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Issues in neurological risk assessment for occupational exposures: The Bay Bridge welders☆

Robert M. Park [a,*], Rosemarie M. Bowler [b], Donald E. Eggerth [a], Emily Diamond [c], Katie J. Spencer [a], Donald Smith [d], Roberto Gwiazda [d]

[a] Risk Evaluation Branch, Education and Information Division, NIOSH, Centers for Disease Control and Prevention, Cincinnati, OH, USA
[b] San Francisco State University, San Francisco, CA, USA
[c] The Wright Institute, Berkeley, CA, USA
[d] University of California, Santa Cruz, CA, USA

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Abstract

The goal of occupational risk assessment is often to estimate excess lifetime risk for some disabling or fatal health outcome in relation to a fixed workplace exposure lasting a working lifetime. For sub-chronic or sub-clinical health effects measured as continuous variables, the benchmark dose method can be applied, but poses issues in defining impairment and in specifying acceptable levels of excess risk. Such risks may also exhibit a dose–rate effect and partial reversibility such that effects depend on how the dose is distributed over time. Neurological deficits as measured by a variety of increasingly sensitive neurobehavioral tests represent one such outcome, and the development of a parkinsonian syndrome among welders exposed to manganese fume presents a specific instance. Welders employed in the construction of piers for a new San Francisco–Oakland Bay Bridge in San Francisco were previously evaluated using a broad spectrum of tests. Results for four of those tests (Rey–Osterrieth Complex Figure Test, Working Memory Index, Stroop Color Word Test and Auditory Consonant Trigrams Test) were used in the benchmark dose procedure. Across the four outcomes analyzed, benchmark dose estimates were generally within a factor of 2.0, and decreased as the percentile of normal performance defining impairment increased. Estimated excess prevalence of impairment, defined as performance below the 5th percentile of normal, after 2 years of exposure at the current California standard (0.2 mg/m^3, 8 h TWA), ranged 15–32% for the outcomes studied. Because these exposures occurred over a 1–2-year period, generalization to lifetime excess risk requires further consideration of the form of the exposure response and whether short-term responses can be generalized to equivalent 45-year period. These results indicate unacceptable risks at the current OSHA PEL for manganese (5.0 mg/m^3, 15 min) and likely at the Cal OSHA PEL as well.
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1. Introduction

The goal of risk assessment is to characterize risk in relation to exposure in a manner that informs regulatory decision-making. For cancer or other chronic, disabling or fatal disease outcomes, where appropriate exposure metrics have been identified and where the exposure–response relationship has been well-described, excess lifetime risk estimates can be readily generated (Biological Effects of Ionizing Radiation (BEIR) IV, 1988). For health outcomes that fall on a continuum where the demarcation between impaired versus not impaired or able versus disabled is not obvious, and where reversibility may apply, the task for risk assessment is more difficult.

1.1. Benchmark dose procedure

The benchmark dose (BMD) procedure is able to address continuous outcomes in risk assessment in a manner that is not dependent on specifying *No-Observed-Adverse-Effect Levels*

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* Corresponding author. Present address: Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Education and Information Division, MS C-15, 4676 Columbia Parkway, Cincinnati, OH 45226, USA. Tel.: +1 513 533 8572; fax: +1 513 533 8224.
E-mail address: rhp9@cdc.gov (R.M. Park).

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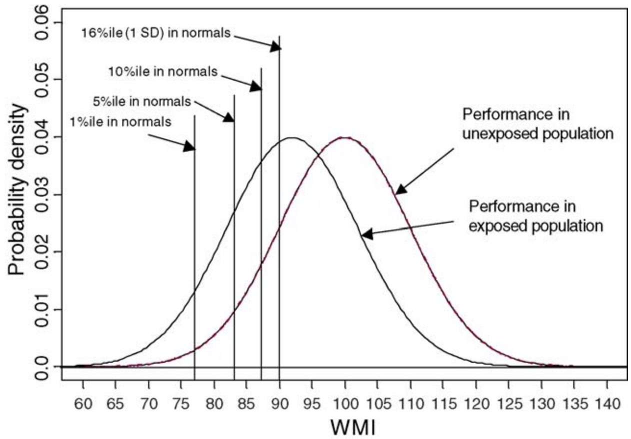

Fig. 1. Benchmark dose procedure, showing alternate definitions of impairment threshold for working memory index (WMI).

(NOAELs) and *Lowest-Observed-Adverse-Effect Levels* (LOAELs) (Crump, 1984; Crump, 1995). These latter are often statistical artifacts because most animal and human studies have limited statistical power in the low dose range or categorical dose classification. The BMD procedure describes the distribution of some outcome attribute in a normal (unexposed) population and then estimates, using a model of exposure–response, how much that distribution is altered by an exposure experience, e.g., a shift in the mean of the outcome distribution (Fig. 1). By specifying some ''cutpoint'' or threshold for impairment, it is then possible to describe the increase in impairment prevalence or cumulative incidence as a function of exposure level (Crump, 1995, Bailer et al., 1997). The BMD approach not only presents the challenge of defining impairment but also poses issues in specifying what are acceptable increases in impairment prevalence, and in relating acute responses over relatively short time periods to lifetime risks. The commonly used 1/1000 excess lifetime risk criterion for mortality or clearly disabling diseases (Infante, 1995) is not unambiguously applied in these situations.

One definition of impairment threshold commonly used is the 5th percentile of performance on some outcome measure in the general population, chosen partly for statistical convenience (Bailer et al., 1997; Clewell et al., 2003): i.e, a level unlikely to have occurred by chance. One concern, however, is that some proportion of the performance deficit below the 5th percentile in the general population could be attributable to known risk factors. In the case of neurological assessments, such risk factors might include chronic alcoholism, cumulative trauma disorders, past infectious diseases, pre-clinical neurological disease or chronic depression, conditions that would normally be considered candidates for preventive intervention. Basing the threshold on the 5th percentile in a selected population free of known risk factors affecting the performance measure would be much more justifiable, but not necessarily feasible. Alternatively, choosing an impairment threshold corresponding to higher percentiles in the normal population might provide a more appropriate level for dealing with subtle but important deficits.

Similar to the impairment threshold issue, deciding what constitutes an acceptable increase in impairment prevalence, the ''benchmark response'' (BMR), is another important question. An increment of 10% is often used in risk assessments, which together with defining impairment at the 5th percentile, results in a three-fold increase in impairment prevalence (from 5 to 15%) among those exposed at the BMD. A benchmark response of 10% corresponds to a 100/1000 excess risk, which often could have accrued in much less than a lifetime of exposure. For irreversible effects, this choice of BMR would be unacceptable in most public health settings. For reversible effects, less precedence is available for guidance.

Neurological effects from occupational exposures provide examples of risk assessment using the BMD and other procedures. Extensive development of neurobehavioral measures of performance provides many opportunities to characterize impairment and describe the natural history of conditions (Fiedler et al., 1996; Anger, 2003; Hattis et al., 1996) but further specifications are needed to implement risk assessment (Bailer et al., 1997; Hattis et al., 1996).

1.2. An application: the San Francisco–Oakland Bay Bridge welders

In order to illustrate choices made in the application of the BMD procedure for neurological outcomes, a population of welders exposed to manganese that had been evaluated for neurobehavioral outcomes was analyzed. Sustained, high exposures to manganese, as in some mining and ferroalloy operations, induce severe manganism, a well-described syndrome (Levy and Nassetta, 2003) that falls within the broad category of parkinsonism: neurological diseases involving degradation of the basal ganglia in the extrapyramidal motor pathways of the central nervous system. Early manganism is less well described and the extent to which it shares common pathophysiology with classical idiopathic Parkinson's disease, itself a complex and possibly multiple entity (Calne et al., 1994), remains controversial (Racette et al., 2001; Josephs et al., 2005).

A number of investigators have observed symptoms and signs consistent with onset of a parkinsonian syndrome in welders (Sjogren et al., 1990, 1996; Moon et al., 1999; Jin et al., 1999; Bowler et al., 2003), similar to observations in other worker populations exposed through inhalation to manganese fume, such as ferroalloy or dry-cell battery workers (Roels et al., 1987a,b, 1992; Mergler et al., 1994; Kim et al., 1994, 1998, 1999; Lucchini et al., 1995, 1997, 1999). The exposure–response relationship has not been well characterized. Important aspects of the manganese effect at these exposure levels are largely unknown, such as, what features of the time-course of exposure best predict deficits, how the particle size distribution affects response, what the exposure–response relationship is using an optimum exposure metric, and to what extent and under what conditions deficits are reversible. Several risk assessments for neurobehavioral effects of manganese exposures have appeared previously (Clewell et al., 2003; Roels et al., 1992; McClure and Odin, 1998), based on studies of manganese-exposed workers in battery (Roels et al., 1992) and chemical (Gibbs et al., 1999) production.

A population of welders employed for up to 2 years on a project constructing piers for a new bridge in California was evaluated using neurobehavioral measures. Manganese exposures arise as a respirable fume from arc welding using welding rods, wire and flux containing manganese, which is important for weld integrity. Under U.S. OSHA regulation, the maximum permissible exposure to manganese is 5.0 mg/m^3 (averaged over a 15-min period) (U.S. Occupational Safety and Health Administration, 2000); in California, the Cal OSHA maximum allowable exposure is 0.2 mg/m^3 (averaged over an 8-h period) (California Code of Regulations, 2003). Thus, this bridge welder population, which was usually in compliance with the Cal OSHA standard, offers an opportunity to examine possible effects occurring at substantially below the current U.S. OSHA limit. The present study was intended to describe the exposure–response relationship between Mn and several neurobehavioral outcomes, and then use these findings in a BMD procedure for risk assessment.

2. Materials and methods

2.1. Study population

This study evolved out of workers' compensation evaluations that were originally stimulated at least in part by public reports of health effects and litigation concerning manganese exposures in other welders. The study population was drawn during 2004/2005 from the group of welders building the piers for the new San Francisco–Oakland Bay Bridge as described elsewhere (Bowler et al., 2005). These welders worked in confined spaces in the piles and adjoining chambers being constructed in the piers, using both manual and automated welding and cutting processes, predominantly metal-inert gas (MIG) welding. The workers and supervisors who were evaluated reported that they included almost all those who had been welding for more than a few months on this project. In order to verify that most long-term welders from the bridge project were included in the evaluation, confined space entry logs that the employer is required to maintain daily were examined for a sample of six occasions covering the period May 2003–March 2004. Of the 83 unique individuals identified on the 6 logs (by an assigned ID number; names were not generally known), 24 appeared on only 1 of the logs, very likely representing visitors, inspectors or others not involved in welding production. Of the remaining 59, 48 appeared on 3 or more of those logs and 34 appeared on 4 or more logs. Thus, it appears that 48 or more workers (59 at most) were employed for sustained periods working on the bridge project during 2003–2004 (some workers may have been absent from work on the date of 1 or more of the 6 logs). Those actually evaluated, who also numbered 48, are believed to largely coincide with the 48 appearing on 3 or more logs, and thus were representative of long-term welders on this project.

The health evaluation consisted of a clinical interview and a comprehensive battery of cognitive, motor, sensory and behavioral assessments (Bowler et al., 2005), which were individually administered typically requiring a full day during December 2004–April 2005. On a separate day, a neurological evaluation, neurophysiological tests, a test of olfaction, spirometry to evaluate lung function and an EKG were performed. Additionally, blood and urine samples were drawn for analysis of manganese and other metals. For the present investigation, a subset of four illustrative neurobehavioral tests was analyzed for risk assessment purposes: the Rey–Osterrieth Complex Figure Test (Spreen and Strauss, 1991), the Working Memory Index (Wechsler, 1997), the Stroop Color Word Test (Golden, 1978) and the Auditory Consonant Trigrams Test (Mitrushina et al., 1999) (Table 1). These tests were selected because they were judged to be pertinent to a parkinsonian syndrome and because they showed clear exposure–response relationships in this welder population that were not due to chance.

2.2. Work history

A work history questionnaire was administered as part of the clinical history and medical evaluations (Bowler et al., 2005). From this questionnaire, as well as from a follow-up interview, the following were obtained: employment dates, shifts worked, average hours of work per day and days per week, and proportion of time spent doing MIG versus stick welding during

Table 1
Neurobehavioral outcomes studied

Test	*n*	Normal mean	Normal S.D.	Observed mean	Observed S.D.
1. Rey–Osterrieth CFT—immediate copy[a]	46	50	10	38.20	14.13
Rey–Osterrieth CFT—delayed copy	46	50	10	38.35	14.31
2. Working Memory Index[b]	43	100	15	90.51	13.50
3. Stroop Color and Word Test[c]	45	50	10	39.82	13.17
4. Auditory Consonant Trigrams—3 s[d]	47	0	1	−1.22	1.63
Auditory Consonant Trigrams—9 s	47	0	1	−1.39	1.33
Auditory Consonant Trigrams—18 s	47	0	1	−1.24	1.08

[a] Spreen and Strauss (1991).
[b] Wechsler (1997).
[c] Golden (1978).
[d] Mitrushina et al. (1999).

the bridge project. No systematic record of workers' daily assignments in terms of pile versus chamber or type of operation was maintained by the employer. Workers' responses were generic to their entire period on the bridge project so that time-dependent exposure characterization was not possible beyond average trends exhibited by air samples.

2.3. Exposure assessment

In the course of building coffer dams, assembling and sinking piles, and building up the final pier structure, some of the welding and cutting activities took place in the open air but most were in confined spaces below sea-level. There were two shifts operating approximately 6 a.m. to 3 p.m. and 5 p.m. to 2 a.m. Collected for compliance purposes, under a contract with the employer, 126 gravimetric air sampling results for airborne manganese were available from early in the project, February 2003, until May 2004, consisting of 49 area samples and 75 personal breathing zone samples of which 62 came from automated welding operations (two samples were not characterized as personal versus area). Total manganese was reported, and for some samples, total particulate and other metals were also reported. Levels of metals other than manganese or iron, such as for lead or cadmium, were very low. Most samples were taken for approximately 8 h. Other sampling addressed fibers, and concentrations of CO and other gases were continuously monitored. Peak values from CO monitoring (over 4 h intervals) were almost always below 20 ppm, and usually below 10 ppm. Sampling records identified the operation being sampled as well as the location (pile, chamber). Chamber exposures were generally approximately double the pile exposures; unfortunately, worker assignments were not available at that level of detail. Elevated temperatures and humidity, due to the necessity of warming the structural steel with electric heaters prior to welding, constituted another adverse condition in the confined spaces, possibly influencing Mn metabolism and neurobehavioral performance.

Cumulative exposure to manganese (cumMn) was calculated for each worker up to the time of their neurobehavioral evaluation using average process exposure estimates assigned to three 6-month periods: January–June, 2003, July–December 2003, January–June 2004 and workers' reported proportion of time doing automated versus stick welding. For the period July–December 2004, for which no sampling data were available, exposures were assumed to be the same as in the preceding 6-month period. For this investigation, an attempt was made to account for time-of-day of sampling due to the plausible possibility that levels increased over the course of the day, by regressing the time-weighted average sample exposure on the time-of-day of the mid-point of the collection interval. This resulted in a small increase for the night shift exposures by about 6%. Adjustment was also made for the shorter hours reportedly worked on the night shift (confirmed by data sampled from the confined space logs: day, 7.25 h versus night, 6.25 h). The end-result was an estimated exposure level for each worker over their time of employment on the bridge project. The cumulative exposure was calculated as follows:

$$\text{cumMn} = \sum_{i,j}^{t} [X_{ij} \times P_i \times S \times \text{dur}_j] \quad (\text{mg/m}^3 \times \text{month})$$

where X_{ij} is the estimated exposure level, ith activity, jth period (activity 1: automated MIG, 2: stick, 3: other); P_i the reported proportion of time, ith activity; S the work shift and days/week adjustment and dur_j is the employment duration in jth 6-month interval.

2.4. Outcomes studied

The Rey–Osterrieth Complex Figure Test (ROCFT) (Spreen and Strauss, 1991) assesses planning, organizational skills and problem-solving strategies and perceptual, motor and memory functions. It also is considered to be helpful in assessing visuo-spatial constructional ability and visuo-spatial memory in brain injured persons (Lezak, 1995) and has also been shown to be sensitive in Parkinson's disease (Ogden et al., 1990) and frontal lobe damage (LeGall et al., 1990). This investigation used a copy trial followed by immediate (after 3 min) and delayed (after 30 min) recall trials (Bowler et al., 2005). Generally, ''norms'' data indicate how normal populations perform in neurobehavioral tests, with age, gender and education adjustment available. ROCFT results were generated as T-Scores, which are scaled to be gaussian with expected mean of 50 and S.D. of 10 in normal populations (Table 1). For welders whose ROCFT scores were below 20 and not able to be given a score, a value of 15 was assigned ($n = 6$).

The Working Memory Index (WMI, from WAISIII) (Wechsler, 1997) measures short-term memory, concentration, attention and the ability to work with numbers. The normal values for the WMI have mean, 100, and S.D., 15 (Table 1).

The Stroop Color Word Test (CWT) (Golden, 1978) is a test of cognitive flexibility. It measures the relative speeds of reading names of colors, naming colors and naming colors used to print an incongruous color name. It consists of three trials: word reading, color naming and an interference condition (reading color words printed in a different color ink) with 45 s per trial. CWT scores are generated with normative mean, 50, and S.D., 10.

The Auditory Consonant Trigrams Test (ACT) (Mitrushina et al., 1999) is considered to be sensitive to deficits both in short-term auditory verbal memory and in divided attention/working memory. Poor performance may be associated with frontal system dysfunction (e.g., as in parkinsonism). The ACT test requires the memorization of three consonants and uses subtractions from 100 by 3 as a distractor for intervals of 3, 9 and 18 s before asking the subject to recall the initially presented consonants. Z-Scores relative to observations (at 3, 9 and 18 s) were calculated relative to observations in normal populations.

2.5. Analysis of exposure response

The exposure–response relationship was estimated using simple linear regression in S-Plus (Mathsoft, 1999). Associations with employment duration alone were also examined. A preliminary test of non-linearity of the neurobehavioral response with respect cumulative exposure was accomplished by including a quadratic term as well.

2.6. Risk assessment

From the distribution of the neurobehavioral test expected in a normal population thresholds of impairment were defined based on the 1st, 5th, 10th, 16th (IS.D.) and 20th percentiles of performance. From the regressions, the distribution of the neurobehavioral response was described in terms of the mean as a function of exposure level and the standard deviation (from the regression residual standard error, assumed to be constant over exposure levels). Exposures were then calculated that over a 2-year period would shift the distributions such that there was an absolute increase in impairment prevalence (BMR) by 1, 2, 5, or 10% for each outcome. These calculations were performed using the cumulative normal distribution function provided in S-Plus (Mathsoft, 1999) applied for specified percentiles to vectors of cumulative exposure (0–4.8 mg/m^3 × month).

3. Results

3.1. Study population

The study population was composed of 45 men and 3 women and had a diverse ethnic composition: 52% white, 31% Hispanic, 11% African American and 6% other (Table 2). The average age was 43 (S.D. = 10) and mean education: 12.5 years (S.D. = 2.2). The mean duration of employment on this bridge project was 16 months (S.D. = 6.4; Table 2).

3.2. Manganese exposures

Two-thirds of the available environmental samples were taken during January–June 2004, and almost all were for automated (MIG) welding (Table 3), reflecting concerns over higher exposures with that activity. For full shift breathing zone samples from welders doing automated or stick welding between July 2003 and May 2004 ($n = 54$), the geometric mean manganese concentration was 0.14 mg/m^3, with a GSD of 2.33 (arithmetic mean: 0.19, S.D.: 0.15) (Table 2). The minimum and maximum exposures were 0.03 and 0.67, respectively. The relatively low GSD probably reflects confined space conditions where more uniform concentrations would tend to develop over time. The mean cumulative exposure at the time of evaluation was 3.37 mg/m^3 × month (median: 3.45) with a minimum and maximum of 0.16 and 7.97. Blood manganese, a measure of exposure over the prior several months (Anderson et al., 1999), showed a clear association with cumulative Mn (Mn(B) = 7.88 + 0.473 × cumMn, in μg/L; $R^2 = 0.173$, $p = 0.006$; Fig. 2). Manganese levels in the blood vary widely in the general population (3–12 μg/L) due to dietary and metabolic differences (Anderson et al., 1999).

3.3. Outcomes

For all four outcomes studied, a smaller result represents inferior performance. The means observed for the four

Table 2
Study population characteristics

	n	%
Gender		
Men	45	93.75
Women	3	6.26
Ethnicity		
White	25	52.1
Black	5	10.5
Hispanic	15	31.5
Other	3	6.3
Disabled at evaluation		
Yes	5	10.4
No	43	89.6

	Mean	S.D.	Minimum	Maximum
Age	43.3	9.8	23	66
Education (years)	12.5	2.2	6	17
Date of hire (month)	March 2003	4.4	February 2002	February 2004
Duration employed (months)	15.9	6.4	4.9	29.2
Mn concentrations, welders[a] (mg/m^3)	0.14	2.33	0.03	0.67
Mn concentrations, welders[b] (mg/m^3)	0.19	0.15	0.03	0.67
Mn cumulative exposure (mg/m^3 × month)	3.37	2.31	0.16	7.97
Mn(blood) (μg/L)	9.58	2.54	5.13	15.3

[a] Personal samples for metal-inert gas (MIG) and stick welders ($n = 54$); geometric mean and geometric standard deviation.
[b] Arithmetic mean, S.D.

Table 3
Exposure assessment: compliance air sampling for full shift total Mn during January 2003 to May 2004

Activity[a]	January–June 2003		July–December 2003		January–June 2004		All	
	n	Mean[b]	*n*	Mean	*n*	Mean	*n*	Mean
1. Automated welding	5	0.278	20	0.154	82	0.417	107	0.361
2. Stick welding	1	0.110	3	0.054			4	0.068
3. Arc/torch cutting			6	0.134			6	0.134
4. Foreman/assistant					2	0.033	2	0.033
5. Splicing	2	0.076					2	0.076

[a] Breathing zone (75) and area (49) samples; most samples approximately 8 h; some half-shift samples. Short-term (STEL) samples were excluded ($n = 3$).
[b] Arithmetic mean concentration (mg/m^3 Mn).

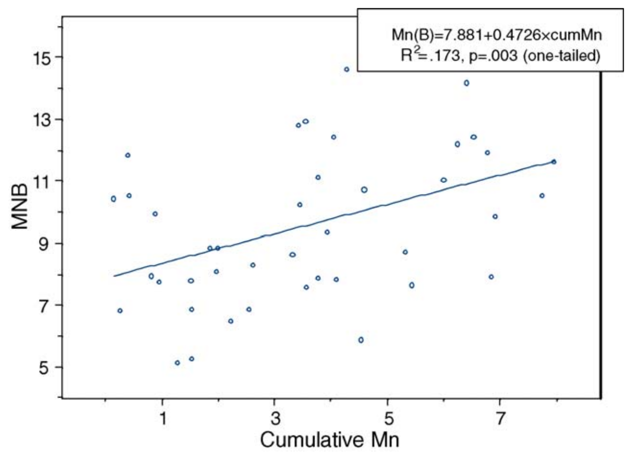

Fig. 2. Cumulative Mn exposure (mg/m^3 × month) and blood manganese (μg/L).

neurobehavioral measures were all smaller than expected, and S.D.s were larger except for WMI (Table 1). The observed means fell more than 1S.D. below the normative means, except for the WMI. With regression models, except for the WMI, intercepts still remained smaller than norms would predict (Table 4). For the ROCFT, immediate copy test, the decline with cumulative Mn (cumMn) was significant ($p = 0.028$, one-tailed) (Table 4; Fig. 3). The same pattern was observed for the ROCFT – delayed – but with less statistical significance. The intercept (performance predicted for zero exposure) for both ROCFT subunits (44.4, 43.3) were well below the expected 50.0. For the WMI working memory test, the intercept was almost exactly as predicted (99.7 versus 100) and a highly significant decline was observed with cumMn ($p = 0.0010$) (Table 4, Fig. 4). The Stroop Color Word Test showed a non-significant decline with cumMn and an intercept below the norm (44.6 versus 50, $p = 0.06$) (Table 4). Removal of one outlier with a very low score (9) and a low cumulative exposure (0.89 mg/m^3 × month) would strengthen this association. This individual had low scores on all four tests and was a support worker, not actually welding and reported no prior welding. The ACT tests not only showed significant declines at all three delays (3, 9, 18 s; $p = 0.009$, 0.006, 0.0014, respectively) but also had intercepts depressed below expected (0.0) (Table 4).

The test for a quadratic departure from linearity in predicting outcomes using cumulative exposure was statistically insignificant for all four neurobehavioral tests (Table 4; *p*-values for model b). For the ROCFT scores, the test approached significance and suggested a faster than proportional decline with increasing cumulative exposure (Fig. 3).

3.4. Excess prevalence

Excess risk of impairment (difference between risk predicted for exposure and risk predicted without exposure) was calculated. For WMI, for example (Table 5), at zero exposure the observed impairment prevalences corresponding to impairment at the 1st, 5th, 10th, 16th and 20th percentiles in

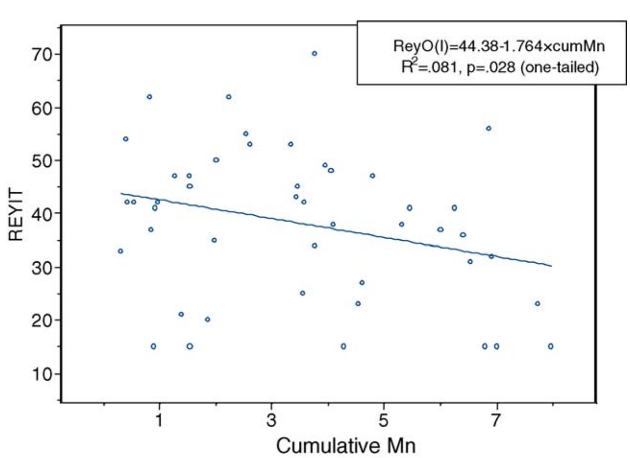

Fig. 3. Cumulative Mn exposure (mg/m^3 × month) and ROCFT-immediate.

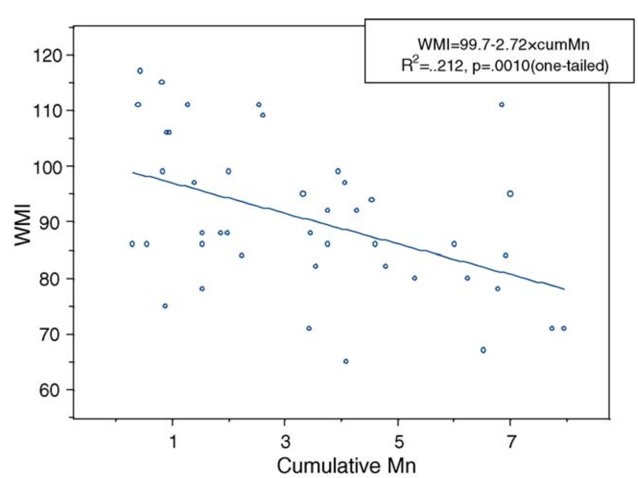

Fig. 4. Cumulative Mn exposure (mg/m^3 × month) and Working Memory Index.

Table 4
Regression models for neurobehavioral effects with linear and quadratic terms in cumulative exposure (mg/m^3 × month)

Model	Intercept	Linear	Quadratic	p^a	R^2	Residual standard error
1. Rey–Osterrieth Complex Figure—immediate copy						
(a)	44.4	−1.76	–	0.028	0.080	13.70
(b)	36.8	4.26	−0.78	0.077	0.146	13.36
2. Rey–Osterrieth Complex Figure—delayed copy						
(a)	43.3	−1.42	–	0.066	0.050	14.10
(b)	36.9	3.68	−0.66	0.149	0.096	13.92
3. Working Memory Index						
(a)	99.7	−2.72	–	0.0010	0.212	12.13
(b)	101.4	−4.08	0.18	0.664	0.216	12.25
4. Stroop Color and Word Test						
(a)	44.6	−1.35	–	0.06	0.053	12.96
(b)	42.0	0.66	−0.26	0.544	0.062	13.05
5. Auditory Consonant Trigrams—3 s						
(a)	−0.379	−0.25	–	0.009	0.118	1.55
(b)	−1.027	0.29	−0.07	0.149	0.159	1.53
6. Auditory Consonant Trigrams—9 s						
(a)	−0.664	−0.21	–	0.006	0.134	1.25
(b)	−0.814	−0.088	−0.016	0.682	0.138	1.26
7. Auditory Consonant Trigrams—18 s						
(a)	−0.551	−0.20	–	0.0014	0.183	0.99
(b)	−0.783	−0.009	−0.025	0.420	0.195	0.99

[a] p-Value for linear (model a) or quadratic (model b) terms.

normals were: 0.2, 2.2, 5.9, 11. 2 and 15.3%, respectively, indicating that the study population was predicted to have fewer than expected deficits at zero exposure, despite an intercept close to expected (due to a smaller than expected S.D.: 12.1 versus 15). An excess risk of 1% (above the 2.2% for the baseline 5th percentile definition) for a total impairment of 3.2%, corresponded to a 2-year exposure at about 0.029 mg/m^3 (Table 5, Fig. 5). Specified excess risks and impairment definitions determine benchmark dose levels (Table 6). At the 16th percentile impairment definition for WMI, excess risks of 2, 5 and 10% correspond to 2-year exposures of 0.018, 0.043 and 0.077 mg/m^3, respectively.

The benchmark exposures estimated for impairment definitions and excess risk levels (Table 6) show considerable concordance across the different neurobehavioral tests, varying by less than a factor of 2.0 except for the WMI which diverges to higher BMDs with impairment defined at lower (1st, 5th) percentiles in normals. If the same cumulative exposures accrued over time intervals longer than 2 years, corresponding smaller benchmark exposures would result (making several important assumptions such as linearity of exposure response and irreversibility of effects). The excess risks predicted for exposure at the current Cal OSHA PEL (0.20 mg/m^3) range 0.035–0.375 for the four neurobehavioral tests, and 0.171–0.375 for the ACT (18 s) (Table 7).

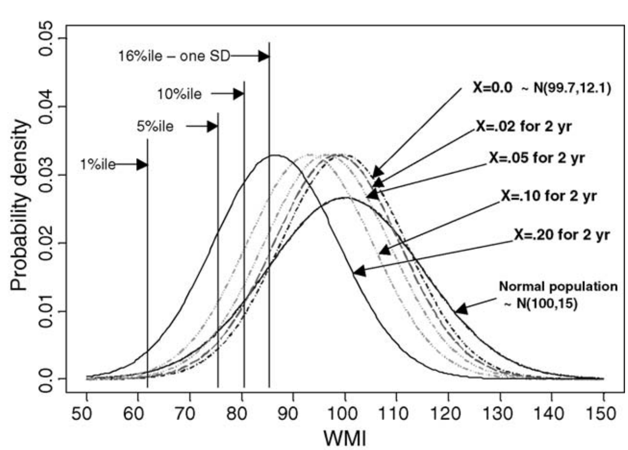

Fig. 5. Benchmark dose procedure, showing shift of predicted performance distributions with Mn cumulative exposure.

3.5. Other risk factors for neurobehavioral deficits

The choice of which percentile of performance in normals constitutes impairment might be informed by examining the neurobehavioral performance in groups with known organic brain disease. ROCFT-delayed scores were compiled from populations classified as (1) potential for toxic encephalopathy (Diamond et al., 2003), (2) psychiatric and quasi-psychiatric (Diamond et al., 2003), (3) diverse diagnoses (e.g., traumatic head injury, stroke, anoxia, encephalitis, Korsakoff' syndrome; Wilson and Watson, 2003), (4) brain-injured (Meyers and Meyers, 1995) and (5) psychiatric (Meyers and Meyers, 1995). ROCFT scores were adjusted for age, gender and education (by polynomial regression using a normal population; Ardila and Rosselli, 2003). Many of these groups scored at levels above the 1st, 5th and even 10th percentile of the ROCFT for normals (Table 8), suggesting that material impairment may be present above the 5th percentile.

Table 5
Estimated risk of impairment as function of exposure level (mg/m^3 Mn) for Working Memory Index

Cumulative exposure (mg/m^3 × month)	Equivalent exposure for 2 years (mg/m^3)	Predicted mean WMI	Prevalence of impairment				
			Percentile defining impairment in normals				
			1	5	10	16, 1S.D.	20
0.00	0.000	99.7	0.002	0.022	0.059	0.112	0.153
0.02	0.001	99.7	0.002	0.023	0.059	0.113	0.154
0.04	0.002	99.6	0.002	0.023	0.060	0.114	0.155
0.06	0.003	99.6	0.002	0.023	0.061	0.115	0.156
0.08	0.003	99.5	0.002	0.023	0.061	0.116	0.157
0.10	0.004	99.5	0.002	0.023	0.062	0.117	0.158
0.12	0.005	99.4	0.002	0.024	0.062	0.118	0.159
0.16	0.007	99.3	0.002	0.024	0.063	0.119	0.162
0.20	0.008	99.2	0.002	0.025	0.064	0.121	0.164
0.24	0.010	99.1	0.003	0.025	0.066	0.123	0.166
0.32	0.013	98.9	0.003	0.026	0.068	0.127	0.171
0.40	0.017	98.6	0.003	0.027	0.070	0.130	0.175
0.48	0.020	98.4	0.003	0.029	0.073	0.134	0.180
0.60	0.025	98.1	0.003	0.030	0.077	0.140	0.187
0.80	0.033	97.5	0.004	0.034	0.083	0.151	0.199
1.00	0.042	97.0	0.004	0.037	0.090	0.161	0.212
1.20	0.050	96.5	0.005	0.041	0.098	0.173	0.226
1.50	0.063	95.6	0.006	0.047	0.110	0.190	0.246
2.00	0.084	94.3	0.008	0.060	0.133	0.222	0.283
2.40	0.100	93.2	0.010	0.071	0.153	0.250	0.314
4.80	0.200	86.7	0.038	0.176	0.313	0.445	0.521

Table 6
Benchmark dose: manganese exposure levels that, over a 2-year period, result in specified increases in prevalence of impairment above a defined baseline threshold of impairment

Threshold of impairment (percentile of normals)	Excess risk (%)	Benchmark dose (mg/m^3 total airborne Mn)				
		1st	5th	10th	16th	20th
Working Memory Index	1	0.112	0.030	0.014	0.009	0.007
	2	0.156	0.053	0.028	0.018	0.015
	5	0.229	0.102	0.061	0.043	0.035
	10	0.294	0.157	0.105	0.077	0.066
Rey–Osterrieth Complex Figure–immediate copy	1	0.018	0.011	0.009	0.008	0.008
	2	0.034	0.021	0.018	0.017	0.016
	5	0.079	0.052	0.045	0.042	0.041
	10	0.143	0.099	0.088	0.083	0.082
Rey–Osterrieth Complex Figure–delayed copy	1	0.020	0.013	0.011	0.011	0.010
	2	0.039	0.026	0.023	0.022	0.021
	5	0.091	0.063	0.056	0.053	0.052
	10	0.167	0.121	0.109	0.105	0.104
Stroop Color and Word Test	1	0.025	0.014	0.012	0.011	0.010
	2	0.048	0.028	0.023	0.021	0.021
	5	0.108	0.067	0.057	0.052	0.051
	10	0.191	0.128	0.111	0.103	0.101
Auditory Consonant Trigrams Test (3 s)	1	0.013	0.009	0.008	0.007	0.007
	2	0.026	0.018	0.015	0.014	0.013
	5	0.063	0.044	0.038	0.035	0.033
	10	0.113	0.082	0.073	0.069	0.067
Auditory Consonant Trigrams Test (9 s)	1	0.014	0.008	0.007	0.006	0.006
	2	0.028	0.017	0.013	0.013	0.013
	5	0.064	0.039	0.033	0.031	0.031
	10	0.113	0.075	0.066	0.062	0.062
Auditory Consonant Trigrams Test (18 s)	1	0.023	0.009	0.007	0.005	0.005
	2	0.042	0.018	0.013	0.011	0.011
	5	0.088	0.042	0.032	0.028	0.026
	10	0.142	0.061	0.078	0.054	0.052

Table 7
Excess risks of impairment for exposures at current Cal OSHA PEL (0.20 mg/m^3 Mn) for 2 years

Threshold of impairment (percentile of normals)	Excess risk in 2 years				
	1st	5th	10th	16th	20th
Working Memory Index (WMI)	0.035	0.153	0.254	0.333	0.368
Rey–Osterrieth—immediate	0.153	0.217	0.237	0.243	0.242
Rey–Osterrieth—delayed	0.124	0.173	0.187	0.191	0.189
Stroop Color and Word Test	0.106	0.165	0.188	0.197	0.198
Auditory Consonant—3 s	0.205	0.277	0.289	0.295	0.294
Auditory Consonant—9 s	0.211	0.296	0.315	0.313	0.306
Auditory Consonant—18 s	0.171	0.315	0.365	0.375	0.368

Table 8
ROCFT (delayed) scores and percentiles in populations with known neurological deficits

	n	Age	Education	Gender	ROCFT	ROCFT adjusted	%iles
Epilepsy[a]	1	56.00	14.0	0.0	17.00	20.85	
Psychiatric[b]	11	47.60	14.2	0.0	18.40	19.86	
Toxic encephalopathy[b]	11	48.80	14.0	0.0	15.00	16.86	
Psychiatric[c]	30	33.20	12.4	0.5	16.00	16.81	
Left stroke[a]	20	45.40	14.0	0.0	15.21	16.28	
						16.21	20
Epilepsy[a]	1	25.00	14.0	1.0	17.00	16.11	
						14.96	10
Right stroke[a]	23	42.13	14.0	0.0	14.52	14.91	
						13.09	5
Right stroke[a]	12	49.66	14.0	1.0	7.77	12.20	
Cerebral tumor[a]	9	37.88	14.0	0.0	12.33	11.97	
Stroke and head injury[a]	5	46.40	14.0	1.0	8.40	11.85	
Other stroke[a]	3	52.00	14.0	1.0	6.16	11.34	
						10.99	2
Cerebral tumor[a]	5	32.80	14.0	1.0	10.40	10.67	
Traumatic head injury[a]	82	27.54	14.0	0.0	12.24	10.66	
Left stroke[a]	5	42.20	14.0	1.0	8.00	10.31	
						9.60	1
Traumatic head injury[a]	27	28.62	14.0	1.0	9.81	9.40	
Brain injury[c]	30	38.10	12.8	0.5	7.60	8.95	
Anoxia[a]	2	32.00	14.0	1.0	8.75	8.88	
Anoxia[a]	7	32.14	14.0	0.0	9.64	8.50	
Encephalitis[a]	4	32.50	14.0	1.0	6.30	6.51	
Encephalitis[a]	5	49.60	14.0	0.0	4.40	6.46	
Other stroke[a]	4	52.00	14.0	0.0	3.75	6.45	
Korsakoff syndrome[a]	3	48.00	14.0	0.0	3.00	4.67	

[a] Wilson and Watson (2003).
[b] Diamond et al. (2003).
[c] Meyers and Meyers (1995).

4. Discussion

Neurobehavioral assessments for chemical exposures are needed for the regulatory process (Hattis et al., 1996; Dick and Ahlers, 1998). This study examines an episode of confined space welding where, initially (until mid-2004), there was inadequate protection and ventilation according to workers, state regulatory authorities and an independent contractor performing air monitoring. Study strengths include (a) a high level of participation of long-term welders on the Bay Bridge project, (b) a relatively extensive environmental assessment, (c) confined space exposures that might tend to be more uniform than other welding environments, (d) duration of exposures of less than 2 years which simplified exposure–response modeling and (e) administration of an extensive array of neurobehavioral tests.

The definition of impairment and interpretation of neurobehavioral tests are critical steps in the evaluation of exposed workers. Clinical judgment on these bridge welder results is discussed elsewhere (Bowler et al., 2005); the results presented here accommodate a range of impairment definitions. The choice of 5th percentile definition can be questioned, for example, in the context of the ROCFT, where impairments plausibly exist above that threshold. The neurobehavioral deficits observed in this welder population appear to have considerable potential impact on the required working skills for welders (see: http://online.onetcenter.org/link/details/51-4121.03 for skill characterization of category ''welder/fitter''). Previously, Bowler et al. (2003) observed significant deficits for the Working Memory Index and Stroop Color Word Tests among long-term welders (average welding duration: 24.9 years) working in open welding shops; the ACT and Rey–Osterrieth tests were not administered in that population.

4.1. Limitations of study

There are limitations in this risk assessment. The exposure assessment did not allow precise assignment of worker exposures over time because air sampling was very limited (or absent) in some time periods and because welder work history did not permit direct mapping to the reported air sampling results. Thus, there was considerable potential for exposure misclassification, which was likely to be non-differential with respect to outcomes and would tend to diminish estimates of effect. Misclassification could partially account for the low intercepts observed in exposure–response analyses. Ventilation improvements reportedly took place during the second half of 2004 but are not accounted for in this analysis, which would tend to cause over-estimation of actual exposures (and under-estimation of exposure response). Mechanistic aspects of the Mn response remain almost entirely unaddressed, issues such as clearance, particle size and reversibility of deficits; if addressed, a superior exposure metric and model specification could provide a more precise estimate of the exposure–response relationship. The relatively brief exposure interval makes the results generalizable for other workplaces over similar time intervals.

Previous work with manganese exposure by the bridge welders was not accounted for. Duration in previous welding was reported but with no indications of levels of Mn exposure. Most of the bridge workers reported not having worked previously in confined spaces. Nevertheless, some initial deficit may have been present, which could also partially explain the low intercepts observed in the regressions for most outcomes. Further complicating the comparison is the possibility of a simultaneous healthy worker effect which might be expected in a workforce of highly skilled workers requiring precision in eye–hand coordination, good working memory skills and visuo-spatial abilities. This effect would increase baseline performance above expected norms.

4.2. Comparisons with other risk assessments for manganese

The study by McClure and Odin (1998) using 5th percentile-defined impairment, found benchmark doses for a measure of eye–hand coordination in the range 0.016–0.183 mg/m^3 Mn with different models and excess risks of 1–10%, which compares well with results from this study: 0.011–0.124. Clewell et al. (2003) derived a benchmark dose for eye–hand coordination deficit of 0.155 mg/m^3 for a 10% excess risk above a 5% baseline versus 0.061–0.124 estimated here. Earlier, Roels et al. (1992) concluded that risk of tremor increased for a lifetime cumulative exposure to respirable Mn exceeding 0.73 $mg/m^3 \times$ year, corresponding to BMD of 0.15 mg/m^3 for 5 years, or 0.016 for 45 years.

4.3. Benchmarks corresponding to OSHA Guide of 1/1000 Lifetime Risk

If an effect is reversible and if impairment has not occurred in an individual after 5 years at some exposure level, perhaps it will not subsequently occur, in which case, it could be stated that the lifetime risk is equivalent to the 5-year risk. While it is clear that very high manganese exposures lead to severe irreversible deficits, the situation for low levels, e.g., below 0.20 mg/m^3, is unknown. Further complicating the situation is the uncharacterized response of the Mn homeostasis under time-varying respiratory exposures. If there are irreversible effects at low levels, then the benchmark dose based on a 2-year exposure will need to be further reduced to accommodate 45-year exposures.

4.4. Risk assessment

The results reported here indicate that in this workforce of bridge welders working in confined spaces, possibly experiencing heat stress as well, the prevalence of attributable neurological impairment after the equivalent of 2 years at levels of 0.2 mg/m^3 was 15–32%, depending on impairment definition. A prevalence of 2–5% excess impairment would be expected after 2 years at 20–50 $\mu g/m^3$ Mn. Conceivably, this work force experienced higher cumulative exposures than others with the same time-weighted average levels because workers were unable to exit the confined space with the freedom that other workers have to move away from the source of contaminants.

5. Conclusion

The bridge welders studied here constitute a diverse, highly skilled and proud workforce with strong concerns about their future livelihood. They have not only exhibited a dramatic decline in performance over a 2-year period on many neurobehavioral tests but also show symptoms and signs consistent with a parkinsonian syndrome (Bowler et al., 2005). These welders have been advised (RB) to seek employment that does not place workers in confined spaces without supplied-air respirators. Their experience indicates that continuous exposures to Mn at levels in the vicinity of the Cal OSHA PEL in confined spaces have caused impairment as assessed with a variety of tests and definitions of impairment. Future follow-up of this bridge welder group may provide insights into the reversibility of effects from relatively low Mn exposures. Studies of diverse exposure histories with more precise and detailed exposure assessments are needed to resolve remaining issues in the exposure response for Mn neurological effects.

DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

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