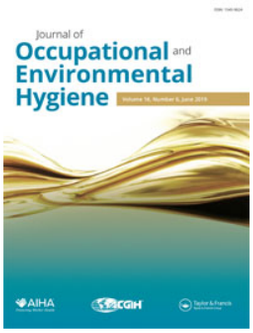

Taylor & Francis
Taylor & Francis Group

Journal of Occupational and Environmental Hygiene

ISSN: 1545-9624 (Print) 1545-9632 (Online) Journal homepage: https://www.tandfonline.com/loi/uoeh20

Influence of welding fume metal composition on lung toxicity and tumor formation in experimental animal models

Patti C. Zeidler-Erdely, Lauryn M. Falcone & James M. Antonini

To cite this article: Patti C. Zeidler-Erdely, Lauryn M. Falcone & James M. Antonini (2019) Influence of welding fume metal composition on lung toxicity and tumor formation in experimental animal models, Journal of Occupational and Environmental Hygiene, 16:6, 372-377, DOI: 10.1080/15459624.2019.1587172

To link to this article: https://doi.org/10.1080/15459624.2019.1587172

JOURNAL OF OCCUPATIONAL AND ENVIRONMENTAL HYGIENE
2019, VOL. 16, NO. 6, 372–377
https://doi.org/10.1080/15459624.2019.1587172

Taylor & Francis
Taylor & Francis Group

COMMENTARY

Influence of welding fume metal composition on lung toxicity and tumor formation in experimental animal models

Patti C. Zeidler-Erdely[a,b], Lauryn M. Falcone[a,b], and James M. Antonini[a]

[a]Health Effects Laboratory Division, National Institute for Occupational Safety and Health, Morgantown, West Virginia; [b]West Virginia University, School of Medicine, Morgantown, West Virginia

KEYWORDS
A/J mice; chromium; iron; lung cancer; welding

Millions of workers in the United States and worldwide are exposed to complex, metal-rich welding fumes. Although welding is a crucial industrial process, the generated fumes are known to cause acute and chronic health effects when inhaled. The International Agency for Research on Cancer (IARC) classified welding fumes as *carcinogenic to humans* (Group 1) in 2017, based on sufficient epidemiological evidence and limited evidence in animals, an upgrade from the former Group 2B (*possibly carcinogenic to humans*) classification. There is evidence that both iron-abundant mild steel (MS) as well as chromium- and nickel-containing stainless steel (SS) welding fumes contribute to an increased risk of lung cancer. Recent animal studies show that welding fumes may act as lung tumor promoters, regardless of the presence or absence of potentially carcinogenic metals, such as chromium and nickel.

Welding processes and fume characterization

Approximately 1.2 million workers are regularly exposed to welding fumes in the U.S.[1,2] Given the variety of welding processes used in the workplace, welders are a diverse and heterogeneous group. The most common metal fusion process is electric arc welding. Specific types of arc welding include manual metal arc (MMA; also known as shielded manual metal arc [SMA]), gas metal arc (GMA), flux-cored arc (FCA), gas tungsten arc (GTA), submerged arc (SA), and plasma arc (PA). In arc welding, high temperatures of 5,000°C or more melt the joint between two metal work pieces as well as a filler material placed between them.[3] These extremely high temperatures are produced when an electric arc is established between the work pieces and a consumable wire electrode. As temperatures cool, the bond solidifies, firmly fusing the work pieces together. The bond created by welding is unique in that it is a mixture of the metal work pieces and the electrode filler material, making the bond extremely strong as it retains the strength of both initial metal parts.[1,3]

Welding fumes are a byproduct of the process and generally arranged as chain-like agglomerates of nanometer-sized primary particles when generated.[4] The size of the welding particles formed varies depending on the process but can range from 10 nm to 20 µm. However, the mass median aerodynamic diameter of most welding fumes has been measured to be 0.2–0.5 µm.[5–8] The welding aerosol composition also varies depending on the specific type of welding process and materials used (e.g., SS vs. MS consumables). However, it is typically composed of a combination of a mixture of vaporized metal oxides from the electrode and/or flux material used.[3] Surface coatings or paint on the base metal or electrode can also contribute to the fume. Due to the contribution by the flux, the morphology of particles generated during MMA welding is different and more complex than GMA welding particles.[5,6] Also, because of the presence of alkali metals in the flux, MMA particles are more soluble (and thus potentially more biological reactive due to the availability of solubilized metals) compared to GMA fumes that are relatively insoluble.[9]

The most common metals present in generated welding fumes are listed in Table 1. Iron (Fe) is the primary metal in most welding fumes and usually

CONTACT Patti C. Zeidler-Erdely paz9@cdc.gov National Institutes for Occupational Safety and Health, Health Effects Laboratory Division, 1095 Willowdale Road (M/S L2015), Morgantown, 26505 WV.
P. C. Zeidler-Erdely and J. M. Antonini contributed equally to this work.

Table 1. Metal composition of common welding fumes.

Welding fume samples	Metal (weight %)*	Soluble/insoluble ratio
GMA-mild steel	Fe 85.0 Mn 14.0	0.020
GMA-stainless steel	Fe 57.0 Mn 13.8 Cr 20.2 Ni 8.8	0.006
Shielded MMA-stainless steel	Fe 41.0 Cr 29.0 Mn 17.0 Ni 3.0	0.345 Soluble metals: Cr 87% Mn 11%

*Relative to all metals analyzed; modified from Antonini et al.[9]

composes >80% of MS fumes. Fume primarily made up of Fe has long been considered a nuisance dust with a small likelihood of causing chronic lung diseases. However, Fe has been shown to accumulate in the lungs of long-time welders and often causes a mostly benign lung condition known as siderosis.[10] Manganese (Mn), a known neurotoxicant, is a common component of most welding fumes as it improves metallurgical properties and acts as a deoxidizing agent to increase hardness and strength of the resultant weld.[11] Chromium (Cr) is common in SS welding fumes, existing in both Cr^{3+} and Cr^{6+} oxidation states.[12] The Cr^{3+} state cannot enter cells as readily and has low toxicity, whereas Cr^{6+} easily passes into cells, is highly toxic and is classified as a carcinogen.[13] The permissible exposure limit (PEL) of Cr was lowered from 52 to 5 $\mu g/m^3$ in 2006 due to its harmful effects.[14] Nickel (Ni) also is a component of SS welding fume and classified as a human carcinogen.[15] Ni alloys are becoming increasingly popular in welding as a potential alternative to Cr-containing materials.[16]

Lung cancer in humans

Recently, the International Agency for Research on Cancer (IARC) classified welding fumes as carcinogenic to humans (Group 1),[17] an upgrade from the Group 2B (possibly carcinogenic to humans) classification in 1990.[15] This reclassification for welding fumes was based on sufficient evidence in humans for lung cancer and limited evidence in experimental animal studies. A majority of the cohort and case-control studies across different countries, time periods, and occupational settings reported an elevated risk of lung cancer for workers employed as welders or have reported being exposed to welding fumes. Potential confounders, such as tobacco smoking and asbestos exposure, were considered important, however, co-exposure to either agent could not explain all of the observed excess risk of lung cancer among welders. It has been suggested that welding with MS consumables, which account for the majority of all welding, posed little risk for lung cancer development because of the absence of carcinogenic metals, such as Cr and Ni, in the generated fume. However, numerous worker studies have been unable to associate an elevated risk of lung cancer directly with Cr- and Ni-containing SS welding compared to MS welding.[18–20] Based on the conclusions of the IARC review, an increased risk of lung cancer was observed regardless of the welding process/method or material/consumable used, and there was no evidence that the increased cancer risk was limited to exposure to Cr- and Ni-containing SS welding fumes.[17] However, because a majority of welders often used multiple processes and consumables, the observed results of the reviewed studies may reflect other underlying and unexplained workplace differences, thus making these associations difficult. To address these difficulties, well-controlled animal studies may provide insights into pulmonary responses to welding fumes. The overall goal of the studies was to examine the influence of welding fume metal composition (e.g., SS vs. MS welding fume) on lung toxicity and tumor development.

Lung toxicity in experimental animal models

Inhalation studies, typically 3 hr/day up to 10 days, in rodent models have examined parameters of lung toxicity including inflammatory cell influx and cytotoxicity at different time points after cessation of the exposure. The freshly generated welding fumes used in these studies were nearly identical in particle size, solubility, and morphology. Lung tumor-susceptible (A/J), and tumor-resistant (C57BL/6) mice were exposed by inhalation to Cr- and Ni-containing GMA-SS welding fume at 40 mg/m^3.[21] Significant and sustained lung toxicity, without recovery, was found in both mouse strains. In a follow-up study of the same design, lung toxicity of an GMA-MS fume, which lacks carcinogenic metals, was evaluated.[22] Unlike with the SS welding fume, no significant adverse lung response occurred after exposure to the MS welding fume up to 84 days post-exposure. A similar pattern of response was found in rats exposed to the same two welding fumes.[23] Inhalation of GMA-MS fume had no significant toxic effect on the lungs at any time point, whereas lung toxicity was significantly increased and persisted up to 21 days after exposure to the GMA-SS fume.

Other experimental animal studies used intratracheal instillation, a method that delivers a bolus of welding fume, suspended in a buffered saline solution,

directly to the lungs of rats. Taylor et al.[24] compared GMA-SS, GMA-MS, and MMA-SS welding fumes and evaluated parameters of lung toxicity as previously described. Results indicated that these fumes which differed in metal composition and water solubility (Table 1) caused varied responses in the lungs of rats with an order of toxicity of MMA-SS > GMA-SS > GMA-MS fumes. In addition, when MMA-SS fume was separated into soluble and insoluble fractions, it was found that although the soluble > insoluble fraction, the toxicity was not greater than the complete fume.[23,25] The overall conclusions from the rodent studies was that SS welding fumes caused greater pulmonary toxicity than MS.

Lung carcinogenesis in experimental animal models

Predicated on a document from an IARC advisory group on the Monograph priorities for 2010–2014 that listed welding fume as a high priority agent for further evaluation of carcinogenic risk to humans, a series of studies examining welding fume and lung tumorigenesis in experimental animals was initiated at the National Institute for Occupational Safety and Health.[26] In 2008, Zeidler-Erdely et al.[27] compared lung tumor-susceptible (A/J) and tumor-resistant (C57BL/6J) mouse strains exposed to GMA-MS, GMA-SS, and MMA-SS fumes via oropharyngeal aspiration. The oropharyngeal aspiration exposure technique in mice is similar to intratracheal instillation except that the suspension is aspirated into the lungs by the animal rather than instilled directly.[28] The GMA-SS fume induced an acutely greater and prolonged lung toxicity in A/J mice, persisted in the lung tissue the longest, and showed a trend toward an increased tumor incidence as compared to the other two welding fumes. The authors concluded that GMA-SS fume was not a potent initiator for lung tumorigenesis using this experimental model and exposure regime.

Based on this preliminary finding, subsequent studies focused on whether GMA-SS fume acted as a lung tumor promotor using a two-stage (initiation-promotion) mouse lung tumor bioassay. Male A/J mice were treated with a chemical initiator known to induce lung tumors, 3-methylcholanthrene (MCA), or corn oil (vehicle control) and then exposed to two different doses of GMA-SS fume via oropharyngeal aspiration.[29] After 30 weeks post-initiation, lung tumors were counted. In the presence of MCA, GMA-SS fume significantly increased lung tumor number compared to MCA/control (12.1 ± 1.5 tumors/mouse for low dose GMA-SS and 14.0 ± 1.8 tumors/mouse for high dose GMA-SS vs. 4.77 ± 0.7 tumors/mouse in MCA/control). This study provided the first experimental animal evidence that GMA-SS welding fume acts as a lung tumor promoter *in vivo*.

A similar two-stage (initiation-promotion) model using inhalation as the exposure route was completed to confirm the results of the oropharyngeal aspiration study with GMA-SS fume. Inhalation is the preferable route for animal studies because it more closely simulates workplace welding fume exposure with respect to particle size and surface properties of the generated fume. Furthermore, it has been shown previously that "freshly-generated" GMA-SS welding fume is more reactive and toxic to the lungs than "aged" welding fume that is commonly used for oropharyngeal aspiration studies.[30] Male A/J mice were initiated with MCA or corn oil vehicle then exposed by whole-body inhalation to filtered air or GMA-SS fume for nine weeks.[31] At 30 weeks post-initiation, average tumors per mouse lung were determined. Mice initiated with MCA and then promoted with GMA-SS fume had significantly greater average lung tumor numbers compared to MCA/air-exposed controls (16.11 ± 1.18 vs. 7.93 ± 0.82). Taken together, the findings from these studies provided conclusive evidence that a Cr- and Ni-containing SS welding fume acts as a lung tumor promoter in an experimental animal model.

Epidemiology studies report that MS welders are also at an increased risk for lung cancer, which calls into question the contribution of known carcinogenic metals to this risk. Therefore, the potential of GMA-MS fume that lacks these carcinogenic metals to cause lung tumorigenesis in the A/J mouse was examined.(22) Using the same inhalation exposure regime and two-stage model as described above, GMA-MS fumes significantly promoted lung tumors in A/J mice initiated with MCA (21.86 ± 1.50) compared to MCA/air-exposed mice (8.34 ± 0.59). Importantly, this study demonstrated that inhalation of Fe-abundant GMA-MS fume promoted lung tumors *in vivo* and aligned with findings from worker studies that showed MS welders were at risk for lung cancer, even with less or no exposure to carcinogenic metals, such as Cr and Ni.

Future directions

Welding fumes, as a single entity, currently has no workplace exposure limit. Recent emphasis has been placed on regulating exposures in the workplace to

the most toxic metals contained in welding fume, such as Cr. However, this may not be the best practice as questions remain in regards to other metals associated with welding fumes that have been typically categorized as less toxic or a nuisance, such as Fe. Two main topics that need to be evaluated in future experimental animal models: (1) the contribution of the individual welding fume metals or combination of metals in the development of lung toxicity and tumorigenesis; and (2) the mechanisms by which welding fumes and the associated metals cause tumorigenesis.

A recent study that compared the pulmonary toxicity of the individual metal oxides commonly found in GMA-SS welding fume preliminarily addressed the first topic.[32] This study also examined the tumorigenic potential of the metal oxides. The pattern for lung toxicity for the metal oxides, administered as weight percentages as found in GMA-SS fume, was Fe (as Fe_2O_3) > Cr mixture (as Cr_2O_3 + $CaCrO_4$) > Ni (as NiO). Overall, lung toxicity was negligible for Ni, acute but not persistent for the Cr mixture, and persistent for the Fe. Lung toxicity was the greatest for the total GMA-SS welding fume compared to the individual metal oxide components, suggesting a possible interactive effect of the metals in combination. This is consistent with the findings of previous studies that have reported the metal components or soluble/insoluble fractions to be less toxic than the total welding fume.[27,33]

Using the two-stage (initiation-promotion) model, Falcone et al.[32] exposed A/J mice by oropharyngeal aspiration to the different metal oxides and found that Fe (as Fe_2O_3), but not the Cr mixture or Ni alone, significantly promoted lung tumors in the presence of MCA. Although these findings demonstrated that Cr or Ni alone did not have a significant effect on lung tumor promotion, previous studies have shown that GMA-MS and GMA-SS welding fume promoted lung tumors.[29,31] It may be that Fe is the primary component that drives the persistent or chronic lung responses (e.g., cancer) to welding fume. Cr and Ni may have the greatest effect on the acute lung cytotoxicity effects (e.g., inflammation) and perhaps interact with Fe to cause carcinogenicity. Overall, these findings provide further evidence that Fe is an important mediator of welding fume toxicity and support previous epidemiology and the recent IARC reclassification for welding fume.

Examination of the mechanisms by which welding fumes cause lung cancer is another area in need of further research. It has been hypothesized that the primary carcinogenic characteristics of welding fume include their ability to cause immunosuppression and chronic inflammation.[34] Epidemiological and experimental animal studies clearly demonstrate that welding fume exposure is associated with increased susceptibility to infection and immunosuppression.[35–39] Although there is some evidence that welding fume exposure causes chronic lung inflammation *in vivo*, it does not seem essential for tumorigenesis.[21,27,39] More studies are necessary to understand the mechanisms that contribute to the development of lung cancer associated with welding fume exposure.

Despite lacking known carcinogenic metals and without causing significant lung toxicity, Fe-abundant MS welding fume promotes lung tumors in an animal model to the same degree as a SS welding fume. Iron (as Fe_2O_3), which is currently a Group 3 or "not classifiable as to its carcinogenicity to humans," was found to be the primary mediator versus Cr or Ni for metal-induced lung carcinogenesis in experimental animals. A set of exposure limits that take these results into account is necessary to protect workers from welding fumes, especially those that contain different metal mixtures. Future work is needed to fully understand the mechanisms, in the context of individual metals and metal mixtures, which drive welding fume toxicity and carcinogenicity.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention.

References

[1] **Antonini, J.M.**: Health Effects Associated with Welding. In *Comprehensive Materials Processing, Volume 8*, N. Bassim (ed.). Oxford, UK: Elsevier Ltd., 2014. pp. 49–70.

[2] **Pfarr, M.**: Combating the welding shortage. *Weld. J. 96(11)*:34–37 (2017).

[3] **The James F. Lincoln Arc Welding Foundation:** Arc-welding Fundamentals. In *The Procedure Handbook of Arc Welding*, Fourteenth *Edition*, The James F. Lincoln Arc Welding Foundation (ed.). Cleveland, OH: The James F. Lincoln Arc Welding Foundation, 2000. pp. 1.3–1.

[4] **Antonini, J.M., M. Keane, B.T. Chen, et al.**: Alterations in welding process voltage affect the generation of ultrafine particles, fume composition, and pulmonary toxicity. *Nanotoxicology. 5(4)*:700–710 (2011).

[5] **Zimmer, A.T.**: The influence of metallurgy on the formation of welding aerosols. *J. Environ. Monit. 4*(5):628–632 (2002).

[6] **Jenkins, N.T., W.M.-G. Pierce, and T.W. Eagar**: Particle size distribution of gas metal and flux cored arc welding fumes. *Weld. J. 84(6)*:156s–163s (2005).

[7] **Antonini, J.M., A.A. Afshari, S. Stone, et al.**: Design, construction, and characterization of a novel robotic welding fume generation and inhalation exposure system for laboratory animals. *J. Occup. Environ. Hyg. 3*(4):194–203 (2006).

[8] **Sowards, J.W., A.J. Ramierz, D.W. Dickinson, and J.C. Lippold**: Characterization of welding fume from SMAW electrodes – Part II. *Weld. J. 89*(4):82s–90s (2010).

[9] **Antonini, J.M., N.J. Lawryk, G.G. Murthy, and J.D. Brain**: Effect of welding fume solubility on lung macrophage viability and function in vitro. *J. Toxicol. Environ. Health, Part A. 58*(6):343–363 (1999).

[10] **Kalliomaki, P.L., M.L. Junttila, K. Kalliomaki, E.L. Lakomaa, and R. Kivela**: Comparison of the retention and clearance of different welding fumes in rat lungs. *Am. Ind. Hyg. Assoc. J. 44*(10):733–738 (1983).

[11] **Harris, M.K., W.M. Ewing, W. Longo, et al.**: Manganese exposures during shielded metal arc welding (SMAW) in an enclosed space. *J. Occ. and Environ. Hyg.* 2(8):375–382 (2005).

[12] **Keane, M., S. Stone, B. Chen, J. Slaven, D, Schwegler-Berry, and J. Antonini**: Hexavalent chromium content in stainless steel welding fumes is dependent on the welding process and shield gas type. *J. Environ. Monit. 11*(2):418–424 (2009).

[13] **Cohen, M.D., B. Kargacin, C.B. Klein, and M. Costa**: Mechanisms of chromium carcinogenicity and toxicity. *Crit. Rev. Toxicol. 23*(3):255–281 (1993).

[14] "Occupational exposure to hexavalent chromium. Final rule," *Federal Register 71*:39. 2006. pp. 10099–10385.

[15] **International Agency for Research on Cancer**: Chromium, Nickel, and Welding. In *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, World Health Organization (ed.). Geneva, 1990. pp. 447–525.

[16] **Sowards, J.W., D. Liang, B.T. Alexandrov, G.S. Frankel, and J.C. Lippold**: A new chromium-free welding consumable for joining austenitic stainless steels. *Weld. J. 90*(4):63s–76s (2011).

[17] **International Agency for Research on Cancer**: Welding, Molybdenum Trioxide, and Indium Tin Oxide. In *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Volume 118, World Health Organization (ed.). Lyon, France, 2018. pp. 36–265.

[18] **Sorensen, A.R., A.M. Thulstrup, J. Hansen, et al.**: Risk of lung cancer according to mild steel and stainless steel welding. *Scand. J. Work Environ. Health. 33*(5):379–386 (2007).

[19] **Moulin, J.J.**: A meta-analysis of epidemiologic studies of lung cancer in welders. *Scand. J. Work Environ. Health. 23*(2):104–113 (1997).

[20] **Langard, S.**: Nickel-related cancer in welders. *Sci. Total Environ. 148*(2-3):303–309 (1994).

[21] **Zeidler-Erdely, P.C., L.A. Batelli, S. Stone, et al.**: Short-term inhalation of stainless steel welding fume causes sustained lung toxicity but no tumorigenesis in lung tumor susceptible A/J mice. *Inhal. Toxicol. 23*(2):112–120 (2011).

[22] **Falcone, L.M., A. Erdely, V. Kodali, et al.**: Inhalation of iron-abundant gas metal arc-mild steel welding fume promotes lung tumors in mice. *Toxicol. 409*:24–32 (2018).

[23] **Antonini, J.M., J.R. Roberts, S. Stone, et al.**: Persistence of deposited metals in the lungs after stainless steel and mild steel welding fume inhalation in rats. *Arch. Toxicol. 85*(5):487–498 (2011).

[24] **Taylor, M.D., J.R. Roberts, S.S. Leonard, X, Shi, and J.M. Antonini**: Effects of welding fumes of differing composition and solubility on free radical production and acute lung injury and inflammation in rats. *Toxicol. Sci. 75*(1):181–191 (2003).

[25] **Antonini, J.M., G.G. Krishna Murthy, R.A. Rogers, R. Albert, G.D. Ulrich, and J.D. Brain**: Pneumotoxicity and pulmonary clearance of different welding fume particles after intratracheal instillation in the rat. *Toxicol. Appl. Pharmacol. 40*(1):188–199 (1996).

[26] **International Agency for Research on Cancer**: Report of the advisory group to recommend priorities for IARC. Monographs during 2010–2014. Lyon, France: Internal report 08/001 (2008).

[27] **Zeidler-Erdely, P.C., M.L. Kashon, L.A. Battelli, et al.**: Lung inflammation and tumor induction in lung tumor susceptible A/J and resistant C57BL/6J mice exposed to welding fume. *Part. Fibre Toxicol. 5*(12):1–16 (2008).

[28] **Rao, P.C. S., S. Tinkle, D.N. Weissman, et al.**: Efficacy of a technique for exposing the mouse lung to particles aspirated from the pharynx. *J. Toxicol. Environ. Health, Part A. 66*(15):1441–1452 (2003).

[29] **Zeidler-Erdely, P.C., T.G. Meighan, A. Erdely, et al.**: Lung tumor promotion by chromium-containing welding particular matter in a mouse model. *Part. Fibre Toxicol. 10*(45):1–10 (2013).

[30] **Antonini, J.M., R.W. Clarke, G.G. Krishna Murthy, et al.**: Freshly generated stainless steel welding fume induces greater lung inflammation in rats as compared to aged fume. *Toxicol. Lett. 98*(1-2):77–86 (1998).

[31] **Falcone, L.M., R. Salmen, A. Erdely, et al.**: Inhalation of gas metal arc-stainless steel welding fume promotes lung tumorigenesis in A/J mice. *Arch. Toxicol. 91*(8):2953–2962 (2017).

[32] **Falcone, L.M., A. Erdely, R. Salmen, et al**: Pulmonary toxicity and lung tumorigenic potential of surrogate metal oxides in gas metal arc welding-stainless steel fume: Iron oxide as a primary mediator compared to chromium and nickel oxides; *PLoS One 13*(12):1–25 (2018).

[33] **Antonini, J.M., M.D. Taylor, A.T. Zimmer, and J.R. Roberts**: Pulmonary responses to welding fumes: Role of metal constituents. *J. Toxicol. Environ. Health, Part A. 67*(3):233–249 (2004).

[34] **Guyton, K.Z., I. Rusyn, W.A. Chiu, et al**: Application of the key characteristics of carcinogens

in cancer hazard identification. *Carcinogenesis. 39(4)*:614–622 (2018).

[35] **Lockey, J.E., M.B. Schenker, D.G. Howden, et al.**: Current issues in occupational lung disease. *Am. Rev. Respir. Dis. 138(4)*:1047–1050 (1988).

[36] **Palmer, K.T., J. Poole, J.G. Ayres, J. Mann, P.S. Burge, and D. Coggon**: Exposure to metal fume and infectious pneumonia. *Am. J. Epidemiol. 157(3)*:227–233 (2003).

[37] **Coggon, D. and K.T. Palmer**: Are welders more at risk of respiratory infections? *Thorax. 71(7)*:581–582 (2016).

[38] **Antonini, J.M., S. Stone, J.R. Roberts, et al:** Effect of short-term stainless steel welding fume inhalation exposure on lung inflammation, injury, and defense responses in rats. *Toxicol. Appl. Pharmacol. 223(3)*:234–245 (2007).

[39] **Antonini, J.M., J.R. Roberts, S. Stone, B.T. Chen, D. Schwegler-Berry, and D.G. Frazer**: Short-term inhalation exposure to mild steel welding fume had no effect on lung inflammation and injury but did alter defense responses to bacteria in rats. *Inhal. Toxicol. 21(3)*:182–192 (2009).