THESIS

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Literature review on Metal Fume Fever: a critical review of the theories of pathomechanism.

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1. List of abbreviations

ASAT	Aspartate aminotransferase
BAL	Bronchoalveolar lavage
Caspase	Cysteine-dependent aspartate specific protease
CPK	Creatine phosphokinase
Cyt-c	Cytochrome-c
ECG	Electrocardiogram
EDTA	Ethylenediamine tetraacetic acid
ENT	Ear, Nose, and Throat
FNB	Food and Nutrition Board of the National Academies of Sciences Engineering, and Medicine
ICP-AES	Inductively coupled plasma atomic emission spectroscopy
IL-1	Interleukin-1
IL-6	Interleukin-6
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
LETH	Lysosome-enhanced Trojan horse
LDH	Lactate dehydrogenase
MFF	Metal fume fever
MOMP	Mitochondrial outer membrane permeability
NP	Nanoparticle
OEL	Occupational exposure limit
PFF	Polymer fume fever

PFT	Pulmonary function testing
RAST	Radioallergosorbent test
SAA	Serum amyloid A
ROS	Reactive oxygen species
TEM	Transmission electron microscopy
TNF-α	Tumor necrosis factor α
TP	Total protein
TrxR	Thioredoxin reductase
UV	Ultraviolet light
ZnONPs	Zinc oxide nanoparticles

2. Introduction

Metal fume fever (MFF) is a disease that has had various names throughout history. Namely, it is also known as brazier's disease, spelter shakes, the galvanizer's poisoning, brass chills, zinc chills, welder's ague, smelter's chills, copper fever, Monday morning fever, and foundry fever [1]. It results from the inhalation of heavy metal, mainly zinc oxide nanoparticles (ZnONPs) that lead to inflammation of lung tissues. This disease occurs after inhalation of subtoxic doses of nanoparticles for a prolonged period of time. This is a pathology that is poorly understood and underdiagnosed in the field of pneumology, although it could be effectively controllable by simple prevention methods [2].

Despite being underdiagnosed, MFF is not rare among welders and others smelter and metal workers [3]. Within hours after exposure, symptoms start to appear: a fever of 39-40 ° C, chills, myalgia, chest pain, upper airway irritation, cough, chest tightness, metallic taste in the mouth, leukocytosis, and headaches. Lung auscultation and additional examinations (X-ray, PTF) are generally normal. The diagnosis of MFF is troublesome in light of the fact that these clinical features are similar to various other respiratory diseases, such as respiratory viruses including influenza or the common cold [4].

MFF is usually a benign self-limited disease. Indeed, the symptoms typically appear within 48 hours of exposure and resolve after 1–2 days following cessation of exposure [5]. So, its evolution is generally favorable within 24 to 48 hours. Nonetheless, severe cases of the disease have been reported. There is also a severe form of MFF, such as secondary exposure to military fumes [3]. Apart from this, a tolerance phenomenon is described, this tachyphylaxis is especially present in patients with ongoing metal fume exposure over the course of a workweek. Among them, there's an attenuation of symptoms during regular exposure. Usually, the most severe symptoms may reappear after a subsequent exposure or typically after a pause from exposure over the weekend, hence one of the disease's names is 'Monday morning fever'. This tolerance would therefore be short-term [6].

Taking a thoughtful anamnesis of the occupational history in patients that present the above-mentioned symptoms is critical to make a diagnosis. In fact, identifying MFF is made especially difficult considering the low frequency, the non-specific symptomatology

of this disease, and the lack of specific laboratory tests. Symptoms usually resolve on their own or with symptomatic treatment within 3 to 5 days [7]. Such treatments include bed rest, analgesics, hydration, and antipyretic. However, the backbone of treatment lies in prevention. In fact, forestalling subsequent exposure to harmful metals is primordial. For instance, symptoms may disappear after putting on a protective mask during work activities.

On the other hand, a twin disease to MFF is Polymer fume fever (PFF), which has similar clinical effects, onset, and duration of effects to those of MFF. It appears following the inhalation of fluorinated polymer decomposition products. One of the most common causes is overheating polytetrafluoroethylene, which can be found as coating on cookware. In particular, the famously trademarked one known as Teflon®. To distinguish between diseases, the diagnosis is based on the mechanisms of their exposure. In the case of MFF, it occurs most commonly as an occupational disease among welders and other metal workers. Whereas PFF was also initially identified as an occupational disease, but thanks to the strengthening of regulations, there has been a decrease in incidences in the work environment. As alluded to earlier, nowadays the most common cause of PFF is due to household air pollution, more specifically following the overheating of Teflon®-coated cookware or other fluorinated polymers [3]. Accordingly, by looking at the clinical presentation itself, it is impossible to distinguish MFF from PFF, only the anamnesis of the exposure history can discern the two diseases.

Nanoparticles are nowadays more and more often used materials, but also are important pollutant materials as well. Further clarifying, these are ultrafine particles which means their size is 100nm in diameter [5]. ZnONPs show the following characteristics: large surface area/volume ratio, high ultraviolet (UV) light absorption, and long half-life [8].

This kind of material has a wide spectrum of usability. Thanks to their broad use, a lot of research has been done. Most commonly they are found in sunscreens but they are also common in cosmetics, paints, and coating for their UV blocking effect. ZnONPs may also be used as drug carriers, in medical filling materials, gene delivery, cancer therapy, angiogenic therapy, and biomedical imaging [9]. Furthermore, ZnONPs are also greatly studied as a food additive where they could potentially be used as an alternative to antibiotics [10]. Indeed, upon ingestion, ZnONPs have promising growth-promoting and antimicrobial properties [11]. Consequently, it's used as a dietary supplement in some of the major food manufacturing sectors: for instance, in fish and poultry production [12].

Welding means joining metal by partial melting of them by using various kind of energy. For this to happen, it requires a high temperature causing physical and chemical changes of the involved elements when they reach their melting point, meanwhile some metallic content get oxidized thus creating a fume. The inherent dangers in welding processes are diverse, such as the risk of burns, the risk of fire, explosion of the workplace, as well as the risk of radiation and electrocution. Beyond these accidental risks, there is also the underestimated risk that represents the inhalation of the welding fumes. Consequently, there is a dire need to further deepen the knowledge about the gaseous and particulate pollutants whose nature and toxicity depend on the solid materials involved. Indeed, the welders are exposed to the different components of the fumes which differ according to the filler metal or welding process used. Moreover, the concentration of particles inhaled depends on the working conditions, such as the welding technique, the ventilation of the workplace, and the existence of personal protective equipment [13].

To protect the workers' health, occupational exposure limits (OEL) have been established for different metals. In many countries (such as the USA, UK, Australia, Canada, Germany, Netherlands, Sweden, Demark), at workplaces, this OEL is set to 5.0 mg/m³ of ZnO [7,3,14,15]. Consequently, if that dose level is not exceeded, the fume containing ZnONPs is considered to not be harmful to health. However, researches suggest that this limit is not only over-defined but also needs a reassessment .

Concerning the pathomechanisms behind the toxicity of MFF, it has not been precisely determined yet. Current assumptions suggest that pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), neutrophil activation, the formation of oxygen containing free radicals, and allergic processes are involved including a direct toxic effect on the lungs that may also be involved since workers can develop MFF a couple of hours after the very first exposure [16,17].

3. Scientific goals

The aim of this thesis is to focus on the biological effects of ZnONPs after inhalation that lead to the development of MFF. The objective here was to gather the current knowledge on MFF, getting a better clinical understanding of the disease, as well as focusing on the pathomechanisms leading to its toxicity. Indeed, the toxicokinetics of ZnONPs absorbed by the respiratory system are uneasy to understand, which makes the interpretation of its biomonitoring problematic. Hence, this literature review gathered and summarize history, clinical cases, and research work that could help us to have a better understanding and overview of the effects of the inhalation of ZnONPs in vivo. In this paper, we focused on the researches that studied ZnONPs generated during welding, and in the other kinds of metal working processes.

4. Description of the disease

As we mentioned in the introduction, after inhalation of fumes containing metal oxides in the form of aerosols, one can get a fever known as "metal fume fever", which is characterized by a rapid rise in temperature preceded by intense chills of pseudo-malaria type. This fever is accompanied by tremors of the lower limbs, severe headache, myalgia, and arthralgia. There is also tachycardia, tachypnea, nausea with sometimes vomiting, and often a red skin complexion. The feverish picture generally improves in a few hours after profuse sweats. By then, the above-mentioned symptoms disappear and the worker can resume his work the next day. During the febrile attack, an increase in blood pressure is often reported with a mild leukocytosis. The cause of this morbid syndrome has been mainly attributed to the inhalation of ZnO containing fume, which is one of the metals used in metal works and which evaporates and ignites at high temperatures in oxygen containing atmosphere. This is how it can be inhaled by the worker. Indeed, it is among welders of galvanized iron sheets that this syndrome has been most often observed, however other metals can cause metal fume fever such as copper, manganese, lead, etc.

4.1 History of the disease

The chronological approach of the discovery and study of MFF throughout history is particularly interesting. Indeed, the etiopathogenesis of this disease remains at the present time, partially mysterious. Moreover, the small number of cases studied and reported does not facilitate the study. Finally, the historical struggle in gaining progressive knowledge on this disease, illuminate, by their successes as by their failures, its global understanding.

Although the first medical description of MFF was only in 1822 by Potissier, it is very likely that this condition is as old as the art of melting metals (around 2500 to 3000 BC) [18].

The literature mentions a case of a famous Italian sculptor Benvenuto Cellini (1500-1571), who suffered from it in 1550 when he was making a bronze statue of Perseus for the Duke Cosimo De Medici. He made a dramatic mention of it in his memoirs [19].

In 1831, an English doctor from Birmingham, Doctor Tackrah (1795-1833), made a clinical description of the disease, documented by numerous cases occurring in founders of brass, an alloy mainly based on copper, giving it its first name: Brass founder's ague [20].

Subsequently, the nineteenth century brought only a few publications, among brass founders, including Blandet, in 1845. Only in 1862 did Edward Headlam Greenhow (1814-1888) identify zinc oxide as the cause of the disease. The disease was then titled to brass chills [21].

In 1850, Landouzy and Maumene described among workers of galvanized metal what then named zinc chills [22].

Lehmann, in 1910, following experiments on himself, noted that the MFF looked, not like a poisoning by a metallic element in its symptomatology, but like a bacterial infection or an injection of exogenous proteins. Thus, he developed the first etiopathogenic theory of the disease, advancing the fact that the fever is caused by the resorption of a protein. Indeed, inhalation of ZnO would destroy cells of the respiratory tract, releasing these proteins, which then form complexes with the metal oxide particles of zinc. It would be the metabolization of these zinc protein complexes which would induce fever. But Lehmann stumbled on a major problem: he could not explain why the ordinary powder of ZnO could not cause the symptoms of this disease [23].

During the time, several metallic elements were suspected to be the cause the symptoms of the MFF. In the beginning, mostly the heavy metals were supposed to cause the disease (mercury, lead, cadmium or antimony, later other metals were also thought to play role in the pathomechanizm, like manganese, zinc or copper [24].

In 1925, Turner and Thompson carried out important work on the epidemiology of the disease, and several experiments on animals [20].

In 1927 and 1928, Drinker et al., significantly improved the knowledge of MFF, by demonstrating, on one hand, the importance of ZnO particles in the intoxication (thus solving the riddle that Lehmann had not been able to answer), and, on the other hand, by evoking the temporarily acquired tolerance if exposed repeatedly with ZnONPs during the symptomatic period, through clinical studies and animal experiments (cats, rabbits, and rats) [25].

By the time of 1927, MFF was experimentally induced in two healthy subjects by exposing them to freshly generated zinc oxide fumes [26].

From 1926 to 1936, several studies by Balsac et al, made it possible to affirm the benign character of this acute syndrome, which always results in spontaneous and rapid recovery, without sequelae [27]. Although in 1935, Williman published what remains still today, one of the rare exceptions to this rule: a case of fatal complication by a type of pneumonia [28].

Schiötz, in 1945, described a new form of the disease called Iron Fever, in workers carrying out electric welding [29].

In 1946, Kuh et al., published an original etiopathogenic hypothesis, according to which the fever is due to the absorption of endotoxins, released into the respiratory tract by the destruction of the Gram-negative bacteria that are usually present in the airways. Temporary tolerance, in this case, would come from the relative sterilization of the respiratory airway by the previous exposures [30].

In 1947, Dreessen published an important American governmental survey on the health of arc welders and also reported many cases among welders on galvanized sheet tubes [31].

In France, Ollivier and Brun, in 1949, reported fourteen similar cases [32].

In 1951, Doig and Duguid confirmed the possibility of complications, such as pneumonia [33].

Fay et al., in 1957, showed experimentally the role of irritative substances produced at the same time as zinc oxide, during welding with acetylene (nitrogen oxide, ozone, etc.) as cofactor [34].

In the year 1960, the two etiopathological theories were published, that became the most commonly accepted :

- Pernis et al., explained the symptoms of the disease by the production of endogenous pyrogenic substances by leukocytes [35].
- Mac Cord put forward the theory which remained, the most frequently adopted: the immunological theory according to which the symptomatology of the disease is explained by immunoallergic mechanisms [36].

After 1960, most of the publications concerning MFF, mainly focused on developing knowledge of the disease in terms of additional biological, radiological, and functional examinations (notably PFT), except the report of interesting clinical cases, such as those of Papp in 1968, Fishburn and Zenz, in 1969, Anseline, in 1972, or Jaremin, in 1973 [37-40].

More recently, the medical literature reported cases of asthmatic reactions, or true asthma, associated with MFF: Vogelmeier in 1987, Malo, and Kawan in 1988 [41,42].

Likewise, Farrell, in 1987, published a case of a cutaneous and respiratory anaphylactoid reaction during an acute episode of MFF [2].

All these data provided a new momentum to the study of this condition, by orienting research towards a phenomenon having an etiological immunological origin and thus opening up new perspectives about MFF.

4.2 Circumstance of onset

Various professional activities linked to the industry can create the conditions that are leading to the occurrence of MFF (as referred to in the Introduction and in the Zinc as an element chapter 4.3). That implies that inhalation of freshly formed metal oxide containing fume or durst can lead to MFF [43,44].

Lehmann et al., in 1910, had found that zinc oxide powder was incapable by itself to reproduce the effects of intoxication. In fact, they showed that it is rather immediately after its formation which is during heating the zinc to high-temperature in oxygen containing atmosphere such as during welding soldering, that ZnO led to the disease. This is explained by the fact that, in the nascent state, the ZnO particles are very small in size (between 0.1 and 1µm), and they can then cross the pulmonary alveolar-capillary barrier. Whereas, very quickly after their formation, the ZnO particles will form aggregates that

increase their overall size, and this will prevent them to go through the blood-air barrier. An experimental animal study by Ohmoto et al confirmed these findings in 1974 [45].

Furthermore, the degree of hydration of the fumes significantly influences their level of toxicity: the less hydrated (therefore the closer we are, over time, to their formation) the more toxicologically active they are. The humidity of the ambient air could, in this way, play a certain role in the pathomechanics. Although it has not yet been quantitatively studied on how much it influences the intensity of the expression of clinical signs [44]

Circumstances of occurrence of MFF therefore only occurs in workers working in a place where one of the metals "at-risk" is brought to a temperature above the boiling point (907°C for zinc): cast iron, oxy-acetylene welding or arc welding, thermal cutting of sheets, etc. On another note, work in an overheated environment would be an additional risk factor for the occurrence of intoxication [46].

For the MFF to develop it is necessary the fumes to be inhaled at a sufficient concentration. The smoke produced in large quantities, poor ventilation conditions, and working in confined places, are important factors. For zinc, Batchelor et al, in 1926, showed that no case occurred in an atmosphere where a concentration of less than 15 mg/mm³ prevailed. Inhalation, allowing access of the fumes to the pulmonary alveoli, presupposes the absence of a filter such as a face mask, or of an unsuitable filter such as one with a very thick mesh [47].

Finally, it is very important to take the other elements into account (they can be metallic or chemical) that are involved in the industrial processes:

- The contaminants: for example, cadmium, which is frequently extracted in small quantities with zinc, is thought to have a role as a cofactor, by its toxicity which is similar but more potent than zinc [48,49].
- The irritants: such as ozone, zinc dioxide, and certain acids for instance ZnCl2 that are produced during industrial heating operations at the same time as ZnO, are thought to have an irritant effect. Thus, favoring the action of ZnO [35,50]. See also Chapter 7. "Etiopathology".

4.3 Zinc as an element

As previously mentioned, most cases of MFF are due to ZnO [39,49], to the extent that the other forms, can be considered anecdotal considering their incidence. This is explained by the very frequent use of zinc in itself; but also, by the fact that zinc is

widely used in paint production manufacturing, metal casting processes, and galvanizing (a process consisting of covering a metal element with a layer of insulation for the purpose of protecting it from this air, thus avoiding oxidation) [51].

4.3.1 Physicochemical aspects

Zinc is a bluish-white metal, not very ductile, and poorly malleable at room temperature. It is shiny on the freshly cut surface. Zinc-ore is mined for the most part in the form of blende: the ore consists mostly of zinc sulphide but also contains iron, cadmium, lead, manganese, and arsenic.

Its chemical symbol is Zn. Its atomic number is 30, its atomic weight 65,38. Its valence is 2, its melting point is 419.5 °C, its boiling point at 908 °C. When heated to fusion, zinc evaporates and burns in the air, with a blue-green flame, and an oxide cloud (ZnO) occurs.

The density of zinc at 25 °C is 7,14 g/cm ^{3} [52].

The workers are in contact with the zinc in [53]:

- zinc mines

- ore processing sites

- galvanization

- the alloy industry (brass which is a mixture of zinc and copper)

- the use of pigments and salts

- ZnO: paints, varnishes, textiles

- $ZnCl_2$: wood preservation

- $ZnSO_4$: astringent and disinfectant
- P_2Zn_3: rodenticide

4.3.2 Zinc metabolism

<u>4.3.2.1 Intake</u>

Dietary daily intake: It is always greater than 10-15 mg of zinc per day in the diet of industrialized countries [54].

Zinc content in foods:

- for the meat: 10 to 50 mg/kg
- for cereals and fruits: less than 5 mg/kg
- for milk: 3 mg/liter
- sea water and drinking water: 1 to 10 μg/liter

In ambient air, the zinc concentration is less than l μg/m³ [49].

<u>4.3.2.2 Absorption</u>
a) Pulmonary absorption of ZnO:

In an industrial environment, zinc that is in the form of dust, fumes, or aerosols, and that could also be in the form of zinc metal, ZnO, and $ZnCl_2$ passes easily through the alveolar-capillary barrier [55].

b) Intestinal absorption of ZnO:

It is regulated by proteins such as metallothionein, thionein and zinc transporters that act as follows [56]:

- low bodyweight or zinc deficit in the organism cause an increase in the digestive absorption of zinc,
- a diet containing high doses of zinc or a diet rich in calcium will lead to a decrease in the absorption of zinc.

c) Dermal absorption of ZnO:

It was mostly studied during safety evaluation of sunscreens. Indeed, sunscreens containing traceable form of zinc were applied topically. The dermal absorption was then assessed measuring the radioisotope tracers of zinc in the internal organs as well as measuring the serum amyloid A (SAA) level in blood. This study revealed that [57]:

- there is a dermal absorption and then a distribution of ZnO.

- the ZnO absorbed by the skin appears to not cause a disturbance in the zinc homeostasis.

Based on the existing data on dermal absorption, zinc compounds absorption from the skin is approximated at 2%. For the durst exposure to zinc, a 10-fold lower default value of 0.2 % is applied [58].

4.3.2.3 Distribution

The total amount of zinc contained in the body of a healthy adult is estimated to be around two grams. Zinc is a cofactor in over 200 enzyme systems and appears to be distributed throughout all tissues and tissue fluids. Its concentration is maximum in the prostate, then the retina, the bones and muscles [48]. Zinc is transported in the blood by binding to albumin and alfa2 macroglobulin. The alfa2macroglobulin is a zinc-binding protein, it has a very high affinity to zinc and an inhibitor of matrixmetalloproteinases [59].

In relative value, the quantity of zinc incorporated in different organs is showed in the Table 1 [49].

Organ	Relative Zn content
skeletal muscles	63%
Bones	20%
Liver	3%
Blood	2%
digestive tract	1.7%
Skin	1.3%
other organs	9%

Table 1. Zinc content of different organs relative to the total body content.

4.3.2.4 Excretion

Daily zinc excretion represents about 1% of the total zinc in the body. Its biological half-life is between 162 and 500 days. The excretion is distributed as follows: 3/4 by the digestive tract and 1/4 by the urine. It has been experimentally found that the elimination by the urine was markedly increased the chelate-forming agents, such as ethylenediaminetetraacetic acid (EDTA) which is administered at high intraperitoneal doses to rats during toxicological studies. To a lesser extent, the excretion of zinc is done also via saliva, hair loss, sweat and milk [48].

4.3.3 Physiopathological aspect

The zinc is a biogenic element, the minimum zinc needs, in humans, defined by the Food and Nutrition Board (FNB) of the National Academies of Sciences, Engineering, and Medicine, United States of America, are the following [60]:

- 15 mg per day in adults
- 25 mg per day in breastfeeding women

Zinc deficiency can have the following consequences:

- failure to thrive in children
- delayed puberty
- anemia
- hepatosplenomegaly
- hyperpigmentation

All these pathologies are reversible, with oral supplements of 30 mg per day [48].

The disturbed zinc may cause the following [61]:

- acne
- delays in skin healing
- acrodermatitis enterohepatica (a hereditary disease): defect in the absorption of zinc by the intestine.

In the body zinc has several roles [62]:

- it is necessary for the functioning of metalloenzymes such as alcohol dehydrogenase, alkaline phosphatases, carbonic anhydrases, carboxypeptidases, etc.
- it is a component of the DNA polymerase. This enzyme is responsible for the replication of DNA, therefore for the cellular replication. The zinc deficiency will lead to a decrease in the production of RNA and DNA, therefore resulting in a decreased of protein synthesis.

Moreover, zinc has anti-inflammatory properties [63]:

- stabilization of lysosomal membranes
- inhibition of prostaglandin synthesis
- interaction with the complement system
- inactivation of macrophages

Zinc is needed for the regulation of the endocrine system on several levels, as well as for the regulation of the carbohydrate and lipid metabolism. It's exact mode of action is poorly understood [55].

Finally, insulin also contains zinc.

The toxicity of zinc, let alone MFF, is expressed by the intermediate of [64]:

- ZnO, in its powder form, which has a high cutaneous toxicity causing for example papulopustular dermatitis when it's manipulated by workers
- $ZnCl_2$ which exerts a caustic action on the skin and breasts, and which is thought to ease the occurrence of MFF when produced at the same time as ZnO
- zinc salts, which are very corrosive to the skin and irritating for the digestive tract. It is also highly emetogenic, in high dose, when they are ingested. However, Zn do not represent a risk for general intoxication because it is very poorly absorbed from the gastrointestinal tract.

5. Clinical symptoms of the disease

Generally, MFF is an acute disease, which mimic the symptoms of an upper respiratory infection (nasopharyngitis), tracheitis, or bronchitis, or even an influenza-like syndrome [39].

After exposure to metal oxide containing fumes, the first clinical signs appear only after an exposition free interval, varying from a few dozens of minutes to a few hours. The maximum delay is the one given by Jaremin, which is approximately 20 hours [40]. Concerning the minimum of time before the onset of clinical sign, it is very difficult to distinguish between the different authors, because some have calculated it considering the end of work in a contaminated atmosphere, whereas others do situate the appearance of the clinical signs according to this same labor (without mentioning its duration).

However, it seems to be admitted by all that the longest lapse of time frequently observed is of 2 to 4 hours.

As a result, the first symptoms are generally perceived during work, at the end of the afternoon, or, even more often, in the early evening on their return home [20].

The parameters influencing the exposition free interval are not clearly defined, but it appears to us, according to the published clinical cases, that they depend on one hand, to the inhaled dose (concentration of smoke, local ventilation, duration of exposure), and, on the other hand, the individual patient sensitivity (identical history of toxic contamination, previous clinical condition) [65].

5.1 Early clinical signs

The clinical expression of MFF almost always begins with signs of irritation of the upper airways:

- pharyngolaryngeal irritation
- the feeling of dryness in the throat
- non-productive cough
- the feeling of nasal obstruction

Sometimes, from this stage onwards, we see appearing respiratory functional signs:

- chest tightness, with the subjective impression of a difficulty in breathing; feeling of breathlessness
- true dyspnea (with a slight increase in respiratory rate) [40].

Digestive signs come next, with the short difference in time, when they are not concomitant:

- sweet metallic taste in the mouth (which is an almost constant sign at the point of being quasi-pathognomonic)
- alteration of taste perceptions: when it comes to the food, but also and especially while smocking tobacco, it gives an unpleasant sensation when you smoke [48].
- pronounced thirst
- anorexia
- ptyalism
- nausea [37].
- vomiting (grayish color)
- diarrhea, with greyish color
- upper abdominal pain (epigastric)

A transient polyuria has had already been observed, but we can ask the question of whether there's a possible link with the polydipsia that is directly induced by the disease. It may or may not be accompanied by urination burns [20].

Neurological signs can sometimes accompany the onset of the disease:

- headache, very frequent, often bilateral frontal, leading to insomnia-related pain.
- a feeling of emptiness
- tremors of the extremities
- paresthesia of the extremities [37]
- dizziness
- more rarely, a disturbed vision, ringing in the ears, delusional speech [66], convulsions [48].
- cases of sudden initial loss of consciousness were even reported [38].

Summarized, the patient feels general discomfort [17].

5.2 Fever

Fever is a constant clinical feature in MFF. It occurs early and is one of the first symptoms of the disease. Most often, it is between 38.5°C and 39.5°C and can be even as high as 40.6 °C [39]. The fever has mostly an undulating character. During the thermal

ascent phase, it is associated with chills and tremors. It reaches its maximum around tenth-twelfth hour after the appearance of the signs and it then decreases very quickly until it generally completely disappears on the very first night. As it is vanishing, profuse sweating occurs, which contribute to the insomnia [67].

Aside from the mentioned main symptoms, generally other signs are often accompanying with the MFF: asthenia, drowsiness, or even prostration. Finally, eye burns are frequently cited in the description of cases in the literature. They have no specificity of the disease and are only the parallel consequence of the work which provoked the intoxication [68].

5.3 Symptoms in different organs

The patient presents for medical assessment, in the first hours, slightly feverish, the face marked with a certain level of pallor, prostrated, complaining of asthenia, irritation of the upper airways with dry cough. The symptoms of the patient are not very specific, the clinical picture evokes a banal infectious syndrome. The clinical signs are usually non-pathognomonic, and does not provide any specific diagnostic guidance. The clinical history, including the workplace information helps to lead to the correct diagnosis [69].

5.3.1 Respiratory system

There are never any signs of acute respiratory failure. The respiratory rate is never significantly increased, although it is rather in the upper limits of normal.

Pulmonary auscultation is, in the vast majority of cases, completely normal. Very rarely, bronchial rales are reported, in this case, it can be localized or diffuse [37,70].

Others report, described rhonchi lung sounds, [66], wheezing [39], or localized pleural friction [38] in some cases.

Ear, nose and throat (ENT) examination shows neither edema nor pharyngeal redness.

5.3.2 Other organs and tissues

Cardiac auscultation is always unremarkable. Blood pressure is also normal. Heart rate is predominantly measured as unchanged, otherwise, it is observed with moderate sinus tachycardia [70].

Skeletal and myocardial injuries are extremely seldom, although it was reported in one case [71].

The nervous system is always without peculiarities.

Concerning the digestive system, the examination finds, at most, only a diffuse sensitivity of the abdomen [72].

Following chronic exposure to high concentrations of ZnO fumes, long term effects such as asthma, dermatitis, conjunctivitis and gastrointestinal disturbances may be associated with MFF [7].

5.4 Prognosis of the disease

The evolution of the acute stage is always favorable, in 6 to 48 hours, at maximum. Most often, after a very symptomatic night (headache, fever, profuse sweating, digestive disorders, etc.), the signs have improved, and the patient can resume work the next day. At most, we can observe a certain weakness, a weariness, but the clinical recovery is total [73].

5.5 Induced temporary tolerance

In the event of new exposure to fumes on the following day, we see that the signs of the disease do not reappear. It is this phenomenon which has been called: temporary immunity [48].

This symptomless period lasts as long as there is a daily exposure or at least every other day.

If there is an interruption in the exposure of two or more days, the manifestations can occur again. Hence the name "Monday fever" which was sometimes given to the disease, the workers being preferentially affected when they return to work on Monday, after two days spent at home. Hence also the particularly recurrent nature of the fever of metals in workers irregularly exposed to fumes [1].

6. Supplementary clinical examinations

6.1 Blood examinations

6.1.1 Blood cells

Leucocyte count: The increase in the total number of leukocytes is a constant finding in the MFF. The leucocyte count is considered to be elevated when it is greater than 10 000/mm³ [74]. In case of MFF, we find, in general: 12 000 to 200 000 leucocytes/mm³. This leukocytosis occurs very early, and it is rare that it is not in the first medical examination. It begins to decrease after 12 hours of apyrexia [39,75].

In some cases, neutrophilia has been found, sometimes a lymphocytosis, but it is not characteristic in every case.

Quite often the sedimentation rate is slightly increased, and this for only 2-3 days [39].

6.1.2 Blood proteins

Measuring the protein content and the enzyme activity in the patient's blood, the followings can be experienced:

- a decrease in albumin
- an increase in globulins (especially for alpha 2 globulins) [40].

There is an increase in the overall level of lactate dehydrogenase (LDH), and in particular of the pulmonary specific isoenzyme: LDH3.

Total creatine phosphokinases (CPKs) are high, and there is an increase in the activity of aspartate aminotransferase (ASAT), which however is not constant [71].

6.1.3 Blood gases

In most cases, these parameters are found within normal ranges. Vogelmeier et al., in 1987, found experimentally in one case, a decrease in partial pressure of oxygen of

9 mmHg (from its normal value which is 80 mmHg), after exposure to zinc oxide fumes during one hour [42].

6.2 Metal elements

Zinc: Some cases of elevation of zinc in the plasma have been identified in acute phase but mostly it is within normal values which is 10 to 20 µmol/l [38]. A very rare abnormal elevation of urine zinc has been observed in certain cases. It should be noted that zincuria in exposed workers, even if it remains within normal range, is found to be in higher rate than in the general population. There is no other recognized urinary pathology [70,76].

Copper: It is significantly elevated in both blood and plasma in the case of MFF was induced by copper fumes [77].

6.3 Radiology signs

It is mostly found as normal, however, some cases, present some anomalies such as:

- signs of bilateral hypervascularization
- opacity signs that are micronodular.

In all cases, the normalization of the radiological image is obtained within 24 to 48 hours [1].

6.4 Lung function test

Amdur et al, in 1982, showed experimentally, using guinea pigs, that inhalational exposure of zinc oxide for a period of one hour did not cause any increase in resistance of the upper airways, but there was a statistically significant decrease in lung compliance. The decrease was of 9%, at the end of the exposure compared to the control values (p-value less than 0.01). One hour after the end of the exposure, that decrease was of 16% (p-value less than 0,001) and the value was 27% two hours post-exposure [78].

Vogelmeier et al., in 1987, found experimentally in a patient that had previously MFF (6 months ago) an increase of the total pulmonary resistance. That increase was measured after one hour of welding on galvanized sheet tubes. It was found that the value returned to normal within an hour post-work. The onset of clinical signs of MFF appeared in the second-hour post work.

After the end of fume exposure, a significant decrease of the vital capacity, a reduction of the transfer factor (the transfer factor allows an assessment of the alveolar-capillary diffusion) of 40% of the initial value, and a decrease of the partial pressure of oxygen of 9 mmHg was recorded as was stated earlier.

The next day, functional respiratory exploration returned to normal, except for the transfer factor, which was only at 77% of its initial value.

Six months after this experience (without the occurrence of a pathological episode in the meantime), after exposure to zinc oxide fumes in the same conditions as the first exposure, the results of the respiratory functional exploration were entirely similar to those obtained at the time of the first exposure. Thus, the reproducibility of observed phenomena was demonstrated.

The conclusion of these experiments was that the metallic fumes of ZnO lead to peripheral pulmonary damage, which basically seems to be an inflammation [42].

Malo and Cartier, in 1987, observed, increased bronchial responsiveness to histamine (see chapter 7.1.3 Theory immunoallergical) [41].

6.5 Bronchoalveolar lavage

During the experimentation of Vogelmeier et al., in 1987, BALs were performed:

- one day after exposure (after 1 hour of arc welding on galvanized pipes), while all symptoms had disappeared and after that, the pulmonary function testing (PFT) results had normalized. It was then found that the number of total cells in the sample was of 90,000,000 which is 10 times greater than normal. Furthermore, an abnormally high proportion of polymorphonuclear leukocytes was also present.

- after seven weeks without contact with the zinc oxide fumes, the total number of cells had returned its physiological value. Indeed, the cells count of 7,300,000 cells was measured, but there was still a residual polymorphism of macrophages which, moreover, were more multinucleated than usual.

In both cases, the bronchi were macroscopically normal, and there were no bacteria in the fluid collected [42].

7. Ethiopathology

7.1 Historical theories

Zinc oxide fume inhalation is known to cause clinical signs upon exposure for a long period of time. The clinical signs involved are diverse and grouped under the name of MFF. It is a set of symptoms including generally a transient fever, nausea, pneumonia, nausea, fatigue, etc.

Consequently, inhalation of ZnONPs is well established for being toxic but the pathophysiology behind it is not well understood yet. A clear understanding of its mechanism of action would be fundamental in order to improve the safety of exposed people.

The first attempt to explain pathogenic mechanisms of MFF was done by Lehmann in 1910. He argued that zinc, in the respiratory tract or lungs, would destroy cells, causing their cytoplasmic contents to be released. Some proteins, thus released, would firstly form complexes with the zinc, and then these complexes would be reabsorbed and passed into the bloodstream. The destruction of these zinc-protein complexes would then lead to metabolic phenomenon that is highly pyrogenic.

But there were weak points in this hypothesis:

- There was no evidence either biologically or radiologically to suspect the existence of histological lesions of the respiratory, or pulmonary alveoli.
- The rapid and complete recovery, which follows an acute episode of MFF, does completely contradict this explanation. Indeed, the reparation of the hypothesized damage must have had taken much longer.
- Inhalation of gases, that are known to cause such organic lesions, causes a symptomatology that is different from what is experienced in MFF cases [23].

7.1.1 Theory of bacterial necrosis

In 1946, Kuh et al. argued that the metal fumes could not destroy the cells of the respiratory tract except the saprophytic flora occupying it. This flora contains, according to the authors, Gram-negative bacteria, which are releasing endotoxins when the cells are damaged or killed, that can then be absorbed by the host. An onset of fever would be the resulting from it, with a certain latency time (which is the time required for the systemic passage of endotoxins). Temporary immunity would then be explained by the relative sterilization of the airways, leading to a quantitative decrease in endotoxins releasable during a new exposure. This hypothesis, attractive in principle, has now fallen in disuse, supplanted by more recent ones [79,30].

7.1.2 Theory of endogenous pyrogens

In 1960, Pernis et al., gathered the work done in 1953 by Bennet and Beeson in one hand and the work of Atkins and Wood in 1955 on the other hand, to develop the foundations of the theory of endogenous pyrogens, by experimenting it in rabbits.

This study tends to show that MFF is due to the direct action of zinc oxide fumes on a protein having a pyrogenic action. This protein is thought to be contained in the cytoplasm of the polymorphonuclear cells.

The experiments showed that:
- MFF "attacks" could be provoked, in rabbits, by inhaling zinc oxide fumes, after inhalation of an aerosol of diluted acetic acid (without prior irritation by the acid, the results were much less convincing, which illustrates perhaps the role of cofactors and irritants in the occurrence of intoxication).
- an immediate fever attack can be caused, in healthy rabbits, by transfusion of 10 ml of plasma from sick rabbits.
- there is a very strong increase in the number of polymorphonuclear cells in the pulmonary capillaries of affected rabbits.

The conclusion of the experiment was, according to the authors, that:
- zinc oxide fumes do not act by the release of endotoxins, but by inducing the release of an endogenous pyrogenic substance thanks to their action on the polynuclear leukocytes.

- the contact between zinc oxide fumes and leukocytes, in the rabbit is facilitated by the accumulation of these cells in the capillaries. This accumulation is caused by prior irritant action of the aerosol of acetic acid.

The time interval, between the exposition and the clinical signs, would here firstly be due to the time necessary for the initial accumulation of polymorphonuclear cells in the pulmonary capillaries, and secondly due to the release of endotoxins in sufficient quantity.

The temporary tolerance is explained by the time requirement of the synthesis and the massive storage of the pyrogenic substance (assuming that there is no continuous release during the continuation of the exposure) [80,81,35].

7.1.3 Theory immunoallergical

In 1960 Mac Cord released his research according to which the MFF results from an immunoallergological mechanism.

His understanding is as follows:
- newly formed metal oxides are more active than others

- when they reach the respiratory system, these oxides are irritants and cause inflammation
- this is followed by a release of histamine, or a histamine-like substance, which is responsible for the first episode of MFF, which can therefore be considered as a "histamine shock"
- the mucous membranes of the respiratory system, subjected to inflammation, produce zinc-protein complexes, which are allergens. On further exposure to fumes, there is an immunological reaction with the formation of antigen-antibody complexes
- this antigen-antibody complex (A), which is a molecule that is foreign to the organism, causes the appearance of antibodies (B)
- there is an A-B conflict
- the activity of B antibodies is lower than that of A complexes, and requires perpetual renewal, through repeated exposure to metal fumes
- in the absence of frequent contact with the fumes, the complex antigen-antibody A dominates, and an allergic reaction occurs during exposure

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- in the presence of continuous stimulation, B antibodies dominate and an acute poisoning is prevented
- in the event of massive and sudden exposure, the protective mechanisms are overwhelmed and disease occurs anyway.

As the author points out himself, none of these postulates have been proven, they are acceptable only by sign-hypothesis analogy. Therefore, they created a plausible hypothesis, that is needed to be verified experimentally or clinically [36].

The immuno-allergological origin is through today to be one of the most likely cause of the symptoms of MMF, in the form described by Mac-cord, and it was further researched to determine its exact pathomechanism (see 7.2.2 Allergy).

Allergic manifestation associated with MFF:

Based on the theory that MFF has an immunological several authors, after Griffon and Derobert in 1942, have reported cases of allergic reactions, having manifested concomitantly with an acute episode of the disease [82].

Farrel, in 1987, reported the case of a man, having for allergic clinical history only once had hives after ingestion of tomatoes during his childhood (episode that had not reproduced itself thereafter). After exposure to zinc fumes for four days, he developed MFF, followed a few hours later by generalized hives, with pruritus and enlarged edema.

His complementary assessment showed:

- a normal PFT.
- an RAST positive for timothy grass and negative for all others allergens tested
- slightly increased total IgE (106 U/ml for a value upper limit normal to 100) with normal IgA, IgG, and IgM.
- normal plasma level of complement fractions C3 and C4.
- the rest of the biological, blood and urine assays were normal.

The radiological examination of the patient's chest showed no pathologic signs.

In order to verify the possible existence of a link between MFF and these allergic reactions, an experience of new exposure to zinc oxide fumes was attempted, after a

completely asymptomatic time. The experience was performed at the patient's home to avoid any foreign allergen exposure that could be associated with the workplace. The result was the recurrence of the signs of MFF and, about twelve hours later, a generalized urticaria that lasted almost a week was also seen.

It was consequently postulated that secondary allergic reactions (hives, edema) could be the delayed phase of the MFF. The initial phase would then be being made up of the usually described clinical signs. Thus, the two phases could be immunologically associated [2].

Three cases of asthmatic dyspnea were reported in two welders who also had an acute episode of MFF. Bronchial reactivity to histamine, which was markedly increased in one case, and was seen at the upper limit of physiological level in the other, argued in favor of an acute reaction to an allergen (specific and non-irritative reaction) [83,41].

These pathologies, with immuno-allergological determinism, do not seem to occur simultaneously with MFF by coincidence, but appear to be closely related to ZnO.

These clinical facts facilitate the immuno-allergic pathomechanism in triggering MFF but was still in needs to be proven.

7.2 Current theories

7.2.1 Oxidative stress and inflammation

As the investigations moved on, the new results suggested that newer theories should be formed on the bases of the previous ones. As the part of this process, recent study found that endogenous pyrogens substances may be released following oxidation stress and inflammation.

To begin with, the basis of the hypothesis is that the zinc oxide nanoparticles cause inhalation symptoms through oxidative stress and this effect leads to a resulting inflammation. Oxidative stress would be caused by the endocytosis of the ZnONPs. In fact, after the uptake of ZnONPs by the lysosome, it undergoes digestion due in its acidic environment. This leads to a high content of free zinc ions which cause intracellular toxicity by destabilizing the lysosomal cell membrane, thus leading to cell damage [84].

To test this hypothesis different experiments have been performed. Some of them are based on comparing particles based on their different properties. To do so, the toxicity of different kinds of metal-containing NPs were compared. Indeed, the goal is to see the key role of endocytosis as well as the role in the corrosion made by the acidic lysosomal content in releasing free metallic ions [85].

To achieve this, the toxicity of different gold particles that differ only by their endocytosis properties has been experimentally compared. The measured parameters to look at were the cellular level of ROS, the caspase-3 activation, the occurrence of apoptosis, the thioredoxin reductase (TrxR) enzyme activity, etc. A significant increase of ROS was found when the gold particles were able to enter by endocytosis (after 48 hours: 118% ROS generation for 20 nm of gold nanoparticle that underwent endocytosis compared to the control that is at 100% ROS generation). Similarly, a dose dependent activation of the caspase-3 could be measured (after 48 hours: 132% caspase-3 activity for 20 nm of gold nanoparticle that underwent endocytosis compared to the control that is at 100% caspase-3 activity).

In vivo experiments were also performed. The test organism was the fruit fly (Drosophila melanogaster), besides of the mentioned parameters, the lifespan of the fly was also measured. It has been found that the average lifespan was reduced by 47% compared to the control when treated with gold particle that are able to undergo endocytosis whereas the average lifespan was not significantly changed when they were treated with gold particles that were not able to endocytose [85].

In addition, the toxicity of particles that are able to release ions compared to others particles that lack this property has also been studied. Other ways to demonstrate that the toxicity of NPs comes from the release of ions is by adding chelating agents that sequestrate ions or by adding lysosomotropic agents that prevent the acidification of the lysosome, thus reducing the levels of ions [85].

On the cellular level, oxidative stress is thought to depend on the disturbance of the lysosomal membrane integrity. This effect can be demonstrated by an acridine orange staining [84].

Furthermore, experiments to demonstrate in vivo toxicity of ZnONPs were performed using rats exposed to intratracheal NPs containing fume. Following this exposure, the animals were examined checking their inflammatory and oxidative stress response. The examination of their body response was assessed by histopathology of their lung tissues, BAL, and biochemistry examination. In the blood testing, parameters such as antibodies level (IgA and IgE) were examined. The BAL fluid was studied checking for its cytokines, chemokines, LDH, and TP levels. The levels of TP, LDH and IL-13 in the BAL were significantly increased at 24 h after instillation with the 150 cm²/rat of ZnONPs:

- TP: 1.5mg/mL compared to 0.1mg/mL in the control group
- LDH: 11 fold vs vehicle compared to 7 fold vs vehicle in the control group
- IL-13: 80pg/mL compared to 30pg/mL in the control group

The histopathology was evaluated using TEM as well as lung tissues staining method in order to evaluate the pulmonary fibrosis, the atelectasis, and the goblet cells detection [84].

To point out the importance of the lysosomal pH in the degradation of metal NPs, the method was using inductively coupled plasma atomic emission spectroscopy (ICP-AES) comparing the lysosomal environment (mimicked by citrate buffer) to a cytoplasmic environment (mimicked by water) in the release of ions from NPs. Respectively a significant zinc ions release to the citrate buffer and no release into the water was observed. This shows that acidity matters since it causes the degradation of the NPs that will release the toxic ions [85].

In conclusion, the pathomechanism is thought to be the following: the ZnONPs is inhaled, it is phagocytosed by macrophages, and enters its lysosome, the ZnONPs loses its stability in the acidic environment which leads to the dissolution of the solid particles and to the creation of metallic ions that cause oxidative stress consequently to inflammation. Inflammation occurs when ROS are produced in excessive quantity. Indeed, physiologically there's a balance between the oxidative stress and the antioxidant system.

The excessive production of ROS in the cells leads to oxidative stress because the antioxidant system cannot counteract it. In the case of MFF, the macrophages that phagocyted ZnONPs will release an increased number of ROS. This will lead to an oxidative stress-mediated signaling mechanisms that is defined as the opening of inter-endothelial junctions and as the promoting of the migration of inflammatory cells across the endothelial barrier. It has been shown that ROS cause the disruption of this endothelial barrier due to an activation of the Ca^{2+} signaling pathway by enhancing the generation of H_2O_2. In fact, H_2O_2 change the ionic current which increase the endothelial barrier permeability, thus triggering inflammation Besides, the accumulated macrophages producing oxidative stress will also lead to direct tissues damage by apoptosis. In fact, their release of large quantities of highly reactive cytotoxic oxidants and pro-inflammatory cytokines also called chemokines (such as TNF-α, Interleukin-1 (IL-1) and Interleukin-6 (IL-6)) will lead to cells death. The released chemokines and reactive oxidants will lead to cell death via a cysteine-dependent aspartate-specific proteases (caspases) activation that happen through an extrinsic or an intrinsic pathway. The precise mechanisms involved are described as followed.

High oxidative stress will induce the following pathways:

- The extrinsic pathway is mitochondrial independent. The activation of the caspase is made through the binding of cell death receptors (for example the TNF receptors and Fas receptor) with their ligand (for example the TNF-α and Fas ligand).

- The intrinsic pathway is dependent on the mitochondria. Indeed, the increased mitochondrial outer membrane permeability (MOMP) will lead to the release of apoptogenic proteins (especially Cytochrome-c (Cyt-c)) release in the cytoplasm. These apoptogenic protein will form complex in the cytoplasm called apoptosome. The apoptosome will then lead to the activation of caspase-dependent mechanisms.

These enzymatic pathways connect the ROS to the end result of being inflammation [86,87]. The parameters of inflammation that can be seen, are diverse such as interleukin levels, changes in white blood cells such as in the eosinophils count, changes in inflammatory cells, direct tissues damage, etc. [84].

In fact, that has been proven by measuring different key parameters (such as ROS level, the cellular membrane integrity, the apoptosis rate, the redox potential, etc.) after the instillation of different modified NPs. It was also further demonstrated by adding up chelating agents. Consequently, by modifying the free ions released from NPs, or reducing

the free ions content originating from NPs, the role of oxidative stress in the metal fume fever is clearly shown. Indeed, less free ions released from metal NPs or more neutralized free metal ions both lead to a significant reduction of the NPs toxicity [88,85,89].

This shows that there's a "lysosome-enhanced Trojan horse effect" (LETH mechanism). This is a toxicity model which describes that the endocytose of NPs will lead to the release of toxic ions as degradation product. Indeed, the acidic environment of the lysosome instead of protecting the cell is rather enhancing the toxicity of ZnONPs by leading to its autophagy [85].

7.2.2 Allergy

Another feasible idea about the pathomechanism of the MFF is that the NPs are causing the activation of the immune system and thus, causing a hypersensitivity reaction. Inhalation of metal nanoparticles causes metal fume fever that is expressed through various body responses. Most commonly, the signs and manifestations that the patients present are influenza-like symptoms that include fever, nausea, exhaustion, chills, shortness of breath, etc. There are also some reported about symptoms that rather show a clinical presentation that is similar to an allergic reaction [2]. These symptoms were described for the first time in 1986 following a medical report on a worker of a zinc smelting plant. In this case, a man showed both: an acute and a late phase reaction. The acute phase reaction is the immediate one that is termed anaphylactoid reaction. Later on (12 hours after exposure), other symptoms were described such as pruritis, urticaria, and angioedema which are part of the delayed anaphylactoid reaction. These symptoms were so severe that emergency care was needed and his condition resolved with the same treatment as the one applied in an acute allergic reaction which is a combined injection of adrenalin, glucocorticoid, and antihistaminic. He also presented the more common clinical signs of MFF. Later on, after each exposure to zinc oxide fume, this anaphylactoid reaction quickly reoccurred in this subject. That suggests that the toxic effect of the ZnONPs could be through the exact same pathomechanism as an allergic reaction.

Allergic reactions can be classified in the following types of reactions, according to the Gel-Coombs classification (Table 2):

Classification	Immunoreactants	Clinical Presentation
Type I	Mast cell mediated, IgE dependent (anaphylactic, and	Anaphylactic shock, urticaria, angioedema, asthma, and allergic

	IgE independent)	rhinitis
Type IIa	Antibody-mediated cytotoxic reactions (IgG and IgM antibodies and complement often involved)	Immune cytopenias
Type IIb	Antibody-mediated cell-stimulating reactions	Graves disease and chronic idiopathic urticaria
Type III	Immune complex–mediated reactions, complement is also involved	Serum sickness and vasculitis
Type IVa	Th1 cell-mediated reactions macrophage activation	Type 1 diabetes and contact dermatitis (with IVc)
Type IVb	Th2 cell–mediated reactions eosinophilic inflammation	Persistent asthma and allergic rhinitis
Type IVc	Cytotoxic T cell-mediated (perforin/granzyme B involved)	Stevens-Johnson syndrome and toxic epidermal keratinocytes
Type IVd	T-cell-mediated neutrophilic inflammation	Acute generalized exanthematous pustulosis and Behcet disease

Table 2., The Gel-Coombs classification of hypersensitivity reactions

Type I or IgE mediated reactions are the best characterized. Indeed, they represent the immediate allergic reactions to physiologically indifferent substances that are more commonly called allergens. It is linked to the excessive production of IgE specific to various allergens, most often inhaled or ingested. The local symptoms which may then appear are respiratory (rhinitis, spasmodic cough and asthma), ocular (most often conjunctivitis), digestive (vomiting, abdominal pain, diarrhea), skin (atopic dermatitis, urticaria and / or angioedema). The systemic symptom results in anaphylaxis which is a severe life-threatening hypersensitivity reaction.

The other three types of hypersensitivity reaction are respectively referred to as non-immediate, late and non-IgE-mediated allergies. They are less common and more recently known.

The type II hypersensitivity reaction is linked to antibodies (IgM, IgG) which bind to antigens expressed constitutively. These antibodies induce the destruction of cells by activating the complement system through the classical pathway and / or by opsonization of phagocytic-cytotoxic cells (monocytes and macrophages or natural killer cells). The manifestations linked to this type of hypersensitivity are mainly cytopenia (hemolytic anemia, thrombocytopenia, leukopenia), and certain interstitial and tubulointerstitial nephritis induced by drugs. Cytotoxic hypersensitivity is also involved in some

autoimmune diseases, such as Goodpasture syndrome, pemphigus and bullous pemphigoid, etc.

The type III hypersensitivity reaction is linked to the formation and deposition of antigen-antibody complexes in tissues. Indeed, the antigen induce the production of large number of antibodies, forming immune complexes that are then deposited in the walls of small blood vessels. These immune complexes are then eliminated by activation of the complement proteins though the classical pathway and the neutrophil granulocyte and macrophages. The clinical signs of a type III hypersensitivity reaction are localized where the smallest blood vessels are found in the body which is the kidneys, the joints and the eyes. The main allergic conditions relating to type III hypersensitivity reaction are hypersensitivity pneumonitis, either linked to the repeated inhalation of organic antigens (diseases of the lungs of farmers, bird breeders, etc.), either induced by drugs ingested or injected. Certain nephropathies, vasculitis and skin rashes, mainly due to drugs, are also part of this type III reaction. Namely, we have infectious diseases such as serum sickness and classical and African swine fever and we also have autoimmune disease such as lupus erythematosus and rheumatoid arthritis.

The type IV hypersensitivity reaction results from the recruitment and activation, at the level of target organs and tissues, of various effector cells (monocytes and macrophages; effector and cytotoxic T lymphocytes; Langerhans cells, in the skin), under the effect of cytokines (TNF-α, chemokines, etc.) secreted by T lymphocytes activated by the antigen. The main conditions relating to this type IV are contact dermatitis and tuberculin test [90,91](Valko and Lorincz, 2020; Uzzaman and Cho, 2012).

In the case of MFF, the reaction is very similar to the type I hypersensitivity reaction. It takes place as follows: after the presentation of the allergen by the dendritic cells to the T helpers cells, there is a mobilization via production of cytokines of eosinophils granulocytes (IL-3 and IL-5) and B cells (IL-4 and IL-13). The B cells will produce immunoglobin E (IgE). The late phase of the type I hypersensitivity reaction is defined by an eosinophilic inflammation: the eosinophil granulocytes are activated through an immunoglobin E (IgE)-mediated allergic response [90]. Consequently, the well-known parameters of a type I hypersensitivity reaction are the eosinophilic granulocytes and the level of IgE. These two parameters have been seen as increased following metal oxide NPs toxicity. For instance, an eosinophilic inflammation termed pulmonary eosinophilia was reported following metal oxides exposure. Concerning the IgE, it has also been reported as increased. This supported the hypothesis that metal oxide

NPs induce an allergic process [92]. In the case described by Farrel et al., 1987, in the studied patient, the blood level of IgE was increased (106.1 U/ml) which is why his condition was termed IgE-mediated acute and delayed reaction [2].

Upon inhalation of ZnONPs, an immune complex reaction is thought to be formed by two means. On one hand, the oxide particle itself is an hapten that forms an antigen together with a protein and this will trigger directly the formation of an antigen-antibody complex. On the other hand, the oxide particle also causes inflammation which results in the release of histamine or histamine-like substances. This leads to the damage of tissue from the respiratory tract and subsequently to the released of tissue particles which will also be bound and form an immune complex. These complexes could induce an allergic reaction when the allergen meets the antibody again. However, an immunocomplex antibody (secondary antibody) is also formed and accumulated after prolonged exposure and thus, diminishes the symptoms. That explains why tolerance is established and this also explains another name of the disease: Monday morning fever. Indeed, during the weekend, there is an exposure-free period, workers are not inhaling metal oxide NPs. But the following Monday, at the beginning of their work week their symptoms are occurring strongly as reexposure occurs because the antibody-allergen complex is then dominating. So, upon reexposure, we have an exacerbated response of the body. The symptoms will diminish again as the week progresses and tolerance develops as the results of the anti-antibody becoming the majority again [1].

8. Conclusion

As it can be seen the ethiology of the MFF is rather diverse and there are multiple theories to explain the pathomechanical process of it. Here we would like to summaries and compare the available theories. The main points of the currently accepted theories are shown in the Table 3.

The theory of **bacterial necrosis** is questionable on several points. The theory is that the metal fumes only destroy the saprophytic flora present in the lungs and have no harmful effect on the cells. It is the endotoxin released from the decaying bacteria that would causes the symptoms. Among other things, it has been disproved that the metals do not enter the cells. The bacteria are not necessary to cause the fever. The theory does not explain how zinc induces the destruction of bacteria. The endotoxin shock could cause much more severe symptoms [79].

The theory of **endogenous pyrogens** is, as far as we know, valid on several points. The idea is that zinc oxide causes the release of a protein from the cytoplasm of polymorphonuclear cells that causes fever. This theory was described before the discovery of cytokines, but it is now clear that the production of IL-1, IL-6 and TNF-α by macrophags, among other factors, is associated with the onset of symptoms. In the experiments, acetic acid inhalation was used too in rabbits, but the results were inconclusive in the absence of acetic acid inhalation. However, the acidic environment may indeed promote cell irritation [35].

The most common hypothesis today is that **oxidative stress** caused by inhaled zinc oxide the symptoms of MFF.

While the absorption of zinc from the intestine is a regulated process, the absorption of the inhaled zinc is not controlled by the host, thus it can cause a lot of symptoms. Welders and other metal workers can be exposed to zinc oxide for long periods of time as a result of their work. Symptoms of self-contamination can also develop from inhalation of subtoxic amounts of zinc oxide. Zinc is an essential transition metal, that enters the cells via metal transporter. However, excess transition metals, such as zinc, can also form covalent bond to the thiol groups of proteins; enzymes, structural proteins, transporters, signaling proteins, so they can cause an inhibitory, inactivating effect.

Glutathione and metallothionein, which bind toxic metal ions with their -thiol group, play a major role in detoxification. As the concentration of zinc ions increases, the formation of Zn-metallothionein also increases.

The hydroxyl radicals released during the Fenton reaction, i.e. the oxidation of transition metals (such as iron, copper, zinc), play a key role in modifying the toxicity of metal ions. The reactive hydroxyl radicals lead to cell damage. Damage Associated Molecular Pattern (DAMP) is formed after the cell lysis, that attracts phagocytes, which will produce various cytokines and provoke inflammation [93].

The nanoparticles, that are considered as solid particles between 1-100 nm in diameter, could cause cell damage in a different way than the larger zinc oxide molecules. Nanoparticles are characterized as having a high surface area to mass ratio. Their biological activity depends more on their physical and chemical properties than on their qualitative composition [5,94,95].

Metal-containing NPs smaller than 500 nm enter the cell by endocytosis, then these are entering the acidic lysosome. Sabella et al., 2014 define this process the "Lysosome-Enhanced Trojan Horse (LETH) effect. This mechanism is depend mainly on the size of the NPs. The NP entering the cell through endocytosis produce show a much more toxic effect in the cell than if they had entered the cytoplasm with neutral pH [85].

Experts are divided whether the fever could be an **allergic reaction** after inhaling the zinc oxide or not. Researchers are thinking about how the zinc, as an essential metal, can be an allergen or antigen for the immun system. It is suspected that zinc could act as a hapten and then forms an antigen together with a protein. It is high possible, but still unproved that the immunsystem create an antibody against the Zn-containing antigen and these together form an immune complex. Researchers also suggest that the body also produces a secundary antibody (with a different structure) against the complete immune complex. According to the theory of hypersensitivity reaction, depending on whether the immune complex or the secondary antibody contrentration is dominant, the organism either shows tolerance or develops MFF. In our opinion, the fever and other symptoms are caused via the oxidative stress theory, but it does not exclude the possibility that occasionally the processes also has some level of allergic background [2].

Theory	Oxidative stress	Allergy

Theory	Oxidative stress	Allergy
Process	1. Zinc oxide NP enters the cell's lysosome by endocytosis. 2. In the acidic environment of the lysosome creates a large amount of soluble zinc ion 3. Zinc ions disrupt the integrity of the membrane of the lysosome. 4. Danger signal is released when the cell breaks down 5. Fever is produced by cytokine production by immune cells.	1. ZnNPs, which act as a hapten, bind to a protein to form an antigen. 2. Antibodies are produced against the antigen, which later combine to form an immune complex. 3. The body produce a secondary antibody against the complete immune complex. 4. Depending on immune status and the ratio between the immune complex and the secondary antibody concentration the MFF is developed or immune toleration takes place.
Cells	Neutrophil granulocytes, macrophages	Neutrophil granulocytes, macrophages and eosinophil granulocytes Mastocytes
Cytokines	TNF-α, IL-1, IL-6	TNF-α, IL-1, IL-6 and IL-5, IL-3
Isotype of Antibody	-	IgE
Other substances released	-	Histamine
Symptoms	Fever, influensa-like symptoms	Fever, influenza-like symptoms and Urticaria, angioedema

Table 3. Comparison of the main properties of the oxidative stress and the allergy theories of the pathomechanism of the MFF.

Several facts complicate the study of the background of the disease. The prevalence of this disease is about 30%, and not all worker suffer from it. It is more common in previously unexplosed workers or workers after prolonged non-exposed period and is associated with the development of tolerance. However, in the majority of cases, symptoms appear within a few hours of exposure to metal fumes.

To determine whether zinc oxide inhalation may lead to an allergic reaction or whether oxidative stress-induced cell death is responsible for the symptoms, several examinations can be performed.

Immediately after exposure, and then 6 hours, 18, 24, 48 hours later, from blood or BALF, the gene expression of some of the cytokines involved in the process, such as TNF-α, IL-3, IL-5, IL-6 could be measured. TNF-α, IL-6 are mainly responsible for the symptoms of fever in various causes. If IL-3 and 5 levels are elevated, an allergic

background may be suspected. We can also detect IgE antibody in serum by ELISA, which also supports the allergic background.

The same blood sample can be analyzed for the number of different granulocytes; if the number of eosinophil granulocytes is elevated, it indicates an allergic process. Also to support this theory the detection of the released histamin also can be performed. In an animal experiment it is also possible to detect the immune complexes in the lung tissue by e.g. Hematoxylin-eosine or Giemsa staining.

Metal fume fever is an acute occupational disease that despite general preventive measures, still exists. The thoughtful questioning of patients makes it possible to link the symptoms to occupational exposure and it also helps to eliminate other types of more serious intoxication.

The prevention involves the business leaders, the workers and all the exposed persons, and, in the medical field, the occupational physician.

The goals of preventive treatment will be to minimize the contact of the fumes with the respiratory system, by:

- reducing the concentration of fumes, or their toxicity
- limiting the duration of exposure
- avoiding the penetration of particles into the respiratory tract.

To reduce the concentration of fumes, all means in order to eliminate the fumes must be implemented. These must be applied to workplaces, and therefore they it should be implemented by company managers, with the advice of the occupational physician [96].

They consist of [18]:

- isolation of furnaces for heating or melting Zinc, Copper, etc. ...
- mechanical ventilation of the premises
- if there is no artificial ventilation system, ensure that there is proper natural ventilation of the working place (opening doors and windows, making an air flow).
- suction of fumes by mobile fume-extractor machines that need to be place above the workstation, or by vacuum.

In order to reduce the toxic effect of the fumes, it is recommended to humidify the air in the workplace, to promote hydration and flocculation of zinc oxide particles [24].

The techniques for measuring suspended metal elements in the ambient air do not currently allow the realization of sensors able to alert in the event of abnormally high rates. It is the responsibility of occupational medicine to periodically check these values, by dithizone solution colorimetric method chloroformed, or by the potassium ferrocyanide method [97].

The limit value for the concentration of zinc in the air has been set at: 5 mg/m³ [98].

To reduce of exposure time, the operations giving off metal fumes must not be always performed by the same person. It is preferable to institute a rotation of the different activities in a team. Likewise, it is desirable to limit the stay in a contaminated atmosphere, and not to stay long in a smoky room, when it is possible (risks of "indirect" exposure) [50].

The protection of the respiratory system is ensured by masks:

- simple masks, which must be suitable for filtering metallic, ultra-thin particles
- the so-called air supplied masks, which are equipped with a fresh air supply system allowing the breathing of unpolluted air, this is the same principle as a diving).

Unfortunately, studies on this subject, in industrial medicine, show that about 80% of the endangered workers (even though a large part of them are convinced of the worthiness of their wear), do not use them, or very rarely. The most common reported reason is the facial discomfort that they cause, especially during abundant sweating, which is the omnipresent in the metallurgical industry where the work is often done in an overheated atmosphere [55].

As for environmental protection aspects, zinc can be removed from industrial emissions by various techniques [99]:

- adsorption in filters or in fluids
- chemical precipitation
- ion exchange
- biological treatment

Concerning curative treatment, it is insured by the practicing physician. Given the absence of complications of the disease, and its rapid course, treatment curative of an acute episode will be mostly symptomatic [100]:

- bed rest

- analgesics and antipyretics

- gastric mucus layer compound, anti-acids

- bronchodilators and, possibly, corticosteroids in the event of asthma-like associated symptoms [101].

In this work, we were intended to summarize the current knowledge about the metal fume fever. We have seen that through the centuries the knowledge about MFF have greatly evolved. Indeed, throughout history, a better understanding of the clinical symptoms and of the laboratory tests results as well as a closer understanding of the causative agent and its related pathomechanism have been achieved. In regards to the pathomechanism of MFF, it has now been possible to prove or disprove previous historical theories. Thus, given us a clearer idea and details of its involved pathomechanism such as the oxidative stress and allergy. Although, there are great efforts to uncover the exact pathomechanical pathways that are leading to develop the MFF, still more research is needed to find the final answers in the future.

9. Summary

Metal fume fever is a well known disease among the miners, metal workers, smelters and welders. However the symptomology of the illness is known for a very long time, the pathomechanism is still not clear. In our work, we were intended to summarize the history of the disease and to compare the currently mostly accepted theories abut the pathomechanism.

It is a common sense in the literature that the cause of the syndrome is most likely the long term – low dose repetitive inhalation of specific metal- or metal oxide particules such as zinc or copper. The symptoms emerge usually in 24 hours after the last exposition. These symptoms are fever, dizziness, flu-like upper respiratory tract signs. The illness is benign, but there are sporadic cases reported that showed much sever conditions, indeed. The incidence of the metal fume fever is very low in the general population, however in the mentioned endangered groups, the incidence can go up to 25-30%.

In the history, there were several theories to explain the causes and the pathomechanism of the disease. Recently, the most accepted theories are the followings:

- the endogenous pyrogen theory, which says that the inhaled particles are causing release of pyrogenic proteins from the host cells, mostly from the polimorpho-nuclear cells.
- according to the oxidative stress theory, the metal oxide particles are causing formation os ROS and these reactice molecular species are causing immunologic changes leadin to the symptoms.
- the allergic reaction theory explains the disease as the inhaled metal particles connect to proteins in the body, forming antigens, and the immune system reacts against these antigens with a hypersensitivity reaction.

There are several examinations reported, including human and animal experiments as well, and the results are inconclusive, or are supporting more than one of the mentioned theories. Since the disease causes considerable losses in the industry, there is a great need to identify the main points of the pathomechanism to be able to perform proper countermeasures and preventive actions in the future.

10. References

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11. Acknowledgement

Declarations

I hereby confirm that I am familiar with the content of the thesis entitled

Literature review on Metal Fume Fever: a critical review of the theories of pathomechanism

. written by …Camille Lemal. (student name) which I deem suitable for submission and

defence.

Date: Budapest, 18 .day……11 ..month …2021……year

....

Csaba Kovago PhD

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Department os Pharmacology and

Toxicology