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Toenail, Blood and Urine as Biomarkers of Manganese Exposure

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Abstract

Objective—This study examined the correlation between manganese exposure and manganese concentrations in different biomarkers.

Methods—Air measurement data and work histories were used to determine manganese exposure over a workshift and cumulative exposure. Toenail samples (n=49), as well as blood and urine before (n=27) and after (urine, n=26; blood, n=24) a workshift were collected.

Results—Toenail manganese, adjusted for age and dietary manganese, was significantly correlated with cumulative exposure in months 7-9, 10-12, and 7-12 before toenail clipping date, but not months 1-6. Manganese exposure over a work shift was not correlated with changes in blood nor urine manganese.

Conclusions—Toenails appeared to be a valid measure of cumulative manganese exposure 7 to 12 months earlier. Neither change in blood nor urine manganese appeared to be suitable indicators of exposure over a typical workshift.

Keywords

Manganese; biomarkers; toenail manganese; blood manganese; urine manganese; low-level manganese exposure; welding fumes; welders

INTRODUCTION

There is growing interest in the health effects of manganese exposure. It has long been recognized that, in occupational settings, significant exposure to manganese (Mn) can occur among workers involved in ferroalloy production, iron, or steel foundries, and welding.[1] Mn in the forms of dust and fume is released in these processes, and enter the body primarily via inhalation and lead to adverse health effects. Short-term assessment of exposure to Mn among workers is generally conducted by measurement of airborne Mn from the worker's breathing zone, which assesses the estimated external dose for the

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duration of measurement. The general population is also exposed to manganese, although generally at lower levels than workers, largely through water, food, or air.[1]

In epidemiologic studies, biomarkers of exposure are useful to verify subject-specific exposures and as an index of internal dose. Blood manganese, urinary manganese, and less frequently nail and hair manganese, have been suggested as biomarkers of exposure.[2] Blood Mn and urinary Mn may reflect exposure over a short and recent period of time (hours to days), while nails and hair are thought to integrate exposure over longer periods of time and thus represent exposures over several months or longer.[3-6] These biological markers can provide important information on the relationship between exposure, the biologically effective dose of an agent at a susceptible site, and the eventual development of clinically-apparent outcome.[7-8]

The utility of blood and urine Mn as biomarkers of Mn exposure is questionable based on the findings from several studies.[2, 5, 9-10] A recent study among occupationally exposed adults [5] found a complex and limited relation between exposure (as measured by total air Mn level and cumulative exposure indices) and blood Mn levels that may depend upon exposure attributes and the latency of blood measurements relative to exposure. Plasma and urine Mn appeared even less useful as exposure biomarkers. In general, studies have found no or weak relations between blood or urine Mn and exposure, which could be explained by the high variability and short half-life of Mn in blood and urine.

Toenails and hair have been proposed as exposure biomarkers for longer-term cumulative exposure assessment. A number of previous studies have demonstrated that Mn can accumulate in toenails, fingernails, and hair [4, 6, 9, 11-12], and that Mn accumulation is greater in these matrices among high exposure groups than lower exposure groups.[9, 12] These studies, however, have not examined the individual level correlation between external Mn exposure and hair or toenail Mn. A validated biomarker for cumulative exposure to Mn could be of tremendous use in studies of health effects of Mn exposure.

To determine how well toenail Mn reflects cumulative exposures in different exposure windows, we examined the correlation between Mn cumulative exposure indices and toenail Mn concentration among welders at a union welding school. We focused on toenails because hair is thought to be more subject to accumulation of metals due to external contamination, reflecting concentrations out of proportion to the body's actual internal exposure.[4] We studied welders because the determination of external exposures is difficult among the general population whereas specific exposure histories are more easily taken among welders, particularly those with a more limited range of welding jobs like those at the welding school. We also examined the correlation between toenail, blood, and urine Mn concentrations, and the change in blood and urine Mn following Mn exposure over a work shift.

MATERIALS AND METHODS

Study Population

The study was approved by the Institutional Review Board of the Harvard School of Public Health. All individuals recruited for the study were informed of the study objectives before obtaining written consent for their participation. Forty-six welders were recruited from a local boilermaker union in June 2008 (n=28) and January 2009 (n=18). Many of them were apprentice welders with less than 3 years experience in welding while the others were more professional welders. These welders participated in our study at the boilermakers welding school where personal work history data and several biological samples were collected. In June 2008, twenty-eight welders were recruited and completed questionnaires. Twenty-

seven of these welders provided blood and urine samples at the beginning of the day, and 26 of them welded during the day during which they were monitored for Mn exposure. These 26 provided a second urine sample after their welding and 24 provided a second blood sample. In January 2009, another 14 welders were recruited, completed questionnaires, provided toenail samples, but blood and urine samples were not collected. An additional thirteen welders were recruited via mail and returned questionnaires and toenail samples.

The welding school consisted of a large, temperature-controlled room outfitted with ten workstations with local exhaust ventilation where the welders received instruction and practiced welding, cutting, and grinding techniques. These welders primarily performed shielded metal arc welding (SMAW, or STICK) and gas metal arc welding (GMAW, or MIG), most commonly using base metals of mild steel and stainless steel (manganese, chromium, and nickel alloys) with electrodes composed mainly of iron with variable amounts of manganese (1-5%). Plasma arc or acetylene torch cutting and grinding also occurred at the work site. Each participant completed a work log and an exposure diary, to assess the number hours welded, type of welding done, and use of protective equipment and ventilation.

Data Collection

Questionnaires—All participants completed self-administered questionnaires that included items on work history, medical history, and life style variables. A standard food frequency questionnaire (FFQ) which was slightly modified to focus on Mn-rich foods (tomato juice, grape juice, beer, wine, and liquor, and 15 food items such as wheat germ, pecans, oat meal, sweet potatoes, and spinach) was also used. Each participant was asked to consider a typical serving size of each (indicated in the FFQ) for these foods and fill in the one frequency that best reflects his average use of each food in the last year (9 levels from never to 6+ per day). Then, the amount of Mn intake from foods (mg Mn/month) was calculated for each participant based on nutrient tables for foods [13-14] and the consumption amounts reported on the questionnaire. A detailed work history (dates of specific jobs, welding tasks on that job, type of metal welded, total hours welded, and respirator use) was collected for the preceding 12 months. On days that participants welded, each also completed a work log and an exposure diary, to track the number of hours welded, type of welding done, and use of protective equipment and ventilation.

Manganese Exposure Assessment—Personal gravimetric samples were collected over the duration of the work shift. We used KTL cyclones (GK2.05SH, BGI Inc., Waltham, MA) with aerodynamic diameter cutpoint of 2.5 μm, in line with personal sampling pumps (APEX/VORTEX, Casella CEL, UK) drawing 3.5 L/min of air. The cyclone was secured to the participant's shoulder in the breathing zone area, and the pump was placed in a padded pouch that was carried by the participant for the entire workday. The cyclone was fitted with a cassette holding a 37 mm polytetrafluoroethylene (PTFE) membrane filter (Gelman Lab., Ann Arbor, MI). Before and after sampling, filters were weighed in a temperature- and humidity-controlled room using a standard protocol on an MT5 micro-balance (Mettler-Toledo Inc., Columbus, OH). They were then analyzed for elemental components using a portable NITON XL3t Portable XRF (ThermoFisher, Billerica, MA), as previously described.[15-16] Air samples were collected to represent exposures around major tasks at the welding school. Repeated measurements were taken for most of these tasks and the average for a particular task (e.g. STICK welding of mild steel using 7018 electrode) was used in the construction of cumulative Mn exposure index (Mn-CEI) for each individual. [17-18]

Based on the growth rate of toenails [19-20] clippings from all ten toenails would be expected to reflect exposure approximately 7-12 months before the clipping date. Therefore, we calculated Mn-CEIs from the work histories for the following exposure windows prior to the clipping date: months 1-6, months 7-9, months 10-12, months 7-12, and months 1-12, which were treated as measures of average exposure intensity across all exposed tasks in each specific exposure window for each participant.

Mn-CEIs for exposure windows of interest were calculated using each welder's report of specific welding tasks and total hours of welding for that task during the given exposure window, and the reported use of respiratory protection, collected from the work histories. Averaged Mn concentration from air measurements for each specific task was used in the Mn-CEI calculations. Occasionally welders reported a task for which we did not have air measurements from the school itself; in this case we used typical values from the literature. The Mn-CEI for an exposure window in the past 12 months was derived by summing (equation 1) the products of the average Mn exposure intensity, the number of hours worked on that particular task, and an adjustment for the effect of respiratory protection used for each welding task the participant performed during that exposure window (equation 2).

$$CEI_w\ \left(mg/m^3 - hr\right) = CEI_{w1} + CEI_{w2} + CEI_{w3} + \ldots + CEI_{wn} \tag{1}$$

$$CEI_{wi} = (MnA_i)\,(\mathrm{Time}_{wi})\left[\left(\frac{\%\mathrm{respirator}_{wij}}{APF_j/2}\right) + \left(\frac{\%\mathrm{respirator}_{wij}}{APF_j/2}\right) + ...\right] \tag{2}$$

Where MnA_i is the average air Mn concentration for the i^{th} task performed; $Time_{wi}$ is the total hours spent for the i^{th} task performed in the w^{th} exposure window; $\%respirator_{wij}$ is the estimated percentage of time the participant used the j^{th} respirator in the i^{th} task performed in the w^{th} exposure window; and APF_j is the assigned protection factor for the j^{th} respirator used.[21-23] This yields a measure of cumulative exposure across all exposed jobs in that exposure window, in mg/m^3-hr.

Biomarkers of Mn Exposure—Pre- and post- work shift blood samples were collected by phlebotomists in trace metal Vacutainers (Becton-Dickinson and Company, Franklin Lakes, NJ) containing EDTA. Pre- and post- work shift urine samples were collected in plastic cups and were aliquoted into 15 mL tubes for metals analysis. Toenail clippings from all toes were collected from each participant in small envelopes. Participants who could not give toenail samples at the time of our visit were asked to mail them in using pre-stamped envelopes. Participants recruited by mail also mailed in their toenail samples. In each of these cases, the participant indicated the toenail clipping date.

The biological samples were analyzed in the Harvard School of Public Health Trace Metals Laboratory, which is equipped with a class 100 clean room facility and a dynamic reaction cell-inductively coupled plasma mass spectrometer (DRC-ICP-MS, Elan 6100, Perkin Elmer, Norwalk, CT). Quality control measures are routinely performed in the laboratory and included analysis of initial calibration verification standards (NIST SRM 1643d trace elements in water), continuous calibration standards, procedural blanks, duplicate samples, spiked samples, quality control standards, and certified reference material.

Toenail clippings were prepared and analyzed as described by Kile et al., 2007.[24] Briefly, external contamination was removed from nails by sonicating samples in a 1% Triton X-100 solution (Sigma-Aldrich, Inc., St. Louis, MO) for 20 minutes. Toenails were then rinsed

repeatedly in Milli-Q water (Millipore Corp., Billerica, MA), dried, weighed, digested in nitric acid, and analyzed using ICP-MS. Each sample was subjected to five replicate analyses. The net averaged concentration was calculated by subtracting detectable laboratory blank concentrations within each batch.

Data Analysis

Spearman correlations were used when considering toenail Mn measurements because these concentrations were not normally distributed. When toenail Mn was not involved, Pearson correlations were used as the other measures were adequately normally distributed. Correlation coefficients, adjusted for age (year) and dietary Mn (mg/month), were computed to assess the associations between toenail Mn and Mn-CEI for the exposure windows of interest (partial correlation). Correlations between Mn exposure over a work shift and changes in blood Mn or urinary Mn, and the correlations among these 3 biomarkers of Mn exposure were also determined.

Statistical analyses were performed with Statistical Analysis System (SAS Institute Inc., NC) version 9.1.3. Statistical significance was set at alpha = 0.05.

RESULTS

From the personal exposure monitoring over their work shifts, the concentrations of airborne Mn from welding ranged from 2.02 to 137.41 $\mu g/m^3$ (median = 12.89 $\mu g/m^3$). Mn-CEI (median) ranged from 0 – 6.88 (0.52) mg/m^3-hr for the 7-9 month window, 0 – 5.05 (0.44) mg/m^3-hr for the 10-12 month window, 0 – 21.88 (1.23) mg/m^3-hr for the 1-6 month window, 0 – 10.09 (1.15) mg/m^3-hr for the 7-12 month window, and 0 – 24.14 (3.41) mg/m^3-hr for the past 12 months. Blood Mn (n= 27) collected at the beginning of the day ranged from 15.29 to 28.61 ng/ml (mean = 18.88 ng/ml) and beginning of the day urinary Mn (n = 27) ranged from 0.45 to 3.02 ng/ml (mean = 1.50 ng/ml). Collected toenail samples (n=49) had a skewed distribution ranging from 0.05 to 10.41 $\mu g/g$ with a median of 0.80 $\mu g/g$ (25^{th}-75^{th} percentiles: 0.45-1.49). The distribution of toenail Mn by different characteristics and Mn-CEI for the different exposure windows, are presented in table 1. Toenail Mn tended to increase with age, was higher in whites, and increased with the Mn-CEIs for the exposure windows between 7 and 12 months prior to the toenail clipping date. However, toenail Mn did not appear to be higher with increased dietary Mn intake. There was little relation between either blood Mn or urinary Mn and any of the variables (data not shown).

The Spearman correlations between toenail Mn and past Mn-CEI, adjusted for age and dietary Mn intake, were significant for the 3 Mn-CEI windows encompassing months 7-12 before the toenail clipping date (7^{th}-9^{th} months, 10^{th}-12^{th} months, and 7^{th}-12^{th} months), ranging from 0.32 to 0.35 (table 2). The unadjusted correlations were similar but slightly weaker. Pearson correlation analyses on square root transformed toenail Mn and Mn-CEI also yielded similar coefficients. There was little correlation between toenail Mn and any of the other Mn-CEI exposure windows, nor either pre-work shift blood Mn or urinary Mn. In contrast, the adjusted correlation between pre-work shift blood Mn and urinary Mn was reasonably high (r=0.33) and close to significant (p = 0.10). There was little correlation between post-work shift blood and urine (r=0.06; p=0.78), nor between the change in each (r=0.03; p=0.88).

There was no correlation between air Mn exposure over a work shift (mean duration = 5.83 hours; sd = 1.02 hours) and either post-shift blood Mn concentration or change in blood Mn concentration over the work shift (table 3). Air Mn exposure over a work shift was slightly more correlated with post-work shift urinary Mn and change in urinary Mn over the work shift, although these did not reach statistical significance. Pre- and post- work shift

concentrations of both blood Mn and urinary Mn, however, were significantly correlated. Pre- work shift blood Mn and urinary Mn were also each correlated with the change in those measures, although inversely and only statistically significantly for change in blood Mn (table 3).

DISCUSSION

Our study demonstrates that toenail Mn, averaged over clippings from all 10 toes, is correlated with Mn-CEI windows encompassing months 7-12 before the toenail clipping date, which is the exposure window it would be expected to reflect based on toenail growth rates. One of the first estimates reported a toenail growth rate of approximately 0.050 mm per day [19], which would suggest that clippings should reflect exposures, on average, 8-9 months before the clipping date. A recent study [20] found slightly faster nail growth rates, and suggested that the great toenails grow faster than other toenails—at the estimated rate of 2.09 mm/month. Since it is much longer than other toenails, great toenails (average length of 2 cm) may represent exposures more than 10 months before clipping.[20] The average exposure window reflected would be 1-2 months earlier than this if nails from all 10 toes were used. These are consistent with the findings from our study that the correlation between toenail Mn and Mn-CEI was strongest for exposure windows in the 7-12 months before clipping. This is also consistent with a previous study of toenails as markers of selenium intake.[25] Toenail Se concentration was unaffected by dietary intake in the 3 months prior to nail clipping and appeared to provide a time-integrated measure of intake over a period of 26-52 weeks (~6.5-12 months) before nail clipping, which is essentially the same exposure window as ours.

A few studies have suggested that the human toenail could be used as a biomarker of exposure to other elements such as arsenic [24] and selenium.[25-26] However, we are aware of only two studies that looked at toenails as biomarkers of Mn exposure. One study compared toenail Mn to whole blood Mn and fecal Mn collected at the same time among exposed workers.[6] No assessment of individual level external exposures, however, were made in this study. They observed poor correlations between the different biomarkers and concluded that toenails might not be a good biomarker for Mn. Another study in a general population sample compared toenail Mn among multivitamin users to matched controls and found that toenail Mn was not significantly higher among Mn supplement users.[4] This is consistent with our finding that toenail Mn did not tend to increase with dietary Mn, although we did observe slightly stronger correlations with Mn-CEIs after adjusting for age and dietary Mn. Unlike other elements (e.g., As) [24], Mn from food intake may not make a significant contribution to internal dose represented by toenail Mn. It is also possible, however, that increases in toenail Mn from dietary sources could have been masked by a relatively larger amount of occupational exposure to Mn by inhalation.

It was not unexpected that blood Mn and urinary Mn were not well correlated with toenail Mn, nor any of the Mn-CEI given the relatively short half-life (several days) of Mn in blood and urine.[7, 27] A number of previous studies suggested that blood Mn and urinary Mn may be used to discriminate groups of exposed and non-exposed subjects, but not differences in exposure on an individual basis.[2, 5, 9-10] Morning blood and urine samples were reasonably well correlated with each other, suggesting that the exposure windows they reflect are similar. Because of the shorter time frames of blood Mn and urinary Mn as exposure biomarkers, we were interested in how well these biomarkers reflected Mn exposure across a work shift. However, changes in both blood Mn and urinary Mn over a work shift were not well correlated with air Mn exposure over that time. Intriguingly, there was a strong significant inverse correlation between pre-work shift blood Mn and change in blood Mn over the work shift. This suggests that there may be homeostatic pressures that

limit the rise in blood Mn such that those who have a high blood Mn concentration before the work shift do not increase blood Mn concentration as much as those whose blood Mn is lower before the work shift. There was a similar although less strong and significant trend for urinary Mn. Small sample size for blood and urine may limit our ability to observe such relationship.

A strength of our study is that the population was recruited from a welding school, which meant that the range of their welding exposures to Mn over the prior year was more limited than in many other settings and we were able to take air measurements during most of the types of welding tasks they performed over the past year. These factors should have helped increase the accuracy of our Mn-CEI. Nonetheless, Mn-CEI created on the basis of retrospective work histories likely have some error that would reduce the correlation between toenail Mn and true Mn exposure for a given window. Thus, the correlations we found may still underestimate correlations with actual air Mn exposures.

A broader implication of our results relate to the use of toenails as a biomarker of Mn exposure in non-occupational settings. In our occupational study setting air Mn exposures are likely far more variable than in the general population because the exposures depend heavily on job or training-related exposure and these can vary substantially from month to month (welders often have periods of intense work activity followed by periods of no work activity and these can vary month to month). As a result air Mn exposure in months 1-6 prior to toenail clipping are less correlated with air Mn exposure 7-12 months prior to clipping than they might be in a general population sample. Thus, the utility of toenail Mn as an exposure metric in an occupational setting is likely restricted to a period 7-12 months prior to the clipping date. However, to the extent that external exposures are more consistent, as might be expected in a general population setting, toenail Mn may be a better biomarker for more general cumulative exposure. Furthermore, toenails have important practical advantages over other samples such as blood and urine in that they are easier to collect (e.g. they can be collected by mail with no special mailing requirements) and store.

Hair and fingernail tissues are similar to toenail and have also been explored to some extent as biomarkers of Mn exposures, although they are generally thought to be more subject to external contamination because they are more frequently open to the external environment than toenails. This may explain in part why the few studies that have explored these tissues as biomarkers of Mn exposure suffered from a relatively great variation as well as from analytical problems.[9, 11]

CONCLUSIONS

Our study is, to our knowledge, the first to assess the relation between external exposure to manganese and toenail Mn concentration on an individual basis. Among this population of boilermaker welders, neither blood nor urine was reflective of cumulative exposure in the prior year and changes in Mn concentration in these media over a welding work shift did not correlate well with Mn exposure over that time. Toenail Mn, however, was well correlated with exposures 7-12 months earlier. While we conducted this study among occupationally exposed workers in order to better assess the external exposures, the results may be applicable to the general population, where toenail Mn may well be reflective of a more extended exposure window since external exposures in the ambient settings are likely more consistent than in occupational settings.

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REFERENCES

1. Agency for Toxic Substances and Disease Agency (ATSDR). Toxicological Profile for Manganese. US Department of Health and Human Services; Atlanta, GA: 2000.
2. Apostoli P, Lucchini R, Alessio L. Are Current Biomarkers Suitable for the Assessment of Manganese Exposure in Individual Workers? Am J Ind Med. 2000; 37:283–290. [PubMed: 10642418]
3. Aschner ME, Erikson KE, Dorman DC. Manganese Dosimetry: Species Differences and Implications for Neurotoxicity. Crit Rev Toxicol. 2005; 35:1–32. [PubMed: 15742901]
4. Guthrie JM, Brockman JD, Morris JS, Robertson JD. The “One Source” Cohort – Evaluating the Suitability of the Human Toenail as a Manganese Biomonitor. J Radioanal Nucl Chem. 2007:1–7.
5. Smith D, Gwiazda R, Bowler R, et al. Biomarkers of Mn Exposure in Humans. Am J Ind Med. 2007; 50:801–811. [PubMed: 17924418]
6. Wongwit W, Keawkungwal J, Chantachum Y, Visesmanee V. Comparison of Biological Specimens for Manganese Determination among Highly Exposed Welders. Southeast Asian J Trop Med Publ Health. 2004; 35(3):764–769.
7. Barceloux DG. Manganese. Clin Toxicol. 1999; 37(2):293–307.
8. Levy BS, Nassetta WJ. Neurologic Effects of Manganese: A Review. Int J Occup Environ Heal. 2003; 9:153–163.
9. Bader M, Dietz MC, Ihrig A, Triebig G. Biomonitoring of Manganese in Blood, Urine, and Axillary Hair Following Low-dose Exposure During the Manufacture of Dry Cell Batteries. Int Arch Occup Environ Health. 1999; 72:521–527. [PubMed: 10592004]
10. Jarvisalo J, Olkinuora M, Kiilunen M, et al. Urinary and Blood Manganese in Occupationally Nonexposed Populations and in Manual Metal Arc Welders of Mild Steel. Int Arch Occup Environ Health. 1992; 63:495–501. [PubMed: 1577529]
11. Mehra R, Juneja M. Fingernails as Biological Indices of Metal Exposure. J Biosci. 2005; 30:253–257. [PubMed: 15886462]
12. Loranger S, Zayed J. Environmental and Occupational Exposure to Manganese: A Multimedial Assessment. Int Arch Occup Environ Health. 1995; 67:101–110. [PubMed: 7545647]
13. Department of Preventive Medicine, Northwestern University. Nutritional Fact Sheet: Manganese. www.feinberg.northwestern.edu/nutrition/factsheets/manganese.html
14. International Programme on Chemical Safety. Environmental Health Criteria for Manganese. World Health Organization (WHO) Publication; Geneva: 1981.
15. National Institute for Occupational Safety and Health (NIOSH). NIOSH Manual of Analytical Methods – 4th Edition Method #7702 Lead by Field Portable XRF. Cincinnati, OH: 1998. DHHS – NIOSH Publication No. 98-119
16. Laohaudomchok W, Cavallari JM, Fang SC, et al. Assessment of Occupational Exposure to Manganese and Other Metals in Welding Fumes by Portable X-ray Fluorescence Spectrometer. J Occup Environ Hyg. 2010; 7(8):456–65. [PubMed: 20526948]
17. Bowler RM, Roels HA, Nakagawa S, et al. Dose-effect Relationships between Manganese Exposure and Neurological, Neuropsychological and Pulmonary Function in Confined Space Bridge Welders. Occup Environ Med. 2007; 64:167–177. [PubMed: 17018581]
18. Nieuwenhuijsen, MJ. Exposure Assessment in Occupational and Environmental Epidemiology. Oxford University Press; New York: 2003.
19. Edwards LF, Schott RG. The Daily Rate of Growth of Toenails. Ohio J Sci. 1937; 37:91–98.
20. Yaemsiri S, Hou N, Slining MM, He K. Growth Rate of Human Fingernails and Toenails in Healthy American Young Adults. J Eur Acad Dermatol Venereol. 2009:1–4.

21. National Institute for Occupational Safety and Health (NIOSH). NIOSH Respirator Selection Logic. Cincinnati, OH: 2004. DHHS – NIOSH Publication No. 2005-100

22. Occupational Safety and Health Administration (OSHA). Assigned Protection Factors for the Revised Respiratory Protection Standard. Salt Lake City, UT: 2009. U.S. Department of Labor – OSHA Publication No. 3352-02

23. Heirbaum, J. OSHA's Assigned Protection Factors for Respiratory Protection. www.workplacemagazine.com/contedchooseest.asp

24. Kile ML, Houseman EA, Breton CV, et al. Association between Total Ingested Arsenic and Toenail Arsenic Concentrations. J Environ Sci Health A. 2007; 42:1827–1834.

25. Longnecker MP, Stampfer MJ, Morris JS, et al. A 1-y Trial of the Effect of High-selenium Bread on Selenium Concentrations in Blood and Toenails. Am J Clin Nutr. 1993; 57:408–413. [PubMed: 8438776]

26. Satia JA, King IB, Morris JS, et al. Toenail and Plasma Levels as Biomarkers of Selenium Exposure. Ann Epidemiol. 2006; 16:53–58. [PubMed: 15961316]

27. Feldman, RG., editor. Occupational and Environmental Neurotoxicology. Lippincott Williams & Wilkins; Boston, MA: 1998.

Table 1

Distributions of toenail Mn by different characteristics of the participants and their cumulative exposure index levels (Mn-CEI) over different windows.

Characteristics			Toenail Mn, μg/g	
	n	Mean (SD)	Median	25^{th} – 75^{th} Percentiles
Age				
− < **35 years**	17	26.9 (4.6)	0.46	0.26 – 1.49
− **35 to 50 years**	15	41.1 (4.5)	0.79	0.50 – 1.17
− > **50 years**	17	55.5 (3.6)	1.10	0.56 – 1.95
Years of Welding				
− < **5 years**	19	1.66 (0.8)	0.69	0.30 – 1.59
− **5 to 10 years**	15	7.58 (1.8)	0.80	0.54 – 1.13
− > **10 years**	15	25.6 (7.1)	0.81	0.35 – 1.61
Race				
− **White**	40		0.91	0.51 – 1.54
− **Non-white**	9		0.46	0.11 – 0.46
Body Mass Index				
− **≤25**	7	23.15 (1.0)	0.56	0.30 – 1.40
− **25-30**	26	27.18 (1.2)	0.81	0.45 – 1.26
− **>30**	14	34.12 (3.1)	0.74	0.46 – 1.44
Dietary Mn				
− **≤40 mg/month**	15	25.55 (12.2)	0.65	0.37 – 1.76
− **40-85 mg/month**	17	58.57 (11.5)	0.86	0.58 – 1.24
− **>85 mg/month**	17	145.4 (51.7)	0.79	0.44 – 1.27
Mn-CEI				
For months 1–6				
− < **0.7 mg/m^3-hr**	19	0.17 (0.24)	0.79	0.27 – 1.49
− **0.7 – 4.0 mg/m^3-hr**	14	1.75 (0.98)	0.93	0.32 – 1.63
− >**4.0 mg/m^3-hr**	16	7.92 (4.30)	0.76	0.54 – 1.21
For months 7–9				
− < **0.3 mg/m^3-hr**	16	0.06 (0.09)	0.39	0.19 – 0.93
− **0.3 – 1.0 mg/m^3-hr**	16	0.52 (0.20)	0.84	0.57 – 1.49
− >**1.0 mg/m^3-hr**	17	2.28 (1.03)	1.10	0.51 – 1.70
For months 10–12				
− < **0.3 mg/m^3-hr**	18	0.05 (0.07)	0.58	0.27 – 0.81
− **0.3 – 1.0 mg/m^3-hr**	18	0.57 (0.24)	0.98	0.40 – 1.49
− >**1.0 mg/m^3-hr**	13	2.63 (1.16)	1.19	0.56 – 2.13
For months 7–12				
− < **0.7 mg/m^3-hr**	19	0.20 (0.26)	0.46	0.21 – 0.81

Characteristics			Toenail Mn, μg/g	
	n	Mean (SD)	Median	25th – 75th Percentiles
− **0.7 – 2.0 mg/m^3-hr**	15	1.29 (0.36)	1.07	0.54 – 1.59
− >**2.0 mg/m^3-hr**	15	4.61 (2.12)	1.10	0.54 – 1.70
For past 12 months				
− < **1.5 mg/m^3-hr**	20	0.64 (0.76)	0.62	0.21 – 1.37
− **1.5 – 7.0 mg/m^3-hr**	14	3.99 (1.42)	1.17	0.53 – 1.76
− >**7.0 mg/m^3-hr**	15	11.86 (4.84)	0.80	0.53 – 1.23

Table 2

Associations between Toenail Mn (μg/g), pre-workshift blood and urine Mn (ng/ml), and Mn-CEI (mg/m^3-hr) exposure windows.

	Partial Correlation[a]					
	Toenail Mn, μg/g		Blood Mn, ng/ml		Urinary Mn, ng/ml	
	ρ	P-value	ρ	P-value	ρ	P-value
	(n = 21)					
Blood Mn, ng/ml	0.11	0.66	1.00			
	(n = 21)		(n = 27)			
Urinary Mn, ng/ml	−0.18	0.46	0.33	0.10	1.00	
Mn-CEI, mg/m^3-hr	(n = 49)		(n = 27)		(n = 27)	
− **Months 1–6**	0.07	0.62	0.05	0.82	−0.04	0.84
− **Months 7–9**	0.35	**0.016**	0.12	0.58	0.02	0.94
− **Months 10–12**	0.32	**0.031**	0.17	0.42	0.06	0.77
− **Months 7–12**	0.32	**0.027**	0.07	0.75	0.01	0.97
− **Past 12 months**	0.19	0.19	0.15	0.46	−0.01	0.98

[a] Adjusted for age (year) and dietary Mn (mg/month). Spearman correlations were used when toenail Mn or CEI was involved.

Table 3

Correlations between work shift Mn exposure ($\mu g/m^3$), and blood/urinary Mn (ng/ml).

	n	Pearson's Correlation ρ (p-value)	
		Post-shift	Change[a]
Blood			
Pre-shift	27	0.63 (< **0.01**)	−0.66 (< **0.01**)
Air Mn Exposure	26	−0.07 (0.75)	−0.06 (0.80)
Urine			
Pre-shift	27	0.45 (**0.02**)	−0.22 (0.30)
Air Mn Exposure	26	0.14 (0.52)	0.21 (0.32)

[a] Change over work shift: Post-shift concentration minus pre-shift concentration.