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Abstract

Welders are exposed to relatively high concentrations of manganese (Mn) and while the neurotoxicity of Mn is well documented, few studies have investigated the cardiac effects of occupational Mn exposures. The goal of this study was to investigate the cardiac effects of Mn exposures among welders, specifically boilermaker construction workers, using a repeated measures study design where workers were monitored twice or more over a 6-month period. A total of 78 male welders were recruited from a union hall out of Quincy, MA. In total, 118 worker-days were collected with 28 (36%) workers monitored at two or more time points. Blood, hair, and nail samples were collected as biomarkers of Mn exposure (Table 1). Hair samples were only available on 33% of participants due to short hair. Detailed work histories were collected to calculate a Mn cumulative exposure index (CEI). The cardiovascular health of each worker was assessed by ambulatory electrocardiogram (ECG) and inflammatory markers. A sub-study of 49 welders with toenail, blood and work history collected at one time-point was used to determine the relationship between blood and toenail Mn and CEI. Collected toenail samples had a skewed distribution ranging from 0.05 to 10.41 ng/g with a median of 0.80 ng/g (25^{th}-75^{th} percentiles: 0.45-1.49) (Table 2). Toenail Mn increased with the Mn-CEIs for the exposure windows between 7 and 12 months prior to the toenail clipping date. These results were confirmed when the Spearman correlations between toenail Mn and past Mn-CEI, adjusted for age and dietary Mn intake, were evaluated (Table 3). Biomarker and cardiovascular health endpoints analysis is on-going. We hypothesize that occupational exposure to Mn will be associated with detectable changes in cardiovascular autonomic control as assessed by 24-hr heart rate variability (HRV) as well as changes in inflammatory markers as assessed by C - reactive protein and fibrinogen.

The top findings from this pilot study are:

1. Toenails provide a useful biomarker of intermediate Mn exposures. 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.
2. Toenail and blood Mn concentration showed no correlation and likely represent different exposure windows.
3. Boilermaker construction workers with variable Mn exposure have detectable blood and toenail manganese concentrations.
4. Toenail and blood samples are easily provided by welders while hair samples are difficult to collect.
5. We were able to recruit 78 individuals into our study over the 18-month period. However, due to variable work schedules, it was difficult to monitor participants more than once (only 36%). Future studies should account for the variable work schedule among boilermaker construction workers.

T able 3. Associations as assessed by partial spearman correlation coefficients between Toenail Mn (ng/g), blood Mn (ng/mL) and Mn-CEI (mg/m^3-hr) exposure windows.

	Toenail Mn, ng/g		**Blood Mn, ng/ml**	
	£	**P-value**	**£**	**P-value**
	(n = 21)			
Blood Mn, ng/ml	0.11	0.66	1.00	
Mn-CEI, mg/m^3-hr	**(n = 49)**		**(n = 27)**	
- Months 1-6	0.07	0.62	0.05	0.82
- Months 7-9	0.35	0.016*	0.12	0.58
- Months 10-12	0.32	0.031*	0.17	0.42
- Months 7-12	0.32	0.027*	0.07	0.75
- Past 12 months	0.19	0.19	0.15	0.46

[a] Adjusted for age (year) and dietary Mn (mg/month).

Introduction

Welders are exposed to relatively high concentrations of manganese during the process of welding. Inhalation exposure occurs when molten mild or stainless steel, or manganese-containing electrodes is volatilized. While the neurotoxicity of manganese exposure and the neurological health effects among welders are well documented (Sjogren, Iregren et al. 1996; Bowler, Gysens et al. 2003; Bowler, Gysens et al. 2006; Bowler, Roels et al. 2007), few studies have investigated the cardiac effects of occupational manganese exposures, despite the fact that welders are at increased risk for ischemic heart disease (Newhouse, Oakes et al. 1985; Moulin, Wild et al. 1993; Sjogren, Fossum et al. 2002).

The goal of this study was to investigate the cardiac effects of manganese exposures among welders using a repeated measures study design with two assessment points. Welders, specifically boilermaker construction workers, were recruited from a union hall out of Quincy, MA. A number of biomarkers of Mn exposure were collected including blood, hair, and nail. In addition, detailed work histories were also collected.

Cardiovascular health of each worker was assessed by ambulatory electrocardiogram. We expanded the original aims of the study by monitoring inflammatory ma7s8tC w1(expanded th)C2w(x)4lWe

Background and Significance

Welders and manganese exposure

Welders are exposed to manganese during the process of welding when molten metal from mild or stainless steel or from manganese containing electrodes or wires is volatilized. Volatilized welding fume is small in size, mainly spherical particles ranging from 50 to 300 nm in diameter (Zimmer 2002). These small particles have the ability to reach deep into the alveolar region of the lung where they can initiate health effects. Alternately, toxicological studies suggest that the small particles may be transported via the olfactory nerves where they can initiate a cascade of central nervous system effects (Doty 2008).

Short-term, cross-shift exposures to occupational manganese exposure are best captured using personal sampling. The appropriate quantification of longer-term manganese exposures is less clear and can be quantified by a number of techniques including calculating a cumulative exposure index (CEI) of manganese dose based on detailed work histories and previous personal air manganese measurements or through use biomarkers of manganese exposure which provide cumulative internal manganese dose.

Biomarkers of manganese exposure

Numerous biological media including whole blood, serum, urine, nails, and hair have been investigated as potential biomarkers of manganese exposures. Monitoring occupational and environmental exposures to manganese is challenging because manganese is an essential element and concentrations of internal manganese are regulated by homeostatic mechanisms governing absorption, disposition and excretion. In general, the whole-body half-time of manganese is estimated to be about 37 days for healthy individuals without occupational exposures and anywhere from 15 to 28 days in healthy miners with or without chronic manganese poisoning (Michalke, Halbach et al. 2007).

Among workers with occupational manganese exposure, biomarkers of manganese exposure have been evaluated in welders (Ellingsen, Dubeikovskaya et al. 2006; Smith, Gwiazda et al. 2007), ferroalloy workers (Lucchini, Selis et al. 1995; Apostoli, Lucchini et al. 2000; Smith, Gwiazda et al. 2007) as well as manganese oxide and salt production workers (Roels, Lauwerys et al. 1987). In terms of acute manganese exposures, associations have been observed with workday air manganese and post-shift urine manganese (Apostoli, Lucchini et al. 2000; Ellingsen, Hetland et al. 2003). However, since over 95% of manganese is excreted via the bile to feces (Klaassen 1974), excretion in urine is low, making urine manganese a poor biomarker. Likewise, serum manganese concentrations have also been shown to be a poor biomarker as compared to manganese in whole blood (Smith, Gwiazda et al. 2007).

Both short-term (daily work shift) and long-term (months to years) manganese exposures have been related to whole blood manganese concentrations with mixed results. In terms of acute exposures, among the manganese oxide and salt workers, there was no relationship between workday air manganese concentrations and post-shift manganese in whole blood (Roels, Lauwerys et al. 1987). Yet, among the ferroalloy workers, a statistically significant linear exposure-response relationship was observed between work shift air manganese and post-shift whole blood manganese (Apostoli, Lucchini et al. 2000). Further evaluation of this cohort found heterogeneity in the linear association between whole blood manganese with consistent results observed in the low (median = 0.42 g/m^3

participants reporting a number health problems including hypertension as well as skin disease, mental stress, diabetes, respiratory trouble, and ophthalmic disease (Mehra and Juneja 2005). Overall, studies have shown that manganese exposures deposit in both hair and nails.

Cardiovascular effects of manganese exposures

While the neurotoxicity of manganese exposure and the neurological health effects among welders is well documented (Sjogren, Iregren et

markers of inflammation. CRP has been found to be a useful inflammatory biomarker of cardiovascular risk. In fact among healthy populations, elevated CRP is associated with increased risk of future myocardial infarction, strove, peripheral vascular disease and cardiovascular death (Blake and Ridker 2002).

Methods

Study design

A repeated measures study design was used (Table 1) to determine how changes in cardiovascular autonomic control and inflammation relate to manganese exposures. A major strength of this study design is that rather than compare workers to each other, each worker is compared to himself by examining the association between HRV and manganese exposures at two points in time, 6-months apart.

Table 1. Sampling Scheme

	Baseline	**6 months**
HRV	X	X
Questionnaire	X	X
Toenail Collection	◆———	———◆
Hair Collection	◆———	———◆
Blood Collection*	X	X

*For both metal content and inflammatory markers

Participants were recruited from a local boilermaker union, in Quincy, MA. Boilermakers are construction workers trained to weld upon round vessels, often located within power plants. Due to rotating energy needs throughout the year, boilermakers' work is cyclic with intense periods of work and welding exposures occurring over a 5-6 month time period, followed by a down period when workers are laid off for up to 3-months time and have little or no welding exposures. Our original goal was to monitor workers during the no exposure period (when workers had been laid-off and were free from welding exposures for a minimum of 6-weeks) and then a second time at the end of the peak exposure period, approximately 6-months later. However, due to time constraints and availability of participants, workers were monitored at their convenience without regard to previous exposure. We believe that this change in the protocol will still allow us to evaluate the original study aims.
To eliminate the acute effects of welding, monitoring occurred on a day when participants were not exposed to welding fumes. Participants were fitted with an ambulatory ECG at the Boilermaker Union Hall and were asked to return 24-hrs later to return the ECG equipment.

At baseline and subsequent monitoring periods a self-administered questionnaire was used to collect medical history and medication use. Demographic and lifestyle information including smoking history and occupational history were also collected.

Ni	20	11.43	9.50	5.68	1.32 - 23.73

*n=1 below detection limit
**n=3 below detection limit

Table 4: Summary of blood inflammatory markers and lipids

	N	Mean (SD)
Inflammatory Markers		
C-Reactive Proteins (mg/l)	77	1.94 (2.08)
Fibrinogen (mg/L)	40	232 (59)
Lipid Levels		
Total Cholesterol (mg/dL)	71	196 (45)
Triglycerides (mg/dL)	71	169 (142)
HDL (mg/dL)	71	44 (15)
LDL (mg/dL)	67	117 (33)

Evaluation of Biomarkers of Mn at one time-point

A sub-study of 46 welders with toenail, blood and work history collected at one time-point was used to determine the relationship between blood and toenail Mn and cumulative exposure index. Results of this sub-study of 46 welders are presented. Correlation coefficients, adjusted for age (year) and dietary Mn (mg/month), were computed

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
- 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

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 (7th-9th months, 10th-12th months, and 7th-12th months), ranging from 0.32 to 0.35 (Table 6). 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. 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. (Figure 1)

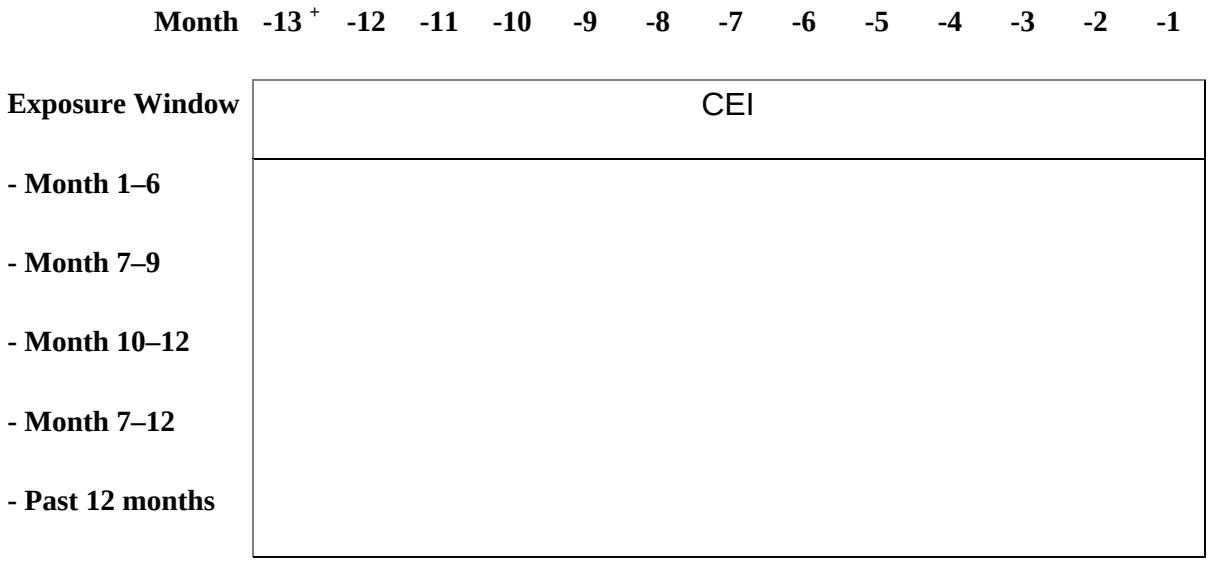
Table 6. Associations as assessed by partial spearman correlation coefficients between Toenail Mn (ng/g), blood Mn (ng/mL) and Mn-CEI (mg/m^3-hr) exposure windows.

	Toenail Mn, ng/g		**Blood Mn, ng/ml**	
	!	**P-value**	**!**	**P-value**
Blood Mn, ng/ml				

Mn-CEI, mg/m^3-hr	(n = 49)		(n = 27)	
- Months 1–6	0.07	0.62	0.05	0.82
- Months 7–9	0.35	0.016*	0.12	0.58
- Months 10–12	0.32	0.031*	0.17	0.42
- Months 7–12	0.32	0.027*	0.07	0.75
- Past 12 months	0.19	0.19	0.15	0.46

[a] Adjusted for age (year) and dietary Mn (mg/month).

Figure 1. Exposure windows of interest for Mn-CEI and toenail Mn.



Summary

We have surpassed the original aims of the small study project. Our original proposal projected 40 participants over 80 worker-days. We have monitored 78 workers over 118 worker-days. In addition to examining cardiovascular autonomic health using HRV, we were also able to monitor inflammatory markers an additional independent predictor of cardiovascular disease. Some changes to the original study design were made. Due to participant availability, we were unable to monitor each participant twice over a 6-month period. However, we believe we have sufficient sample size to examine the relationship of interest. We were also unable to collect hair samples on the majority of the participants. However,

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