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The Utility of Biological Monitoring for Manganese in Ferroalloy Smelter Workers in South Africa

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Abstract

Five hundred and nine workers at a manganese (Mn) smelting works comprising eight production facilities and 67 external controls were studied cross-sectionally. Exposure measures from personal sampling included inhalable dust, cumulative exposure indices (CEI) and average intensity (INT = CEI/years exposed) calculated for the current job at the smelter and also across all jobs held by subjects. Biological exposure was measured by Mn in the blood (MnB) and urine (MnU) and biological effect was measured by serum prolactin. Average lifetime exposure intensity across all jobs ranged from near 0 (0.06 μg/m³) for unexposed external referents to 5 mg/m³. Atmospheric exposures and MnB and MnU distributions were consistent with published data for both unexposed and smelter workers. Associations between biological exposures and groups defined by atmospheric exposures in the current job were substantial for MnB, less so for MnU and absent for serum prolactin. Random sampling of MnB measurements representative of a group of workers with more than 1–2 years of service in the same job and notionally homogenous exposure conditions could serve as a cross-sectional predictor of atmospheric Mn exposure in the current job, as well as for surveillance of Mn exposure trends over time. Correlations at the individual level were only modest for MnB (33% of the variance in log atmospheric Mn intensity in the current job was explained by log MnB), much worse for MnU (only 7%). However, a receiver operating characteristic (ROC) analysis was performed which showed that it is possible to use a MnB cut-off of 10 μg/l (the 95th percentile in the unexposed) to good effect as a screening tool to discriminate between individual exposures exceeding and falling below a relatively strict atmospheric Mn exposure threshold at the ACGIH threshold limit value (TLV) of 0.2 mg/m³. MnU has no utility as a measure of biological exposure nor does serum prolactin as a measure of biological effect.

Keywords: Manganese; Exposure; Biomarkers; Prolactin; Surveillance

INTRODUCTION

As part of a study examining atmospheric and biological manganese (Mn) exposures in relation to neurobehavioural outcomes among large numbers of ferroalloy workers, information was sought on

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associations between measures of biological exposures (manganese concentrations in blood (MnB) and urine (MnU)), biological effect (serum prolactin), and atmospheric exposure (intensity and cumulative exposure in the current job or across all exposed jobs). The potential of these biological measures for group surveillance, and for individual screening in relation to exceedances of commonly used exposure limits such as the ACGIH threshold limit value (TLV), was also explored.

There are some uncertainties about the value of biological exposure or biological effect monitoring in the estimation of workplace exposure (which can be difficult, expensive and impractical to determine) and exposure-related effects (Smargiassi and Mutti, 1999). Blood and urine Mn have been found to be inconsistently related to atmospheric Mn (MnA) exposure (whether measured as exposure intensity or as cumulative exposure either in the current job or across all exposed jobs); to each other; and also to biological effect measures and other (e.g. neurobehavioural) outcomes.

This applies both to group comparisons as well as to individually based correlations. Roels et al. (1987) found that in chemical plant workers MnB was not associated with MnA on a group basis, and that there was neither correlation between MnB and MnU, nor between either of these and atmospheric Mn exposure at the individual level. In a 1992 study of battery workers exposed to MnO_2, Roels et al. found that only MnU, but neither MnB nor serum prolactin, was significantly associated with MnA on a group basis. They found no relationship between MnB or MnU and atmospheric exposures measured as duration, current intensity or cumulative exposure at the individual level. Only cumulative exposure to atmospheric Mn was associated with neurobehavioural abnormalities.

On the other hand, Lucchini et al. (1995) found significant associations between MnB and MnU, and between both of these and the cumulative exposure index (CEI), at the individual level in ferroalloy workers who had been temporarily laid off. Furthermore, both MnB and MnU were associated with neurobehavioural abnormalities. As these relationships, especially for MnB, were strengthened after cessation of exposure, MnB was thought to reflect the Mn body burden more accurately without confounding by acute exposure. By contrast, for currently employed workers, Lucchini et al. (1999) found neither a relationship between biological exposure measures and CEI on the one hand, nor with neurobehavioural test results on the other. There was, however, an association between MnB and exposure intensity.

More recently, Apostoli et al. (2000) investigated the suitability of MnB and MnU for exposure assessment, and concluded that while MnB and MnU can discriminate between exposed and unexposed groups of workers, and while there was a linear relationship between MnB and atmospheric Mn intensity in the current job, variability was too high (with only 13% of the variance explained) to be of use in individual biological monitoring.

Roels et al. (1992) found that serum prolactin as a presumptive measure of effect was not related to atmospheric Mn exposure, while Mutti et al. (1996) and Smargiassi and Mutti (1999) found raised levels in ferroalloy workers. Mutti et al. (1996) also found that MnB and MnU were associated with serum prolactin levels.

Occupational health practitioners responsible for Mn exposed workers require surveillance tools to help reduce exposure and prevent adverse health effects. The utility of biological exposure and effect measures has become increasingly important to establish as occupational and environmental exposure limits for manganese have been set increasingly lower in recent years in order to prevent early nervous system effects. Exposure–response relationships with neurobehavioural outcomes are dealt with in a companion paper (Myers et al., 2003).

MATERIALS AND METHODS

A cross-sectional study was conducted on 509 manganese exposed subjects drawn from one of eight production environments in a Mn smelting works in South Africa. Different plants or activities at the works were divided into notionally high (three ferro- and silico-Mn smelters), medium (one ferro-silicon smelter, raw and finished materials handling plants) and low (quality control laboratories, administration and security workers, and a chemical plant making no use of Mn). The low exposure group served as an internal control with no direct Mn exposure. The smelter has been producing Mn ferroalloys for about 50 years and is one of the largest global producers of Mn. Ore comes in by rail to a raw materials handling yard where it is crushed and sorted, and conveyed to the smelter plant furnaces where it is smelted using the Soderberg process. Molten ore is then tapped from the bottom of the furnaces and poured into ladles from where it is separated from slag and transported to casting bays. When the casts have cooled they are transported by front end loader to the final products yard where they are crushed, sorted and dispatched. The two non-manganese producing plants at the works are a dense ferro-silicon smelter and a chemical factory producing phosphates. Apart from water misters in the materials handling yards there were no engineering controls limiting exposure to workers in place, particularly not at the furnaces. Where personal protective equipment was in use this involved disposable filtering face piece respirators. Few changes affecting occupational hygiene had been made over the years. Additionally, 67 external unexposed reference workers from an electrical fittings assembly plant were included in the study.

There were 1380 production workers at the works of which 200 subjects were randomly selected in each of three subjectively determined exposure groups. Maintenance workers with highly variable exposures were excluded. High exposure was considered to be above 2 mg/m^3, medium between 2 and 0.1 mg/m^3, and low exposure below 0.1 mg/m^3.

Sampling for atmospheric Mn measurements followed a NIOSH method (NIOSH, 1977) to capture at least one individual from the highest 10% of an exposure group with 90% confidence. Subjects were drawn from all homogeneous exposure locations and/or jobs in smelter and control plants.

Full-shift personal breathing zone inhalable dust and fume samples were collected. Employees wore Gilian® Gilair constant-flow personal air sampling pumps using Institute of Medicine inhalable dust sampling heads with 25 mm × 1.2 μm pore size, mixed cellulose-ester membrane filters, connected to pumps by Tyvek® tubing. Pumps operated at 2 l/min. Blood and urine specimens were collected for the determination of MnB, MnU and serum prolactin as described elsewhere (Myers et al., 2003).

All air samples were analysed by using a modified NIOSH method 7300, which was designed to optimise for the presence of Mn including insoluble SiMn (NIOSH, 1994). The IOM cassettes were first rinsed with deionised water to remove any dust, which might have remained in the cowl of the IOM filter cassette holder. The rinsate was added to the filter samples. Filters were digested using a CEM MARSX microwave digester. A combination of hydrochloric, nitric and hydrofluoric acid were used together to digest the Mn and any silica compounds, which might have bound to Mn compounds. A Varian® Vista simultaneous inductively coupled plasma optical emission spectrometer (ICP-OES) was used for all the analyses.

Three levels of in-house quality control were prepared by spiking blank filters with stock manganese solution. The filters were digested and analysed in the same manner as the samples with each batch of analyses. The mean recovery was 102%. The CV ranged between 3.41 and 3.48%. Three levels of Certified Reference Material (CRM) from United States National Institute of Standards and Technology no. 2676d were digested and analysed in the same manner. Mean recovery was 101.6% (standard acceptable range 95–105%).

Heparinised whole blood samples were diluted 10 times using Triton X100 and manganese content on the diluent was measured by a Varian® graphite furnace atomic absorption spectrophotometer (Varian® Spectra AA 30) coupled with a Zeeman effect background correction system (Varian® Zeeman graphite tube atomiser). Standards and CRM (Seronorm™ trace elements, whole blood, level II) were run at the beginning, during and at the end of each batch of samples that were analysed. The mean and the CV of all the results obtained from the CRM was 11.0 (10.3–11.7) μg/l (recommended value 13.0 μg/l) and 6.45%, respectively.

Urine samples were diluted five times with 0.1N nitric acid and analysed by a Varian® AA 975 atomic absorption spectrophotometer equipped with GTA-95 furnace and autosampler. Standards and CRM (Seronorm™ trace elements, urine and BIO RAD Lyphocheck® level I) was run at the beginning, during and at the end of each batch of samples that were analysed. The mean and the CV of all the results obtained from the Seronorm R was 10.51 (8.23–11.8) μg/l (recommended value 13.0 μg/l) and 12.2%, respectively. The mean and the CV for BIO RAD Lyphocheck® level I was 6.3 (5.4–7.2) μg/l (recommended 5.9 (4.4–7.0) μg/l) and 14%, respectively.

Two different types of exposure intensity and cumulative exposure measures were calculated, reflecting lifetime and current job exposure. For all jobs in a working lifetime, a cumulative exposure index was calculated for each subject by multiplying the mean Mn inhalable dust concentration characteristic of each job or activity by the number of years worked in that job, and summing these products over all jobs worked by each subject at the works. The CEI was divided by total years of service at the works (LOS) to yield a measure of mean exposure intensity over all jobs at the works (INT). The same was done for exposures in the current job.

Uni- and bivariate data exploration were used to describe the atmospheric and biological exposure variables and explore their inter-relationships. The non-parametric distributions of MnB, MnU and serum prolactin were examined within categories (Table 1) of different atmospheric exposure variables including exposure intensity and cumulative exposure in the

Table 1
Categorisation of exposure variables

Category	Exposure range (mg/m^3)	Significance	n
Average exposure intensity across all jobs (mg/m^3)			
0	0	Unexposed controls	67
1	$0 < x \leq 0.1$	LOAEL[a] in literature	105
2	$0.1 < x \leq 0.2$	ACGIH TLV (1996)	50
3	$0.2 < x \leq 1$	SA OEL[b] for fumes	235
4	$1 < x \leq 2$	Company advisors' safe level	59
5	>2		59
Cumulative exposure index across all jobs (mg-years/m^3)			
0	0		67
1	$0 < x \leq 1.3$		104
2	$1.3 < x \leq 5.4$		98
3	$5.4 < x \leq 10.6$		103
4	$10.6 < x \leq 22.4$		101
5	>22.4		102

[a] Lowest observable adverse effect level.
[b] South Africa occupational exposure limit.

current job and across all jobs held, as well as with total years of service at the smelter. Conclusions about the nature of associations between biological and atmospheric exposures at the grouped level are based on examination of coefficients in categorical exposure modelling using multiple regression. Individual correlations of log-transformed data were examined using Pearson's r correlation coefficient.

To address the question of whether MnB or MnU might be used as a surrogate for job history based exposure measures to flag individuals exceeding certain average exposure intensity levels, a receiver operating characteristic (ROC) analysis was carried out. Stata 6.0 software was used (STATA, 1999). Associations of biological exposure and effect measures with neurobehavioural outcomes are examined elsewhere (Myers et al., 2003).

The study was approved by the ethics and research committee of the Health Sciences Faculty of the University of Cape Town. Informed consent was signed by all participants. A Research Reference Panel was set up with representatives of workers and their trade unions, management and researchers to oversee all aspects of the study and to assist the research team. The reference panel served as a conduit for stakeholder input to the research process. Although the study was funded by the company, independence of the researchers in the design, conduct, analysis and interpretation and reporting of the results was ensured in the research contract which included the right to presentation and publication of findings in the scientific media.

RESULTS

Some 442 personal inhalable dust samples were measured in various homogeneous exposure zones for jobs in different production locations enabling the construction of exposure indices shown in Table 2.

Arithmetic means, geometric means and maxima for intensity of exposure in the current job were 0.006, 0.005 and 0.01 within the chemical plant; 0.04, 0.03 and 0.11 for security; 0.04, 0.03 and 0.04 for administrative personnel; 0.21, 0.16 and 0.52 for the ferrisilicon smelter; and 0.36, 0.26 and 0.56 for materials handling. The three Mn smelter plants had exposures ranging from a low of 0.80, 0.69 and 1.29 through 1.40, 1.16 and 2.82 to a high of 2.70, 1.97 and 5.08.

No association was found with serum prolactin and any measure of atmospheric or biological exposure. With one exception, 27 μg/l, all values fell within the normal laboratory range of 2.1–17.7 μg/l for males. Fig. 1 typifies the absence of association in the case of cumulative exposure across all jobs. The results for exposure in the current job are similar.

Table 2
Atmospheric and biological exposures

	n[a]	Mean (S.D.)	Geometric mean (G.S.D.)	Minimum	Maximum
Cumulative exposure index across all jobs (mg-years/m^3)	508	16.0 (22.4)	5.1 (6.7)	0	137.6
CEI in current job only	511	12.7 (21.3)	3.3 (7.9)	0	137.6
Average intensity across all jobs (mg/m^3)		0.8 (1.1)	0.3 (5.5)	0	5.1
INT for the current job only	507	0.9 (1.2)	0.3 (6.3)	0.003	5.1
Total length of service	576	17.2 (8.1)	14.7 (2.0)	0.4	42
MnB (μg/l)	482	11.7 (5.6)	10.6 (1.6)	3.3	44
MnU (μg/l)	481	9.2 (19.1)	3.3 (3.9)	0.5	170
Serum prolactin (μg/l)	456	6.1 (2.9)	5.5 (1.5)	1.7	27

[a] For workers in the smelter works only.

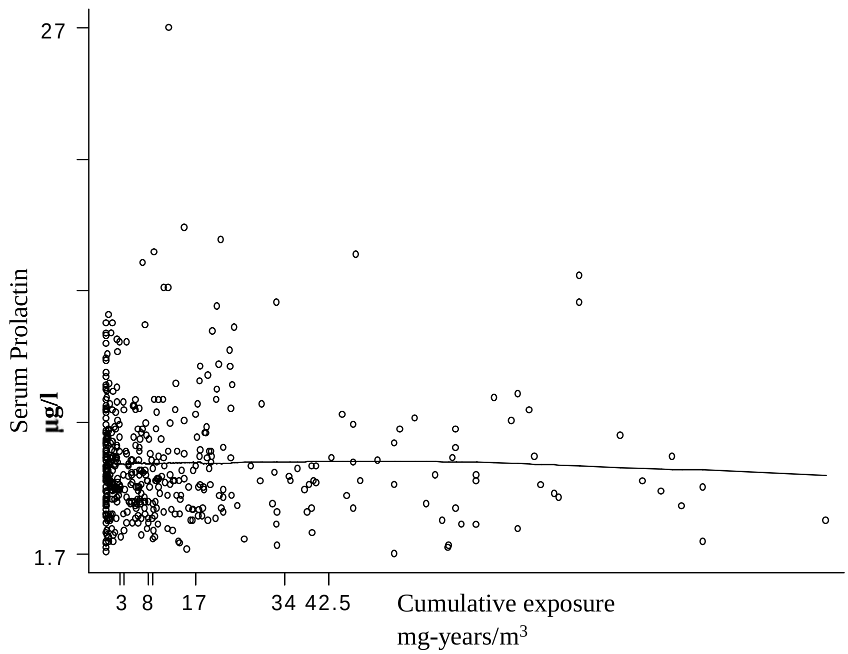

Fig. 1. Smoothed bivariate plot of serum prolactin vs. cumulative exposure across all jobs.

Table 3 shows non-parametric distributions for MnB by different exposure categories. The median values are very close to the geometric means 6.2, 7.5, 10, 11.1, 14.2 and 15.2, respectively. Multiple regression analysis shows that mean log MnB in every exposed category is significantly different from the unexposed, and also increases significantly for each higher category of current job exposure intensity amongst the exposed. The same is not true for average intensity across all exposed jobs in that the mean does not always increase significantly for each consecutive higher exposure category.

Fig. 2 shows the distribution of blood Mn by different exposure categories. Multiple regression analysis shows that mean log MnU for any category of atmospheric Mn exposure is significantly higher than in the unexposed, but that there is no significant increase in the geometric mean between any two exposure categories (Table 4).

Table 5 shows that individual correlations with logged exposure intensity in the current job are relatively good for log MnB. Fig. 3 shows some saturation at 2 mg/m^3. Individual correlations with log exposure intensity in the current job are relatively poor with log MnU. The log MnB and log MnU are significantly correlated ($r = 0.43$, $P < 0.0001$).

Fig. 4 shows the estimated ROC curve for MnB used as a screen to identify individuals whose exposure intensity in the current job exceeds the ACGIH TLV level of 0.2 mg/m^3. The discrimination here is quite good. For instance, if a threshold for MnB of 10 µg/l is used (based on the 95th percentile in the unexposed

Table 3
MnB vs. current job exposure intensity

Intensity in current job (mg/m^3)	MnB (µg/l)					
	n	Minimum	Maximum	Median	10th percentile	90th percentile
Unexposed	63	3.3	10.9	6.2	4.7	9.1
Total exposed	419	3.3	44	11.4	7	19.4
Intensity range						
$0 < x \leq 0.1$	64	3.3	19.3	7.6	5.1	10.7
$0.1 < x \leq 0.2$	67	4.6	41.2	9.4	6.4	14.7
$0.2 < x \leq 1.0$	127	5.1	44	11.7	7.4	16.3
$1.0 < x \leq 2.0$	67	8.2	43.3	13.1	9.5	21.0
>2.0	92	5.5	38.7	14.8	10.4	24.3

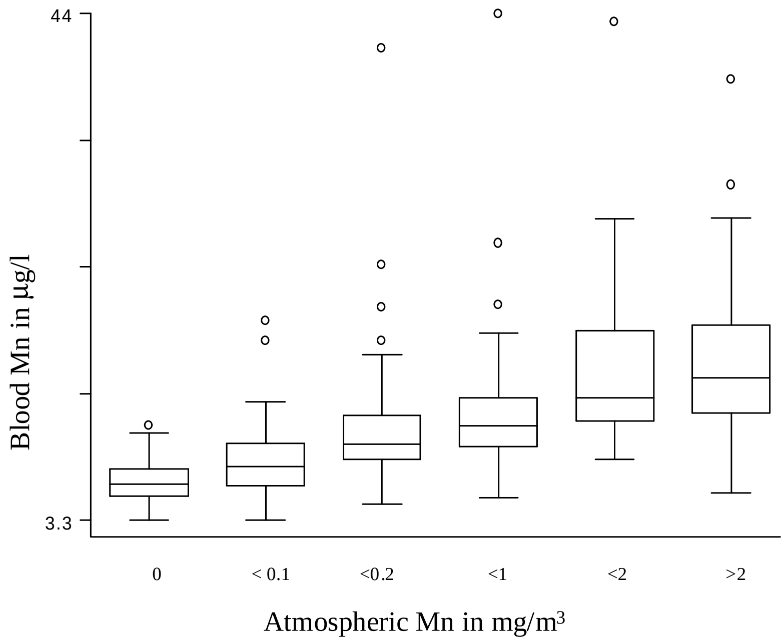

Fig. 2. MnB vs. category of exposure intensity in the current job.

Table 4
MnU vs. current job exposure intensity

Intensity in current job (mg/m^3)	MnU (µg/l)					
	n	Minimum	Maximum	Median	10th percentile	90th percentile
Unexposed	66	0.5	35	0.7	0.5	1.7
Total exposed	419	0.5	170	4	0.8	23.4
Intensity range						
$0 < x \leq 0.1$	64	0.5	51	1.4	0.6	16
$0.1 < x \leq 0.2$	64	0.5	98.7	3	0.6	17.9
$0.2 < x \leq 1.0$	130	0.5	124	4.1	0.9	17.4
$1.0 < x \leq 2.0$	64	0.6	48.4	6.2	1.3	26.4
>2.0	90	0.7	170	5.7	1.4	55.4

referent group) to discriminate, the estimated sensitivity (percent of those truly in exceedance of the ACGIH threshold who are correctly identified) is 80% (95% confidence interval: (75, 85%)); and estimated specificity (percent of those truly below the ACGIH threshold who are correctly identified) is 81% (95% confidence interval: (76, 86%)). The estimated positive predictive value (percent of those flagged by blood Mn who are truly in exceedance of the ACGIH threshold) is 87% (95% confidence interval: (82, 92%)). The ROC curve for average exposure intensity across all jobs is similar but the performance is somewhat poorer.

Table 5
Individual correlations (Pearson's *r*) between logged values for MnB and MnU and logged environmental Mn

Atmospheric Mn	MnB	MnU
Mean in current job	0.57	0.26
CEI in current job	0.53	0.25
Mean across all jobs	0.44	0.23
CEI across all job	0.44	0.20
Length of service	0.27	0.16

Table 6 shows the results of a sensitivity analysis with estimated sensitivity, specificity, positive and negative predictive values and overall percent correctly identified for a blood Mn threshold of 10 µg/l used to identify individuals with exposure intensity levels in the current job and also average exposure intensity across all jobs in exceedance of 0.2, 0.5, 1 and 2 mg/m^3, respectively. Performance for MnU was much poorer, and similar analyses with selected neurobehavioural outcomes performed even worse.

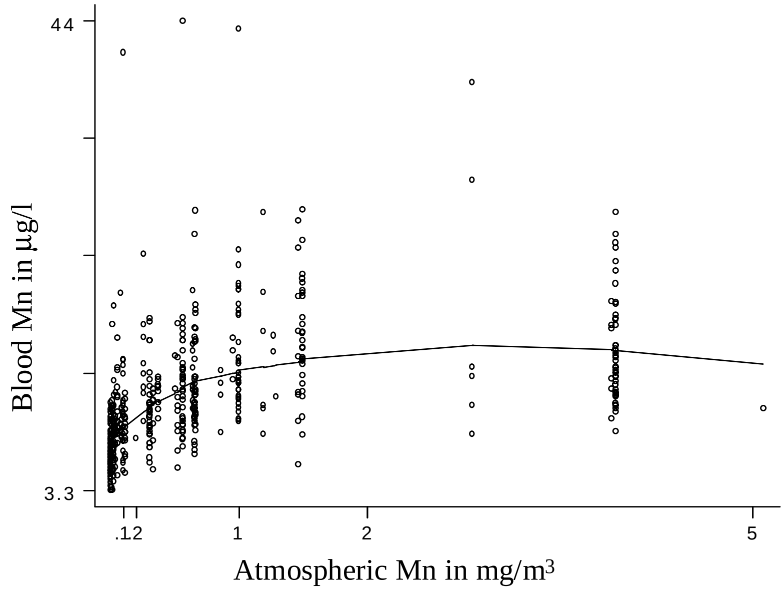

Fig. 3. MnB vs. current job exposure intensity.

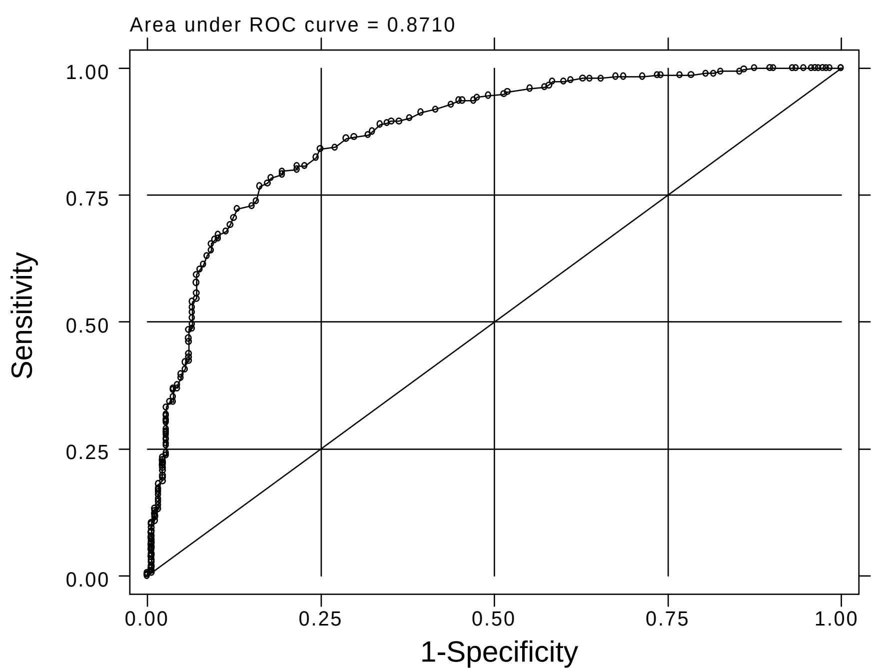

Fig. 4. ROC analysis for MnB screening for exposure intensity in the current job exceeding the ACGIH TLV (0.2 mg/m^3).

DISCUSSION AND CONCLUSIONS

These findings contribute to the inconsistent picture in the literature. Overall, the distributions of our biomarkers were remarkably similar to those reported by Apostoli et al. (2000) whose ferroalloy workers had similar exposures. Serum prolactin was not associated with any measure of atmospheric or biological exposure, nor with neurobehavioural test results (Myers et al., 2003). This agrees with Roels et al. (1992) but not Mutti et al. (1996) who found values of 9.77 (S.D. = 1.69) in exposed ferroalloy workers and 4.65 (S.D. = 1.78) in controls. The latter also found associations with MnB and MnU. Smargiassi and Mutti (1999) later reported a positive association between serum prolactin and atmospheric Mn at low exposures. Serum prolactin was in our study, however, negatively associated with smoking status, as has been previously reported.

Significant associations at the group level were found between both log MnB and log MnU and any

Table 6
Performance of MnB is screening for atmospheric exposure intensity at different thresholds

Exposure threshold	Sensitivity	Specificity	PPV	NPV	Correct (%)
Exposure intensity in the current job					
0.2 (ACGIH)	80	81	87	71	80
0.5 (UK)	84	71	73	82	77
1	92	52	34	96	60
2	93	51	20	98	56
Average exposure intensity across all jobs					
0.2 (ACGIH)	76	77	84	65	76
0.5 (UK)	83	65	65	82	73
1	89	51	32	95	59
2	96	48	18	99	54

measure of exposure intensity or cumulative exposure—whether in the current job, averaged across all jobs, or as a measure of chronic exposure (leaving out the last year). There were no meaningful differences between our measures of chronic cumulative exposure and intensity, and those measured across all jobs. Lucchini et al. (1995) observed associations between MnB and CEI across all jobs in workers who were not currently exposed. In 1999, Lucchini et al. observed associations between MnB and current exposure intensity in currently exposed workers, but not with cumulative exposure. Apostoli et al. (2000) and Lucchini et al. (1995, 1999) propose that MnB reflects mainly the body burden of Mn in currently unexposed workers, and that this is why it is correlated with neurobehavioural outcomes in such workers. For those currently exposed, and for whom MnB reflects the impact of current exposure as well as body burden, such correlations are not found. Our results showing stronger associations for current job measures, especially intensity, provide some confirmation for Apostoli et al.'s (2000) and Lucchini et al.'s (1995) observations that the biomarkers of exposure significantly reflect current atmospheric exposure intensity while workers are exposed, as opposed to simply reflecting the body burden of Mn when workers are removed from exposure. Additionally, neither MnB or MnU in our study were associated with neurobehavioural test results, providing further confirmation of this interpretation although this is not surprising as there were few convincing neurobehavioural effects of Mn exposure found in our study (Myers et al., 2003). Had there been clear effects it would have been possible to further explore the utility of MnB as a screening device.

At the individual level there were significant correlations between log MnB and all other exposure variables—more strongly for intensity and cumulative exposure in the current job. There were no meaningful differences between correlations for atmospheric manganese based on chronic measures or those based on cumulative exposure across all jobs which is not surprising since the mean years of service was high at 17.2. MnB explained a relatively modest 33% of the variance in atmospheric Mn. This was somewhat higher than the 13% found by Apostoli et al. (2000) who concluded that MnB is a poor biomarker of exposure due to its high variability.

However, a ROC analysis was performed which showed that it is possible to use an MnB cut-off of 10 μg/l to good effect as a screening tool to discriminate between individual exposures exceeding or falling below a relatively strict atmospheric Mn exposure threshold at the ACGIH TLV of 0.2 mg/m^3. If the Mn exposure threshold is calculated from exposure intensity in the current job, an MnB exceeding 10 discriminates well for current exposure exceeding the TLV. If the threshold is calculated from the average intensity across all jobs MnB still discriminates well between a body burden resulting from long-term exposure intensity at the ACGIH TLV. For exposure intensity in the current job, MnB exceeding 10 μg/l also performs well at an exposure threshold of 0.5 mg/m^3, which is the exposure limit currently proposed by the UK Health and Safety Executive (HSE). The value 10 μg/l usefully corresponds to the 95th percentile of the MnB distribution in the unexposed referents.

While exceeding a MnB of 10 μg/l may be useful to identify individuals in exceedance of strict thresholds such as the ACGIH, its utility diminishes with more lenient exposure thresholds due to increasingly poor specificity. Similar analyses for MnU at a cut-off of 2.8 μg/l (95th percentile in the unexposed) at the ACGIH TLV threshold showed poor discrimination (sensitivity only 62% at specificity of 75%).

An important objective of the study was to identify useful tools for surveillance and screening at group and individual levels. Occupational hygiene surveys, and construction of complicated job exposure matrices, and linking exposure to health outcome data at a workplace are all demanding, time-consuming and expensive tasks. Surrogate measures for estimating exposure and risk are therefore very attractive. Of the three measures investigated here, MnB alone has utility for group exposure surveillance. The mean calculated from randomly sampled MnB measurements representative of a homogenous exposure group of workers with more than 1 year of service in their current job, could serve as a cross-sectional predictor of atmospheric Mn exposure (Table 3). It could also serve well for surveillance of atmospheric Mn exposure intensity trends over time for that group/job, helping to monitor success in lowering workplace exposures. NIOSH sampling strategies could be employed (NIOSH, 1977).

At the individual level, it is possible to use an MnB of 10 μg/l cut-off to good effect as a screening tool discriminating well between individual exposures exceeding and falling below a relatively strict atmospheric Mn exposure range between the current ACGIH TLV of 0.2 mg/m^3 and the level currently being considered by the UK HSE (0.5 mg/m^3). Positive predictive values will decline if exposure conditions improve in relation to this threshold range resulting in a declining prevalence of exceedances. MnU has poor utility as a measure of biological exposure as does serum prolactin as a measure of biological effect. These findings are not generalisable beyond those with similar exposures to manganese ferroalloy smelter workers.

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