Relation of cumulative exposure to inorganic lead and neuropsychological test performance

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Abstract

Objectives—To determine if measures reflecting chronic occupational lead exposure are associated with performance on neuropsychological tests.

Method—467 Canadian male lead smelter workers (mean (SD) age 43.4 (11.00) years, education 9.8 (3.18) years, years of employment 17.7 (7.43), and current blood lead concentration (B-Pb) 27.5 (8.4) $\mu\text{g dl}^{-1}$) were given a neuropsychological screening battery. Time weighted average (TWA) and time integrated blood levels (IBL) were developed from B-Pb records obtained through regular medical monitoring (mean (range) TWA 40.1 (4.0–66.4) $\mu\text{g dl}^{-1}$, mean IBL 765.2 (0.6–1625.7) $\mu\text{g-y dl}^{-1}$). 14 neuropsychological variables were included in three multivariate analyses of covariance, with each exposure variable as the grouping variable (high, medium, and low) and age, education, score on a measure of depressive symptoms, and self reported alcohol use as the covariates. Groups did not differ in history of neurological conditions.

Results—Neither the B-Pb, TWA, nor IBL was significant by multivariate analyses of covariance (MANCOVA). When years of employment, a suppressor variable, was included as a covariate, IBL exposure groups differed significantly on digit symbol, logical memory, Purdue dominant hand, and trails A and B.

Conclusions—A dose-effect relation was found between cumulative exposure (IBL) and neuropsychological performance at a time when current B-Pb concentrations were low and showed no association with performance.

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Keywords: lead; smelter workers; neuropsychological tests

Research findings on the neurobehavioural effects of occupational lead exposure are inconsistent. Relations between occupational lead exposure and neuropsychological measures have included reaction time, visuomotor functioning, verbal memory, and dexterity.^{1–5}

With few exceptions, most studies use current blood lead (B-Pb) as the exposure index. The B-Pb reflects recent exposure with a half life of 30 days. People with equivalent B-Pb may have significantly different past exposure.⁶ Some authors suggest that reliance on current

exposure measures may mask differences in neuropsychological functioning related to chronic, low dose exposure.^{5,7} Measures of chronic exposure include time weighted average (TWA), a weighted average of B-Pb over the duration of exposure, and time integrated B-Pb (IBL), a measure of cumulative B-Pb concentrations over the period of exposure.

Baker *et al* found a relation between TWA (for B-Pb) and verbal memory and motor dexterity.⁴ However, TWA reflected only the previous 15 months of exposure, and was not a weighted average over the entire duration of exposure. Parkinson and colleagues used current B-Pb, TWA, peak exposure, and proportion of B-Pb values greater than 60 mg/100 ml as exposure indices. These authors did not find a relation between exposure variables and neuropsychological measures after adjustment for the effects of age and education.⁵ Hogstedt *et al* found differences between exposed and non-exposed controls in reaction time, learning, and memory. However, when the exposed group was analysed by TWA terciles, no significant differences (dose-effect) were found.¹

A recent review noted that the relation of chronic exposure and neuropsychological functioning remains unexamined.⁸ Our study examined the effects of chronic occupational lead exposure on neuropsychological performance.

Method

PARTICIPANTS

We held small group informational sessions with all employees to describe the purpose and procedure of the study. The 467 Canadian men currently and previously employed in a lead smelter (370 current, 97 former; mean (SD) age 43.4 (11.00), years of education 9.8 (3.18), years employed 17.7 (7.43)) who agreed to participate, represented about 87% of current employees. No company records were available to measure the number of former employees. Participants were not paid for their involvement, and current employees completed the evaluation at the start of their shift. A consent form explaining the purpose of the study was reviewed with each participant. Because the smelter was in a bilingual area, workers chose to be tested in either French ($n = 129$) or English ($n = 329$). Nine men chose to be evaluated with a combination of French and English.

PROCEDURE

The participants completed an individual two hour neuropsychological screening battery.

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Trained examiners blind to the participant's exposure history gave the tests in a standard order. Current employees were evaluated at the beginning of their shift to avoid the effects of fatigue. Four of the 15 examiners were bilingual.

MEASURES

Exposure

The smelter recorded multiple B-Pb concentrations of each employee annually since the opening of the plant in 1966. Integrated B-Pb (or cumulative lead) was calculated from these values based on Haber's Law that states that $\Sigma (c_i t_i) = k$, where c_i is the mid-interval average calculated from B-Pb measurements during the time period t_i , and k is a cumulative dose estimate. The TWA was calculated by dividing the IBL by the number of years exposed, resulting in a weighted average exposure when employed.⁹

Neuropsychological variables

Fourteen neuropsychological variables were selected from a larger battery to serve as the dependent variables. Variables were selected on the basis of the psychometric properties and the intercorrelations of the measures, as well as findings from earlier research. The variables included: WAIS-R digit span forward, digit span backward, block design and digit symbol¹⁰; WMS-R story A logical memory (initial recall), WMS-R verbal paired associates (initial and delayed recall)¹¹; finger tapping (dominant hand)¹²; trail making test (parts A and B)¹²; Rey auditory verbal learning test (RAVLT) (total words recalled and delayed recall)¹³; Purdue pegboard (dominant hand and assembly).¹⁴ Scores on individual measures greater than four SDs from the mean of their exposure group were removed from the analysis as outliers: the same three men's scores were found to be outliers in each analysis. Four variables showed evidence of significant skewness and kurtosis after outliers were removed and were transformed. Square root transformations were used for digit span backward and Purdue pegboard dominant hand, whereas logarithmic transformations provided the best adjustment of trails A and B.

DATA ANALYSES

Data were analysed with the statistical package for social sciences (SPSS) for Windows.¹⁵ To examine the hypothesis that chronic measures of exposure are related to neuropsychological performance, separate analyses were performed on B-Pb, TWA, and IBL. The sample was divided into low, medium, and high exposure terciles based on each of these exposure variables and separate multivariate analyses of covariance (MANCOVA) were performed for each exposure index. Age, education, language, depression, neurological disorders, and alcohol use were considered as potential confounders for each analysis. The assumptions of normality, homogeneity of the variance-covariance matrices, multicollinearity, and linearity were met for each analysis. Twenty seven men were removed from each analysis

due to missing data on one or more of the measures.

Results

COVARIATES

Potential covariates included age, education, language, score on a measure of depression, head injury or other neurologic disorder, and alcohol use.

Age and education

Age and education differences between groups were examined through three analyses of variance, with tertiles as the between subject variables. The B-Pb groups differed significantly in age ($F(2,402) = 10.2$, $P < 0.0001$) and education ($F(2,402) = 10.9$, $P < 0.0001$), as did TWA groups (age $F(2,460) = 68.22$, $P < 0.001$, education $F(2,460) = 59.47$, $P < 0.001$) and IBL groups (age $F(2,464) = 150.9$, $P < 0.001$, education $F(2,464) = 68.6$, $P < 0.001$). Higher levels of exposure were associated with older age and fewer years of education in each analysis. Age and education were therefore retained as covariates in each analysis. Table 1 shows the demographic data for each group.

Language

Language differences between tertile groups (B-Pb, TWA, and IBL) were examined in three χ^2 analyses. The proportion of men tested in either English or French was not significantly different for any analysis. There was no relation between language and any neuropsychological variable (Student's t test), and no earlier literature supported such a relation. Therefore, language was not retained as a covariate.

Depression

Previous research has shown an association between depression and neuropsychological performance.¹³ Depressive symptoms were measured with the self reported questionnaire on depression (CES-D) from the center for epidemiological studies.¹⁶ Three separate multiple regression procedures were used to find if the CES-D score was significantly related to

Table 1 Demographic data for exposure groups (mean (SD))

	Low	Medium	High
<i>B - Pb groups</i>			
n	119	142	140
Age	33.9 (10.4)	40.8 (9.9)	43.6 (8.4)
Education	11.1 (2.9)	10.2 (2.6)	9.6 (2.9)
Years employed	15.2 (8.5)	16.9 (7.8)	19.6 (6.0)
B-Pb ($\mu\text{g dl}^{-1}$)	17.6 (4.3)	27.0 (2.6)	36.5 (4.3)
<i>TWA groups</i>			
n	146	141	139
Age	35.9 (10.1)	44.1 (8.2)	47.6 (9.0)
Education	11.8 (2.0)	9.7 (2.7)	8.7 (3.0)
Years employed	11.1 (7.9)	20.1 (4.6)	21.4 (4.7)
TWA ($\mu\text{g dl}^{-1}$)	26.1 (7.2)	41.9 (3.2)	52.8 (4.0)
<i>IBL groups</i>			
n	145	145	136
Age	34.1 (8.4)	43.4 (8.2)	50.4 (7.2)
Education	12.0 (2.0)	9.5 (2.8)	8.7 (2.8)
Years employed	9.1 (6.2)	19.6 (3.1)	24.1 (2.0)
IBL ($\mu\text{g-y dl}^{-1}$)	268.6 (195.3)	820.7 (121.6)	1227.7 (145.3)

exposure. The CES-D score was significantly skewed towards low scores (less depressive symptoms) and therefore was transformed with a square root transformation. The CES-D was included as the dependent variable with age, education, and exposure as independent variables; age and education were significantly related to CES-D score. No exposure variable was related to CES-D score after adjustment for age and education. The CES-D score was found to be significantly correlated with the neuropsychological variables after adjustment for age and education, and was included as a covariate to reduce the error variance.

Neurological disorders

Review of medical histories found 69 men with a history of neurological disorders, including history of head injury with loss of consciousness ($n = 37$), hypertension controlled by medication ($n = 38$), childhood seizure disorder ($n = 3$), Arnold Chiari syndrome ($n = 1$), history of meningitis ($n = 3$), history of hallucinations or psychosis ($n = 4$), and a history of bipolar disorder ($n = 1$). Men with seizure disorder, meningitis, Arnold Chiari syndrome, and previously diagnosed psychiatric illness were excluded from the analysis, yielding a final total of 426. The men in each exposure group who reported either head injury or hypertension were examined with three χ^2 analyses (B-Pb, TWA, and IBL). As the proportion of men who reported these conditions was not significantly different between exposure variables, they were not included as a covariate.

Alcohol use

Previous research has shown an association between alcohol use and neuropsychological performance.¹³ Partial correlations were used to examine the relation between the exposure variables and self reported units of current alcohol use (one unit = 12 oz of beer, six oz of wine, or one oz of hard liquor). Alcohol use was not related to IBL or TWA after controlling for age and education, but was related to B-Pb (partial r ($df = 415$) = 0.13, $P < 0.01$). Self reported alcohol use was also significantly correlated with six of the 14 neuropsychological variables, and was retained as a covariate to reduce the error variance.

ANALYSIS OF B-Pb

Although the plant had a history of high levels of exposure in the past, improved industrial hygiene including increased use of personal protective gear over the past decade has resulted in reduced exposure. Because of the current low levels of exposure, B-Pb concentrations were measured every three to six months. Of the 426 workers 401 had a B-Pb concentration recorded within six months (372 within one month) of neuropsychological assessment.

The 401 workers were divided into exposure terciles based on B-Pb concentration. A MANCOVA was performed for the 14 neuropsychological measures with exposure group as the between subjects variable, and age, edu-

cation, CES-D score, and current alcohol use as the covariates. Table 1 shows the demographic information for these three groups. The combined multivariate effect of the covariates was significant (Wilks' $F(56,1480) = 8.9$, $P < 0.0001$). The B-Pb tertile effect was not significant (Wilks' $F(28,760) = 0.97$).

TWA

To examine if the TWA of lead exposure is related to neuropsychological outcome, the 426 participants were divided into three groups based on TWA (table 1). A second MANCOVA was performed with TWA group as the between subjects variable, and age, education, CES-D score, and current alcohol use as the covariates, and the 14 neuropsychological measures as the combined dependent variable.

The combined dependent variables were significantly related to the covariates (Wilks' $F(56,1578) = 7.3$, $P < 0.0001$). The TWA tertile effect was not found to be significant (Wilks' $F(28,810) = 1.31$, $P = 0.13$).

IBL

The 426 participants were divided into tercile based IBL (table 1). The 14 neuropsychological variables were included in a MANCOVA, with age, education, CES-D score, and current alcohol use as covariates and IBL terciles as the grouping variable. The combined dependent variables were significantly related to the covariates (Wilks' $F(56,1578) = 6.45$, $P < 0.0001$). The IBL tertile effect was not significant (Wilks' $F(28,810) = 0.95$).

SUPPRESSOR VARIABLE

Examination of the data showed the presence of a suppressor variable, a variable which improves the overall predictive validity of another variable by removing irrelevant variance. A suppressor variable is recognised statistically by the pattern of regression coefficients and correlations of each independent variable with the dependent variable: the β weight and correlation have opposite signs.¹⁷ In the present study, years of employment was acting as a suppressor variable, and was negatively correlated with neuropsychological functioning—that is, greater years of employment was associated with decreased test performance. However, when the partial correlation (removing the effects of age and education) was examined, years of employment was positively related to neuropsychological functioning—that is, greater years of employment was associated with improved test performance. With a neuropsychological variable as the dependent variable, years of employment was entered into a regression equation with age, education, and IBL. The β weight for years of employment had the opposite sign of the full correlation. The IBL and years of employment were not collinear.

To show this effect, means adjusted for age and education in the digit symbol subtest are

Table 2 Digit symbol subtest scores by IBL and years employed quartiles

	Years employed*			
	0-10	10-15	15-20	>20
IBL quartile:				
0-400:				
Mean	41.9	45.1	46.2	—
SD	(10.17)	(10.37)	(5.50)	—
n	72	23	5	—
400-850:				
Mean	32.8	40.2	42.6	45.5
SD	—	(10.97)	(12.52)	(12.23)
n	1	33	67	27
850-1100:				
Mean	—	41.4	39.9	41.9
SD	—	—	(12.59)	(12.78)
n	—	1	43	62
>1100:				
Mean	—	—	35.9	42.3
SD	—	—	(156.29)	(12.36)
n	—	—	6	109

*Means adjusted for age and education.

presented by years of employment and IBL exposure quartile (table 2). Note that IBL and years of employment are highly correlated ($r = 0.89$). However, increased IBL is associated with *decreased* digit symbol means, whereas increased years of employment is associated with *increased* digit symbol means.

Years of employment was found to be a suppressor variable only for IBL; this effect was not found when examining either TWA or B-Pb tertiles. Years of employment was therefore included as a separate covariate in the IBL MANCOVA. The same 14 dependent variables were included, with IBL tertile as the grouping variable.

The combined effect of the covariates was found to be significant (Wilks' $F(70,1928) = 5.57$, $P < 0.0001$). The multivariate effect of IBL tertile was also significant ($F(28,808) = 1.65$, $P < 0.02$). Examination of the univariates showed five variables which were significantly different between groups: digit symbol, logical memory (story A) immediate recall, trails A, trails B, and Purdue pegboard dominant hand. Forward digit span approached significance. All means were in the expected direction such that poorer performance was associated with greater lead exposure (table 3).

Table 3 MANCOVA results for neuropsychological test scores by IBL tertile group

Variable	IBL tertile (mean (SD))*			F	df = 2, 417	P value
	Low	Medium	High			
Digit symbol	45.0 (11.00)	41.2 (12.03)	41.3 (11.52)	3.03		0.049
Logical memory-story A	11.1 (4.62)	9.5 (4.21)	9.1 (3.72)	3.29		0.038
Purdue dominant†	14.6 (1.55)	13.8 (1.88)	13.7 (1.79)	4.89		0.008
Trails A†	35.5 (10.47)	40.1 (15.20)	38.7 (15.95)	3.89		0.021
Trails B†	88.9 (31.13)	95.3 (38.63)	111.1 (61.83)	3.20		0.042
Forward digit span	8.0 (2.10)	7.3 (2.42)	6.9 (2.13)	2.93		0.055
Finger tap dominant	53.7 (8.50)	50.7 (8.90)	50.1 (9.55)	2.04		0.131
Backward digit span†	6.3 (2.14)	5.8 (2.18)	5.7 (1.93)	1.19		0.304
Block design	28.3 (7.94)	26.3 (9.97)	26.6 (9.35)	1.09		0.338
RAVLT total	43.7 (10.20)	41.5 (9.62)	40.6 (10.00)	1.34		0.263
RAVLT delayed	8.4 (3.14)	7.9 (3.39)	7.5 (3.31)	1.00		0.370
Verbal paired associates	13.9 (4.15)	13.6 (4.40)	14.6 (4.30)	1.87		0.155
VPA delayed	6.0 (1.24)	5.9 (1.75)	6.1 (1.64)	0.48		0.618
Purdue assembly	27.9 (7.03)	27.0 (6.40)	27.8 (6.83)	0.73		0.484

*Mean adjusted for age, education, self reported alcohol use, CES-D score, and years of employment.

†Variable was transformed before data analysis; mean represents untransformed variable.

Discussion

This study showed a relation between cumulative lead exposure and neuropsychological performance. Monitoring of B-Pb was available for all years of employment at the smelter. The IBL incorporated past years of high exposure and more recent years of lower lead exposure due to improved industrial hygiene and use of personal protective equipment. It may be that the pattern of exposure that was captured in IBL allowed the relation between IBL and neuropsychological performance to be observed.⁶

In contrast with earlier research, the current study did not find an association between neuropsychological performance and B-Pb or TWA. One explanation is the relatively low B-Pb values in the current study; mean B-Pb value for all workers was $36 \mu\text{g/dl}^{-1}$, which is lower than the value reported by studies that showed an association between B-Pb and neuropsychological performance. These lower B-Pb concentrations, present for about 12 years, were incorporated into the calculation of the TWA. The TWA is not sensitive to exposure duration or peak exposures, as these are averaged out in the measure.¹⁸ Maizlish *et al* reports similar results from a group of Venezuelan smelter workers with a mean B-Pb concentration of $42 \mu\text{g/dl}^{-1}$ and a mean TWA of $31.5 \mu\text{g/dl}^{-1}$, neurobehavioural performance was not associated with current or TWA measures of lead exposure.¹⁹

The possibility that a healthy worker effect influenced the TWA analysis must be considered. The plant had been in existence for 26 years, with very high exposure for about the first 13 years, followed by 13 years when B-Pbs were lower. Men who left the plant during the first 13 years would be expected to have increased TWAs. Assuming that these men with high TWA values would have had poorer neuropsychological performance, their absence from this study may have biased the TWA results towards the null.

A recent review noted that the relation between chronic exposure and neurobehavioural performance had not been adequately examined.⁸ In the present study, chronic exposure (IBL), was found to be related to neuropsychological performance. This relation was not evident until the effect of a suppressor variable, years of employment, was taken into consideration. As expected, years of employment was highly correlated with IBL. However, when included simultaneously in a statistical analysis, these variables exert *opposite* influences on neuropsychological performance (table 2). A greater number of years of employment was associated with better scores after adjustment for age and education on several neuropsychological measures.

One possible explanation for the suppressor effect is that years of employment represents continuing education for older employees. Years of education in the older population were lower after demographic—for example, the long distance to schools—and socioeconomic factors—for example, leaving school to support the family were considered. As such,

education was not an accurate reflection of native ability. The company was committed to educating its employees, and regularly offered formal courses in subjects such as language, reading, and mathematics. Employees participated in these courses, which included homework and written papers as part of the class requirements. In this population, years of employment is a surrogate for additional schooling. Also, men with greater years of employment were more likely to have worked up through the ranks to managerial positions. An examination of the data confirmed that, within each IBL exposure level, the proportion of men working in managerial positions increased as years of employment increased. For example, 228 workers had an IBL between 0 and 850 $\mu\text{g-y dl}^{-1}$; of those employed less than 10 years 12% were managers, whereas of those employed for more than 20 years 21% were managers. Years of employment acted as a suppressor variable only for IBL, and not TWA. As noted in the results section, a suppressor variable eliminates irrelevant variance in either the dependent or independent variable, and must provide significant adjustment to the dependent variable. This pattern was only recognised in regression equations with IBL as an independent variable, and not TWA. This is because IBL and years of employment are strongly related, even after controlling for age and education (partial $r = 0.81$). In contrast, TWA and years of employment have a partial correlation of $r = 0.41$ after controlling for these variables. The relation between IBL and years of employment produces a very strong cohort effect in the IBL tertile analysis. Table 1 shows that years of employment is nearly the same in the medium and high TWA tertiles, but differs greatly in the same IBL tertiles. Therefore years of employment does not provide a significant adjustment in the TWA tertiles.

Previous research has shown a relation between visuomotor functioning and measures of B-Pb and TWA lead exposure.^{1-3 20 21} The current findings provide evidence of a deleterious effect of cumulative exposure on visuomotor skills. Psychomotor speed and dexterity, as measured by Purdue pegboard dominant hand, trails A and B, and digit symbol, declined with increasing IBL values. Block design was not significantly associated with lead exposure, although the adjusted means changed in the expected direction (table 3).

Digit span forward, a measure of attention, has likewise been associated with B-Pb and TWA lead exposure in previous research, although results have been inconsistent.^{4 5 20-23} In contrast, digit span backward was not associated with IBL exposure group in the present study. Pasternak *et al* reported similar results: exposed workers exhibited decreased digit span forward performance and intact digit span backward scores.²² This result is not unexpected given the different skills tapped by these measures. Digit span forward is a relatively pure measure of attention, whereas digit span backward requires the ability to manipu-

late the numbers, a more complex skill of working memory.²⁴ The complexity of digit span backward resulted in a floor effect. Examination of the data provides some support for these findings. The differences between these two subtests for the low, medium, and high exposure group were 1.8, 1.5, and 1.2, respectively. Across exposure groups, digit span forward had a 50% greater decrement than digit span backward (1.2 v 0.6).

Although verbal memory has been infrequently associated with lead exposure in previous research, present findings indicated that the immediate recall of logical memory story A, differed significantly between IBL groups. Higher IBL was associated with poorer recall of the details of this narrative passage. The adjusted means for RAVLT total and RAVLT delayed also changed in the expected direction, although these results were not significant. The difference in these tasks may account for the results. The RAVLT requires the learning of 15 discrete words repeatedly presented, whereas logical memory entails the immediate recall of a prose passage after a single presentation.

In conclusion, the study found an association between cumulative exposure to lead and neuropsychological performance. This association was found at a time when current blood concentrations were low and not related to neuropsychological performance. The relation between IBL and neuropsychological performance was clarified once a suppressor variable, years of employment, a surrogate for education, was included in the model.

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