Zinc Exposure in Chinese Foundry Workers

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Background: *Inhalational exposure to zinc oxide fumes is associated with metal fume fever, a self-limited but very uncomfortable condition closely resembling influenza. Very little is known regarding the toxicokinetics of inhaled zinc, making the interpretation of zinc measurements in serum and urine problematic.*
Methods: *Twenty workers in a zinc foundry in Baiyin, Peoples' Republic of China, were investigated with serial examinations by a physician, chest radiographs, and spirometry. Exposure assessment consisted of the measurement of zinc in serum, urine, and personal air samples.*
Results: *No cases of metal fume fever were observed during the study period despite exposures to as high as 36.3 mg/m^3 over less than 4 hr. In addition, no radiographic or functional changes were noted. Serum zinc levels of all workers were within the reference range and did not correlate with external exposure measurements. However, elevations were noted in urinary zinc levels, which showed a significant association (Spearman's correlation coefficient = 0.47, P = 0.04) between exposure to zinc and urine zinc.*
Conclusions: *These results provide exposure measurements for zinc at which workers demonstrate tolerance to the development of metal fume fever. Furthermore, they suggest that urine may be the preferred biological medium for the assessment of zinc exposure.* Am. J. Ind. Med. 35:574–580, 1999. *© 1999 Wiley-Liss, Inc.*

KEY WORDS:* *zinc; biological monitoring; metal fume fever

INTRODUCTION

Inhalational exposure to zinc oxide may result in metal fume fever, a very uncomfortable condition closely resembling influenza. It typically begins 4–6 hr after exposure, with symptoms resolving after 24–48 hr without specific treatment. One peculiar feature of metal fume fever is the phenomenon of tachyphylaxis, or rapidly acquired tolerance in which workers are asymptomatic following repeated exposures to zinc oxide. Those at risk of developing metal fume fever include individuals flame cutting or welding galvanized steel, zinc or brass foundry workers, and zinc sprayers.

Very little data is available on air concentrations of zinc oxide associated with metal fume fever. Much of our current understanding of this condition is based on a series of human experiments by Drinker and colleagues published in 1927 [Sturgis et al., 1927; Drinker et al., 1927a,b,c]. Two volunteers in whom metal fume fever was reproduced breathed an estimated concentration of 600 mg/m^3 for 5 and 12 min, respectively [Sturgis et al., 1927]. In a study of 26 welders subjected to welding fume challenges with an estimated mean air zinc oxide concentration of between 70–140 mg/m^3, two individuals developed a clinical picture consistent with metal fume fever [Blanc et al., 1991, 1993]. In a recent study, Fine et al. [1997] produced a mild fever

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Accepted 23 February 1999

TABLE I. Summary of Methodology in a Study of Chinese Foundry Workers Exposed to Zinc

Pre-shift	Mid-shift	Post-shift	24 Hr post-shift
Clinical assessment			
Baseline medical interview and physical examination	Medical interview and physical examination	Medical interview and physical examination	Medical interview and physical examination
Spirometry	Spirometry	Spirometry	Spirometry
Chest radiograph		Chest radiograph	
Exposure assessment			
Timed urine collection	⟶		
Personal air sampling	⟶		
		Serum and whole blood collection	

(reported as a mean increase of 1.4 ± 0.3°F) in 10 of 13 subjects inhaling zinc oxide at 5 mg/m^3 for 2 hr.

In case reports of metal fume fever, zinc has usually been measured in serum. Zinc levels described as elevated, normal, and below normal in metal fume fever have all been reported [Noel and Ruthman, 1988]. Many of the results are difficult to interpret because the timing of the sample in relation to exposure is not provided.

To gain further insight into workplace concentrations of zinc oxide that lead to the development of metal fume fever, as well as to explore the relationship of external zinc levels to those of serum and urine, a study was undertaken of workers potentially exposed to high levels of zinc oxide.

MATERIALS AND METHODS

Study Population

The study was carried out on 20 workers in a zinc foundry within the Northwest Lead/Zinc Foundry Complex of Baiyin Corp., in the industrialized city of Baiyin, about 200 km northeast of the city of Lanzhou. The industry in this area is based on refining ore from a local mine which contains copper, lead, and zinc. In the particular foundry studied, zinc ingots from an adjacent smelter are melted and undergo a final refining step. Work is divided into three 8-hr shifts beginning at 8 AM. There are four groups of workers who work rotating shifts.

Ethics approval for the study was obtained from the Research Ethics Board of the Faculty of Medicine and Oral Health Sciences, University of Alberta, prior to the study. Informed consent was obtained from all workers prior to participation in the study protocol.

All workers studied were performing an 8 AM to 4 PM shift. They were examined before the start of the shift, in the middle of the shift, after the shift, and 24 hr post-shift. This timing was chosen to minimize disruption in the workplace. Four subjects were studied daily on five consecutive days.

Workers were all male between the ages of 24 and 44 with a mean age of 29.8 years. Eighteen of the workers had worked in the foundry since it opened 6 years earlier. Fifteen subjects were active smokers. Three subjects gave a history of fever or chills in relation to work in the past; two of these also reported additional symptoms of metal fume fever with these episodes of fever/chills. In total, 13 subjects reported at least one of the symptoms associated with metal fume fever (nausea, dyspnea, cough, headache, sweet or metallic taste, throat irritation, or fatigue).

When asked about symptoms noted when they first started work in the foundry, all but one subject (who later recalled experiencing work-related nausea) recalled symptoms. Ten experienced throat irritation, seven experienced sweet or metallic taste, four experienced cough, three experienced nausea, and three experienced dyspnea.

Investigations

Investigations were performed in two broad areas: a clinical assessment aimed at ascertaining cases of metal fume fever and an exposure assessment for zinc. The various investigations are summarized in Table I.

The clinical assessment consisted of an interview and examination performed by a physician, chest radiographs, and spirometry. Spirometry was performed according to American Thoracic Society standards [ATS, 1995]. Exposure assessment consisted of external sampling through personal air sampling as well as measurement of zinc in serum and a cross-shift (approximately 8 hr) urine collection.

Separate air samples were taken during the first half of the shift in the morning and the second half in the afternoon. One sampler broke down during the study; therefore, personal air sampling data are not available for subject #5 or subject #13 during the morning half of the shift. Matched weight, mixed cellulose ester filters with a pore size of 0.8 μm in preloaded closed-faced 37 mm diameter cassettes

TABLE II. Zinc Measurements in Air, Serum, and Urine in Chinese Foundry Workers

Subject no.	AM air sample zinc concentration (mg/m^3)	PM air sample zinc concentration (mg/m^3)	Mean air sample zinc concentration (mg/m^3)	Serum zinc (μmol/L)	Urine zinc (μmol/L) approx. 8 hr shift
1	0.62	0.53	0.58	10.3	1.89
2	0.74	1.9	1.3	12.2	5.51
3	0.79	1.1	0.94	12.1	8.28
4	1.6	1.1	2.7	11.5	4.25
5	Not available	Not available	Not available	15.8	2.94
6	0.89	2.0	1.5	11.5	4.18
7	0.24	0.56	0.40	12.5	1.85
8	5.2	17	11	12.0	4.59
9	0.30	0.22	0.26	10.0	0.87
10	2.6	3.0	2.8	9.1	5.02
11	3.5	0.49	2.0	12.4	3.33
12	3.2	0.72	2.0	9.9	2.71
13	Not available	5.9	3.0	13.6	2.79
14	0.88	36.2	18	12.3	2.28
15	9.8	4.8	7.3	10.6	3.74
16	0.47	2.0	1.2	11.0	3.66
17	0.33	0.09	0.21	12.1	2.08
18	0.97	1.1	1.0	11.8	3.32
19	0.43	6.7	3.6	9.3	7.48
20	0.48	0	0.24	10.2	2.64

(Omega Specialty Instrument Co., Chelm's Ford, MA) were used for all air sample collections. Sample collection and analysis was performed according to National Institute of Occupational Safety and Health methods [NIOSH, 1984].

Cross-shift urine samples were collected from each study subject. Workers were asked to void just prior to the shift and all urine produced until the end of the shift was collected. Post-shift blood sampling consisted of serum zinc measurement and a complete blood count with differential (manual determination). Measurement of zinc in serum, air sample digests, and urine was performed using flame atomic absorption spectrometry at the University of Alberta Hospital Trace Elements / Environmental Toxicology Laboratory.

Data and Statistical Analyses

Although workers were exposed to zinc in the form of zinc oxide, by convention all exposure measurements and reference ranges are expressed in terms of metallic zinc. For consistency, when zinc results from biological matrices have been reported in milligram units, these have been converted to molar units (1 mg = 15.29 μmol).

Morning and afternoon air sampling results were measured separately and averaged to obtain mean values for the entire shift for each subject. For purposes of obtaining an average value for subject 13, in whom only an afternoon air sampling result was available, a morning value of 0 mg/m^3 was used.

Urine zinc levels for statistical analyses were calculated by multiplying the measured concentration (in units of μmol/L) by the volume of urine collected to derive the amount of zinc in the cross-shift collection (in μmol) (Table II).

Nonparametric methods were chosen to examine the relationship between zinc measured in air, serum, and urine using Spearman's rank correlation method. Two-tailed tests of significance at the 0.05 level were used. No statistical adjustments were made for multiple comparisons. Data were analyzed using standard statistical packages [SAS Institute Inc., Cary, NC, and SPSS Inc., Chicago, IL].

RESULTS

No cases of metal fume fever were observed in the study cohort as evidenced by the medical examinations and normal post-shift white counts (mean of $7.9 \pm 1.4 \times 10^9$ cells/L). With respect to spirometry, the mean FEV_1 of the 20 subjects increased by 2% (3.77 ± 0.53L), 5% (3.88 ± 0.58L), and 6% (3.91 ± 0.53L) of the pre-shift measurement (3.68 ± 0.56L) at the mid-shift, post-shift, and 24-hr post-shift assessments. Similarly, mean FVC increased by 0% (4.65 ± 0.53L), 2% (4.78 ± 0.57L), and 2% (4.78 ±

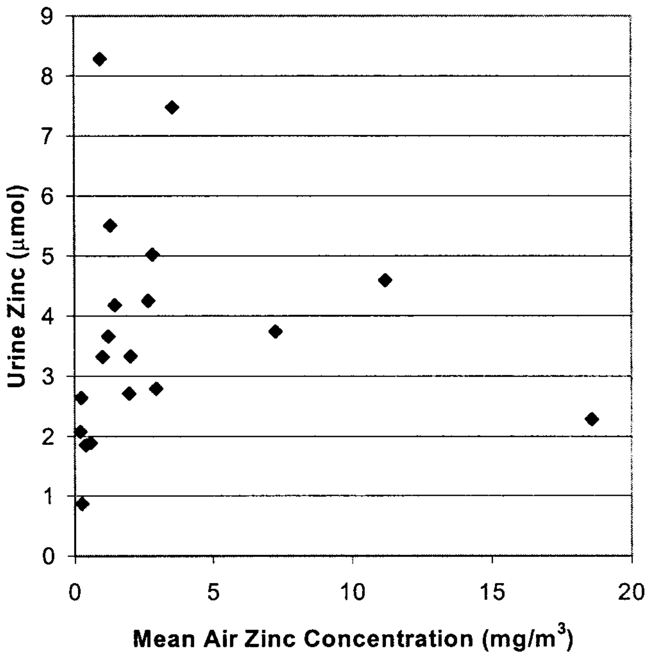

FIGURE 1. Cumulative urine zinc against mean air zinc (Spearman's correlation coefficient = 0.47, $P = 0.04$).

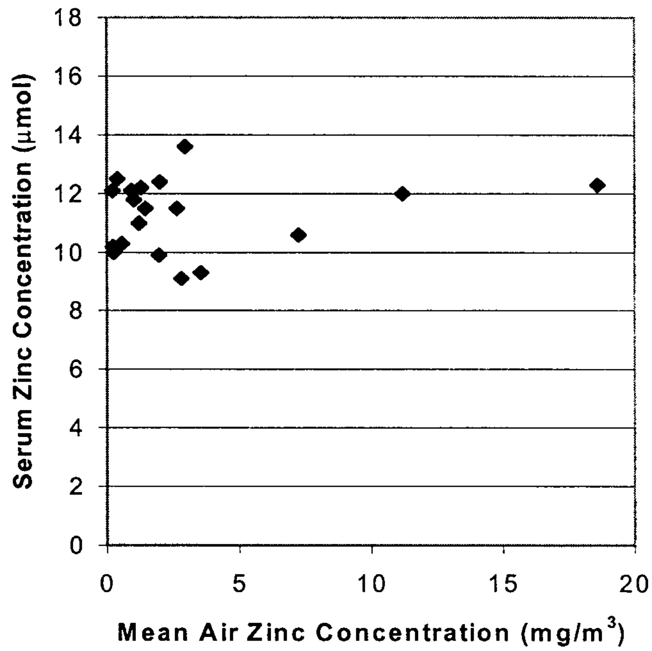

FIGURE 2. Serum zinc against mean air zinc (Spearman's correlation coefficient = 0.05, $P = 0.84$).

0.58L) from the pre-shift measurement (4.67 ± 0.51L). No radiographic changes were noted.

Most of the mean air sampling levels of zinc were below the recommended 8-hr TLV of 5 mg/m^3 (Table I). However, three subjects exceeded this value. These were subjects 8 (11.2 mg/m^3), 14 (18.6 mg/m^3), and 15 (7.3 mg/m^3). The highest single measurement was for the afternoon half of the shift for subject 14 (36.3 mg/m^3).

Figure 1 is a plot of the mean air sample zinc measurement against the measured value of zinc in the cross-shift urine collection for each subject. There was a statistically significant association ($P = 0.04$) between mean air sampling values of zinc and urine zinc measured during the shift with a Spearman's correlation coefficient of 0.47.

Although this association was largely driven by the afternoon shift air sampling values ($P = 0.02$, Spearman's correlation coefficient of 0.55) the association with the morning shift values did approach conventional statistical significance ($P = 0.09$, Spearman's correlation coefficient of 0.41).

Regarding mean air sampling values, if the three subjects with levels above 5 mg/m^3 are excluded from the analysis, Spearman's correlation coefficient increases to 0.61 with a P value of 0.01.

Serum zinc levels ranged from 9.1–15.8 μmol/L (Table II). These values fall within or below a widely accepted plasma reference range of 10.7–22.9 μmol/L [Milne, 1994], recognizing that serum levels of zinc may be as much as 16% higher than plasma levels [Abu-Hamdan et al., 1981]. No statistically significant association was observed between serum zinc levels and either mean air sample levels ($P = 0.84$, Spearman's correlation coefficient = 0.05, Fig. 2) or the morning or afternoon air sample levels. Similarly, no association was observed between serum and urine zinc measurements.

DISCUSSION

Clinical Assessment

No convincing cases of metal fume fever were observed in the course of this study. Subject 14 reported a constellation of symptoms (myalgias, nausea, headache, feeling feverish) consistent with metal fume fever at the mid-shift assessment. However, these symptoms were not noted at subsequent assessments and were not accompanied by either a rise in oral temperature or a peripheral leukocytosis in the post-shift blood count.

The American Conference of Governmental Industrial Hygienists (ACGIH) recommended 8-hr time-weighted average (TWA) for zinc oxide fume is 5 mg/m^3, which is intended to be protective for metal fume fever [ACGIH, 1993]. Three subjects had estimated 8-hr exposures of 7.5 (subject 15), 11.2 (subject 8), and 18.6 (subject 14) mg/m^3. Subject 14's exposure was particularly high over the afternoon half of the shift (36.4 mg/m^3). Thus, despite sufficient exposure, metal fume fever did not develop in the workers studied.

TABLE III. Summary of Studies Measuring Zinc Levels in Biological Matrices

Reference	Matrix	Sample Timing	Result	Reference Range [Milne, 1994]
Hamdi [1969]	Plasma 24 hr urine	Chronically exposed workers, no attempt to time samples	Statistically significant difference between clinically exposed workers for 24 hr urine but not for plasma	
Anthony et al. [1978]	Urine	Tenth day of hospitalization	400 mg/L (6,100 μmol/L)	2.3–18.4 μmol/day (24 hr collection)
Armstrong et al. [1983]	Single void urine	48 hr after exposure	0.05 to 1.8 mg/L (0.76 to 27.5 μmol/L)	2.3–18.4 μmol/day (24 hr collection)
Ulvik [1983]	Serum	6 hr after onset of symptoms 23 hr after onset of symptoms 6 days after onset of symptoms	11.3 μmol/L 9.5 μmol/L 13.3 μmol/L	10.7–22.9 μmol/L (plasma)
Vogelmeier (1987)	Serum ?	Not reported	6.9, 7.0 mg/L (105, 107 μmol/L)	10.7–22.9 μmol/L (plasma)
Noel and Rothman [1988]	Serum	12 hr after exposure	179 μg/dL (27.4 μmol/L) 161 μg/dL (24.6 μmol/L)	10.7–22.9 μmol/L (plasma)
Blanc et al. [1991]	Serum	6 hr after exposure 20 hr after exposure	14.8 ± 2.3 μmol/L 11.5 ± 2.6 μmol/L Inverse correlation between zinc exposure and serum zinc	10.7–22.9 μmol/L (plasma)
Pasker et al. [1997]	Urine	Post-shift	Statistically significant difference in levels between exposed and unexposed workers	

There is, however, a well-known, rapidly acquired tolerance to zinc exposure, termed tachyphylaxis. The precise duration of tachyphylaxis in the absence of ongoing exposure is not known. It has been demonstrated in human subjects receiving a second zinc exposure given within 24 hr of the first exposure [Drinker et al., 1927b]. Subject 8 finished a shift 16 hr previously, subject 14 finished a shift 36 hr previously, and subject 15 finished a shift 24 hr previously. Therefore, it is quite possible that tachyphylaxis may explain why no cases of metal fume fever were observed.

Exposure Assessment

Attempts to measure zinc in serum have yielded inconsistent results, as summarized in Table III. In a case investigated by Vogelmeier et al. [1987], the serum zinc at an unspecified interval following two separate exposures was markedly elevated (6.9 and 7.0 mg/L, equal to 105 and 107 µmol/L, compared to a reference range of 10.7–22.9 µmol/L). Although a methodology for serum zinc determination was cited in the text of the article, the authors refer to ‘‘the blood level of zinc.’’ This statement, together with the magnitude of the observed elevation, suggest that the measurement may have been made on whole blood, in which case the elevation was spurious.

In 14 welders investigated by Blanc et al. [1991], the mean serum zinc was not elevated at 6 and 20 hr post-exposure (14.8 ± 2.3 µmol/L and 11.5 ± 2.6 µmol/L). Noel and Ruthman [1988] reported serum zinc levels 12 hr after exposure in two laborers cutting galvanized steel who developed metal fume fever. They describe values of 179 µg/dL (27.4 µmol/L) and 161 µg/dL (24.6 µmol/L) as elevated compared to a range of 55 to 150 µg/dL (8.4–22.9 µmol/L). The upper limit of this range is usually cited for plasma, whereas the sample measurements were made on serum. Since serum zinc measurements have been reported to be up to 16% higher than plasma [Abu-Hamdan et al., 1981], these results are difficult to interpret and are at best described as being marginally elevated or at the upper limit of the reference range.

A more likely possibility is that circulating levels of zinc decline in metal fume fever. In studies on welders with metal fume fever, Blanc et al. [1991] found a statistically significant inverse correlation between cumulative zinc exposure and serum zinc. Ulvik [1983] presented a compelling case report of a man with metal fume fever in whom serum zinc decreased. Three measurements were made during the course of his illness. Six hours after the onset of symptoms serum zinc was 11.3 µmol/L; 23 hr after the onset of symptoms, 9.5 µmol/L; and 6 days after symptom onset, 13.3 µmol/L. Ulvik [1983] noted that low serum zinc is a feature of several other inflammatory conditions, as well as myocardial infarction. He speculated that the decline in serum zinc in metal fume fever may be ‘‘an unspecific [sic] response to a local inflammation in the lung tissue'' [Ulvik, 1983]. Ulvik proposed a sequestering of circulating zinc from plasma into the liver. Hirano et al. [1989] demonstrated a dose-dependent induction of the low molecular protein metallothionein following intratracheal instillation of zinc oxide in the lung. Leber and Miya [1976] have shown that zinc induces the synthesis of hepatic metallothionein in mice, suggesting a possible role for metallothionein in this process.

Much less information is available on measurements of zinc in urine in metal fume fever. Anthony et al. [1978] presented a case report of a welder exposed to both zinc and cadmium fumes whose clinical picture was more consistent with a toxic pneumonitis with pulmonary edema than metal fume fever. A urine zinc on the tenth hospital day was 400 mg/L (6,100 μmol/L). The authors do not specify whether this measurement was made on a single void specimen or a 24-hr collection.

Armstrong et al. [1983] investigated an outbreak of metal fume fever in 26 workers cutting brass pipes with carbon-air torches. The outbreak was ascribed to copper since the piping was found to consist of 90% copper and 10% nickel, with only trace amounts of zinc and markedly elevated urinary copper levels were measured in single void samples in 5 of 12 workers. Urinary zinc was also modestly elevated, with a reported range of 0.05 to 1.8 mg/L (0.76–27.5 μmol/L) [Armstrong et al., 1983].

A recent study by Pasker et al. [1997] included zinc measurements from end-of-shift urine samples. Although the data were not presented, small but statistically significant higher levels were reported in exposed workers compared to unexposed [Pasker et al., 1997].

Hamdi [1969], in a study of 12 furnace operators in a brass foundry and 10 unexposed controls, reported statistically significant differences in zinc concentrations in 24-hr urine collections but not plasma. Although a statistically significant difference was also reported for whole blood, most authorities regard plasma as the metabolically active fraction of zinc [Cousins, 1985]. Although zinc levels in urine tend to be more consistently elevated, the available studies suggest there is also quite a large degree of variability in the reported levels.

The present study was designed to describe the functional, radiographic, and clinical changes in cases of metal fume fever rather than to obtain detailed toxicokinetic information on zinc exposure. Accordingly, a small number of subjects underwent several different investigations with the aim of obtaining detailed descriptive data. Therefore, in view of the small sample size, the results of this study should be regarded as preliminary.

With these caveats in mind, possible elevations were found in urine zinc levels. Since reference ranges are usually based on 24-hr collections, multiplication of the cross-shift urine collections from this study yielded elevated values for subjects 3 (24.9 μmol) and 19 (22.4 μmol) using a reference range of 2.3–18.4 μmol/day [Milne, 1994]. A statistically significant association was also found between air exposure to zinc and the amount of zinc measured in cross-shift urine collections (Spearman's correlation coefficient = 0.47, $P =$ 0.04).

If this association is real, inhaled zinc oxide must be taken up from the lungs by the circulation and cleared through the kidneys very rapidly. Studies in rats have indicated that zinc oxide is cleared from the lung with an estimated half-life of 14 hr following intratracheal instillation [Hirano et al., 1989]. No estimates of the half-life of zinc in circulation could be identified. It is possible that inhaled zinc, when taken up by the circulation, may be present in a labile form amenable to rapid renal clearance. In any event, such rapid clearance was also suggested by the study by Pasker et al. [1997], in which the relative elevation in urinary zinc levels was noted in end-of-shift samples.

A second question relates to the three subjects with the highest mean air sampling values for zinc. With these outliers excluded from the analysis, the association between air sample and urine zinc levels appears to be strengthened. It is, of course, possible that the air samples on these three subjects were contaminated. If, however, these measured levels are accurate, this finding may suggest a threshold for the renal clearance of zinc, above which further elevations in the amount of zinc in the personal breathing zone are not accompanied by proportional increases in zinc in the urine.

As most of the workers had completed shifts 16–24 hr prior to the study shift, the urinary zinc measurements may actually reflect exposure prior to the start of the study. Furthermore, variations in urine output may not have been adequately accounted for in this study. Therefore, further attempts to confirm these findings should be performed on workers without recent exposure to zinc and include 24-hr urine collections and/or measurements of urine creatinine, which were not made in the present study.

Since serum appears to be a poor choice of body fluid for establishing inhalational exposure to zinc, future studies of zinc exposure and metal fume fever should include measurements of zinc in urine.

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