

# Metal Fume Fever among Galvanized Welders

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## ABSTRAK

Demam uap logam/metal fume fever (MFF) adalah sindroma demam inhalasi pada tukang las baja seng, yang menggabungkan dan memotong komponen-komponen logam dengan menggunakan lidah api atau percikan listrik dan sumber panas lainnya. Inhalasi oksida logam tertentu yang baru saja terbentuk akibat proses pengelasan dapat menyebabkan MFF sebagai suatu penyakit akut swasirna yang menyerupai flu (acute self-limiting flulike illness). Penyebab MFF yang paling umum adalah inhalasi seng oksida (ZnO). Inhalasi partikel ZnO dapat mencetuskan sejumlah respons klinis yang disertai oleh perubahan komposisi cairan bilasan bronkoalveolar/ bronchoalveolar lavage (BAL) fluid, yang meliputi peningkatan sitokin pro-inflamasi dini, penanda inflamasi dan rekrutmen sel-sel inflamasi di paru-paru. MFF ditandai oleh demam, batuk, pengeluaran dahak, mengi, sesak di dada, lelah, menggigil, demam, mialgia, batuk, dispnea, leukositosis dengan pergeseran ke kiri, rasa haus, rasa metalik dan salivasi. Diagnosis MFF didasarkan pada temuan klinis dan riwayat pekerjaan. Gejala menyembuh spontan. Pengobatan MFF sepenuhnya bersifat simptomatik, tidak ada pengobatan khusus yang diindikasikan untuk MFF. Tatalaksana utama MFF adalah pencegahan paparan selanjutnya dari unsur logam yang membahayakan; termasuk membangun kesadaran masyarakat dan para dokter tentang MFF agar dapat mengurangi tingkat kejadian penyakit ini.

**Kata kunci:** demam uap logam, seng oksida, inflamasi, pencegahan.

## ABSTRACT

The metal fume fever (MFF) is an inhalation fever syndrome in welders of galvanized steel, who join and cut metal parts using flame or electric arc and other sources of heat. Inhalation of certain freshly formed metal oxides produced from welding process can cause MFF as an acute self-limiting flulike illness. The most common cause of MFF is the inhalation of zinc oxide (ZnO). The inhalation of ZnO particles can provoke a number of clinical responses of which accompanied by changes in composition of bronchoalveolar lavage (BAL) fluid, including early increase in pro-inflammatory cytokines, inflammatory marker, and recruitment of inflammatory cells in the lungs. The MFF is characterized by fever, cough, sputing, wheezing, chest tightness, fatigue, chills, fever, myalgias, cough, dyspnea, leukocytosis with a left shift, thirst, metallic taste, and salivations. The diagnosis of MFF diagnosis is based on clinical finding and occupational history. The symptoms resolved spontaneously. The treatment of MFF is entirely symptomatic, no specific treatment is indicated for MFF. The mainstay of management of MFF is prevention of sub-sequent exposure to harmful metals. Including public and physician awareness of MFF may help to reduce the occurrence of the disease.

**Key words:** metal fume fever; zinc oxide, inflammation, prevention.

## INTRODUCTION

Metal fume fever (MFF) is an inhalation fever syndrome long recognized in metal workers. It was first described in the mid-1800 as brass founders' ague in brass foundry workers, and in 1900s in welders of galvanized steel (the metallurgical combination of zinc and steel as the corrosion protection), particularly in the shipyard industry.<sup>1</sup> The international standard classification of occupations (ISCO) defined welders are workers who join and cut metal parts using flame or electric arc and other sources of heat.<sup>2</sup> Inhalation of certain freshly formed metal oxides, produced from welding process, can cause MFF, an acute self-limiting flulike illness.

The most common cause of MFF is the inhalation of ZnO, which is generated from molten bronze or welding galvanized steel.<sup>3</sup> It is estimated that more than 700,000 workers in the United States are involved in welding operations, so the potential for inhalational exposure and MFF is great. An estimated minimum of 1,500-2,000 cases of MFF occur each year in the United States.<sup>4,5</sup> A prevalence of 31% for MFF and a prevalence of over 35% was reported, but an exact definition was not provided.<sup>5</sup> When zinc is heated to its melting point, zinc oxide fumes are generated, The particle size of the generated fumes ranges from 0.1-1.0  $\mu\text{m}$  in diameter, although aggregation with the formation of larger particles occurs readily. The underlying pathogenesis of MFF is not completely understood, although there is evidence from controlled human exposure studies that zinc oxide fume inhalation induces leukocytes recruitment to the lungs with an associated release cytokines, which causes systemic symptoms.<sup>3</sup>

The diagnosis of MFF is based on clinical finding and occupational history. The symptoms resolved spontaneously. The MFF linked with inhalation of fumes of ZnO is characterized by fever, cough, sputing, wheezing, chest tightness, fatigue, chills, fever, myalgias, cough, dyspnea, leukocytosis with a left shift, thirst, metallic taste, and salivations. The treatment of MFF is entirely symptomatic, no specific treatment is indicated for MFF.<sup>5-7</sup> Prevention relies on appropriate engineering controls and/or personal

protective equipment to reduce exposure. There are no good data on the long term sequelae of repeated exposures.<sup>3</sup>

## PATHOGENESIS

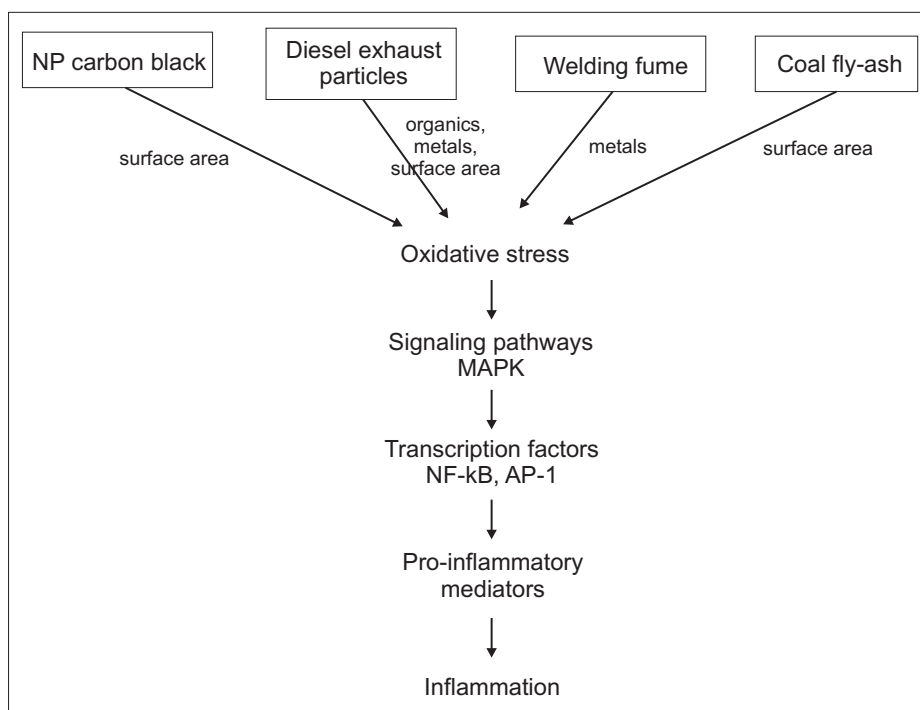
The ZnO is a common constituent of particulate air pollution and if inhaled in fine or ultra-fine fractions with a particle size smaller than 0.5 $\mu$ -1 $\mu$  and at a concentration exceeding 500  $\mu\text{g}/\text{m}^3$  for 2 hours can induce acute systemic effects.<sup>6</sup> A severe acute inflammation of peripheral bronchoalveolar structures following zinc fume is sign by a distinct increase of the total cell count and number of the polymorphonuclear (PMN) leukocytes. There are several hypothesis of the MFF's pathogenesis, such as the release of endogenous pyrogens from leukocytes, and the production of metal proteinases (composed of the inhaled particles and the damaged pulmonary tissue) that are recognized as antigens and lead to the formation of allergen-antibody complexes which cause the clinical symptoms, but the precise mechanism is still un-clear.<sup>6,7</sup>

Inhalation of ZnO particles can provoke a number of clinical responses of which accompanied by changes in composition of BAL fluid, including early increase in tumor necrosis (TNF)- $\alpha$  followed by interleukine (IL)-8 and IL-6, matrix metalloproteinase (MMP)-9, myeloperoxidase (MO),  $\alpha$ 2-macroglobulin levels, and numbers of PMN. There is also an increase in C-reactive protein (CRP) in blood.<sup>6,8</sup> The cytokine networking mediated by the release of pro-inflammatory cytokines by pulmonary macrophages causes both local pulmonary inflammatory cellular (neutrophils recruitment) and systemic response, and also increased of reactive oxygen species (ROS) production.<sup>9</sup> The IL-8 level peaked at 8 hours whereas IL-6 value steadily increased with the time after exposure and reached a maximum concentration at 22 hours. The TNF- $\alpha$  level is elevated as soon as 3 hours after exposure, and it plays a large role in the initial response of MFF, whereas IL-6 and IL-8 are likely involved in the later response. The TNF- $\alpha$  also has been shown to induce IL-8 production.<sup>6,10</sup> The mechanism by which zinc may induce cell signaling, nuclear translocation of nuclear factors in the cytokines

production, is not clear. It is postulated that zinc-induced pulmonary inflammation may involve endothelial growth factor receptor-mediated activation of mitogen-activated protein kinase (MAPK).<sup>11</sup>

The ZnO contained in the welding fume is likely to be deposited in the bronchiolar and alveolar regions of the lungs, and will generate more free radical activity leading to oxidative stress, of which one pathway is the formation of ROS, and thus induce a greater inflammatory response.<sup>12</sup> The high level of ROS cause a change in the redox status of the cell, thereby triggering a cascade of events associated with inflammation and, at higher concentrations, apoptosis. Typically ROS are formed in cells through the reduction of oxygen by biological reducing agents such as reduced nicotinamide adenine dinucleotide (NADH) and reduced nicotinamide adenine dinucleotide phosphate (NADPH).<sup>13</sup> The oxidative stress is leading to activation of MAPK-dependent nuclear factor-kappa beta (NF- $\kappa$ B), protein kinase C (PKC), and activator protein (AP)-1 (Figure 1).<sup>10,14</sup>

The lung is an important source of inflammatory cytokines as well as the target organ for the effects of these mediators.<sup>14</sup> The acute effects of the exposure to Zn results in activation of the extra-cellular signal-regulated kinase (ERK), c-Jun NH2-terminal kinase (JNK) as a member of AP-1, and p38 MAPK pathways.<sup>15</sup> The MAPKs are an important group of serine or threonine signaling kinases that play a major role in converting mitogenic and stress stimuli into nuclear responses. Three major groups of MAPK have been identified. The ERK1 and ERK2 pathways transmit signals due to mitogenic and differentiation stimuli. The JNK and p38 pathways transmit stress signals resulting from oxidative stress or stimulation with inflammatory cytokines, such as TNF- $\alpha$  which may induce phosphorylation of p50 and p65 sub-units of NF- $\kappa$ B. Activation of these signal transduction pathways leads to either phosphorylation of transcription factors in the nucleus or translocation of nuclear factors, such as NF- $\kappa$ B, to turn affect gene expression.<sup>16</sup>



**Figure 1.** The different components of different combustion-derived nanoparticles can cause oxidative stress that acts through well-documented redox-sensitive pathways, such as MAPK and NF- $\kappa$ B, to cause inflammation.<sup>14</sup>

The activation of the p38 MAPK pathway is critical for many immune response-related functions, including T-cell differentiation and death, macrophage and neutrophils effector functions (e.g., respiratory burst, granular exocytosis, etc.), and the production of pro-inflammatory cytokines including TNF- $\alpha$ . There are 4 isoforms of p38 MAPK: p38 $\alpha$ , p38 $\beta$ , p38 $\delta$ , and p38 $\gamma$ ; and it seems that p38 $\alpha$  and/or p38 $\beta$  is responsible for induction of TNF- $\alpha$  and IL-6 mRNA.<sup>17,18</sup> The c-Jun and the activating transcription factor (ATF)-2 proteins are known targets of JNK kinase family members, and are phosphorylated on residues within the N-terminus trans-activation domain. The trans-activation activation of ATF-2, as a substrate for p38 MAPK, is regulated post-translationally by phosphorylation, particularly by the JNK and p38 group of MAPK, after exposure to cellular stress. The ATF-2 has also been implicated in mediating a transcriptional response to c-Jun promoter, and may interact with NF- $\kappa$ B in a DNA-independent manner, leading to increase transcriptional activity.<sup>19,20</sup> The ZnO exposure may increase the binding of p65 of the NF- $\kappa$ B to IL-8 gene promoter and also increased the phosphorylation of p65 at ser276 and ser536.<sup>21,22</sup>

### CLINICAL PRESENTATION

The MFF has been defined as a “flulike” illness that develops after inhalation of metal fumes. The clinical symptoms of MFF begin in 3-10 hours after exposure to ZnO in welding fume. The workers develop tachyphylaxis, that is symptoms appear only when the exposure, not when there are regular repeated exposures.<sup>3,5</sup> Moreover, as MFF can be experienced on the first day by a new employee in the welding profession, without any latency, whereas airway obstruction and respiratory symptomatology require some latency periods, it is conceivable that MFF, occurring shortly after exposure, could be a risk factor for the further development of respiratory symptoms and/or increased bronchial responsiveness.<sup>5</sup>

Initially, there may be a sweet metallic taste in the mouth associated with throat irritation, accompanied by a worsening dry cough and shortness of breath. Fever and shaking chills

often develop and the worker feels ill.<sup>3,5</sup> The principle elements of the systemic symptoms according to the clinical description of MFF, included the following: history of a particular taste in the mouth (such as a sweet metallic taste), flue-like symptoms (such as fever, feeling of flue, general malaise, chills), myalgia, arthralgia, throat symptoms (such as dry, itchy, or constricted throat, dry cough, hoarseness), digestive symptoms (such as loss of appetite, nausea, abdominal cramps), fatigue (such as weakness, yawning, difficulty concentrating), and history of respiratory symptoms (such as wheezing, chest tightness, shortness of breath, and cough).<sup>4</sup> A case study of MFF in 25 year old male welder with MFF showed that he was suffering from aseptic meningitis with pericarditis, pleuritis, and pneumonia.<sup>6</sup>

### DIAGNOSTIC PROCEDURES

The ZnO welding fumes were associated with a marked-dependent increase in the number of polymorphonuclear leukocytes recovered in BAL fluid in 22 hours following exposure, although it was not associated with a clinically significant change in pulmonary function or airway reactivity.<sup>6</sup> In non-smokers, welding fume exposure was associated with a mean increase in white blood cell (WBC) count by  $0.8 \times 10^3/\mu\text{l}$ . Likewise, neutrophil counts in non-smokers increased by  $1.0 \times 10^3/\mu\text{l}$ , indicating that the increase in WBC count following exposure may be mostly attributable to the increased neutrophil counts. The acute exposure to welding fume is associated with the increased levels of systemic inflammatory markers. Additionally, smoking is found to modify the effect of welding fume on specific inflammatory markers. Immediately following welding fume exposure, non-smokers experience a significant increase in circulating WBC counts, specifically absolute and relative neutrophil counts, and a significant decrease in fibrinogen level. Sixteen hours after exposure, both non-smokers and smokers will experience significantly increased levels of CRP.<sup>23</sup>

The chest roentgenogram of MFF is usually normal but may show bilateral pulmonary infiltrates.<sup>24</sup> A study in New Zealand in 1996, found that an acute decrease in FEV1 was more

prevalent among welders than the comparison group of non-welders, and more common among welders without local exhaust ventilation.<sup>23</sup> Another study in Denmark between 1987 and 2004 among 68 steel welders and 32 non-welding production workers, found that long-term exposure to welding emissions may accelerate the age-related decline of lung function but at exposure level levels in range of 1.5 to 6.5 mg/m<sup>3</sup> the average annual excess loss of FEV1 is un-likely to exceed 25 ml in smokers and 10 ml in non-smokers.<sup>23,25</sup>

The definitive diagnosis of MFF is based on clinical findings and is confirmed by the occupational history combined with the rapid resolution of the symptoms which generally peak at 18 hours and resolve spontaneously with complete resolution of abnormalities within 1-2 days.<sup>3,24</sup> The differential diagnosis includes common respiratory viral diseases, inhalation injury from polymer fumes or smoke, and true chemical pneumonitis following exposure to fumes from cadmium, manganese, mercury, or nickel. In the later cases, the condition is progressive and sometimes complicated by non-cardiogenic pulmonary edema.<sup>24</sup>

## TREATMENT AND PREVENTION

The treatment of MFF is entirely symptomatic. The treatment including the control of elevated body temperature by anti-pyretics, analgetics, and oxygen therapy for hypoxemia may be required.<sup>3,24</sup> The mainstay of management of MFF is prevention of sub-sequent exposure to harmful metals. Including public and physician awareness of MFF may help to reduce the occurrence of the disease.<sup>24</sup>

The respiratory protective devices are used in only 20-30% of the work situations where they are needed, and this was attributed to environmental conditions, physical work demands, psychological and social factors, and the individual characteristic of the wearer.<sup>26</sup> There is occupational exposure limits (OELs), as the maximum permissible concentration of a hazardous substance that most healthy adults may be repeatedly exposed to without suffering adverse health effects. There maybe increased risk, for example, for a smoker, a person with

pre-existing health problems or individuals who suffer from allergies. The OELs are often assigned three values. One value is based on normal working conditions of 8 hours per day, over an average lifetime of exposure. If more than 8 hours are worked, this value must be adjusted. A second value provides a limit for 15 minutes, short term exposure. This is a value to which a worker may be exposed for 15 minutes, a maximum of 4 times per shift, with at least 1 hour between exposures. In this case, the 8 hour OEL can not be exceeded. A third value is the ceiling limit. This limit must never be exceeded. If one or more than one type of contaminant is present, as in most welding situations, and the effects of exposure to each is similar, an exposure limit for the mixture is calculated. This value is lower than the limits set for exposure to individual contaminants. The amount of exposures are measure in parts-per-million (ppm) or milligrams per cubic meter (mg/m<sup>3</sup>), using sophisticated instruments and techniques.<sup>27</sup>

The ways to avoid hazard from welding, are by keeping the head out the fumes, do not breath the fumes, use enough ventilation, exhaust at the arch or both to keep fumes and gases from the breathing zone and the general area (**Figure 2** and **3**), if adequacy of the ventilation or exhaust is un-certain or not used than approved respirators or air-supplied should be worn to remove the fumes from breathing zone, wear protective work clothing, and wash thoroughly immediately after exposure to ZnO.<sup>27,28</sup> The steps to reduce the welding fumes and gases are by substituting less hazardous flux materials, introducing engineering control by using enclosures and improving ventilation, developing administrative controls, such as implementing work-rest, and wearing respiratory protection.<sup>28</sup>

There is need for proper education of this economically viable group on workplace hazards, the types and proper use of the different protective devices in order to safeguard the welders health. There is also need for a strong welder's union that should make adequate and proper representation to the appropriate tier of government. The ministry of labour in conjunction with the ministry of health should collaborate to provide health care for this group



**Figure 2.** Enough ventilation, exhaust at the arc, or both, to keep fumes and gases from your breathing zone and the general area.<sup>28</sup>



**Figure 3.** The portable exhaust ventilation unit. These units moved 740 cubic ft. of air per minute and were positioned to pull the fume out of the welder's breathing zone. The units are lightweight and are easily manipulated by employees. The combination of local exhaust and general ventilation reduced the amount of welding fume exposure by 51 percent.<sup>28</sup>

of workers, as close as possible to where they live and work, in keeping with one of the principles of the primary health programme.<sup>2</sup>

## CONCLUSION

Metal fume fever (MFF) is a disease caused by inhalation of certain freshly formed metal oxides, most common cause is the inhalation of ZnO. It is an acute self-limiting flulike illness, marked by changes in composition of bronchoalveolar lavage (BAL) fluid, including early increase in pro-inflammatory cytokines, inflammatory marker, and recruitment of inflammatory cells in the lungs. It may be accompanied by leukocytosis

and reduced in lung function, especially in those who have repeated exposure and smoking. The treatment of MFF is entirely symptomatic and rest. The mainstay of management of MFF is prevention of sub-sequent exposure to harmful metals. Including public and physician awareness of MFF may help to reduce the occurrence of the disease.

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