Environmental Health Engineering and Management Journal 2024, 11(2), 237-256
http://ehemj.com
doi 10.34172/EHEM.2024.24

Environmental Health Engineering and Management Journal

Review Article

Environmental Health Engineering and Management

Open Access Publish Free

Health risks of welding fumes: A review to investigate the relationship between oxidative stress levels and trace metals in body fluids of welders

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Abstract

Background: Welding fumes (WFs) contain heavy metals that can induce oxidative stress and health issues in welders. This review investigated the relationship between oxidative stress biomarkers and trace metals in welders' bodily fluids.

Methods: Online databases such as Scopus, PubMed, Web of Science, Science Direct, EMBASE, and Google Scholar were reviewed, with a specific emphasis on the effects of metal fume exposure during welding. Specific keywords such as "welding fumes", "metal fumes", "antioxidant enzymes", "biomarkers", and similar terms were employed to search for articles published between 2004 and 2023. After the evaluation of article titles and abstracts, this study reviewed a total of 19 articles.

Results: Studies suggest that welders experience oxidative stress due to changes in trace metals in their body fluids, affecting antioxidant enzymes and oxidative stress biomarkers. Elevated heavy metals in welders' biological samples lead to oxidative stress and inflammation, even at low levels. Certain metals in blood and urine, such as lead (Pb), manganese (Mn), iron (Fe), chromium (Cr), and cadmium (Cd), positively correlate with serum superoxide dismutase (SOD) and glutathione peroxidase (GPx) levels. There is also a significant positive correlation between serum/EBC MDA and blood/urine Pb, Mn, Cd, Cr, and Fe, indicating cellular damage, lipid peroxidation, and reduced antioxidant capacity. Additionally, welders may experience more DNA damage compared to non-welders.

Conclusion: Exposure to WFs significantly altered oxidative stress biomarkers in bodily fluids, underscoring the importance of the relationship between oxidative stress and trace metal imbalances in WF-related injuries. These factors could serve as valuable biomarkers for monitoring workers exposed to WFs.

Keywords: Oxidative stress, Antioxidants, Welding, Body fluids, Biomarkers

Citation: Karimi Zeverdegani S, Mohammadi F, Mohammadalipour A, Hashemnia M, Mohebian Z. Health risks of welding fumes: a review to investigate the relationship between oxidative stress levels and trace metals in body fluids of welders. Environmental Health Engineering and Management Journal 2024; 11(2): 237-256 doi: 10.34172/EHEM.2024.24.

Article History:
Received: 14 January 2024
Accepted: 4 March 2024
ePublished: 8 June 2024

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Introduction

Welding is a vital and highly skilled process, but the research on its health implications is still ongoing. Currently, there are 800 000 to 1 000 000 full-time welders worldwide, with an estimated 5 million people engaged in welding-related occupations (1). This workforce is regularly exposed to toxic metals, gases, radiation, and fumes. The main source of exposure is welding fumes (WFs), which have diverse chemical compositions based on variables like welding technique used, electrode material, filler metals, fluxes, shielding gases, and base metals (2). In 2010, aluminum (Al), cadmium oxides (Cd), copper (Cu), iron oxide (Fe), manganese (Mn), nickel (Ni), zinc oxides (Zn), beryllium (Be), chromium (Cr), fluoride (F), lead (Pb), mercury (Hg), molybdenum (Mo), antimony (Sb), and vanadium (V) were identified as common metals found in WFs (3). Additionally, Be, Cd, arsenic (As), hexavalent chromium compounds (Cr(VI)),

and Ni compounds have been categorized as carcinogenic agents by the International Agency for Research on Cancer (IARC) due to occupational exposure, with sufficient evidence linking them to lung cancer in humans (4). In 2017, IARC updated its classification of WFs to group 1, identifying them as carcinogenic to humans (5).

WFs are predominantly less than 0.50 μm in diameter, with ultrafine particles (0.01 to 0.10 μm) posing a challenge for removal once lodged in the small airways (6,7). Heavy metals can penetrate the body through ingestion, inhalation, or dermal contact, and even low-level exposure can result in toxic bioaccumulation (8,9). Exposure to WFs has been linked to health conditions such as bronchitis, metal fume fever, cancer, and functional alterations (10), metabolic syndrome (11), cardiovascular disease (12,13), type 2 diabetes (14), DNA and RNA damage (15,16), and an increased risk of neurological diseases (17). Non-smoking or minimally smoking welders face an increased risk of lung, pharynx, and larynx cancer due to prolonged WFs exposure (18-21).

Inhalation of WFs can cause systemic oxidative stress, reduce intracellular oxygen levels, and increase oxygen free radicals, hydroxyl radicals, superoxide anions, and hydrogen peroxide (22). Welders who were exposed to metal compounds during welding have been found to have higher levels of oxidative stress and lower antioxidant capacity compared to the control group (1,23-26).

Iron oxide is the most abundant metal found in WFs, followed by Mn, Cr, and Ni (27,28). Trace elements, including these metals, are concerning due to their potential to generate reactive oxygen species (ROS) and increase lipid peroxidation. ROS including superoxide anion, hydrogen peroxide, and singlet oxygen, act as messengers within cells, playing a role in processes such as mitogenic signal transduction and gene expression. However, excessive ROS production or impaired defense systems, both enzymatic and nonenzymatic, can be harmful (29,30). The accumulation of oxidative stress from ROS overproduction may contribute to cellular damage and death, potentially causing neuronal harm and cell apoptosis (31).

Biological monitoring is essential for individuals exposed to WFs, as it allows early detection of health risks (32). This helps prevent long-term effects and reduces treatment costs. Studies show that oxidative stress, trace element imbalance, and inflammation are significant factors in WF-related injuries (3,24). These factors can serve as biomarkers to assess occupational risks. Epidemiological studies support this hypothesis. For instance, some studies on welders have demonstrated that exposure to WFs leads to a disruption in the balance of trace elements in the body's circulation, which in turn triggers oxidative stress (33,34). It has been shown that welders have lower levels of glutathione (GSH) and activities of catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) compared to a control group, indicating increased oxidative stress (2,24,34,35). In addition, high levels of malondialdehyde (MDA), 8-hydroxy-2-deoxyguanine (8-OHdG), and 8-iso-PGF2α have been reported for welders (2,24,36-38). However, some authors have reported inconsistent results. Two studies found that welders had higher activities of erythrocyte CAT and SOD, with one study showing no significant changes in MDA levels and the other indicating lipid peroxidation in the erythrocyte membrane (24,39).

Up to today, few epidemiological studies have demonstrated a relationship between trace elements and heavy metals and oxidative stress biomarkers in the body fluids of welders. The purpose of this review article was to provide an overview of the current state of knowledge of the following: First, to investigate the potential impact of occupational exposure to metals-containing WFs on the balance of essential trace elements in biological fluids, thus, affecting homeostasis; second, to assess the levels of oxidative stress in professional welders after prolonged exposure by employing oxidative biomarkers; and third, to determine the relationship between trace metals and oxidative stress levels in body fluids of welders.

Materials and Methods

The articles reviewed in this study consist of original research articles and cross-sectional descriptive studies focusing on the levels of heavy metals and their association with oxidative stress biomarkers in welders' body fluids, published in the English language in either Iranian or international journals. The selection criteria specifically focused on inhalation as the exposure route. This review included all available full-text articles published between 2004 and 2024. Any studies that did not meet these criteria were excluded from the review. Therefore, neither the congress articles nor the abstracts of the articles were reviewed in any way. Initially, the method for extracting data from the articles was determined through discussions and consensus between researchers and article authors. Subsequently, the extracted data from the articles underwent multiple reviews, with any discrepancies being identified through discussion and agreement. Various valid databases like ScienceDirect, Scopus, Web of Science, PubMed, EMBASE, and other sites capable of accessing full-text relevant articles were reviewed. General keywords utilized to enhance the search specificity in the comprehensive review comprise WFs, toxic metals, metal fumes, heavy metals, exposure to metal, metal toxicity, welder, oxidative stress, antioxidant enzymes, biomarkers, GPx, SOD, CAT, MDA, 8-OHdG, trace elements, and body fluids. The validity and strength of each study were evaluated through a qualitative assessment of the study's objectives, methods, and the population involved. Using the specified keywords, a total of 1486 papers were identified. After screening based

on titles and abstracts, 1446 papers were excluded, and finally, 19 sources were reviewed in this study.

Results

Common welding techniques and associated metal fumes

Welding processes are mainly categorized into two types, arc welding and non-arc welding types. It is important to mention that arc welding is more popular than non-arc welding. In this technique, through the passage of electricity between two electrical conductors, a temperature exceeding 4000 °C is generated, resulting in the fusion of materials (40). The WFs composition is influenced by various factors such as electrode type, filler wire, fluxes, base metal, shielding gases, and surface coatings. When molten metal comes into contact with oxygen, it vaporizes and forms metal oxides, which then condense and create fumes. Shielding gases can help minimize oxidation. The amount of WFs generated depends on the specific welding procedures used. A recent study has found that consumable electrodes' filler metal and flux coating/core produce 90% to 95% of fumes (41). Submerged arc welding (SAW), gas metal arc welding (GMAW or MIG), and gas tungsten arc welding (GTAW or TIG) utilize shielding gases to minimize oxidation during the welding process, resulting in lower fume emissions when compared to manual metal arc welding (MMAW or SMAW) and flux-cored arc welding (FCAW). However, it should be noted that in GMAW and GTAW, the use of shielding gas can potentially enhance ultraviolet radiation, thereby facilitating the photochemical formation of gases such as O_3 and NOx (42). Some common welding processes are shown in Figure 1. Iron is the primary metallic element in WFs, with 90% being emitted by mass in shielded metal arc welding (SMAW). This is followed by the most abundant metals in SMAW, gas metal arc welding (GMAW), and gas tungsten arc welding (GTAW), including Mn, Zn, Cr, Al, and Cu (43,44). Fumes produced by stainless steel (SS) electrodes typically consist of Fe, Cr, Mn, and Ni, while mild steel (MS) WFs primarily contain 80% Fe with trace amounts of Mn (45). Approximately 90% of welding procedures predominantly employ MS, whereas SS is utilized in only 10% or less of cases (46). Evidence suggests that the inhalation of SS WFs elicits a higher degree of lung inflammation and damage in animals when compared to fumes emanating from MS (45,47). As a result, occupational risks associated with SS welding are higher compared to MS welding, mainly due to potential exposure to two known carcinogens: Cr(VI) and Ni (42). Extensive research has been conducted on the reactivity and capacity of both Cr and Ni to generate ROS in biological systems (48). The demonstrated toxicity of these metals has resulted in the noteworthy and ongoing generation of ROS, leading to consequential damage such

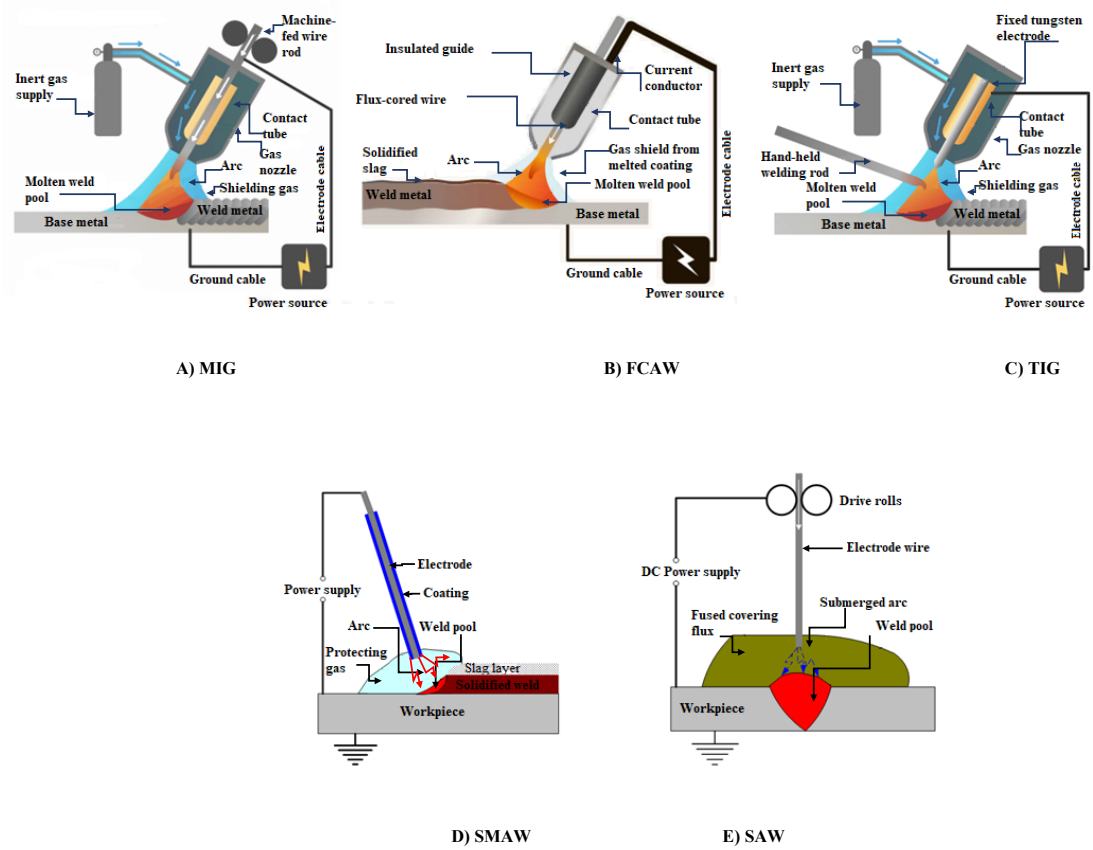

Figure 1. Common welding processes

as lung and DNA damage (49,50). A study showed that the ability to generate ROS and cause damage was significantly affected by the chemical composition of steel, particularly SS containing Cr and Ni, which caused more damage than MS. WFs produced by a gas metal arc robotic welder could lead to lipid peroxidation and H_2O_2 generation in cells (10). Scientific evidence demonstrates that newly emitted fine particulate fumes have a greater detrimental impact on lung health compared to aged fumes. This finding implies that the elevated level of free radicals on the surfaces of freshly generated fumes is accountable for the heightened harm. Hence, individuals working in active welding areas and exposed to recently formed fumes are potentially more susceptible to developing lung diseases (51). It was observed that exposing lung cells to an SS sample with high metal content resulted in higher levels of DNA damage and death of lung macrophages, which was directly proportional to the concentration of the sample. Furthermore, the administration of WFs in vivo led to a rise in the quantity of apoptotic cells observed in lung tissue (50). The results of a study indicated that Fe_2O_3 acts as a promoter of lung tumors in vivo and could be the main metal oxide causing the carcinogenic impact of SS fume (46). Some studies have shown that the clearance rate of WFs from the lungs of rats was observed to be slower for SS fumes compared to MS fumes (52,53). Furthermore, distinct metals present in diverse WFs were observed to be eliminated from the lungs at different rates after exposure. Notably, the highly toxic metals such as Mn and Cr, which were detected in certain WFs, demonstrated a more rapid and thorough clearance from the lungs compared to Fe. This occurrence potentially enhances the transport of these toxic metals from the respiratory system to other organs (54).

Biological monitoring of occupational exposure to welding fumes

Exposure to WFs, whether through inhalation or dermal absorption, can be detected in biological fluids. However, the presence of these elements alone does not necessarily indicate the occurrence of diseases or adverse effects. While blood is commonly used for evaluating potential exposure to organic and inorganic contaminants in human biomonitoring, it does not capture the accumulation of chemicals over time. Human biomonitoring involves directly measuring the presence of environmental contaminants or their metabolites in blood, urine, plasma, sputum, exhaled breath condensate (EBC), saliva, or other samples. The significant advantage of biomonitoring is that it offers conclusive evidence of both exposure and uptake (55). Many occupational exposures to pollutants like metals occur through inhalation, making the respiratory tract the main organ of exposure. Currently, blood and urine are the conventional matrices employed for the biological monitoring of workers exposed to metals. However, non-invasive sampling of EBC and saliva may serve as less-intensive alternatives (56). To evaluate occupational exposure, it has been discovered that not all substances exhibited an increase throughout the work shift. This is because many metals tend to accumulate in the body tissues and are gradually released over extended periods (57). The practice of biological monitoring in the workplace, which involves monitoring levels of toxic substances in the body, can facilitate the early detection of any negative health impacts resulting from occupational exposure to these compounds. Numerous researchers have investigated the health effects of welding on workers using various models. These studies have involved testing workers' blood and urine. For example, Borska et al. reported a statistically significant decrease in the number of cells capable of phagocytosis in the group of welders when compared to the control group (58). It was found that welders had a higher erythrocyte fragility index, indicating that their red blood cells were less tolerant to osmotic shock compared to the non-exposed group. The proportion of sputum neutrophils and eosinophils was also significantly higher in the exposed workers. Furthermore, metal body burden was associated with a significant decline in erythrocyte fragility index in the entire population (59). Some studies reported the blood levels of Cr, Mn, Pb, and Cu have been significantly elevated in the welders compared to the control group (1,33,36,38,39,59). Some other studies have reported higher urinary levels of metals such as Cd, Mn, Pb, Cu, Ni, Fe, Zn, and Co in welders compared to the control group (24,32,36,38,60).

A biological standard limit has been established for Pb concentration in whole blood due to the extensive data collected over a long period (61). Pb poisoning can cause a range of symptoms that vary depending on the duration of exposure (62). Symptoms such as delayed reaction times, irritability, and difficulty concentrating may occur at blood Pb levels of 25 to 60 μg/dL (63). Anemia may develop at levels higher than 50 μg/dL (64). In adults, abdominal colic may occur at blood Pb levels higher than 80 μg/dL (62). Severe manifestations, such as encephalopathy, coma, seizures, and headaches, can occur at levels exceeding 100 μg/dL (64). Hg exposure can be managed by assessing the Hg levels in blood or urine, but for alkyl mercury compounds, urine tests are not reliable (65). Evaluating Cd exposure based on blood and urine concentrations presents challenges, similar to the case of Mn (55,66,67). Permissible limits of urinary concentrations have been recommended for metals such as Ni, Cr, As, and selenium (Se), but knowledge about tolerable concentrations, particularly in blood, is limited for other metals due to the previous unavailability of sensitive methods for detecting trace elements (55). A study conducted on individuals who performed plasma cutting of SS revealed that the half-life of urinary Cr

excretion was 10.75 years (129 months) (68). In another study, after stopping environmental exposure, the half-life of urinary Cd was 16 years in men (69), while it was 12 years in welders who worked with SS (70). This indicates that urinary Cr and Cd can be used as long-term biomarkers to detect the extent of exposure to WFs. By contrast, welders who were exposed to SS WFs showed a significantly shorter half-life of urinary Ni, lasting only 96 hours (71). Information on the toxic characteristics of certain metals present in WFs, as well as reference values for the general population and their biological thresholds for occupational exposure, is presented in Table 1.

Interaction between heavy metals and trace elements

Trace elements, which are vital micronutrients, are necessary in small quantities to support diverse physiological processes in living organisms (76). Although essential elements are necessary for proper cellular function and are involved in the regulation of oxidative stress through metalloenzymes and proteins, studies indicate that changes in their levels are linked to insulin activity, glucose metabolism, cytokine production, inflammation, immune defense, and oxidative stress (77). These components, which are required in daily amounts from 50 µg to 18 mg, consist of a diverse range of elements including Fe, Zn, Cu, Mn, Cr, Se, iodine, and Mo. Although present in small amounts in the human body (78), they play essential roles in various physiological processes such as enzyme activity, cell signaling, DNA synthesis, and overall health maintenance. For example, iron is necessary for oxygen transport and energy production (79), while Zn is crucial for immune function and DNA synthesis (80). The balance between the absorption, distribution, utilization, and excretion of these micronutrients within the body is known as trace element homeostasis. However, the presence of heavy metals like Pb, Cd, Hg, and As can disrupt this delicate balance. Heavy metals have no known biological function and can be toxic even at low concentrations (81,82). They can interfere with the absorption and transport mechanisms of trace elements, leading to their deficiency or excess. For example, Pb exposure can inhibit the absorption of Fe, resulting in Fe deficiency anemia. Similarly, Cd can compete with Zn for binding sites, leading to reduced Zn absorption and subsequent Zn deficiency (83). According to a study conducted on welders working in a vehicle manufacturing plant, the levels of Mn and Fe in their blood were significantly higher than those of the control group. The welders had 4.3 times more Mn and 1.9 times more Fe in their blood compared to the control group. However, the concentration of Pb in their blood increased 2.5 times, and their serum Zn levels decreased by 1.2 times (24). This indicates that chronic exposure to WFs can lead to an imbalance in trace elements, with increased levels of Mn, Fe, and Pb, and decreased levels of Zn. This disturbance in trace element homeostasis may contribute to the development of oxidative stress and subsequent health issues among welders. It was found iron homeostasis remained normal in welders who used low-emission techniques or personal air-purifying respirators (PAPR). However, the regulation of iron could be compromised when the concentration of respirable iron in the air exceeded 1800 µg/m^3 (84). Another study reported significantly higher concentrations of Mn and Cu in the saliva of welders, while salivary levels of Zn were significantly lower. Increased Mn levels in welders could disrupt the balance of Cu and Zn in the body (85).

Trace metals have a notable impact on multiple biological processes, such as regulating enzymatic reactions and influencing the permeability of cell membranes. Additionally, they play a crucial role in the body's detoxification processes, particularly concerning heavy metals. For example, Se is an essential component of GPx, an enzyme involved in detoxifying ROS and heavy

Table 1. Toxicokinetic properties of some elements, reference values (µg/L, µg/g) in biological matrices of general population, and biological limits for occupational exposure

Element	Half-life in urine	Half-life in blood	Reference values in urine (µg/L)	Reference values in blood (µg/L)	Biological exposure limit in urine	Biological exposure limit in blood	Reference
Fe	2 h	6 h	up to 62.4±4.1 µg/g creatinine in healthy subjects	600 to 1700 µg/L	-	-	(72)
Mn	30 h	40 days	<3 µg/g	1 µg/100 mL (10 µg/L)	-	-	(73)
Cr	129 months	40 months	0.22 µg/L	2.0 µg/100 mL to 3.0 µg/100 mL	-	-	(68)
Ni	17-39h	24h	less than 20 µg/L	0.2 µg/L	1µg/L (ACGIH)	-	(74)
Pb	28 days		12–27	1–2 months	-	200 µg/L (ACGIH)	(75)
Cd	7 h	3 to 4 months	0.1–1.5	0.1 to 0.5	2 µg/g (EU) 5 µg/g (ACGIH)	5 µg/L	(75)
Hg	1–3 months	40 to 60 days	1	less than 10 µg/L	20 µg/g (ACGIH)	-	(75)

metals. However, heavy metal exposure can deplete these trace elements, impairing the body's ability to detoxify and eliminate toxic substances (86). Heavy metals can displace trace elements from their binding sites within enzymes, proteins, and other cellular structures. This displacement can impair the normal functioning of these biomolecules, leading to a cascade of adverse effects. For instance, Hg can displace Se from selenoproteins, disrupting their antioxidant activity and impairing thyroid function (87). Other substances within the body can have antagonistic or synergistic effects with Se (88). For instance, As reduces the absorption of Se, leading to a deficiency that may cause diseases of the liver, skin, lungs, and thyroid (89). Other substances such as sulfur, Hg, Cu, Zn, Pb, Cd, and Mn have also been identified as Se antagonists (90). Conversely, vitamins E and A, as well as iodine, have a synergistic effect with Se (91). Vitamin E, for example, boosts the immune system and works better when combined with Se to fight oxidative stress (92).

As shown in Figure 2, apart from Se, Fe, Cu, Zn, and Mn are cofactors of the antioxidant enzymes CAT and SOD. It seems that an excess of essential trace elements such as Zn and Cu can protect against the toxicity of heavy metals like Ni (93). Earlier studies have also shown that Ni reduces the amount of GSH, while Zn either increases GSH levels or prevents GSH depletion. One possible explanation for zinc's protective effects could be that it stabilizes tissue thiols or activates enzymes associated with GSH, such as glutathione transferase (94,95). Zn is a necessary element for SOD, an enzyme located in the cytoplasm of eukaryotic cells. SOD plays a critical role in converting the superoxide radical and protecting cells from harm caused by ROS (96). Cu is an important metal that serves as a cofactor for enzymes engaged in respiration and DNA synthesis, due to its capacity for reversible redox reactions (97).

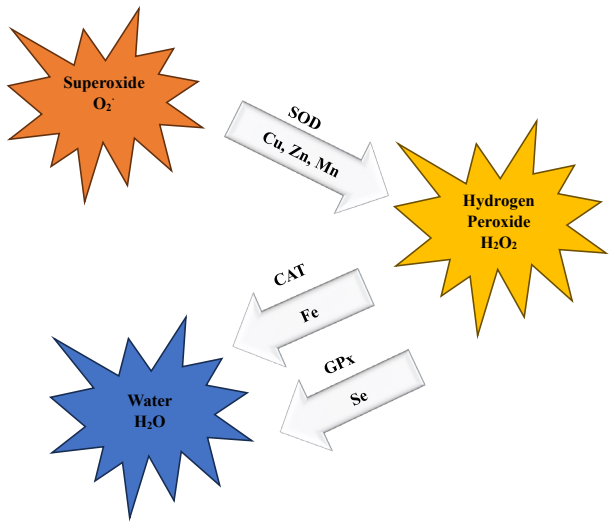

Figure 2. Antioxidant enzymes that utilize trace elements as cofactors

As mentioned earlier, WFs contain a complex mixture of heavy metals including Fe, Cr, Ni, Pb, Mn, etc. Among these heavy metals, Fe plays a crucial role due to its abundance in WFs and its potential interaction with other heavy metals. In the following, the interaction between iron and other heavy metals in the welder's body fluids was investigated, focusing on the implications for homeostasis.

Interactions between Fe and other trace elements

Iron is a crucial nutrient that plays a vital role in various physiological processes, including oxygen transport, energy production, and DNA synthesis (98). WFs contain iron, which is an essential trace element but an excess of iron can lead to toxicity due to Fenton reactions. The interaction between iron and other heavy metals can have profound implications for welders' health. To avoid oxidative harm, surplus iron is attached to ferritin. High levels of serum ferritin (SF), which is a biomarker for iron storage, are associated with inflammation and potentially cancer. A study has indicated that welders with high levels of body iron exposed to high concentrations of airborne iron resulted in higher concentrations of SF, indicating an enhanced uptake of iron through the lungs (84).

Pb, a common contaminant in WFs, can interfere with Fe metabolism, leading to altered Fe homeostasis. Pb competes with Fe for binding sites on transport proteins, such as transferrin, reducing iron's availability for essential functions. This disruption can result in iron deficiency, leading to anemia and impaired immune function in welders (99). Fe deficiency resulting from lead interference can lead to anemia, fatigue, and compromised immune function. Conversely, iron overload due to Cr interaction can increase the risk of oxidative stress, tissue damage, and cancer development (100). It is indicated that welders had higher levels of Pb than normal levels of Pb in their bodies. This was linked to an increase in mixed white blood cell fraction platelets (101).

Mn is an essential trace element that acts as a cofactor in specific enzymes, playing a crucial role in the metabolism of lipids, carbohydrates, and proteins (102). It is also involved in various processes such as reproduction and growth, immunity, energy homeostasis, and antioxidant defense (103). Mn, a prevalent element in WFs, is recognized as an environmental metal that can harm the central nervous system and cause manganism (104-107). Mn generates harmful free radicals, resulting in oxidative stress and neurodegeneration (108). It can enter the brain through the bloodstream using specific carriers as it passes through the blood-brain barrier (109). Surprisingly, Mn inhibits lipid peroxidation caused by Fe and serves as a crucial component of the antioxidant enzyme Mn-SOD (110). In other words, Mn plays a crucial role in scavenging ROS during mitochondrial oxidative stress. Both Mn deficiency and intoxication have been linked

to negative metabolic and neuropsychiatric effects (111). However, exposure to Mn, especially in an iron-deficient state, may exacerbate iron deficiency due to their similar absorption and transport mechanisms (112). Iron deficiency increases Mn absorption in the lungs, while excess iron has the opposite effect (113). Overloading of both Fe and Mn can have an adverse effect on each other since both metals compete for the same binding protein in SF and transportation systems. The accumulation of excess Fe in neurons can lead to oxidative stress at the cellular level, resulting in neuronal damage. Blood Mn and SF levels are commonly used to assess the systemic homeostasis of Mn and Fe. Overloading of Mn or Fe during welding may disrupt this balance (114,115). Some studies have investigated the interaction between Mn and Fe in welders exposed to Mn, which is a primary coating material in welding products such as bars and wires. Cowan et al., reported welders with higher levels of Mn in their biosamples tend to have lower levels of Fe in their plasma and erythrocytes (116). Another study on 241 welders showed that only a few individuals had Fe deficiency. Moreover, there was no significant correlation between blood Mn levels and SF (27). A different study conducted on welders showed a notable increase in the levels of both Fe and Mn in their serum. This increase was accompanied by higher levels of transferrin and lower levels of transferrin receptor. Additionally, an inverse relationship between serum Mn and transferrin levels was reported. This indicates that exposure to WFs can disrupt the balance of Mn, Fe, and the proteins involved in Fe metabolism in the serum (117). Despite limited studies on airborne Mn levels during welding, the effects of prolonged and low-level exposure to Mn or WFs on blood levels of trace metals are uncertain. Nevertheless, it is known that changes in systemic homeostasis of Fe and Mn are linked to neurodegenerative disorders (118,119). The exact mechanism by which Mn causes neurodegenerative damage is still unknown. However, several recent studies have suggested that Mn neurotoxicity, in addition to its interaction with Fe (120-123), may be related to its interaction with other essential trace elements such as Zn (124), Cu (124), and Al (121,122,125). In support of this hypothesis, Wang et al. reported there is a noteworthy connection between the levels of Mn and Cu, as well as between Mn and Zn, in saliva samples. As a result, changes in Mn levels in welders could disrupt the balance of Cu and Zn in the body (85). Toxic metals like Mn, Fe, and Cr in WFs can move to the brain via systemic circulation after accumulating in the lungs. Mn has high water solubility and can quickly translocate to specific brain regions, including dopaminergic areas, while other metal components accumulate in the lungs and other organs but do not translocate to the brain. Although Fe is abundant in the fumes, its lack of accumulation in the brain suggests that it exists as a water-insoluble component in WFs. Therefore, selective translocation of Mn to brain structures occurs after exposure to WFs (126).

Cr is another essential trace metal that can interact with Fe. In WFs, both Cr (III) and Cr (VI) are present in significant amounts, with Cr (VI) existing as K_2CrO_4 and its concentration influenced by the type of shielding gas used (127). Cr (III) is considered to be of low toxicity, while Cr (VI) is highly toxic and classified as a human carcinogen (128). Studies conducted in vitro have demonstrated that Cr reduces the binding of Fe to transferrin. On the other hand, it has been observed that once Cr enters the bloodstream, approximately 90%-95% of this element can bind to transferrin (129,130). High doses of Cr (1 mg/kg/d for 45 days) have been observed to significantly reduce transferrin saturation by iron in animals, deplete tissue Fe stores, and decrease hemoglobin levels (130).

Metal-induced oxidative stress

An imbalance between the production of free radicals and the body's ability to neutralize them leads to oxidative stress, which is characterized by elevated levels of lipid peroxides and free-radical intermediates, as well as a reduction in total antioxidant capacity (TAC) (131). Moreover, when free radicals target cellular components like lipids, proteins, and nucleic acids, it results in impaired cellular function (132-134). In addition to ROS, exposure to metals can also influence the generation of reactive nitrogen species (RNS). The process of metal-mediated free radical generation can result in diverse alterations to the DNA bases and also increase lipid peroxidation (131). Furthermore, metal-induced oxidative stress can contribute to the development of metabolic syndrome, heart disease, diabetes, and stroke, as well as damage to multiple organs, the development of autoimmune diseases, and developmental toxicity (135,136). The main participants in the phenomena of oxidative stress and oxidative signaling include the superoxide anion, hydroxyl radical, hydrogen peroxide (H_2O_2), singlet oxygen, and peroxyl radical (137). It has been demonstrated that even low-level exposure to a combination of heavy metals can have a detectable effect on biomarkers of oxidative stress. These biomarkers could potentially serve as a sensitive, specific, and early diagnostic tool for identifying oxidative stress induced by metal toxicity (57). There are various biomarkers of oxidative stress, including ROSs. However, since ROSs are highly reactive and have a short half-life, it is more appropriate to evaluate oxidative stress by measuring their oxidation target products, such as lipid peroxidation, oxidized proteins, oxidative nucleic acid damage, and markers of antioxidant defense systems (138). Antioxidants can be divided into two categories: enzymatic antioxidants (e.g., SOD, GPx, CAT, and glutathione reductase) and non-enzymatic antioxidants (eg., vitamin C, vitamin E, β-carotene, Se, Zn, GSH, and ferritin) (77). Biomarkers of oxidative stress are shown in

Figure 3. These biomarkers can be measured in various body fluids such as blood (e.g., serum, plasma, red blood cells, granulocytes, or lymphocytes), urine, sputum, EBC, and saliva (139,140).

Elevated levels of metals detected in blood and urine have been linked to an increase in oxidative stress biomarkers such as MDA, 8-OHdG, and changes in the glutathione ratio (141-143). MDA is a byproduct of lipid peroxidation, formed when polyunsaturated fatty acids break down in cell membranes. It acts as a marker for evaluating oxidative stress and lipid peroxidation in biological systems. MDA levels can be detected in urine, blood, and EBC, and elevated levels are associated with cardiovascular disease, cancer, and neurodegenerative disorders (24). 8-Oxo-7,8-dihydroguanosine (8-oxoGuo or 8-OHG) is a commonly used biomarker of DNA damage caused by ROS and free radicals, found in the cytosol, nuclear and mitochondrial DNA, and produced by hydroxyl radicals attacking the C-8 position of deoxyguanosine in DNA, leading to oxidative damage to the DNA, with 8-OHdG being highly stable and not undergoing metabolic processes in human circulation (16). Urinary 8-OHdG is a commonly used approach to assess DNA damage in individuals exposed to cancer-causing substances, including asbestos fibers, tobacco smoke, heavy metals, and polycyclic aromatic hydrocarbons (16). The process of oxidizing RNA, which is generally more abundant and less protected compared to DNA, results in the production of 8-OHdG or 8-oxodGuo (144).

Disrupting metal homeostasis can cause uncontrolled production of harmful free radicals, which can trigger alterations in DNA bases, heightened lipid peroxidation, and imbalanced calcium and sulfhydryl levels (145,146). Some metals such as Fe, Cu, Cr, vanadium (V), and Co participate in redox-cycling reactions, while another group consisting of Hg, Cd, and Ni mainly exert their harmful effects by reducing glutathione levels and bonding with protein sulfhydryl groups. Arsenic (As) is thought to bind directly to essential thiols, although alternative mechanisms such as the production of hydrogen peroxide under physiological conditions have also been proposed. The generation of RNS is a common factor that determines the toxicity and carcinogenicity of all these metals (100). Pb can cause oxidative stress by generating reactive ROS and impairing the antioxidant defense system of cells (147-149). The significant indirect mechanism for oxidative stress caused by redox-inactive metals involves the reduction of major cellular sulfhydryl reserves, including δ-aminolevulinic acid dehydratase (ALAD) (150,151). Pb can replace zinc in many enzymes, rendering them inactive, leading to increased lipid peroxidation and inhibition of enzymes responsible for preventing oxidative damage. Pb-induced oxidative injury can disrupt the pro-oxidant/antioxidant balance, leading to injury to critical biomolecules through oxidative damage. Prolonged exposure to Pb can result in a notable reduction in the activity of tissue SOD and metalloenzymes (Zn/Cu) (152).

Iron is the most prevalent metal in the body, playing a vital role in tasks such as carrying and storing oxygen, but to prevent oxidative damage, iron is tightly regulated, and ferritin stores iron as a protein (153). Ferrous iron can initiate oxidation processes by reducing and decomposing existing hydrogen peroxide (154). Iron-induced oxidative stress has significant consequences, which can be outlined as follows: Firstly, it results in an inability to properly

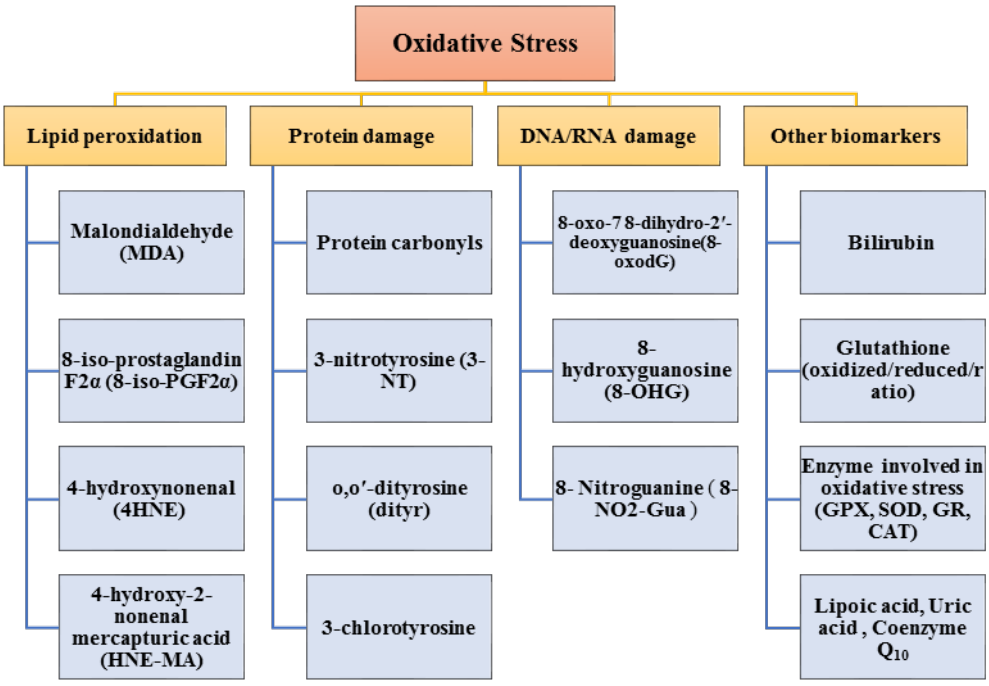

Figure 3. Common biomarkers of oxidative stress

regulate redox reactions, subsequently, leading to damage in DNA, lipid peroxidation, and oxidative impairment of proteins. Secondly, the activation of signal transduction pathways occurs due to the influence of free radicals (100). Iron's electronic structure and its role in one-electron reactions make it essential for the generation and regulation of free radicals in biological systems. It is commonly found in three oxidation states: Fe(II), Fe(III), and to a lesser extent, Fe(IV) (100).

Cu can induce oxidative stress through two distinct mechanisms. Firstly, it acts as a catalyst in the generation of ROS through a reaction similar to Fenton (155). Secondly, when individuals are exposed to high levels of Cu, it leads to a noticeable reduction in the levels of glutathione, an important antioxidant in the body (156,157). The occurrence of Cu at elevated concentrations is associated with the promotion of metastasis in cancerous cells (158).

Cr and other metals can induce oxidative stress by generating superoxide radicals, hydroxyl radicals, and other ROS through the Haber-Weiss/Fenton reaction. Likewise, metals like Ni, Cd, and Pb can also trigger oxidative stress by stimulating NADPH oxidase activity or depleting glutathione and forming bonds with protein sulfhydryl groups (133,134,159,160).

Discussion

Relationship between trace metals and oxidative stress biomarkers in body fluids of welders

This review provides an overview of human studies conducted on some biomarkers of oxidative stress that were evaluated in biological body fluids (e.g., urine, blood, serum, plasma, sputum, saliva, or EBC) of welders and their association with essential trace metals in the body. Assessing and measuring these biomarkers could offer a speedy and straightforward method for detecting and predicting damage, abnormalities, and illnesses in humans (161). Various studies have demonstrated that exposure to WFs can significantly impact the body's antioxidant defense system, particularly in regards to the activities of enzymes like SOD, GPX, and CAT (22,23,38,39). Unfortunately, there are limited data and research on this subject.

Under normal circumstances, two antioxidant enzymes SOD and MDA move reversibly in our body (22). However, multiple factors such as smoking, aging, diet, and intense exercise, have the potential to act as confounding variables, resulting in a marked rise in lipid peroxidation (as indicated by MDA) and a significant decrease in antioxidant enzyme activity (as indicated by SOD) (162). However, in some other studies, there was no correlation between these variables and the levels of oxidative stress biomarkers. Fidan et al. investigated the impact of WFs on biomarkers of oxidation and antioxidant activity in the respiratory system. They found that welders had reduced protein sulphydryl bands and GSH levels, which are important biomarkers. However, factors such as age, BMI, smoking, and years of work experience did not significantly affect this decrease (25). A study of steel mill welders in Poland similarly found that reductions of SOD, CAT, and TAS serum levels in 94 welders were independent of age and smoking effect (163). This suggests that even low levels of airborne metals have minimal impact on oxidative stress and inflammation (3).

The reviewed studies indicate that when investigating the oxidative damage of welders caused by metal fumes, it is important to carefully consider factors such as smoking, length of employment, and the duration of daily and weekly exposure to WFs. Smoking may activate the impact of WFs on antioxidant enzymes, which may demonstrate oxidative stress without causing oxidative damage, as indicated by the absence of correlation with MDA levels. Chronic exposure to WFs can lead to oxidative stress, but it may be balanced by the body's antioxidant defense system (39). In a study by Luo et al heavy smoking (more than 10 cigarettes per day) was found to significantly increase plasma MDA level, indicating that cigarette smoking can increase plasma MDA level. It was also found that smoking and full-time welding were associated with significantly higher levels of urine Zn, Cu, and Ni compared to controls (164). In other studies, an increase in MDA levels and a decrease in SOD and CAT levels have been reported in smoker welders compared to non-smokers (38,165).

The duration of exposure to WFs is correlated with changes in SOD and CAT activities among welders, further supporting these findings (39). In this regard, a study has shown that welders who were exposed to metal oxide fumes for at least 5 years for 10-12 hours per day had significant reductions in blood levels of SOD and GPx activity, as well as TAS concentration. The study found no correlation between age or working years and the decrease in antioxidative system activity but did find that smoking reduced TAS concentration. Exposure to fumes was found to have a significant correlation with TAS and GPx, indicating that exposure to metal fumes can act as an oxidative stressor (22). Li et al reported a significant correlation between the decrease in SOD activity among welders with the duration of employment. Furthermore, it was found that the level of MDA increased as the duration of employment increased, suggesting a higher level of systemic oxidative stress among welders (24). Mainasara et al reported an increase in MDA, SOD, GPx, and CAT enzyme activities as the duration of occupational age increased (166).

According to the literature review, it is clear that inhalation exposure to WFs from various welding processes can lead to an imbalance of trace metal levels in biological body fluids, which in turn can contribute to oxidative stress in welders. The findings of various studies reveal that welders have higher levels of metals, including Mn, Fe, Pb, Cd, Cu, Ni, Zn, and Cr in their blood and

urine compared to non-welders. Studies have shown that the levels of certain metals in blood and urine, such as Pb, Mn, Fe, Cr, and Cd, are positively correlated with the serum level of SOD and GPx (1,22,37). However, some studies have reported a negative correlation between blood and urine levels of Mn, Al, and Pb with SOD and GPx (1,22,24,35). In addition, there are cases where no correlation has been observed between these oxidative enzymes and plasma metals (38,39).

Several studies (Table 2) have suggested a significant positive correlation between serum and EBC levels of MDA and blood and urine levels of Pb, Mn, Cd, Cr, and Fe (24,37,38,165), suggesting increased lipid peroxidation and oxidative damage. However, some other studies did not observe any correlation between these biomarkers (32,39,164). A study found that automobile welders had lower GSH levels due to the interaction of Zn, Cu, and Ni, but this did not increase lipid peroxidation as measured by MDA levels. This study also supported the idea that an excess of essential trace elements such as Zn and Cu can protect against the toxicity of heavy metals like Ni (164). It was observed that the correlation between urinary metal levels and oxidative stress biomarkers further supports the relationship between metal exposure and oxidative stress. Certain studies have indicated a positive association between urine levels of Cr and Ni and biomarkers of oxidative stress such as 8-OHdG or 8-oxoGuo (57,60,167). Additionally, it has been found that urinary Mn, Ni, Cu, Cd, and Pb (excluding Al) had a stronger correlation with 8-iso-PGF2α compared to 8-OHdG. Urinary levels of Fe and Zn demonstrated correlations with both 8-OHdG and 8-iso-PGF2α. This suggests that heavy metals present in WFs play important roles in the regulation of oxidative stress and cardiovascular toxicity (36). These findings indicate that metal fumes from welding processes can induce DNA damage and lipid peroxidation, contributing to oxidative stress. Another study reported a negative correlation between total urinary metals and 8-iso-PGF2α, while a positive correlation was observed between total urinary metals and 8-OHdG (168).

In summary, the cause-and-effect relationship between trace metals and biomarkers of oxidative stress in welders involves the inhalation and accumulation of trace metals from WFs, which leads to oxidative stress through the generation of ROS. This oxidative stress then manifests as elevated levels of biomarkers such as MDA, protein carbonyls, antioxidant enzymes, and 8-OHdG. Understanding these mechanisms is crucial for implementing strategies to mitigate the adverse health effects associated with welding exposure to trace metals.

The limitations and future predictions

This review points out the lack of sufficient data and research on the connection between trace metals and oxidative stress biomarkers in welders' body fluids, indicating a need for further investigation. Factors like smoking, aging, and diet could complicate assessing this relationship accurately. It emphasizes the importance of considering variables such as smoking habits and exposure duration to WFs when studying oxidative damage in welders. Future studies should be conducted thorough analyses to better understand the impact of these factors on oxidative stress. Future research with more details is required to understand how metal fumes affect trace metal levels in body fluids and contribute to oxidative stress, aiding in developing preventive measures. Exploring the role of essential trace elements like Zn and Cu in protecting against heavy metal toxicity such as Ni presents a promising avenue for future research. Investigating how these elements influence oxidative stress and metal toxicity can offer valuable insights for occupational health practices. Future studies may focus on the correlation between metal levels and oxidative stress biomarkers to enhance understanding of the relationship between metal exposure and oxidative stress, particularly in assessing the impact of metal fumes on DNA damage, lipid peroxidation, and overall oxidative stress in welders.

Conclusion

Welders, a group of workers, encounter a range of intricate substances produced by diverse industrial activities. Prolonged and low exposure to WFs can disrupt the equilibrium of trace metals (e.g., Fe, Cr, Ni, Pb, Mn, Cd, etc.) in various body fluids of welders, including blood, plasma, and urine. The prolonged exposure to a mixture of low levels of heavy metals has a notable impact on biomarkers linked to oxidative stress. These biomarkers can serve as an early, accurate, and sensitive diagnostic method for detecting oxidative stress resulting from the toxicity of these metals. Despite these biomarkers are highly sensitive, large-scale human biological monitoring studies are still required to better understand how exposure to WFs can cause oxidative stress, cellular damage, or DNA damage. Although biomarkers can detect these effects, additional biomarkers may be needed to fully understand the relationship between exposure and these health effects. Metal overload, alterations in trace elements in bodily fluids, and the condition of antioxidant enzymes can contribute to the development of oxidative stress in welders. This can result in the generation of free radicals, potentially causing oxidative damage. It has been shown that increased levels of lipid peroxidation in plasma can be associated with a decline in the body's antioxidant capacity. Insufficient information is accessible regarding biomarkers of oxidative stress, antioxidant levels, the extent of peroxidase harm, and the involvement of trace elements in oxidative damage among welders. Studies conducted on trace elements such as Pb, Ni, Mn, Cd, Cr, Cu, Fe, and Zn have shown noticeable alterations in the levels of these elements in

Table 2. Research findings on the relationship between metals in biological body fluids and oxidative stress biomarkers in welders

Studies	Sample size (exposed/ unexposed) Year	Measured Metals in Matrix Studied					Antioxidant biomarker concentration	Welding processes	Study findings
		Blood (µg/L)	Urine (µg/g)	Sputum	Serum (µg/L)	EBC			
Li et al (2004) (24)	37/50	Pb 30.74	Mn (1.5)	-	Mn (0.66) Fe (300.2) Zn (59.37) Cu (75.26)	-	SOD in erythrocytes (483.65 U/g of Hb) MDA in serum (5.46 µmol/mL)	SMAW	Welders had higher levels of Mn, Fe, and blood Pb concentrations, and lower levels of serum zinc compared to controls. Urinary Mn level was also higher than blood Mn in welders. There was no significant difference in serum Cu levels between the two groups. SOD and MDA levels as biomarkers of Mn exposure showed that erythrocyte SOD activity decreased by 24% in welders compared to controls, while serum MDA level increased by 78%.
Lai et al (2021) (168)	49/20	-	Cr (0.0003) Mn (0.0005) Cd (0.00009) Co (0.00009) Ni (0.005) Cu (0.02) Fe (0.014) Zn (0.06) V (0.0001)	-	-	-	8-isoPGF2α in urine (40 pg/g) 8-OHdG in urine (529 pg/g)	TIG	Exposure to metal fumes increased urinary 8-iso-prostaglandin F2-α and 8-hydroxy-2′-deoxy guanosine. Urinary levels of Ni, Co, and Fe were increased among welders. Total urinary metals were negatively correlated with 8-iso-PGF2α and positively correlated with 8-OHdG. The study also found that an increase in urinary IL-6 was linked to higher levels of urinary Ni, Cu, and Fe.
Lai et al (2016) (36)	118/45	-	Al (2) Mn (0.9) Fe (1) Ni (1.2) Cu (1.4) Zn (100) Cd (0.25) Pb (0.19)	-	-		8-OHdG in urine (2.15 µg/g) 8-iso-PGF2α in urine (8.43 µg/g)	MIG	Exposure to metal fumes was found to reduce the survival of cells and increase the levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG) and interleukin (IL)-6. Welding workers showed significant increases in urinary Fe, Cu, Zn, and Cd. The study also found that urinary 8-iso-PGF2α had stronger links with urinary Mn, Ni, Cu, Cd, and Pb than 8-OHdG.
Moitra et al (2018) (59)	15/10	Ni (330) Mn (930) Cd (60)	Ni (0.33) Mn (0.27) Cd (0.13)	Ni (2.01) Mn (1.04) Cd (0.63)	-	-	MDA in plasma (59.3 nM/100 mL)	SMAW	Welders had a higher burden of heavy metals than non-exposed individuals, with significantly higher concentrations of Ni in sputum samples and consistent increases in Mn levels found in blood and sputum. Cd levels were not significantly different between the two groups. The exposed group showed a threefold increase in MDA production, indicating oxidative stress, but the association with metal load did not reach statistical significance.
Prabhu et al (2020) (33)		-	-	-	Fe (94.46) Zn (93.21) Cu (148.93) Pb (14.18)	-	MDA in serum (255.82 nmol/L) TAC in serum (2.16 nmol/L) GSH in serum (10.34 nmol/L)	-	It was found significant differences between welders and controls in terms of MDA, TAC, and levels of iron, copper, and lead in the blood. Welders had higher levels of MDA and lower TAC compared to controls. Additionally, the levels of iron, copper, and lead were significantly higher in welders than in controls. However, there was no significant difference in serum zinc levels between the two groups.

Table 2. Continued.

Studies	Sample size (exposed/ unexposed) Year	Measured Metals in Matrix Studied					Antioxidant biomarker concentration	Welding processes	Study findings
		Blood (µg/L)	Urine (µg/g)	Sputum	Serum (µg/L)	EBC			
Buonaurio et al (2021) (57)	40/13	-	Hg (0.92) Be (0.019) Ni (4.9) Cu (23.7) Sr (157) Cd (0.61) Ba (11) Pb (22) Fe (9.1)	-	-	-	8-oxoGua in urine) 26.87µg/g) 8-oxodGuo in urine (6.68 µg/g)	-	There was a correlation between the heavy metals Ba, Hg, Pb, and Sr and the RNA oxidative stress biomarker 8-oxoGuo. The average levels of 8-oxoGuo were significantly higher in workers than in controls.
Ananian F B et al (2013) (34)	50/30	Pb (81.2)			Mn (3.29) Cr (6.92) Cd (3.29) Fe (156.48)		SOD in serum (148.77 u/ml)	SMAW	It was found negative correlations between the levels of SOD and the levels of Pb, Mn, and Fe, although these correlations did not reach statistical significance. Furthermore, there was a positive correlation between the level of SOD and the levels of Cd and Cr. The correlation was statistically significant for Cr but did not reach statistical significance for Cd.
Imamoglu et al (2006) (39)	35/30	Cr (3.71) Mn (8.38) Cu (0.84)	-	-	-	-	SOD in erythrocytes (1829.24 U/ gHb) CAT in erythrocytes (65.02 U/gHb) MDA in erythrocytes (54.11 U/gHb)	SMAW	The plasma levels of Cr, Mn, and Cu were significantly elevated in the welders compared to the control group. The activities of the antioxidant enzymes CAT and SOD in red blood cells were significantly higher in the welders. However, there were no significant changes in the levels of MDA. The correlations between plasma metal concentrations and antioxidant enzymes, as well as between plasma metal concentrations and MDA, were not significant in the welders.
Su et al (2019) (60)	121/53	-	Cr (2.06) Ni (3.13) Cd (0.69) Pb (4.18)	-	-	-	8-OHdG in urine (4.77 µg/g)	-	Welders had significantly higher urinary levels of Cr, Ni, Cd, and Pb compared to controls. Urinary Cr and Ni were effective predictors of urinary 8-OHdG levels, indicating oxidative DNA damage. There was a positive relationship between urinary metals, particularly Cr and Ni, and 8-OHdG in nonsmoking shipyard welders.
KO et al (2017) (165)	60/49	Cr (2.60) Fe (506.3) Co (16.23) Cu (608.2) Zn (608.2) Mn (16.55) Cd (0.87) Mg (36.10) As (9.05)	-	-	-	-	MDA in EBC (3.98 Mm)	SMAW	The levels of Cr and Mn were significantly higher in welders compared to administrative workers. There were significant positive correlations between the levels of MDA, a marker of oxidative stress, and the levels of Cr and Mn, which are the main components of WFs.
Luo et al (2009) (164)	68/ 29	-	Zn (36.4) Cu (5.8) Ni (8.4)	-	-	-	MDA in blood (0.63 µM/L)	TIG	A significant association was observed between urine metal levels and welding hours. Zinc levels correlated significantly with white blood cells, interleukin-6, and GSH levels. Cu levels were significantly associated with GSH, while Ni levels showed an inverse association. However, there was no significant increase in MDA levels, and these metals did not exhibit a significant relationship with it.

Table 2. Continued.

Studies	Sample size (exposed/ unexposed) Year	Measured Metals in Matrix Studied					Antioxidant biomarker concentration	Welding processes	Study findings
		Blood (µg/L)	Urine (µg/g)	Sputum	Serum (µg/L)	EBC			
Han et al (2005) (1)	197 /150	Mn (1.44) Pb (5.27)	-	-	-	-	GPx in Serum (411.4 mU/ml) Mn-SOD in Serum (0.68 mU/ml) TAS in Serum (0.95 mU/ml)	Co2	The levels of Mn and Pb in the blood were higher in welders than in the control group. There were significant positive associations between Mn levels and GPx, as well as negative associations between Mn levels and Mn-SOD. Additionally, there were significant positive associations between Pb levels and albumin, TAS, and Mn-SOD, and a negative association between GPx and Pb.
Gube et al (2010) (32)	45/24		Cr (0.54) Ni (1.47) Al (9.05)	-	-		MDA in EBC (0.007 pM/µg)	MIG, TIG, MAG and SMAW	Welders had significantly higher levels of Al, Cr, and Ni in their urine compared to the control group. MDA showed no significant differences.
Pesch et al (2009) (167)	238/	Mn (10.3) Cr (<1.50)	Fe (12.5) Cr (1.19) Ni (2.82)	-	Fe (91) Ferritin (131)	-	8-oxoGuo in urine (7.03 µg/g) 8-oxodGuo in urine (4.33 µg/g) 8-oxodGuo in blood (2.35)	GMAW, FCAW, TIG and SMAW	Welders who used techniques with high particle emission rates on stainless steel had higher levels of both urinary 8-oxodGuo and 8-oxoGuo compared to tungsten inert gas welders. It was found a significant non-linear relationship between the concentration of oxidatively damaged guanosines in urine and systemic exposure to metals, particularly with SF and blood Mn. Urinary chromium and nickel also showed associations with modified guanosines in urine. Additionally, oxidatively damaged urinary guanosine is strongly related to body iron stores.
Goyal et al (2020) (38)	51/49	Cd (2.80)	-	-	-	-	MDA in serum (6.95 nmol/mL) CAT in serum (82.19 U/mL) SOD in serum (19.04 U/mL) TAC in serum (0.77 mmol/L)	MMA	Compared to metal handicraft workers, welders had significantly higher levels of cadmium in their blood. Welders also had lower levels of the oxidative stress markers TAC and CAT, while MDA was significantly higher. The level of SOD in welders was low but not significant. It was found a significant negative correlation between cadmium levels and TAC, and a positive correlation between cadmium levels and MDA. The SOD and CAT did not correlate with blood Cd.
Mainasara et al (2022) (166)	54/20	-	-	-	Cu (0.04) Zn (0.9) Mn (0.43)	-	MDA in serum (11.9 NMOL/ ML) SOD1 (1.02 U/ ML) SOD2 (0.91 U/ ML) GPx (2.03 µMOL/MIN/ML) CAT (0.81 KU/L)	SMAW	It was found welders had significantly higher levels of MDA, Cu-Zn superoxide dismutase (Cu-ZnSOD), GPx CAT, Cu, and Mn in their serum compared to non-welders. A robust negative correlation was detected between lung function tests and MDA levels. Similarly, there was a weaker correlation between lung function and antioxidant enzymes.

Table 2. Continued.

Studies	Sample size (exposed/ unexposed) Year	Measured Metals in Matrix Studied					Antioxidant biomarker concentration	Welding processes	Study findings
		Blood (µg/L)	Urine (µg/g)	Sputum	Serum (µg/L)	EBC			
SHRAIDEH et al (2018) (37)	90/20	-	-	-	Pb (14.5)	-	SOD in serum (3.7 U/L) MDA in serum (4.4 µmole/l)	-	It was found that automobile electronics workers had the highest level of lead exposure, while radiator welders had the lowest one. All worker groups had significantly higher levels of plasma MDA compared to the control group. Radiator welders and car painters had the highest increase in SOD activity compared to the control group. The correlation analysis showed a positive correlation between blood lead concentration and biomarkers of oxidative stress and antioxidants in all worker groups studied.
Fouad MM et al (2023) (35)	71/71	Pb (15.03)	-	-	Al (7.71) Zn (101.98) Mn (10.95)	-	SOD in serum (13.62 U/mL)	MIG	Welders had significantly higher mean concentrations of blood Pb, serum Al, and Mn compared to the control group. There was no significant difference in the mean serum Zn concentration between the two groups. The mean levels of testosterone and SOD were significantly lower among welders than the control group. Furthermore, a negative correlation was observed between blood Pb, serum Al, and Mn levels, and testosterone and SOD levels.
Riccelli et al (2018) (3)	50/50	-	Cr-T0 (0.71) Cr-T1 (0.74) Cr-T2 (0.59) Ni-T0 (0.76) Ni-T1 (1.11) Ni-T2 (0.83)	-	-	Cr-T0 (0.0.06) Cr-T1 (0.08) Cr-T2 (<0.05) Ni <0.05 in 3 sampling time	MDA in EBC (T0 = 2.79, T1 = 2.98, and T2 = 2.43 nM)	TIG	The concentrations of both EBC and urinary Cr were higher at pre- and post-shift (T0 and T1) on a Friday than on the following Monday morning pre-shift (T2), while Ni-EBC concentrations remained mostly below the detection limit. MDA-EBC concentrations were higher at T0 and T1 than at T2. There was a weak correlation between Ni-EBC and MDA-EBC. A positive correlation was observed between Cr-U and Ni-U, as well as between Ni-EBC and Cr-EBC. However, there was no correlation between EBC and urinary metal levels.

the blood and urine of welders. There have been only a limited number of clinical studies on the oxidant-antioxidant status of welders. Given that MS, which is composed of over 80% iron, is utilized in almost 90% of welding techniques, it is crucial to investigate the impact of this metal on the body and the resulting peroxidative damage caused by iron overload. Additionally, studies should also examine the use of serum ferritin as an indicator for iron stores, which at high concentrations can lead to inflammation and potentially increase the risk of cancer. Several factors, including smoking habits, aging, diet, alcohol consumption, acute exercise, and exposure to other environmental pollutants, can serve as potential confounding variables. Furthermore, there may be a synergistic effect of these combined exposures on the occurrence of oxidative stress. After reviewing the studies on the status of antioxidant enzymes in welders, it was observed that most welders displayed similar outcomes. While the associations between metal load and oxidative stress did not always reach statistical significance, the overall pattern review of various studies conducted in this field suggests that metal exposure in welding environments poses potential health risks. The findings emphasize the importance of understanding the relationship between metals in biological body fluids and oxidative stress biomarkers in welders. It is crucial to

implement protective measures to reduce metal exposure and mitigate oxidative stress in welders. These measures may include the utilization of suitable personal protective equipment, ensuring sufficient ventilation systems, regular monitoring of metal levels in biological fluids, and administering antioxidants to help minimize oxidative damage and associated complications.

Acknowledgments

The authors would like to express their gratitude and appreciation to Isfahan University of Medical Sciences, for supporting the study.

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Competing interests

The authors declare that there is no conflict of interests.

Ethical issues

In this article, the authors considered all the ethical points in collecting data and certify that this manuscript is the original work of the authors, and all data collected during the study are as presented in the manuscript, and no data from the study has been or will be published elsewhere separately. This article was extracted from a PhD thesis approved (Approval code: 3401606) by the Ethics Committee of Isfahan University of Medical Sciences (Ethical code: IR.MUI.AEC.1401.034).

Funding

This study was financially supported by Isfahan University of Medical Sciences in Iran.

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