III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Occupational contact with zinc oxide may occur either through its use in the manufacture of some product or through its formation as a fume as a result of subjecting either zinc or alloys containing zinc to high temperatures. The principal use of zinc oxide is as a white pigment in rubber formulations where it is also a vulcanizing aid. In 1971, shipments of zinc oxide in the United States were approximately 227,000 tons, about 55% of which was for use in rubber. [1] Next in consumption level to rubber formulation is the photocopying process, followed by the replacement of lead carbonate by zinc oxide as a white pigment in paints, chemicals, and ceramics. Zinc oxide is also used in lacquers and varnishes, as a filler for plastics, in cosmetics, pharmaceuticals, glass, matches, and in dentistry. [1-3]

Total zinc consumption in the United States in 1971 was about 1.7 million tons, of which approximately 1.3 million tons were slab zinc. The zinc content of ore and concentrates used directly to make pigments and salts was about 125,000 tons. Galvanizing consumed 38% of the slab zinc, with 12% going into brass products, 3% as zinc oxide, and 40% into dye casting alloys. [1]

The principal health hazard of zinc oxide arises from inhalation of its fume which is encountered in brass foundries, galvanizing, smelting, welding of galvanized metal or metal coated with zinc compounds, and other processes where zinc is exposed to temperatures exceeding its melting point. The freshly formed fume is considered especially hazardous because

of its small particle size, ranging between 0.01 and 0.4 μm. [3-6] Zinc

oxide is a white or yellowish-white, amorphous, odorless powder. Its

physical characteristics are presented in Table X-1. Table X-2 lists

potential occupational exposures to zinc and its compounds as presented by

Gafafer. [7] Results of individual samples from welding operations are

shown in Tables X-3, X-4, X-5, and X-6. NIOSH estimates that 50,000

individuals in the work force have potential exposure to zinc oxide.

Historical Reports

Metal fume fever, both the most common and the most important

manifestation of occupational zinc oxide fume toxicity, is as old as the

metallurgy of brass which began before the Christian era. [8] According to

Meiklejohn, [9] the earliest recognition that metal fume fever, associated

with the melting and casting of brass, was a result of the inhalation of

zinc oxide fume, was by Thackrah. [9] Thackrah also described

gastrointestinal and respiratory symptoms in brass founders.

Many further reports and clinical descriptions of metal fume fever

were made during the remainder of the 19th century. In the opinion of

Drinker, [8] these episodes may have been largely due to zinc oxide fume, a

fact possibly not recognized by the authors of that time.

In 1910, Lehmann [10] reported from Germany the experiments upon

himself and 3 others, all of whom subjected themselves to fumes from the

combustion of chemically pure zinc. All subjects experienced what Lehmann

described as metal fume fever. Analyses of 100-liter samples of the

experimental chamber area air, filtered through cotton, showed the presence

of 0.1-0.4 mg of ZnO/liter(100-400 mg ZnO/cu m). Lehmann postulated that

zinc oxide might produce the characteristic symptoms of dryness and irritation of the throat with coughing and dyspnea, also pains in the muscles and joints, and general malaise very similar to influenza. Fever then developed, typically associated with the sensation of chills. [8,11-14] These symptoms were thought to be induced by the destructive action upon the epithelial cells of the respiratory passages, followed by absorption of the products of this destruction which were pyrogenic in effect. He also described experiments in which he failed to produce analogous effects in animals by intratracheal injection of zinc oxide powder.

Since 1910, metal fume fever, specifically zinc fume fever, and speculations about its pathogenesis, have received almost all the attention devoted to occupational zinc oxide toxicity in the literature.

Effects on Humans

(a)   Theoretical Considerations

In considering the toxic effects of a metallic salt, it is necessary to study the toxicology of the metal and its ion. Zinc, unlike its neighbors in group II-B of the periodic table, cadmium and mercury, plays a vital metabolic role as a trace element in biological systems. [15-17]

The widespread distribution of zinc in the environment has been mentioned in most of the major reviews. [16-21] According to Schroeder and his associates [15], "Zinc is omnipresent in living organisms and ranks with the most abundant of the trace metals in man."

Schroeder et al [15] listed and evaluated the findings of zinc in human tissue samples he and his colleagues [22] collected from 13 areas of

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the world. Five-eighths of the total body pool of zinc was stored in striated muscle. The highest concentrations (4900-9200 $\mu g/g$) were observed in the prostate, liver, and kidneys. Noting that variations were great, they estimated a daily turnover of 12.6 mg of zinc for humans. Intake was estimated to be 12.0 mg from food, 0.5 mg from water, and 0.1 mg from air. Output was estimated [15] to be 10.6 mg in feces, 0.5 mg in urine, 0.5 mg in sweat, and 1.0 mg each in semen and menstrual blood. These figures are in the same range as those of Drinker et al, [23] which were 0.25-2 mg (average 0.89 mg) daily in urine, and 2.67-19.9 mg (average 9.8 mg) in feces daily. Foods considered by Schroeder et al [15] to be good sources of zinc included seafoods, meats, whole grains, dairy products, legumes, and nuts. Zinc, with cadmium, is present in a wide variety of foods in concentrations ranging from less than 1 $\mu g/g$ in egg white to over 1000 $\mu g/g$ in oysters. All drinking waters examined contained zinc. The authors concluded [15] that "Zinc compounds are relatively nontoxic to living organisms, especially mammals."

Zinc deficiencies in villagers in the Middle East have been described by Prasad. [24] He hypothesized that these deficiencies might involve hypopituitarism or might have a direct effect on DNA synthesis, as severe growth retardation and sexual hypofunction were among the deficiencies noted. Addition of zinc supplement to the diet of affected males led to growth and development of gonads and of secondary sex characteristics.

Using extraction and absorption techniques, Vikbladh, [25] demonstrated zinc in 2 fractions of blood serum, one of which is firmly bound and the other more loosely bound to a serum protein. Lowered zinc levels in blood serum have been observed during the febrile stage of

infectious diseases in humans. Also in patients with "leukemias, malignant tumours, hepatogenic icterus, chronic polyarthritis, and chronic arthritis." Low serum zinc values in cases of untreated pernicious anemia were increased to normal levels by liver therapy.

(b)   Effects of Inhalation

There are many excellent clinical descriptions of zinc fume fever in the literature, for example those of Drinker [8] in 1922, Kehoe [11] in 1948, Rohrs [12] in 1957, Fishburn and Zenz [13] in 1969,and Anseline [14] in 1972.

From 4-12 hours after exposure to freshly formed fumes of zinc oxide, the subject first begins to notice an unusual taste in the mouth. This may be described as a sweetish or "metallic" taste, or it may be some alteration of familiar tastes, including tobacco smoke, which then becomes undesirable. There are also dryness and irritation of the throat with coughing and dyspnea, feelings of weakness, fatigue, pains in the muscles and joints, and general malaise very similar to the prodromal syndrome of a severe coryza or influenza. Fever then develops, typically associated with the sensation of chills. [8,11-14] The body temperature is usually around 102 F but may reach 104 F. There may be febrile shivering or rigors which may be malaria-like in intensity. Historical trade terms such as "metal fume fever," "brassfounders ague," "brass chills," "spelter shakes," "galvo," "zinc chills," "zinc ague," and "Monday-morning fever" [8,11,14,26] refer to this feature. The subject usually sweats profusely, during which process the body temperature begins to fall; occasionally, the chills and sweating may be associated with convulsions. Severe pain in the chest, aggravated by breathing, have been described. [13] Clinical and

symptomatic recovery is usually complete in 24-48 hours. [13] Blood taken during the acute phase of the illness has shown a polymorphonuclear leukocytosis, with the total white cell count rarely going above 20,000 cells/cu mm. The erythrocyte sedimentation rate does not seem to be significantly raised. There may be transient increases in certain serum enzyme levels, especially in the lactic acid dehydrogenase. Fishburn and Zenz [13] found an elevation in isoenzyme Factor 3 but a normal total serum lactic dehydrogenase in a typical case of zinc fume fever. Anseline [14] noted an elevation of the pulmonary isoenzyme for lactic acid dehydrogenase in the serum of another case. During the acute phase, the chest X-ray was either normal or showed merely an increase in bronchiovascular markings. [12,14]

A remarkable feature of zinc fume fever is the rapid development of tolerance to which the term "tachyphylaxis" (literally "quick immunity") was given by McCord [26] in 1960. The author stressed that this "immunity" was both quickly gained and quickly lost. In practical terms, this phenomenon means that a zinc or brass worker is more likely to experience zinc fume fever on his first day back at work after a weekend break or a vacation than during subsequent consecutive days of exposure, hence the term "Monday-morning fever." [11] However, it is a short-lived tolerance and reexposure on consecutive days may lead to repeated attacks of zinc fume fever. [26] The mechanism of zinc fume fever, and of metal fume fever in general, is still the subject of speculation. [10,26,27] Other types of metal fume fever, clinically identical to zinc fume fever, have been attributed to the fumes of other metals including cadmium, [12] copper, [28] and magnesium oxide. [29] Experimental evidence for some of the

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hypothetical mechanisms is discussed later in this chapter under Animal Toxicity. It was suggested by McCord [26] in 1960, and supported by Stilinovic and Grubisic [30] in 1970, that metal fume fever was an immunologic disease.

Mogilevskaya [31] in 1959 reported inflammation of the upper respiratory tract (nasopharyngitis and laryngitis) in 13 of 19 workers employed in zinc powder factories. These changes developed after 2-3 years of work. The author suggested that zinc and zinc oxide powder caused the alterations in the upper respiratory tract, the bronchi, and the peribronchial tissues. It was concluded that persons with diseases of the respiratory tract should be protected or excluded from exposures to zinc powders. Workers involved with zinc or zinc oxide powders and dusts should, according to Mogilevskaya, be given periodic medical examinations with emphasis on the ear, nose, and throat, and X-ray examination should be included. Dzukaev and Kochetkova [32] also reported fibrous changes in the lungs of workers in a zinc oxide production plant. They noted deformation, strengthening, and thickening in the X-rays of the lower and middle areas of the lungs. Details were not given and the supporting animal experiments are questionable because the suspension injected intratracheally into the laboratory animals contained 11-15% lead oxide. The reports [31,32] suggest a potential danger from zinc oxide powder when inhaled over prolonged periods of time.

Following the experimental exposures to pure zinc oxide fume of Lehmann [10] and 3 other subjects described under Historical Reports, Sturgis, Drinker, and their co-workers [5,6,29,33] in 1927 published a series of 4 reports on experimentally induced metal fume fever in humans.

The first report by Sturgis et al [5] in 1927 concerned 2 male subjects aged 32 and 39. Both had previous exposures to unmeasured concentrations of zinc oxide fume, and both experienced metal fume fever on several occasions during the preceding 2 years. With this previous experience, the subjects inhaled the oxide for a length of time and in a manner which each knew would produce a typical reaction of only moderate severity. Both were exposed in the same exposure chamber to an average concentration of 600 mg/cu m of high purity zinc oxide fume calculated as elemental zinc. One subject breathed for 5 minutes at 6 respirations/minute, then for 5 1/2 minutes at 12 respirations/minute. The other breathed for 12 minutes at 15 respirations/minute. It was calculated that the first subject retained 24 mg of zinc and the second 37 mg of zinc during these exposures. Both developed metal fume fever, the maximum febrile reaction being reached in the first subject about 7 hours after exposure, in the second subject about 4 hours after exposure. The body temperature of both subjects returned to normal within 12 hours. The white blood cell counts (WBC) of both individuals peaked (approximately 17,000/cu mm) at about the same time as the peak body temperature was attained. In both cases, the WBC count peaked again at a similar level almost exactly 24 hours after inhalation and remained high for the following 12 hours. In both subjects, the vital capacities, measured at 4-hour intervals, declined synchronously with the rise in body temperature and the initial rise in WBC count. The vital capacity of the first subject was decreased by as much as 18% of baseline and in the second subject there was a diminution of 53%, a seemingly drastic reduction. In both cases, the vital capacity had returned to baseline within 36 hours after exposure. Significant changes in blood

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pressure and chest X-rays were not found.

The second report in the series by Drinker et al [33] covered the same experimental subjects as previously. Estimations were made on the zinc content of the air at a brass foundry for about 5 hours. Subsequent analyses of samples showed that one of the subjects could have inhaled an average of 52 mg Zn/cu m air. That night the subject experienced symptoms of metal fume fever. The following day he worked for 3 hours in an environment containing an average of 330 mg/cu m of Zn and he experienced some of the prodromal symptoms of metal fume fever in the afternoon. On the third day he returned to the same foundry where he was presumably reexposed to similar concentrations of zinc oxide fume as on the previous 2 days, but this time he experienced no untoward reactions. Experimental exposures were then repeated upon the first subject of the earlier report. On the first day he was exposed to zinc oxide at 430 mg Zn/cu m of air for 8 minutes. He developed metal fume fever that night, his temperature peaking about 13 hours after exposure. Twenty-four hours after the first exposure, he was reexposed at 610 mg Zn/cu m and experienced a much milder attack of metal fume fever, peaking at about 12 hours after exposure. The WBC was also followed at 4-hour intervals, peaking at about 15,000/cu mm on the first day about 4 hours before the fever peak. On the second day the WBC was much higher (19,000/cu mm), falling to 11,000/cu mm about 4 hours after exposure and rising again to 17,000/cu mm synchronously with the second fever peak. Both the body temperature and the WBC count then gradually declined over the following 48 hours. It was concluded that acquired resistance to the effects of zinc oxide fume inhalation had occurred, thereby attenuating or preventing the fever altogether, despite

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reexposure on consecutive days.

In their third experimental report, Drinker et al [29] described in passing an experimental exposure of 2 subjects to a well dispersed cloud of very fine zinc oxide powder, the particles of which were of the order of 0.15 μm in size. They observed that such a cloud of very fine zinc oxide dust had approximately the same capacity for causing metal fume fever as the freshly formed fume. Most of this report, however, was devoted to an experimental demonstration that magnesium oxide fume in concentrations ranging from about 4-6 mg/cu m caused a metal fume fever that was clinically indistinguishable from that produced by zinc oxide fume.

In the fourth experimental report in this series, Drinker et al [6] estimated the threshold dose of inhaled zinc oxide, in the form of fume, necessary to induce metal fume fever. They postulated that the occurrence of metal fume fever was determined by the depth of penetration of the oxide particles into the lung, the alveoli being the site of action, with alveolar penetration being increased by slower and deeper inspiration. This postulate was based upon the observation that of 8 subjects inhaling the same concentration of zinc oxide fume for about the same period of time, 5 men who were breathing very deeply at 6 respirations/minute developed typical metal fume fever. Two of the women who were breathing at a rate and depth described as normal developed only minimal symptoms although they had actually inhaled as much oxide as the men. The remaining female subject with low minute volume did not develop any symptoms. The authors explained the difference in symptoms by the degree in alveolar penetration by the zinc oxide particles as influenced by the manner of breathing, ie, slow maximal-depth breathing leading to greater particle

retention than that resulting from breathing at a normal rate and depth for the same minute volume. It was determined experimentally [6] by measuring the zinc oxide content of both the inhaled and the exhaled air and assuming that approximately 1/2 of the inhaled zinc oxide fume was retained in the respiratory tract of the subjects.

A series of 27 inhalation experiments were then conducted [6] at different concentrations of freshly generated zinc oxide fume at varying durations of exposure and different respiration rates and minute volumes. One of the men was subjected to 11 experiments, varying the above experimental conditions, another to 5 experiments, 2 males and 1 female to 2 experiments each, and the remaining 3 males and 2 females to 1 experiment each. From the results obtained from 7 males and 3 females, a dose-response relationship was determined by plotting the calculated retained dose against rise in body temperature. A concentration of 15 mg/cu m of zinc oxide was suggested as the threshold limit for an 8-hour workday. However, this figure does not seem to have been derived from the extensive dose-response calculations described. It appears that an average concentration of 14 mg/cu m, below which fever was not observed, was derived from the report of Batchelor et al, [34] and that the selection of 15 mg/cu m [6] as a TLV was based upon Batchelor's work with zinc oxide powder, not zinc oxide fume. Drinker et al [6] and Batchelor et al [34] used the concentration of 15 mg/cu m as the threshold limit because they found that the men exposed for 8 hours to zinc oxide powder of that concentration in Batchelor's study did not ordinarily acquire fever.

(c)   Gastrointestinal Effects

There are several reports in the literature suggesting that prolonged occupational exposure to zinc oxide fume may be associated with gastrointestinal disturbances. [35-37]   In an insufficiently documented paper on occupational disease of zinc workers in the galvanizing trade, McCord et al [35] in 1926 described histories obtained from workers employed in galvanizing processes for 5-22 years which were suggestive of gastric or duodenal ulcers or hyperchlorhydria. No physical examinations of the workers were performed. The attribution of exposure to zinc is questionable because exposure was diverse and included hydrogen sulfide, arsine, arsenic, mineral acids, ammonia, ammonium chloride, lead, antimony, cadmium, aluminum, as well as zinc, zinc oxide, and zinc salts. [35]

In 1934, Kapp [36] reported 2 cases of gastrointestinal disturbances in zinc workers. One was a 29-year-old mechanic with a history of metal fume fever who spent a few hours 3-4 times each month cutting apart galvanized objects with an oxygen torch.   The other was a galvanizer. After one prolonged exposure ("a few hours") to zinc oxide fume, the mechanic did not recover promptly from the metal fume fever but complained the following day of pressure in the stomach region, nausea, and weakness. Aspirated gastric fluid contained leukocytes. The symptoms responded to a medical ulcer regimen. The galvanizer was exposed for several hours each day to fumes from an oven in which zinc was melted and ammonium chloride was heated. Symptoms of coughing, vomiting, and cramp-like pains in the upper abdomen developed gradually within 6 months. The temporary symptoms of the 2 workers gave the impression of zinc-fume fever and suggested possible gastrointestinal effects from repeated or prolonged exposure to

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zinc fumes.

In 1936, Chrometzka [37] reported observations on 58 electric welders, 18 of whom were seen during episodes of metal fume fever, and the remaining 40 after the symptoms had disappeared. The welding operations were performed on sheets of galvanized iron. Many of the workers complained of pressure or distention of the stomach, loss of appetite, and, in the more advanced cases, cramp-like pains in the upper abdomen. In 12 of the 58 cases the stomach distress was the most pronounced complaint after the fever period. Gastritis was diagnosed in only 1 case, but 12 others had signs of gastric irritation which included acidity, high mucous production, disposition to bleeding, mucous membrane desquamation, and leukocyte infiltration. Ulcers could not be demonstrated in any of the patients, not even with recurrence of poisoning. Four of the patients complained of periodic diarrhea.

In 1969, Hamdi [38] reported a study of 12 Egyptian brass foundry workers who were heavily exposed to zinc oxide fumes for 4-21 years. No environmental data were given. The zinc content of aspirated gastric juice was determined from 8 of the exposed workers and from 7 unexposed controls. There was a statistically significant increase of zinc concentration in their basal fasting gastric juice, in red blood cells, and in whole blood compared to the controls. It was suggested that the increase in zinc concentration in the gastric secretion might have accounted, in part, for gastric complaints present in 10 of 12 workers. The author suggested that other factors such as other environmental contaminants could have been responsible for the pains reported.

McCord et al [35] in 1926, and Du Bray [39] in 1937 have postulated chronic systemic toxic effects from the absorption of zinc following exposure to zinc oxide fume and other zinc compounds but Drinker and Fairhall [40] in 1933, and Hamilton and Hardy [41] in 1949, in review articles on the toxicology of zinc, have expressed doubts as to the existence of chronic systemic effects. To quote Hamilton and Hardy, [41] "On the whole the great weight of evidence is against the existence of chronic industrial zinc poisoning, and the ill health of workers in zinc when it exists should be traced to other sources."

In 1973, Guja [42] reported a prevalence of what was described as a clinically latent dysfunction of the liver in 60% of workers (15 out of 25) exposed to 50 mg ZnO/cu m, measured as zinc. Of the 15 men with evidence of liver dysfunction, (abnormal levels of alanine aminotransferase and cholinesterase were analysed), 3 had radiological evidence of a peptic ulcer. The workers also complained of debility, abdominal pain, acid rebound, heartburn, and loss of weight. The urinary uropepsin levels were significantly higher in the 25 workers exposed to zinc oxide than in 25 unexposed controls. In the opinion of Guja, a raised urinary uropepsin level may be indicative of toxic damage to the gastrointestinal tract.

(d)   Effects on the Skin

Zinc oxide is a constituent of many topical dermatological preparations [43] and has demonstrated a low potential for skin irritation. In 1921 Turner [44] reported that 14 out of 17 men employed in the manufacture of zinc oxide either had or had experienced in the past an occupational dermatitis known in the trade as "oxide pox," which was referred to as a dermatoconiosis due to zinc oxide powder. The lesions

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were described as small red projecting papules, 2-3 mm in diameter, hard and shotlike on palpation, with a white central plug. There was an areola of inflammation at the base of the papule. On the 2nd or 3rd day of the eruption, the central portion of the papule began to soften and develop into a pustule causing intense itching. In 10 of the cases, the skin of the affected parts was dry, and in 4 cases it was moist and eczematous. The eruption usually persisted for a week or 10 days, gradually subsiding and drying up. In 13 of the cases, the pubic region, scrotum, and inner surfaces of the thighs were affected. In 4 cases the axilla and inner surfaces of the arms were also involved. Secondary infection, mostly by Staphylococcus aureus, was thought to play a significant role in the pathogenesis of the skin lesions. Blood agar cultures of material from the lesions were 90% positive for Staphylococcus. It was concluded that zinc oxide had combined with debris and bacteria to block sebaceous glands, resulting in irritation and eventually infection. The workers in the factory reported that the lesions did not occur if they took daily baths. It is evident that the skin disorders in zinc oxide workers occurred mainly because of lack of personal hygiene.

Epidemiologic Studies

In 1926, Turner and Thompson [45] published an extensive survey of the health hazards of brass foundries with some epidemiologic findings but no quantitative environmental data were presented. Qualitative sampling established the presence of zinc as well as iron, cadmium, manganese, antimony, and traces of lead, arsenic, and tin in the airborne dust. Of the 102 brass foundry workers interviewed, 26% had attacks of "brass

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foundrymen's ague" on the average of once a week, 13% once a month, 17% once a year, 11% twice a week, 14% twice a month, 6% twice a year, 2% three times a month, 1% three times a year, and 10% about four times a year. Eighty-eight percent of the men asserted that the attacks occurred only during the winter months (when natural ventilation was inadequate) and 12% said that they were affected without regard to the seasons. All said that during inclement weather they were almost certain to have an attack. Another observation in this report was that a syndrome, similar to "brass foundrymen's ague," was seen in men engaged in the manufacture of zinc oxide powder. Four out of 8 men engaged in the bagging of the freshly formed and still warm oxide dust gave positive histories of "oxide chills" and 7 out of 9 men in the packing room had similar symptoms. No actual cases of the syndrome were observed by the investigator, but several case histories were obtained by questioning the employees. A definite similarity was noted in the symptoms and severity of attacks found in brass foundrymen and the oxide chills reported by the men engaged in the manufacture of zinc oxide powder. The symptoms common to both brass foundrymen and oxide workers consisted of irritation and dryness of the nose and throat, frequent headaches, and occasional digestive disturbances including constipation. It was considered by the authors [45] that the entire sequence of symptoms in all stages was so constant in both situations that the basic causative factor must have been the same.

In 1926, Batchelor et al [34] published a report with epidemiologic features and minimal environmental data on the effect of metallic zinc, zinc oxide, and zinc sulfide on the health of workers. The industrial processes included the smelting of zinc ore for spelter (ingots) and for

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zinc oxide, and the manufacture of zinc oxide, of paint pigment (lithopone, 30% zinc sulfide and 70% barium sulfate), and of zinc dust. Out of a total of 1,620 men employed in the plant, 24 were singled out for special study. These 24 men were defined as having been exposed to zinc metal or zinc oxide, measured as zinc, ranging from 0.03 to 3.7 mg/cu ft (1-131 mg/cu m) for periods ranging from 2 to 35 1/2 years. They were described as being "...on the whole a vigorous, healthy lot of men, giving no histories of significant past illnesses and showing only such general physical conditions as one would expect to find in any similar group of men of the same ages, of the same social status, and doing approximately the same amount of physical work in an atmosphere with a moderate amount of dust, but with no exposure to zinc...." The 24-hour urinary and fecal zinc levels in the zinc workmen differed from 24-hour urine and fecal zinc excretion values for normal (unexposed) subjects on an ordinary mixed diet. The authors' summary conclusion on these measurements was: "...zinc workers absorb and excrete zinc in amounts considerably over the normal, and they maintain constantly a blood zinc content slightly higher than normal...abnormal amounts of zinc may enter and leave the body for years without causing symptoms or evidence, which can be detected clinically or by laboratory examination, significant of gastrointestinal, kidney or other damage...." [34]   Data on excretion levels have been cited in the section on Effects on Humans of this document.

In 1944, Hammond [46] reported on the incidence of metal fume fever in the crushed stone industry. In this industry, zinc containing from 1.6 to 2.2% lead was used to bind and fill voids about the various crushers. When molten zinc was poured in the repairing and relining of the crushers,

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environmental zinc levels ranged from 8 to 12 mg/cu m, with a mean of 10 mg/cu m from 4 measurements. No metal fume fever was observed or recorded during these operations. However, during oxyacetylene torch cutting procedures in the removal of old linings, much higher environmental levels for zinc oxide (as zinc) were measured, ranging from 320 to 545 mg Zn/cu m, with an average of 465 mg Zn/cu m from 5 samplings. Moreover, mean environmental levels of 12.4 mg/cu m of manganese and 1.6 mg/cu m of lead were also noted. The cutters were usually inside the crushers for 1-3 hours without ventilation. It was reported that at one time or another the workers engaged in cutting or burning out of old liners under these conditions experienced metal fume fever.

Animal Toxicity

    (a) Inhalation

    In 1910, Lehmann [10] reported the results of experiments conducted in 1906 in which rabbits were exposed to zinc oxide by inhalation or by intratracheal injection. Lehmann was unable to produce metal fume fever in the animals by either route, inhalation or intratracheal injection.

    In 1926, Turner and Thompson [45] reported studies on guinea pigs to test Lehmann's hypothesis. Monkeys were rejected as being too difficult to handle. An exposure cage was designed to produce a condition similar to that encountered in brass foundry practice, with the additional advantage that the intensity and duration of exposure were reasonably controlled. Temperature, pulse, and respiration rate of the guinea pigs were observed prior to a 1-hour exposure at levels of zinc oxide ranging from 30 to 72 mg/cu ft (1060.0-2543.0 mg/cu m) and again for 46 hours after exposure.

They exhibited "air hunger," with labored and convulsive breathing for about 4 hours after removal from the exposure cages. Their temperatures were subnormal, being most depressed 3-4 hours after exposure. From 8 to 9 hours after exposure, the temperatures were above normal, reaching a peak at 16 hours and returning to normal after 24 hours. When the animals were removed from the exposure cage, their respiration was slow and labored, but increased to a rate above normal for about 42 hours. Microscopic studies of lung tissue from exposed animals showed "infiltration of endothelial cells and polymorphonuclear leukocytes," which were described as being similar to that observed in bronchopneumonia.

Turner and Thompson [45] exposed 6 healthy guinea pigs at 29 mg/cu ft (1024 mg/cu m) of zinc oxide fumes for 1 hour daily for 3 days, followed by 2 days of no exposure, then 6 additional days of 1-hour daily exposure. The animals showed "unmistakable evidence of an accumulative reaction" and required 3-6 days to recover from the effects, which included respiratory irritation, irregular heart action, and weight loss. In further experiments, animals exposed continuously at 70.9 mg/cu ft (2503 mg/cu m) of zinc oxide fume died within 2-5 hours of the start of the exposure. Both the lung tissue and the stomach tissue contained an average of 48 mg ZnO/animal suggesting that as much zinc oxide had been ingested as had been inhaled.

Drinker et al [47] reported in 1925 that zinc oxide was more effectively introduced into the lungs of experimental animals when administered with 10% carbon dioxide.

In 1928, Drinker and Drinker [48] reported results of experiments in which cats, rats, and rabbits were exposed for 15 minutes-3 1/4 hours at

levels of zinc oxide fume ranging between 110 and 600 mg/cu m. The animals showed prolonged temperature depression but no subsequent rise above normal. In addition a delayed but definite increase in polymorphonuclear leukocytes was found. This contrasted with the earlier work of Turner and Thompson. [45] Chemical analyses using an unspecified method of Fairhall's [49] (either gravimetric, turbidimetric, or colorimetric) showed that the quantity of inhaled zinc did not vary directly with the length of exposure, but that most of the zinc accumulated during the first 15-45 minutes of exposure. [48] Cats inhaled proportionately more zinc than did rats. Zinc was removed rapidly from the lungs of cats and rats, returning to normal levels within 4 days after exposure. Zinc concentrations increased in the liver, gall bladder, bile, kidney, and pancreas. It was concluded [48] that the "characteristic reaction of animals to the inhalation of freshly formed metal fume products" was "a fall rather than a rise in temperature...." This statement was partially based on experiments with magnesium oxide in which similar results were obtained.

In 1928, Schmidt-Kehl [50] reported experiments in which rabbits were exposed to freshly formed zinc oxide fume. Serum extracts were prepared from the bronchial and tracheal mucous membranes of rabbits which had inhaled zinc oxide fume. No temperature changes resulted when an extract was injected into the ear vein of an unexposed rabbit. Another experiment was performed using rabbit serum which had been sprayed into an atmosphere of zinc oxide fume. The serum (20-25 cc) was injected into the ear vein and the maximum temperature increase as compared with the controls was present 2-12 hours after the injection and ranged between 0.5 and 1.6 degrees F above normal. The author [50] concluded that either a fever-

inducing zinc and protein combination had formed, or that proteins of the respiratory tract were altered by zinc oxide and became pyrogenic.

In 1960, Pernis et al [51] criticized existing hypotheses regarding the mechanism of zinc metal fume fever and suggested an alternative formation of endogenous pyrogens. Rabbits exposed first to acetic acid and then to zinc oxide fumes were tested for cross-tolerance between metal fumes and endotoxins. Tolerance to endotoxin did not extend to the pyrogenic effect of zinc oxide fumes. They [51] concluded that these results contradicted the suggestion of Kuh et al [27] that metal fume fever was due to endotoxins from bacteria present in the respiratory tract. Pernis et al [51] drew attention to the infiltration of polymorphonuclear leukocytes noted in the lungs of guinea pigs by Turner and Thompson [45] and in cats by Drinker and Drinker [48] in 1928 and noted that conditions existed in the lungs of the experimental animals which permitted contact between leukocytes and zinc oxide particles, perhaps resulting in the release of endogenous pyrogen, thereby causing metal fume fever.

Mogilevskaya [31] in 1959 reported the intratracheal administration to rats of a 1-ml suspension containing 50 mg of zinc oxide powder in sterile physiological solution. All animals survived and no untoward effects were noted. Some of the rats were killed 8 months after the administration of the powder and others after 12 months. Microscopic changes observed in the lungs included hyperplasia and sclerosis of lymphatic follicles, deformations of the bronchi, and occasional peribronchial pneumonia. The changes observed were distinct from those associated with other types of metal dust. Specifically, there was no observation of a nodular process, of diffused sclerosis, or of acute toxic

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action. Pathological changes due to zinc dust were also observed in the upper respiratory tracts of the animals. [31]

Dzukaev and Kochetkova [32] in 1970 administered zinc oxide in sodium chloride solution intratracheally to 38 rabbits at a dose of about 40-80 mg/kg of body weight. Changes were observed in the lungs of the animals, but the zinc solution contained as much as 15% lead, which raises a question concerning their conclusion that the observed changes were due to the zinc oxide.

A review of the literature by Stilinovic and Grubisic [30] in 1970 led these authors to the conclusion that the mechanism of zinc fever onset was still one of speculation.

(b) Ingestion

Turner and Thompson [45] fed guinea pigs daily doses of a zinc oxide suspension in pure olive oil. The total dose over a 12- to 15-day period varied from 600 mg to 80 g/animal. Eight of 16 animals died between the 2nd and the 11th day after ingestion of the mixture. Pulse rates were increased and respiratory rates in some animals were slower than normal. In sick animals respiration was faster than normal and temperatures lower than normal. At necropsy, animals' lungs were found to be congested. Fatty infiltration and parenchymatous degeneration were observed in the livers and kidneys. Control animals fed olive oil alone or zinc oxide in chopped carrots did not exhibit these changes. The authors concluded that zinc oxide, in itself, was probably innocuous when ingested, and that the fatalities resulting from the ingestion of the zinc oxide-olive oil mixture were due to either mechanical disturbances to the digestive system or to a toxic compound formed from the combination of the 2 substances.

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In 1927, Drinker et al [52] conducted long-term feeding experiments with cats and dogs to determine the effects of ingested zinc oxide. The animals received zinc oxide daily in the form of dry powder mixed with the food. The doses were administered daily for 35-53 weeks, ranged from 175 mg to 1 g for the cats and 500 mg to 1 g for the dogs. The authors found no "significant clinical symptom nor obtained any significant laboratory evidence of damage" in the animals. Zinc was excreted mainly in feces. The same authors [52] reported another study in which cats and dogs were fed zinc oxide in food. Three cats receiving high doses showed a weight loss and loss of appetite, which the authors attributed to the disagreeably sweetish taste of the oxide-containing food. Zinc concentrations did not increase in fat, brain, spinal cord, heart, muscle, spleen, thyroid gland, or blood. Zinc increased in the liver, the gall bladder, the gastrointestinal tract, and the kidneys. Fibrous changes were observed in the pancreas of 3 cats given high doses. There was no other clinical or laboratory evidence of damage.

Sadasivan [53] fed rats supplemental pure zinc oxide at levels of 0.5 and 1.0%, both with a stock diet and with a high-fat, low-protein diet. He observed reduction in the weight and fat content of the rat livers. Greater reduction with rats on the high fat diet suggested lipotropic activity of the zinc. At the 1% level, zinc oxide caused a lowered food intake. There was evidence that bone development and mineralization were adversely affected by zinc. This was evident by reduced dry weight and ash content of the bones.

Further experiments by Sadasivan [54] showed that urinary and fecal nitrogen excretion were increased in rats given zinc oxide supplements.

Urinary excretion of phosphorus and sulfur decreased, but fecal excretion of phosphorus and sulfur increased. Urinary excretions of uric acid and creatinine increased with the zinc-supplemented diet.

Grant-Frost and Underwood [55] conducted studies on the interaction between dietary zinc oxide supplements and copper in rats. Rats receiving 0.5% zinc as zinc oxide showed markedly reduced growth, food consumption, hemoglobin levels, copper retention, and body fat. These factorially designed experiments suggested to the authors that the effect of zinc on growth was due to reduced food consumption. Zinc appeared to reduce the copper concentrations in blood and tissues and may have antagonized absorbed copper at the cellular level, according to the authors, [55] who also concluded that the anemia was caused by a zinc-induced copper deficiency.

Witham [56] fed rats a basal diet with 0.4% zinc as zinc oxide and fed controls the basal diet alone. Assays of the homogenized livers from animals killed at 6 weeks showed reduction in the cytochrome oxidase activity in treated animals. The author presented evidence to support the view that this is due to zinc-induced copper deficiency.

(c) Injection

To further test the hypothesis of Lehmann [10] that metal fume fever might have resulted from absorbed lung proteins, Turner and Thompson [45] injected lung extracts from healthy animals, with and without zinc oxide, and extracts of lung from animals exposed to zinc oxide into healthy unexposed animals. The temperatures and pulses of animals given lung extract from healthy unexposed animals were affected in much the same way as temperatures and pulses of animals exposed to zinc oxide fume had been.

Addition of zinc oxide to the lung extract and use of extract from lungs of animals exposed to zinc oxide did not evoke additional effects.

Correlation of Exposure and Effect

The most commonly described and best documented effect of exposure to freshly formed zinc oxide fume in man is the syndrome of metal fume fever.

The first measured exposure to zinc oxide fume recorded is that reported by Lehmann in 1910. [10] Lehmann subjected himself and 3 colleagues to an experimental atmosphere containing from 100 to 400 mg ZnO/cu m of air, and all 4 subjects developed metal fume fever.

Batchelor et al [34] studied the maximum and minimum airborne zinc oxide dust levels in the workplaces of 24 men, out of a total work force of 1,620. The 3 most heavily exposed men were reported never to have had "zinc chills" because 2 of them in fact were exposed to metallic zinc dust in the 6.2-130 mg/cu m range and the 3rd was exposed (16.6-58 mg/cu m as zinc) to highly aggregated "old" zinc oxide, of presumably large particle size. Nine of the 24 men observed were stated to have had the "shakes" within the first few days of their exposure to the suspended oxide. Three of the 9 experienced a recurrence of "shakes" once or twice after the first week or two of employment. Only 1 man in the series remained away from work because of metal fume fever.

The report by Hammond [46] on the incidence of metal fume fever during the overhaul of stone crushers involving the use of zinc and zinc alloys as a binder and filler established 2 basic ranges of zinc oxide fume exposure. At airborne levels of 8-12 mg/cu m of zinc oxide no cases of zinc fume fever were recorded. At airborne levels of 400-870 mg/cu m of

zinc oxide and duration of exposure ranging from 1 to 3 hours, all of the unstated number of exposed workers were said to have had zinc fume fever at one time or another following such exposures. The metal fume contained, besides zinc, 12.4 mg/cu m of manganese and 1.6 mg/cu m of lead. It is difficult to say what role, if any, the manganese and lead fumes might have played in causing the reported symptoms.

The human experimental reports of Sturgis, [5] Drinker, [33] and their colleagues in 1927 offered data on small numbers of subjects. Sturgis et al [5] produced metal fume fever in 2 male adult volunteers by exposing them at a measured average concentration of 600 mg/cu m of high purity, freshly generated zinc oxide fume, 1 for 10 1/2 minutes and the other for 12 minutes. Based on the different rates of respiration of the subjects, it was calculated that one must have retained about 24 mg and the other 37 mg of zinc. Typical febrile reaction occurred followed by marked leukocytosis which persisted for 12 hours after the body temperature returned to normal.

Drinker et al [33] investigated the exposure of a technician in a brass foundry at an average concentration of zinc oxide fume of 52 mg/cu m measured as zinc, for 5 hours. This exposure resulted in an attack of metal fume fever the following night. The next day the same individual was exposed at an average of 330 mg as Zn/cu m for about 3 hours. He experienced no ill effects on the 2nd day, supporting the theory of short-term tolerance or relative immunity to zinc fume fever.

Drinker et al [29] also reported a rise in temperature in 2 volunteers exposed to finely ground zinc oxide powder (0.15 μm particle size) dispersed in air as a stable cloud. The concentration so achieved

was however not reported. This paper suggests that zinc oxide does not have to be generated from zinc metal fume to produce metal fume fever.

Drinker et al [6] conducted 27 experimental exposures on 7 male and 3 female volunteers, varying the concentration of the freshly generated zinc oxide fume, durations of exposure, respiration rates, and minute volumes. Using rise in body temperature of the subjects as the critical response, they constructed a dose-response slope. They proposed a threshold limit of 15 mg/cu m ZnO for an 8-hour exposure.

There are few animal studies reported which contribute to the correlation of exposure and effect in quantitative terms. Turner and Thompson [45] in 1926 reported exposures of guinea pigs for 1 hour to zinc oxide concentrations ranging from 1,000 to 2,600 mg/cu m. The animals exhibited "air hunger" and labored breathing. Their body temperatures were depressed below normal for the first 3-4 hours after exposure, but the animals then became febrile, reaching a peak after 16 hours.

Drinker and Drinker [48] in 1928 conducted experiments in which cats, rats, and rabbits were exposed from 15 minutes to 3 1/4 hours at levels of zinc oxide fume ranging from 110 to 600 mg/cu m. These animals showed prolonged depression of body temperature, but no subsequent rise above normal. The degree and duration of the temperature depression depended on the species of the animal and on the severity and duration of exposure.

Several investigators [35-38] have attributed gastrointestinal effects to zinc oxide at unknown levels of exposure. However these reports have not been substantiated by later studies. [34,41,57] In particular, a study by Natvig [57] in 1937 of 100 workers with a history of repeated attacks of metal fume fever found no evidence of gastrointestinal diseases.