity of UV radiation from welding came from eight partly

overlapping case-control studies and two census-based cohort studies that reported on ocular melanoma. Most case-control studies showed positive associations, with risks of developing ocular melanoma generally increased by between two-fold and ten-fold. Two of three studies that assessed risk by duration of employment as a welder showed positive trends.^{3,4} These studies also showed increased ocular melanoma risk associated with eye burns—a proxy for UV exposure—and one reported a positive exposure-response association for cumulative occupational exposure to artificial UV radiation, including welding.^{3,4} Risks persisted after adjustment for sun exposure, sun bed use, or both.⁴⁻⁶

Welding fumes are produced when metals heated above their melting point vaporise and condense to fine particles (mostly <1 µm in size). Most studies, including more than 20 case-control studies and nearly 30 occupational or population-based cohort studies, reported increased risks of lung cancer in welders or other workers exposed to welding fumes. Exposure-response associations with indices of longer or greater cumulative exposure to welding fumes were also reported in several studies, some of which were large, high-quality studies.⁷⁻¹⁰ Exposure to fumes was assessed indirectly through welding process or material, branch of industry, job title, expert assessment, or self-report.

Asbestos exposure and tobacco smoking, which are important potential confounders, could not explain the observed excess lung cancer risk in welders. Positive associations persisted after adjusting directly or indirectly for smoking, asbestos co-exposure, or both,⁷⁻¹⁰ restricting to non-smokers or low-level smokers,¹¹ and in cohorts with low or minimal asbestos exposure.¹²

Positive associations for occupation as a welder and kidney cancer were reported in nearly all relevant cohort and case-control studies. However, few studies adjusted for solvents used for cleaning metal in tandem with welding, such as trichloroethylene (a risk factor for kidney cancer). Increased risks were consistently reported across countries, occupational settings, and study designs. However, chance, bias, and confounding could not be reasonably ruled out because some findings were not statistically significant, several studies had few exposed cases, and there was little evidence of an exposure-response association.

For all other cancers, the evidence for carcinogenicity was inadequate because of inconsistent findings across studies, insufficient numbers of studies, or the potential for confounding or selection bias. The Working Group concluded that there is “sufficient evidence in humans” that welding fumes cause lung cancer and limited evidence for kidney cancer.

There is limited evidence in experimental animals for the carcinogenicity of gas metal arc-stainless steel welding fumes. In one oropharyngeal aspiration study and one inhalation study in male A/J mice, gas metal arc-stainless steel welding fumes promoted 3-methylcholanthrene-induced lung tumours.^{13,14}

Absorption and excretion of metals (chromium, nickel, and manganese) was shown in people exposed to welding fumes, but data for particle deposition and clearance in welders were scarce. Strong evidence suggests that welding fumes induce chronic inflammation and are immunosuppressive. Lung and systemic inflammation biomarkers were increased in many panel studies (of cross-sectional and cohort design) of various arc welding fumes.¹⁵ Risk for infection (pneumonia) was increased

Published Online

April 10, 2017

[http://dx.doi.org/10.1016/S1470-2045\(17\)30255-3](http://dx.doi.org/10.1016/S1470-2045(17)30255-3)

For more on the IARC

Monographs see

<http://monographs.iarc.fr/>

Upcoming meetings

June 6–13, 2017, Volume 119:

Some chemicals in food and consumer products

Oct 10–17, 2017, Volume 120:

Benzene

IARC Monograph Working

Group Members

J Hansen (Denmark)—Meeting

Chair; A K Nersesyan (Austria);

J Lavoué (Canada); D Luce

(France); W Ahrens (Germany);

S Fukushima (Japan);

H Kromhout, S Peters

(Netherlands); A 't Mannetje

(New Zealand); M Albin

(Sweden); M G Baker,

D C Christiani, J M Fritz,

W M Gwinn, R M Lunn, E J Tokar,

P C Zeidler-Erdely (USA)

Declaration of interests

SP declares that her previous

research unit at the University of

Western Australia received

research support (ceased July,

2014) from WestTrac Ltd (Western

Australia, Australia)—

a construction equipment

supplier—to investigate the

adverse health effects of

environmental asbestos exposure.

All other working group members

declare no competing interests.

Invited Specialists

None

Representatives

Y Chen, for the Health and Safety

Executive (HSE), UK; P Guillou,

for the French Agency for Food,

Environmental and Occupational

Health and Safety (ANSES),

France; F Pega, for WHO, Geneva,

Switzerland; A Ullrich, for WHO,

Geneva, Switzerland

Declaration of interests

All representatives and World

Health Organization members

declare no competing interests.

Observers

A Hall, for the University of

British Columbia, Canada;

S Hubbard, for the International

Molybdenum Association

(IMO), UK; L Levy, for the

International Molybdenum

Association (IMO); A Oller, for Eurometaux, Belgium; V Thomas, for the University Paris Dauphine, France; W Zschiesche, for the Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Germany

Declaration of interests
SH is a consultant for the International Molybdenum Association (IMO), was a recent employee of RioTinto Ltd (until the end of 2015), and has received IMO funding to travel to the IARC meeting. LL provides consulting expertise in occupational health toxicology to the IMO. AO is employed by NiPERA Inc. All other observers declare no competing interests.

IARC Secretariat
L Benbrahim-Tallaa; V Bouvard; R Carel; F El Ghissassi; Y Grosse; N Guha; KZ Guyton; D Hashim; MK Honayyar; R Khlifi; D Loomis; K Muller; L Stayner; K Straif; N Vilahur

Declaration of interests
All secretariat declare no competing interests.

For the **Preamble to the IARC Monographs** see <http://monographs.iarc.fr/ENG/Preamble/index.php>

For **IARC declarations of interests** see <http://monographs.iarc.fr/ENG/Meetings/vol118-participants.pdf>

in epidemiological studies of different designs. In rodents, welding fumes induced chronic pulmonary inflammation and, in fewer studies, impaired resolution of pulmonary infection.

Molybdenum trioxide (MoO₃) is a high-production-volume chemical with rare natural occurrence. Of the >100 000 tons of MoO₃ produced annually, most is used in steel production, with other uses in biocides and increasingly in photovoltaic technology. Environmental exposures to MoO₃ are negligible, but occupational exposures can occur—mainly in mining and metallurgy, steel foundries, welding, and other high-temperature processes using steel. No epidemiological and few toxicokinetic and mechanistic data for MoO₃ were available. In one inhalation study in mice, MoO₃ increased the incidences of bronchioloalveolar carcinoma in male mice and bronchioloalveolar adenoma or carcinoma (combined) in female mice, and caused a positive trend in the incidence of bronchioloalveolar carcinoma in female mice.¹⁶ Molybdenum trioxide was classified as “possibly carcinogenic to humans” (Group 2B) based on sufficient evidence in experimental animals.

Indium tin oxide (ITO) is a low-production-volume chemical, not naturally occurring, which is a mixture of indium oxide (In₂O₃) and stannic oxide (SnO₂). It is mainly used in producing transparent conductive films on glass or plastic panels used in electronic devices. Exposure to ITO occurs mainly in occupational settings,

during ITO production and processing, or during elemental indium recycling. Indium has been detected in exposed workers, but toxicokinetic data for ITO were otherwise sparse. Long-term studies in rats, mice, and hamsters provided strong evidence that ITO induces chronic inflammation. In 2-year inhalation studies, ITO increased the incidences of bronchioloalveolar carcinoma in male and female rats, and caused a positive trend in the incidence of bronchioloalveolar adenoma or carcinoma (combined) in female mice.¹⁷ Indium tin oxide was classified as “possibly carcinogenic to humans” (Group 2B) based on sufficient evidence in experimental animals.

We declare no competing interests.

Neela Guha, Dana Loomis, Kathryn Z Guyton, Yann Grosse, Fatiha El Ghissassi, Véronique Bouvard, Lamia Benbrahim-Tallaa, Nadia Vilahur, Karen Muller, Kurt Straif, on behalf of the International Agency for Research on Cancer Monograph Working Group International Agency for Research on Cancer, Lyon, France

References

- International Agency for Research on Cancer. Volume 118: welding, indium tin oxide, molybdenum trioxide. IARC Working Group. Lyon, France; 21–28 March, 2017. *IARC Monogr Eval Carcinog Risks Hum* (in press).
- International Agency for Research on Cancer. Chromium, nickel and welding. *IARC Monogr Eval Carcinog Risks Hum* 1990; **49**: 1–648.
- Vajdic CM, Krickler A, Giblin M, et al. Artificial ultraviolet radiation and ocular melanoma in Australia. *Int J Cancer* 2004; **112**: 896–900.
- Guenel P, Laforest L, Cyr D, et al. Occupational risk factors, ultraviolet radiation, and ocular melanoma: a case-control study in France. *Cancer Causes Control* 2001; **12**: 451–59.
- Holly EA, Aston DA, Ahn DK, Smith AH. Intraocular melanoma linked to occupations and chemical exposures. *Epidemiology* 1996; **7**: 55–61.
- Seddon JM, Gragoudas ES, Glynn RJ, Egan KM, Albert DM, Blitzer PH. Host factors, UV radiation, and risk of uveal melanoma. A case-control study. *Arch Ophthalmol* 1990; **108**: 1274–80.
- ‘t Mannetje A, Brennan P, Zaridze D, et al. Welding and lung cancer in Central and Eastern Europe and the United Kingdom. *Am J Epidemiol* 2012; **175**: 706–14.
- Matrat M, Guida F, Mattei F, et al. Welding, a risk factor of lung cancer: the ICARE study. *Occup Environ Med* 2016; **73**: 254–61.
- Sorensen AR, Thulstrup AM, Hansen J, et al. Risk of lung cancer according to mild steel and stainless steel welding. *Scand J Work Environ Health* 2007; **33**: 379–86.
- Siew SS, Kauppinen T, Kyyronen P, Heikkilä P, Pukkala E. Exposure to iron and welding fumes and the risk of lung cancer. *Scand J Work Environ Health* 2008; **34**: 444–50.
- Kendzia B, Behrens T, Jockel KH, et al. Welding and lung cancer in a pooled analysis of case-control studies. *Am J Epidemiol* 2013; **178**: 1513–25.
- Steenland K. Ten-year update on mortality among mild-steel welders. *Scand J Work Environ Health* 2002; **28**: 163–67.
- Zeidler-Erdely PC, Meighan TG, Erdely A, et al. Lung tumor promotion by chromium-containing welding particulate matter in a mouse model. *Part Fibre Toxicol* 2013; **10**: 45.
- Falcone LM, Erdely A, Meighan TG, et al. Inhalation of gas metal arc-stainless steel welding fume promotes lung tumorigenesis in A/J mice. *Arch Toxicol* 2017; published online Jan 4. DOI:10.1007/s00204-016-1909-2.
- Kim JY, Chen JC, Boyce PD, Christiani DC. Exposure to welding fumes is associated with acute systemic inflammatory responses. *Occup Environ Med* 2005; **62**: 157–63.
- Program NT. Toxicology and carcinogenesis studies of molybdenum trioxide (CAS no. 1313-27-5) in F344 rats and B6C3F1 mice (inhalation studies). *Natl Toxicol Program Tech Rep Ser* 1997; **462**: 1–269.
- Nagano K, Nishizawa T, Umeda Y, et al. Inhalation carcinogenicity and chronic toxicity of indium-tin oxide in rats and mice. *J Occup Health* 2011; **53**: 175–87.