UDC 615.9:616-009.87:612.57 DOI: 10.32471/umj.1680-3051.262034

Metal fume fever (review). Part 1

O.V. Kravets, V.V. Yekhalov, V.A. Sedinkin, D.A. Krishtafor, D.V. Myronov, O.V. Kovryha
Dnipro State Medical University, Dnipro, Ukraine

Abstract. Metal fume fever is an acute febrile syndrome caused by inhalation of aerosolized metal oxides, classified as an acute occupational disease affecting workers such as non-ferrous metal foundry workers, welders, galvanizers, and tinners. The most common cause is zinc oxide fumes generated from molten bronze, brass, or galvanized steel. However, cadmium, manganese, nickel, chromium, and their oxides are also present in certain welding fumes. Comparing the mechanisms of metal fume fever development reveals that aerosols of various metals can exhibit pathogenicity, including the production of reactive oxygen species, enzyme inactivation, and oxidative stress. This syndrome is distinct from inhalation poisoning. Metal microparticles quickly penetrate the bloodstream and lymphatic system through diffusion or transportation as colloids or protein complexes, exerting systemic resorptive effects. In addition to protein denaturation, the release of pro-inflammatory cytokines and the activation of neutrophils in the lungs play a significant role in the pathogenesis of metal fume fever, leading to pulmonary and systemic inflammatory responses. The entry of metal microparticles into the respiratory system and their subsequent systemic distribution can trigger inflammatory processes, resulting in a febrile syndrome. The lungs serve merely as the entry point rather than the primary site of inflammation. Inhalation of zinc oxide particles can provoke various clinical reactions, such as increasing the number of polymorphonuclear leukocytes in bronchoalveolar lavage fluid and early elevations of pro-inflammatory cytokines like TNF-α, IL-5, IL-6, IL-8, IL-13, myeloperoxidase, immunoglobulin E, γ-interferon, and polymorphonuclear cells. It also induces inflammatory markers, recruitment of inflammatory cells in the lungs, and marked neutrophil infiltration. These responses are time- and dose-dependent concerning the etiological factor but are not associated with bronchospasm or pulmonary dysfunction.

Key words: metal aerosols, occupational disease, metal oxide microparticles, metal fume fever.

Introduction

Metal fume fever (MFF) is an acute febrile syndrome presenting as an influenza-like illness following inhalation of metal aerosols [1–3]. MFF arises from the non-specific effects of metal fumes, where the primary determinant for fever development lies not in the chemical nature of the metal but in its physical properties. Metal fumes, upon cooling and oxidizing in the air, form highly dispersed aerosols that denature cellular proteins upon contact with the bronchial epithelium. Due to their high kinetic energy and significant electric charge, these aerosols interact closely with cellular proteins, inducing their denaturation. The subsequent absorption of these foreign proteins triggers the development of «aseptic, abacterial» protein fever [4], typically described as a self-limiting disease that can be challenging to diagnose or even suspect [1, 2, 5–7]. This condition is poorly studied by the pulmonology community and is largely managed through simple preventive measures [8].

Clear evidence indicates that inhalation of zinc oxide (ZnO) induces reversible systemic inflammation [9]. Welding fumes containing zinc, copper, nickel [10–18], and other metals (aluminum, antimony, beryllium, cadmium, chromium, cobalt, iron, titanium, manganese, magnesium, silver, tin, vanadium) [4, 15, 16, 19–23] have been shown to have pro-inflammatory effects. The prevalence of MFF induced by metals is approximately distributed as follows: zinc — 26%, steel — 15%, iron — 12%, aluminum — 8%, cadmium — 4%, and unidentified metal alloys — 20% [5].

Metal fume fever has a wide range of synonyms, reflecting its historical associations with the production and processing cycles of heavy metals. These include «metal, zinc, copper, brass, and beryllium fever»; occupational terms such as «foundryman's fever» and «tinker's hot cold», «zinc shakes», «smelter's chill», «galvanizer's chill», «tinner's disease», «solderer's chill», «welder's fever» and «boilermaker's fever»; and even more specific names like «monday morning fever», depending on the context of human activity and the course of the condition [4, 6, 7, 19, 24–26].

Relevance

The issue of MFF is likely as old as the art of metal smelting itself. The renowned Italian Renaissance sculptor Benvenuto Cellini suffered from MFF in 1550 while casting the bronze statue of Perseus for Duke Cosimo I de' Medici, as mentioned in his memoirs [7].

MFF was observed in the mid-1800s among brass foundry workers and in the early 1900s among welders of galvanized steel [6, 19, 26]. The first medical description of «foundry fever» was provided by I. Potissier in 1822 [6]. In 1830, H. Tackrah, an English physician from Birmingham, documented numerous cases among brass workers and gave the disease its first name, «brass founder's disease». Since then, the condition has occasionally been discussed by international authors [7, 24]. The impact of heavy metals on human health increased significantly with industrial advancements in the 20th century. Anthropogenic sources, including but not limited to non-ferrous metallurgy, mining, chemical industries, mineral processing, electroplating, and leather tanning, have posed significant risks through the emission of hazardous metal aerosols. Inhalation of these aerosols often leads to MFF [27].

The first attempt to scientifically explain the pathogenic mechanisms of MFF was made by K. Lehmann in 1910. He hypothesized that zinc, upon entering the lungs, destroys cells and forms complexes with certain proteins released from the cytoplasm, potentially triggering a pyrogenic reaction [7, 16].

The first report of a clinical case involving more than ten episodes of MFF in a 32-year-old welder was presented by A.I. Swiller and H.E. Swiller in 1957. In 1960, two etiopathogenetic theories were proposed that became the most widely accepted. B. Pernis and colleagues attributed the symptoms to the production of endogenous pyrogenic substances by leukocytes, leading them to believe that MFF had a bacterial origin. In the same year, C.P. McCord argued that the symptoms of MFF were driven by immuno-allergic mechanisms [7].

Industrial conditions accounted for MFF in 53% of affected cases [5]. According to the Resolution of the Cabinet of Ministers of Ukraine No. 1662, dated November 8, 2000, «On the Approval

of the List of Occupational Diseases», metal fume fever is recognized as an occupational disease [28].

Although MFF is relatively rare in the general population, its prevalence can reach 25–30% among specific high-risk groups, with repeated episodes occurring in some individuals [7].

Globally, there are over 11 million welders and an additional 110 million workers in other professions exposed to welding fumes [29, 30]. In the 1970s, MFF was fairly common among these workers: 31% of welders aged 20 to 59 experienced at least one episode during their careers. A long-term cohort study revealed a prevalence exceeding 35% after an average of 15 months of occupational exposure [7, 16, 23].

In 2006, approximately 700 reports of metal fume exposure were submitted to U.S. Poison Control Centers (PCC). Of these, only about one-third of the affected individuals sought medical attention, while 73% received no medical treatment other than consultation with the PCC [6].

Between 2006 and 2012, over 3,300 cases of this occupational illness were recorded by the U.S. Toxicology Center, though this number likely underestimates the true incidence. Currently, between 1,500 and 2,500 cases are reported annually in the United States. In the state of Victoria, Australia, a retrospective study identified only 85 cases over the previous 5.5 years, suggesting that the epidemiological characteristics of MFF are often underreported [5, 19, 23, 26].

According to the U.S. Bureau of Labor Statistics, more than 420,000 individuals were employed in work involving heavy metals in 2020, with approximately 2,000 cases of MFF reported among them [16]. However, it is believed that MFF occurs far more frequently than reported, with the actual number of undiagnosed cases significantly exceeding the 2,500 reported annually in the United States [7, 31].

MFF primarily affects the adult population, accounting for 99% of cases, while adolescents of school age represent just 1%. Most patients are male (~96%) compared to female (~3.4%). Cases among children and the elderly (>65 years) are exceedingly rare [5].

Modern industrial advancements and the rapid improvement of mechanical devices have introduced new challenges and led to the emergence of previously unencountered illnesses, such as MFF [24].

Etiology

MFF received its colloquial name due to the significant proportion of cases observed in workers in the non-ferrous metallurgy industry, particularly those involved in the melting and casting of molten brass (an alloy of copper and zinc in various proportions), including under high pressure [7, 15, 21, 25, 26, 32]. Inhalation of metal particles in the form of fine dust is considered a route of occupational pathological exposure [15].

Vanadium pentoxide (V_2O_5) as a byproduct of fossil fuels can be present in significant amounts in the slag of the steel industry (ferrovanadium), in the waste of oil refineries, or in soot from boilers burning fuel oil, as they contain considerable amounts of vanadium [33, 34].

Cobalt is used in the production of lithium-ion batteries for electric vehicles and other machinery, magnets, high-speed cutting tools, and in the manufacture of paints and dyes. Poisoning can occur only when the concentration of cobalt dust in the air exceeds 0.5 mg/m^3. Particularly toxic is the vapor of cobalt octacarbonyl $Co_2(CO)_8$ [35].

Exposure to nickel oxide vapor is a rare cause of MFF [20]. Nickel carbonyl is inhaled during nickel refining and when used as a catalyst [33, 34].

Aluminum and its compounds reach high concentrations in the air of workspaces during melting, mold filling, and stamping processes. It has moderate toxicity. Inhalation of aluminum dust can lead to signs of inflammation in the lungs (decreased lung ventilation, and at high concentrations, severe pneumonia) [17].

Iron oxide fumes can cause «metal fume fever» in blacksmiths, metal workers, and similar professions [36].

According to global statistics, the metal fume fever syndrome is most commonly observed in welders and cutters who join or separate metal parts using flames, electric arcs, and other high-temperature sources. Welders are considered a high-risk group for respiratory signs and symptoms due to their exposure to an aerosol mixture containing various gases, vapors, and particles, depending on the composition of the electrodes, materials, and the welding method used [37]. Approximately one million people worldwide are exposed to chemical, thermal, radiation, and other hazards associated with welding [7]. Inhalation of certain metal oxides freshly formed during welding can lead to MFF [1, 3, 5].

Welding is a common method for joining metals in industrial production, where metals are fused by heating or high-pressure compression with or without the use of a filler metal. Welders employ a variety of techniques. The most common technique is using electric current to generate heat, which melts the metals and facilitates their joining. Among the different welding methods, the most common is arc welding, in which extreme temperatures (>4000°C) produce metal vapors that then cool and condense into an aerosol, which can be inhaled by the personnel [1, 16]. These overheated metals include zinc, iron, cadmium, manganese, chromium, and nickel. The most common cause is ZnO, which forms from molten bronze or galvanized steel, but cadmium, manganese, nickel, chromium, and their oxides are also present in some welding fumes [16]. Fifty percent of MFF cases involved working with galvanized metal, mostly with pipes [6, 26].

Galvanization is the process of applying a zinc coating to steel. This process protects the steel from oxidation, corrosion, and wear [16]. The widespread use of galvanized metal sheets can cause serious issues in mechanical engineering, household services, ventilation systems, water supply, and drainage systems. Research has shown that only about 50% of measurements taken near zinc boilers recorded zinc concentrations below 0.1 mg/m^3 [9, 38]. New technologies, such as thermal metal coatings (nickel, chromium, cadmium), can also pose significant hazards [34, 39].

Solderers use a third metal to join two or more metal objects. Metal fumes are generated during soldering of galvanized steel using aluminum bronze wire and the joining of galvanized steel and aluminum with zinc wire. Soldering is used to join dissimilar metals with the help of a filler, thus forming a strong bond between multiple metals. Solderers and tin-platers (tinkers) apply a thin layer of molten solder or tin to the surface of metal products to protect them from corrosion and wear [14, 16, 25].

The production of bimetallic (mostly copper-aluminum) products using the Wood's alloy (tin 12.5%, lead 25%, bismuth 50%, cadmium 12.5%) by explosive welding (mostly with ammonium nitrate) is widely implemented in global industries [40].

Improvements in the acetylene-oxygen torch have led to remarkable advancements in autogenous welding and have greatly facilitated the art of joining and fragmenting metals [24]. Metal cutters use ionized gas, called plasma, which is also heated to high temperatures, to cut metal objects to specific sizes. Plasma cutters can be used for dismantling large objects, such as ships, railcars, and buildings [16]. During welding, soldering, and flame cutting, a common source of cadmium is the welding rod, hard solder, or metal coating, rather than the base metal itself [33].

Welding and cutting of metal structures (especially non-ferrous metal alloys) pose the greatest health risks to workers, especially when the work is performed in enclosed spaces. There have been cases where MFF occurred in workers cutting or welding pipes while inside a structure [6, 21]. In shipbuilding workplaces, welding operations, particularly in confined spaces, produce significant amounts of dust containing manganese and cadmium oxides [4, 39].

Many metalworkers, including plumbers and pipefitters, who perform intermittent welding work, suffer from MFF. Artists, sculptors, and «do-it-yourselfers» may also occasionally use welding techniques, which can lead to MFF. 86% of those affected are men, and only about half are professional welders [16, 19, 26].

Solderers and jewelers typically work with hard solders and small metal components that need to be precisely positioned, such as transistors, computer chips, and jewelry, and are at risk of inhaling cadmium oxide fumes [34, 39]. Significant toxicity is usually a result of working with metal in an enclosed space with inadequate ventilation [14, 16, 39].

Air pollution also occurs during grinding and cleaning operations. In the production environment, dust containing compounds of copper, manganese, zinc, and arsenic can be created, potentially leading to the onset of MFF [4].

The possibility of developing MFF among workers producing nickel-cadmium, nickel-iron, and nickel-zinc battery cells is minimal, but improper disposal (e.g., artisanal smelting of zinc or lead, which may contain significant levels of cadmium contamination) or burning of waste can have significant negative effects due to inhalation of the resulting smoke [34, 39].

There is pulmonary toxicity associated with ZnO nanoparticles used in liquid matrices for glass coatings [19, 26, 41].

Improper safety practices with powdered raw materials for making white lead and paint pigments can pose a risk. Interestingly, aerosolized ZnO powder does not cause symptoms, whereas fresh ZnO does. This is due to differences in particle sizes. The microconglomerates of aged ZnO powder are much larger than freshly produced ZnO particles [16].

A case of severe acute inhalational lung injury was reported following the aspiration of zinc nanoparticles from a food-grade additive (cake decoration powder) [7, 42].

«Copper fog» is a rare cause of MFF. Bordeaux mixture is a well-known cause of hypersensitivity pneumonitis in grape growers, who are exposed to inhalation during vine spraying [20].

Certain beryllium compounds (beryllium oxide, beryllium sulfate, beryllium chloride, beryllium fluoride) are used in industry for the production of X-ray tubes, fluorescent lamps, beryllium steel hardening, and in the ceramics industry. These compounds enter the body through the lungs as fumes and cause «berylliosis» [4].

Inhalation of manganese fumes is a rare cause of inhalation fever and increases the risk of pneumonia [20, 43].

Tributyl tin, used as a mold and mildew inhibitor, is an acute respiratory irritant when inhaled, with cases of MFF being very rare [33].

Accidental inhalational injury from antimony trichloride, zirconium tetrachloride, titanium tetrachloride, and uranium hexafluoride resulting from explosions, pipe bursts, or leaks in chemical plants may lead to inhalation damage, likely due to the halide ions rather than the metal itself [34].

Osmium tetroxide is a potent respiratory irritant with potential as a chemical weapon, and human experience with its inhalation is limited [33].

Cerium oxide is another potential etiological factor for MFF, raising theoretical concerns due to its potential use as a fuel additive and its ability to cause acute inhalation injury in experiments [33].

In mining operations, the extraction process leads to the release of heavy metals from ore, and their use in industrial processes results in certain elements entering the atmosphere through combustion [27]. The concentration of cadmium significantly increases in the air due to soil degradation caused by volcanic activity [39].

Regarding the risk of MFF associated with the use of firearms, artillery, and rocket weapons, information from publicly available literature sources is significantly limited. However, cases of metal fume fever have been reported following exposure to copper-containing vapors and fine dust in military personnel [25, 32].

Various types of firearms can generate distinct chemical aerosol spectra from the products of a gunshot, and the effect of metal fume generation is primarily caused by water-insoluble components containing high levels of copper and bismuth. These elements have been found during rifle firing. Metals are present in the components of the cartridge, including the primer, casing, explosive mixture, bullet jacket, and even the barrel itself, with copper, antimony, and zinc being common. It is likely that microparticles of copper are formed as a result of micro-fragmentation of the bullet jacket due to the high-speed passage through the rifling, and bismuth vapor is formed from heating the remnants of the barrel cleaning agent [44–46], with small amounts of soot, calcium, silicon, sodium, sulfur, and zinc [47]. During heavy gunfire in closed, poorly ventilated spaces, the concentration of copper particulate matter with a diameter of 0.2–0.5 μm significantly exceeds the occupational exposure limits. The total number of reported symptoms was significantly higher among shooters using non-ethylated ammunition compared to those using ethylated or modified non-ethylated rounds. Although it was found that the general symptoms corresponded to the development of metal fume fever, the respiratory symptoms indicated irritation of the respiratory pathways, differing from those observed in foundry fever [45, 48].

During the detonation of ammunition, part of the energy is converted into heat. The explosive (shattering) effect may be observed only at a close distance from the blast site, where the pressure and energy density of gaseous products are very powerful [49].

With an understanding of the components and contents of ammunition, significant emissions of various pollutants, including heavy metals, can be predicted as a result of their use. The most noticeable pollution, especially from heavy metals, is expected in areas of ammunition storage explosions or when ammunition is burned [46, 50].

Dangerous components found in ammunition include explosives and heavy metals. Mercury fulminate (which contains copper) and trisulfide antimony (antimony) are typically found in detonators [51, 52].

Serious inhalation injury and MFF resulting from high exposure to zinc chloride have been associated with the detonation of smoke grenades in military or similar conditions. The use of smoke screens is common during military exercises. The 1A grenade generates 113 m^3 of zinc chloride smoke in 30 seconds. Inhalation of the aerosol containing zinc chloride can lead to MFF, causing severe acute respiratory distress syndrome, a very dangerous condition with a high mortality rate [34, 53].

The explosion is accompanied by key factors such as an almost immediate release of large amounts of heat and a significant emission of aerosol products [54].

Incendiary, armor-piercing, and armor-piercing tracer ammunition typically have a core made from a heavy metal tungsten alloy (tungsten-nickel-iron), a copper or copper-zinc driving band (to increase shooting range), and the shell is entirely steel with a zinc ballistic tip [55]. It's also important to note that ammunition often includes significant amounts of stabilizing and initiating substanc-

es, such as compounds of tin and bismuth (bismuth oxide, carbonate, and nitrate), strontium nitrate, magnesium powder, etc. [46].

Metals are incorporated into explosive materials to enhance the energy of the explosion [49]. Occasionally, small amounts of metals in the form of fine powders (most commonly aluminum powder) are added as flammable impurities to explosive materials. To improve the water resistance of explosives, structural additives containing chromium salts or other metals are included. Detonating agents may contain aluminum powder (10.7%) and calcium or zinc stearate [56].

When a rocket explodes, metal oxides and combustion products from the rocket's electronics are released into the air. Inhalation of fine particulate matter containing heavy metals can cause MFF [46].

Mechanism of action

MFF is the result of inhaling micro- and nanoparticles of ZnO and other metals that are formed when heated above their boiling points. This depends on the type of metallurgical processes (casting, welding, rolling, etc.) and the level of dust in the atmosphere [7, 8, 16, 50].

ZnO particles formed during welding usually range in size from 20 to 3000 nm, with particles smaller than 5000 nm falling into the respirable fraction, meaning they cannot be filtered out by the cilia of the respiratory tract, potentially leading to diseases in the pulmonary alveoli [7]. The majority of primary particles in various welding aerosols range from 5 to 40 nm, but they tend to form chain-like agglomerates. Generally, metal fumes have a wide particle size distribution: from coarse (2.5–10 μm) to fine (0.1–2.5 μm) and ultrafine (≤0.1 μm) [29]. Fine particles are defined as those ranging from 100 nm to 1000 nm, which enter the cytoplasm of the cell via metal transporters. Ultrafine or nanoparticles are defined as particles ranging from 1 to 100 nm with unique properties, which can cause damage to cells different from larger ZnO particles. Nanoparticles have a high surface-to-mass ratio, and their biological activity is more dependent on their physical properties than on their chemical composition [7]. Fine and ultrafine particles with an aerodynamic diameter of 0.01–1 μm can accumulate in the terminal bronchioles or alveoli and cause harmful effects on the respiratory system [1].

Until recently, it was believed that inhaling nanoparticles of ZnO had a stronger negative impact on health compared to the same mass concentration of its microparticles in the air [9, 16, 38]. This hypothesis has now been refuted. Stronger systemic inflammatory responses after inhaling ZnO microparticles can be explained by their higher pathoeffectiveness of deposition in the airways and a specific mechanism of action of the substance, most likely caused by the formation of zinc ions. In other words, micro-sized metal oxide particles that are inhaled cause significantly stronger pathological effects than nanoparticles [9, 34, 38].

The pyrogenic effect of metal fumes is not related to the specific toxic properties of any particular metal but to its unique, extremely active physical state of extreme dispersity when it enters the respiratory tract. This justifies considering metal fume fever as a manifestation of the nonspecific action of metals [28].

Human lung epithelial cells, under the influence of metal fumes, produce reactive oxygen species, pro-inflammatory cytokines (IL-8), and granulocyte-macrophage colony-stimulating factor (GM-CSF), which activate and recruit immune cells. Particles with a high content of copper and zinc activate endothelial cells through a ROS-mediated mechanism, which triggers immune activation (IL-8, GM-CSF), leukocyte adhesion to the endothelium (soluble intercellular adhesion molecule-1), and also stimulate the secretion of acute-phase protein synthesis regulators (IL-6). In whole human blood, after inhalation exposure to metal fumes, platelet activation (release of soluble cluster of differentiation 40 ligand), homodimer of the B-chain of platelet-derived growth factor, vascular endothelial growth factor A, blood coagulation, and the induced concurrent release of pro-inflammatory cytokines from blood leukocytes, which stimulate thrombogenesis, have been identified [50].

The most acceptable modern hypothesis for the development of MFF is the oxidative stress caused by the inhalation of ZnO [7]. Environmental factors (ultraviolet radiation, relative humidity) and the presence of ZnO nanoparticles and other metals contribute to the formation of hydroxyl radicals through the production of gaseous hydrogen peroxide, which exacerbates the inflammatory reaction to ZnO, thus explaining the activation of free radical oxidation as the nature of MFF development [30]. Although the exact pathophysiology of MFF remains unknown, it is suspected that when welding fume particles settle in the bronchiolar and alveolar regions, they induce local formation of radical oxygen species (ROS). These ROS, through cellular signaling pathways, stimulate the release of pro-inflammatory cytokines (TNF-α, IL-6, and IL-8) by pulmonary macrophages, leading to the development of symptoms observed in MFF [7, 30].

NF-kB is a central mediator of the induction of pro-inflammatory genes, as well as regulating the function of innate and adaptive immune cells, apoptosis, and the activation and differentiation of Th-cells responsible for inflammation. The transcriptional signal of the activated nuclear factor kappa B (NF-kB) plays a key role in the connection between inflammation and oxidative stress. It is usually found in the cytoplasm of nearly all cell types in an inactive form. Its activation occurs through stimuli such as stress, free radicals, oxidized low-density lipoproteins, cytokines, ultraviolet radiation, bacterial or viral antigens. Innate immune cells produce pro-inflammatory mediators such as TNF-α, IL-1β, IL-6, and IL-8, which trigger the main symptoms of MFF in response to NF-kB activation. This process is induced by oxidative stress, caused by the liberation of free radicals through the activation of mitogen-activated protein kinases, which promotes the initiation of a cascade mechanism through the activation of NF-kB transcription factors. Activation of the TNF receptor, pattern recognition receptors (PRR), T-helper cell receptor, B-cell receptor, and various cytokine receptors can also induce the NF-kB cascade mechanism. PRRs, including Toll-like receptors, are located on the surface and cytoplasm of innate immune cells, such as macrophages, neutrophilic granulocytes, and dendritic cells, and are designed to recognize pathogen-associated molecular patterns and damage-associated molecular patterns for pathogen elimination. Thus, the accumulation of ROS in cells ultimately leads to the implementation of a fever response [7]. Comparison of the mechanisms underlying MFF shows that different metals can exhibit pathogenicity through similar pathways, including the production of ROS, enzyme inactivation, and oxidative stress [27].

Metallothionein transport proteins, which are rich in cysteine and primarily localized in the Golgi apparatus, may modulate the response to metal oxides. It is hypothesized that this may influence the clinical response and the development of metal fume fever. The lungs are the primary source of cytokines and the organ most affected by these inflammatory agents [16].

Metal aerosols quickly penetrate the bloodstream and lymphatic system through diffusion or transport as colloids, protein complexes, etc. This results in their resorptive action. In addition to protein denaturation, the release of pro-inflammatory cytokines and activation of neutrophils in the lungs also plays an important role in the pathogenesis of metal fume fever, leading to pulmonary and systemic inflammatory responses [5, 28]. *In vitro* experiments on human lung cells and rat alveolar epithelial cells

showed zinc- and copper-mediated toxicity through the generation of ROS, mitochondrial dysfunction, DNA damage, and induction of apoptosis [14].

The lungs serve only as an entry point, not the site of inflammation [11, 12]. Inhalation of ZnO particles can trigger a series of clinical reactions, increasing the number of polymorphonuclear leukocytes in bronchial lavage fluid, including early increases in pro-inflammatory cytokines such as TNF-α, IL-5, IL-6, IL-8, IL-13, myeloperoxidase, immunoglobulin E, γ-interferon, polymorphonuclear cells, markers of inflammation, and recruitment of inflammatory cells in the lungs, along with pronounced neutrophil infiltration. These reactions were dose- and time-dependent, but not associated with the development of bronchospasm or pulmonary dysfunction [3, 7, 16, 20, 34].

The pathogenesis, clinical manifestations, treatment, prevention, and prognosis will be discussed in Part 2 of the literature review.

References

1. Cha E.W., Jeon D., Kang D. et al. (2022) Chemical Pneumonitis Caused by the Inhalation of Zinc Oxide Fumes in an Arc Welder. Int. J. Envir. Res. Public Health, 19(13): 7954.
2. Girao A., Abreu Fernandes J., Valente L. et al. (2023) Metal Fume Fever: An Underdiagnosis. Cureus, 15(2): e34928. DOI: 10.7759/cureus.34928
3. Wardhana, Datau E.A. (2014) Metal fume fever among galvanized welders. Acta Med. Indones., 46(3): 256–262.
4. Kostyuk I.F., Kapustnyk V.A. (2017) Professional diseases. Textbook. 5th ed. Kyiv, VSV «Medicina», 536 p. (In Ukr.).
5. Wong A., Greene S., Robinson J. (2012) Metal fume fever — a case review of calls made to the Victorian Poisons Information Centre. Aust. Fam. Physician., 41(3): 141–143.
6. Ahsan S.A., Lackovic M., Katner A., Palermo C. (2009) Metal fume fever: a review of the literature and cases reported to the Louisiana Poison Control Center. J. La State Med. Soc., 161(6): 348–351.
7. Szűcs-Somlyó É., Lehel J., Májlinger K. et al. (2023) Metal-oxide inhalation induced fever — Immuntoxicological aspects of welding fumes. Food Chem. Toxicol., 175: 113722.
8. Veillard M., Lasnier G., Jouvenot M. et al. (2018) La fièvre des métaux. Revue des Maladies Respiratoires., 35(5): 587. DOI: 10.1016/j.rmr.2018.05.007. (In Franch).
9. Monsé C., Merget R., Bünger J. et al. (2023) Systemic inflammatory effects of zinc oxide particles: is a re-evaluation of exposure limits needed? Arch. Toxicol., 97(10): 2813–2818.
10. Vogel U., Saber A.T., Jacobsen N.R. et al. (2024) Re-evaluation of the occupational exposure limit for ZnO is warranted. Comments on 'Systemic inflammatory effects of zinc oxide particles: is a re-evaluation of exposure limits needed?' by Christian Monsé et al. Arch. Toxicol., 98(2): 567–569. DOI: 10.1007/s00204-023-03634-w.
11. Krabbe J., Beilmann V., Gerhards B. et al. (2019) The Effects of Repeated Exposure to Zinc- and Copper-Containing Welding Fumes on Healthy Volunteers. J. Occup. Environ. Med., 61(1): 8–15. DOI: 10.1097/JOM.0000000000001455.
12. Krabbe J., Hansen C., Otte N., Kraus T. (2023) Short-term exposure to zinc- and copper-containing welding fumes: Effects on pulmonary function in humans. J. Trace Elem. Med. Biol., 78: 127169. DOI: 10.1016/j.jtemb.2023.127169.
13. Szűcs-Somlyó É., Lehel J., Májlinger K. et al. (2023) Immune response to zinc oxide inhalation in metal fume fever, and the possible role of IL-17f. Sci Rep., 13(1): 22239.
14. Bleidorn J., Alamzad-Krabbe H., Gerhards B. et al. (2019) The pro-inflammatory stimulus of zinc- and copper-containing welding fumes in whole blood assay via protein tyrosine phosphatase 1B inhibition. Sci Rep., 9(1): 1315.
15. Hadrup N., Saber A.T., Jacobsen N.R. et al. (2021) Zink oxid: Videnskabelig dokumentation for en helbredsbaseret grænseværdi [Zinc oxide: Scientific basis for setting a health-based occupational exposure limit]. Det Nationale Forskningscenter for Arbejdsmiljø, København, 58 p. (In Danish).
16. Brenner B.E., Keyes D. (2024) Metal Fume Fever. In: StatPearls. Treasure Island (FL): StatPearls Publishing.
17. Lazarenkov A.M., Ivanov I.A., Sadoha M.A. et al. (2024) Impact of Production Environment and Labor Process Factors on the Body of Foundry Workers. Science and Innovation. Int. Sci. J., 3(4): 285–292. DOI: 10.5281/zenodo.11079174.
18. Reisgen M., Thomas K., Beilmann V. et al. (2020) Increased Neutrophil Granulocyte and Myeloperoxidase Levels Indicate Acute Inflammation Due to the Exposure of Zinc- and Copper-Containing Welding Fumes. J. Occup. Envir. Med., 62(8): 618–627.
19. Greenberg M.I., Vearrier D. (2015) Metal fume fever and polymer fume fever. Clin Toxicol (Phila), 53(4): 195–203. DOI: 10.3109/15563650.2015.1013548.
20. Feary J., Cullinan P. (2022) Heavy Metals. Encyclopedia of Respiratory Medicine (2nd Ed.). ScienceDirect. Elsevier, 458–469.
21. Rishko M.V., Prilypko L.B., Vantyukh N.V., Kedyk A.V. (2023) General concepts of occupational diseases: methodical recommendations. Uzhgorod, UzhNU, 46 p.
22. Corrin B., Andrew G., Nicholson A.G. (2011) Chapter 7 — Occupational, environmental and iatrogenic lung disease. Occupational, environmental and iatrogenic lung disease. Pathology of the Lungs (Third Edition). Churshil Livingstone, 327–399.
23. Antonini J.M. (2014) Health Effects Associated with Welding. ScienceDirect. Elsevier. Comprehensive Materials Processing, 8: 49–70.
24. Pfender C.A. (1914) Brazier`s Disease, Brass-Founder`s Ague, or Acute Brass Poisoning. JAMA, LXII(4): 296–297. DOI: 10.1001/jama.1914.02560290046020.
25. Yordanov Y., Cantin D., Le Guerroué G., Pourriat J.L. (2010) La fièvre des fondeurs, une pathologie presque oubliée [Metal fume fever, an almost forgotten disease]. Ann. Fr. Anesth. Reanim., 29(5): 395–396. DOI: 10.1016/j.annfar.2010.03.007.
26. Greenberg M.I., Vearrier D. (2022) Foundry fever and fluoroplastic fever. www.msdmanuals.com/uk/professional/special-subjects/occupational-and-environmental-medicine/metal-fume-fever-and-polymer-fume-fever. (In Ukrainian).
27. Abd Elnabi M.K., Elkaliny N.E., Elyazied M.M. et al. (2023) Toxicity of Heavy Metals and Recent Advances in Their Removal: A Review. Toxics., 11(7): 580.
28. Tkachyshyn V.S. (2023) Metal Fever. Ukr. Pulmonol. J., 31(4): 56–59.
29. Taj T., Gliga A.R., Hedmer M. et al. (2021) Effect of welding fumes on the cardiovascular system: a six-year longitudinal study. Scand. J. Work Envir. Health, 47: 52–61.
30. Suárez G., Niculita-Hirzel H., Correia D. et al. (2022) A proposed synergetic mechanism for metal fume fever involving ZnO and Fe3O4 nanoparticles. Sci. Rep., 12(1): 15643.
31. Kooistra J., de Hosson S.M. (2012) Metaaldampkoorts, vaak niet herkend [Metal fume fever, often unrecognized]. Ned. Tijdschr. Geneeskd., 156(32): A4171.
32. Møller L.B., Aaseth J. (2022) Handbook on the Toxicology of Metals (Fifth Edition) Volume II: Specific Metals. Chapter 10 — Copper., 243–266.
33. Blanc P.D. (2016) Murray and Nadel's Textbook of Respiratory Medicine (6th Ed.). ScienceDirect. Elsevier, 1–68.
34. Nemery B. (2022) Chapter 19. Metals and the respiratory tract. Handbook on the Toxicology of Metals (5th Ed.). Volume I: General Considerations, p. 421–443.
35. Arustamian O.M., Tkachyshin V.S., Arustamian Yu.A. et al. (2022) Features of cobaltand its compounds intoxication. Emergency Medicine (Ukraine), 18(1): 6–11. DOI: 10.22141/2224-0586.18.1.2022.1452. (In Ukrainian).
36. Pohanish R.P. (2015) Short Term Exposure. Sittig's Handbook of Pesticides and Agricultural Chemicals (Second Edition). William Andrew Publishing, 383–457.
37. Wittczak T., Walusiak J., Pałczyński C. (2009) Choroby układu oddechowego u spawaczy [Welding-related respiratory diseases]. Med. Pr., 60(3): 201–208.
38. Monsé C., Raulf M., Jettkant B. et al. (2021) Health effects after inhalation of micro- and nano-sized zinc oxide particles in human volunteers. Arch. Toxicol., 95: 53–65.
39. Koons A.L., Rajasurya V. (2024) Cadmium Toxicity. In: StatPearls. Treasure Island (FL): StatPearls Publishing.
40. Shlionsky P.S. (2020) Explosion welding of copper-aluminum pipes according to the «reverse scheme». Automatic welding, 8: 51–53. DOI: 10.37434/as2020.08.08.
41. Saber A.T., Hadrup N., Williams A. et al. (2022) Unchanged pulmonary toxicity of ZnO nanoparticles formulated in a liquid matrix for glass coating. Nanotoxicology, 16(6–8): 812–827. DOI: 10.1080/17435390.2022.2152751.
42. Moss J., Sinha A., Messahel S., Grime C. (2022) Acute inhalation lung injury secondary to zinc and copper aspiration from food contact dust. BMJ Case Rep., 15: e250152.
43. Shumygay I.V., Yermishev O.V., Manishevska N.M. (2021) Ecological assessment of heavy metal contamination of underground waters of Kyiv region. Agroecol. J., 1: 88–97.
44. Aurell J., Holder A.L., Gullett B.K. et al. (2024) Gas and particle emissions from rifle and pistol firing. J. Hazard Mater., 476: 135196. DOI: 10.1016/j.jhazmat.2024.135196.
45. Kim Y.H., Vance S.A., Aurell J. et al. (2022) Chemistry and lung toxicity of particulate matter emitted from firearms. Sci. Rep., 12(1): 20722.

46. Angurets O., Khazan P., Kolesnikova K. et al. (2023) Ukraine, damage to the environment, ecological consequences of the war. Electronic popular scientific edition. 84 p.
47. McNeilly R., Kirsh J., Hatch J. et al. (2022) Comprehensive characterization of firing byproducts generated from small arms firing of lead-free frangible ammunition. J. Occup. Environ Hyg., 19(3): 169–184. DOI: 10.1080/15459624.2021.2023162.
48. Voie Ø., Borander A.K., Sikkeland L.I. et al. (2014) Health effects after firing small arms comparing leaded and unleaded ammunition. Inhal. Toxicol., 26(14): 873–879.
49. Buller M.F., Robotko V.A. (2022) Explosive production technologies: a course of lectures. Sumy: Sumy State University, 211 p. (In Ukrainian).
50. Elfsmark L., Ekstrand-Hammarström B., Forsgren N. et al. (2022) Characterization of toxicological effects of complex nano-sized metal particles using in vitro human cell and whole blood model systems. J. Appl. Toxicol., 42(2): 203–215.
51. Vergin Y. (2023) War in Ukraine: how ammunition poisons the soil. Nature and ecology. Ukraine.
52. Gaponenko G.M. (2011) Underwater blasting: a tutorial. Kamianets-Podilskyi, 196 p.
53. Mahboob H., Richeson Iii R., McCain R. (2017) Zinc Chloride Smoke Inhalation Induced Severe Acute Respiratory Distress Syndrome: First Survival in the United States with Extended Duration (Five Weeks) Therapy with High Dose Corticosteroids in Combination with Lung Protective Ventilation. Case Rep. Crit. Care, 2017: 7952782.
54. Barbashyn V.V., Nazarov O.O., Ryutyn V.V., Tolkunov I.O. (2010) Basics of organizing pyrotechnic works. Study guide/Ed. V.P. Sadkovoy. Kharkiv: VRVD UTSZU, 353 p.
55. Evans R., Seddon B., Charapich J. (2022) Explosive Ordnance Manual for Ukraine. 2nd Ed. Geneva. Switzerland: GICHD, 224 p. (In Ukrainian).
56. Symanovych G.A., Khomenko O.E., Kononenko M.M. (2014) Destruction of rocks by explosion: training. manual Dnipro: NGU, 270 p. (In Ukrainian).

Лихоманка парів металів (огляд). Частина I

О.В. Кравець, В.В. Єхалов, В.А. Сединкін, Д.А. Кріштафор, Д.В. Миронов, О.В. Коврига

Дніпровський державний медичний університет, Дніпро, Україна

Анотація. Лихоманка парів металів (ЛПМ) — гострий лихоманковий синдром, спричинений вдиханням аерозолів оксидів металів, класифікований як гостре професійне захворювання, що уражує таких працівників, як ливарники кольорових металів, зварювальники, гальванізатори та лудильники. Найпоширенішою причиною є пара оксиду цинку, що утворюється з розплавленої бронзи, латуні або оцинкованої сталі. Однак кадмій, марганець, нікель, хром та їхні оксиди також наявні в деяких зварювальних парах. Порівняння механізмів розвитку ЛПМ показує, що аерозолі різних металів можуть виявляти патогенність, включаючи продукцію активних форм кисню, інактивацію ферментів та оксидативний стрес. Цей синдром відрізняється від інгаляційного отруєння. Мікрочастинки металу швидко проникають у кровотік і лімфатичну систему шляхом дифузії або транспорту у вигляді колоїдів або білкових комплексів, спричиняючи системну резорбтивну дію. Крім денатурації білка, вивільнення прозапальних цитокінів і активація нейтрофілів у легенях відіграють значну роль у патогенезі ЛПМ, що призводить до легеневих і системних запальних реакцій. Потрапляння мікрочастинок металу в дихальну систему та їх подальший системний розподіл можуть спровокувати запальні процеси, в результаті яких виникає лихоманковий синдром. Легені служать лише точкою входу, а не основним місцем запалення. Вдихання частинок оксиду цинку може спровокувати різні клінічні реакції, такі як збільшення кількості поліморфноядерних лейкоцитів у рідині бронхоальвеолярного лаважу та раннє підвищення рівня прозапальних цитокінів, таких як фактор некрозу пухлини-α, інтерлейкін-5, -6, -8, -13, мієлопероксидази, імуноглобуліну Е, γ-інтерферону та поліморфноядерних клітин. Воно також індукує маркери запалення, рекрутинг запальних клітин у легенях і виражену інфільтрацію нейтрофілів. Ці відповіді залежать від часу та дози щодо етіологічного фактора, але не пов'язані з бронхоспазмом або легеневою дисфункцією.

Ключові слова: металеві аерозолі, професійне захворювання, мікрочастинки оксидів металів, лихоманка парів металів.

Information about authors:

Kravets Olha V. — MD, PhD, Professor, Head of the Department of Anesthesiology, Intensive Care and Emergency Medicine, Faculty of Postgraduate Education, Dnipro State Medical University, Dnipro, Ukraine. orcid. org/0000-0003-1340-3290

Yekhalov Vasyl V. — PhD in Medicine, Associate Professor, Department of Anesthesiology, Intensive Care and Emergency Medicine, Faculty of Postgraduate Education, Dnipro State Medical University, Dnipro, Ukraine. orcid.org/0000-0001-5373-3820

Sedinkin Vladyslav A. — PhD in Medicine, Associate Professor, Department of Anesthesiology, Intensive Care and Emergency Medicine, Faculty of Postgraduate Education, Dnipro State Medical University, Dnipro, Ukraine. orcid. org/0000-0002-8894-1598

Krishtafor Daria A. — PhD in Medicine, Assistant at the Department of Anesthesiology, Intensive Care and Emergency Medicine, Faculty of Postgraduate Education, Dnipro State Medical University, Dnipro, Ukraine. orcid.org/0000-0003-0942-4099

Myronov Denys V. — PhD in Medicine, Assistant at the Department of Anesthesiology, Intensive Care and Emergency Medicine, Faculty of Postgraduate Education, Dnipro State Medical University, Dnipro, Ukraine. orcid.org/0009-0003-3769-7585

Kovryha Olena V. — Resident Doctor at the Department of Anesthesiology, Intensive Care and Emergency Medicine, Faculty of Postgraduate Education, Dnipro State Medical University, Dnipro, Ukraine. orcid. org/0009-0007-4778-7823

Інформація про авторів:

Кравець Ольга Вікторівна — докторка медичних наук, професорка, завідувачка кафедри анестезіології, інтенсивної терапії та медицини невідкладних станів факультету післядипломної освіти Дніпровського державного медичного університету, Дніпро, Україна. orcid. org/0000-0003-1340-3290

Єхалов Василь Віталійович — кандидат медичних наук, доцент кафедри анестезіології, інтенсивної терапії та медицини невідкладних станів факультету післядипломної освіти Дніпровського державного медичного університету, Дніпро, Україна. orcid. org/0000-0001-5373-3820

Сединкін Владислав Анатолійович — кандидат медичних наук, доцент кафедри анестезіології, інтенсивної терапії та медицини невідкладних станів факультету післядипломної освіти Дніпровського державного медичного університету, Дніпро, Україна. orcid. org/0000-0002-8894-1598

Кріштафор Дар'я Артурівна — кандидатка медичних наук, асистентка кафедри анестезіології, інтенсивної терапії та медицини невідкладних станів факультету післядипломної освіти Дніпровського державного медичного університету, Дніпро, Україна. orcid. org/0000-0003-0942-4099

Миронов Денис Володимирович — кандидат медичних наук, асистент кафедри анестезіології, інтенсивної терапії та медицини невідкладних станів факультету післядипломної освіти Дніпровського державного медичного університету, Дніпро, Україна. orcid. org/0009-0003-3769-7585

Коврига Олена Василівна — лікарка-інтерністка кафедри анестезіології, інтенсивної терапії та медицини невідкладних станів факультету післядипломної освіти Дніпровського державного медичного університету, Дніпро, Україна. orcid.org/0009-0007-4778-7823

Надійшла до редакції/Received: 30.12.2024

Прийнято до друку/Accepted: 07.01.2025