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Neurobehavioural evaluation of Venezuelan workers exposed to inorganic lead

Neil A Maizlish, Gustavo Parra, Oscar Feo

Abstract

***Objectives*—To assess neurobehavioural effects of low exposure to lead, 43 workers from a lead smelter and 45 workers from a glass factory were evaluated with the World Health Organisation neurobehavioural core test battery (NCTB) in a cross sectional study.**

***Methods*—The NCTB comprises a questionnaire and seven tests that measure simple reaction time, short term memory (digit span, Benton), mood (profile of mood states), eye-hand coordination (Santa Ana pegboard, pursuit aiming II), and perceptual speed (digit-symbol).**

***Results*—Smelter workers were employed on average for four years, and had a mean blood lead concentration of 2·0 µmol/l (42 µg/dl). Glass factory workers had a mean of 0·72 µmol/l (15 µg/dl). Historical blood lead concentrations were used to classify exposure based on current, peak, and time weighted average. Although the exposed workers performed less well than the non-exposed in 10 of 14 response variables, only profile of mood states tension-anxiety, hostility, and depression mood scales showed a significantly poorer dose-response relation with blood lead concentration in multiple linear regression models that included age, education, and alcohol intake as covariates. The frequency of symptoms of anger, depression, fatigue, and joint pain were also significantly increased in the exposed group.**

***Conclusion*—This study is consistent with the larger body of neurobehavioural research of low occupational exposure to lead. The small effects found in this study occurred at blood lead concentrations slightly lower than those reported in several previous studies.**

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Keywords: neurotoxicity; psychological function; smelter; neurobehavioural core test battery

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Since 1978, virtually all of the epidemiological studies of neurobehavioural function in European and North American workers exposed to inorganic lead[1-17] at concentrations at or below permissible exposure limits[18] have reported adverse effects. The specific types of adverse effects have not always been consistent across studies, which may reflect variation in methods, exposure patterns, and population characteristics, among other factors.

Several different standardised neuropsychological test batteries have been given to more than 1000 workers with an average of two to 13 years of exposure and whose blood lead concentrations averaged between 1·0 and 2·7 µmol/l (22-56 µg/dl). Low exposure to lead seems to affect a broad range of psychological functions, including mood,[1 2 7 8] simple and choice reaction time,[6 7 12-14 17] short term memory,[3 4 10 13 17] spatial reasoning,[3 10 13 16] perceptual speed,[6 13 16] and eye-hand coordination.[10 13] Long term follow up of workers has been attempted less often[1-2 10 14] and suggests that psychological function deteriorates with continued exposure,[10] but recovers after the end of exposure.[1]

To correct the lack of standardisation in neurobehavioural assessment, the World Health Organisation (WHO) neurobehavioural core test battery (NCTB)[19] has been advocated as a validated, standardised psychological test battery that has been reported to be transcultural.[20] The purpose of this investigation was to apply the NCTB to confirm whether effects reported in the European and North American scientific literature were also occurring in a population of Venezuelan workers exposed to lead. A specific aim was to explore indices of exposure based on blood lead concentration to determine which were sensitive predictors of altered neurobehavioural function.

Material and methods

STUDY DESIGN AND POPULATION STUDIED

The study was cross sectional in design and subjects were enumerated and drawn from two industrial populations: a secondary lead smelter (exposed group) and a nearby glass factory (non-exposed group) in the state of Aragua, Venezuela.

The smelter workers belonged to a union and were employees of a multinational company that had operated in the same two hectare site since 1986. On average 100 people were employed, including a few managers (< 10%). Stable employment patterns had prevailed until the first quarter of 1993 when nearly one third of the workforce was replaced with new workers. Eligibility to our study was restricted to the 43 long term production workers hired between 1986 and 1992 (inclusive), who were still employed in July 1993, when the workers were studied.

The material handling department (n = 55) at a large glass factory was the source of non-exposed workers. The site was chosen because of the geographic proximity and availability of workers performing tasks with similar mental and physical demands as the lead workers, but without exposure to lead. The department was visited in person by industrial hygienists before the study began to confirm that neurotoxins such as solvents or lead were not present.

Eligibility to participate was restricted to production workers, and because all smelter workers were men, the eligibility of subjects at the glass factory was likewise restricted to men.

EXPOSURE AND CLASSIFICATION OF EXPOSURE

Lead ingot production, roughly 1000 tonnes a month, consisted of cracking and crushing car batteries, separating the lead components from the plastic casings, crushing lead components in a grinder, melting the grindings in induction furnaces, pouring molten lead, removing dross, and casting ingots. The production area, although under a roof, was not walled in, and local exhaust ventilation was not used. A baghouse was present to capture furnace emissions. The maintenance building, yard for stacking batteries, and plastic recycling area were located in the immediate vicinity. Job rotation was a company policy. Shower facilities and clothing change area were separate from, but near the production areas. In recent years, workers were provided with half mask air purifying respirators.

Since 1986, blood lead was monitored under a physician's supervision at the lead smelter. Test results for quarterly screenings for each of several years were available for all of the eligible long term lead workers. At the time of this study, the glass factory workers (non-exposed group) were also requested to provide 10 ml samples of venous blood by venepuncture from a forearm for blood lead analysis. Historical blood lead analyses at the smelter and 1993 samples from the glass factory workers were analysed by the same internationally accredited laboratory with identical methods. Airborne lead measurements were not available for this study.

Based on sampling criteria (exposed and non-exposed) and blood lead concentrations, exposure was classified in four ways that reflected intensity and duration of exposure.

(1) Dichotomous: dichotomous categories (exposed and non-exposed) from the two populations sampled.

(2) Current: defined as the blood lead concentration (μmol/l) taken most recently before testing (usually less than three months).

(3) Peak: maximum blood lead concentration (μmol/l) recorded between 1986 and 1993 for the smelter workers, and the single measurement for glass factory workers, which was assumed to reflect peak concentration.

(4) Time weighted average (TWA): the product of the time and the concentration (μmol/l × years) taken over the course of employment divided by the overall time period. For smelter workers, the TWA exposure is given by:

$$\text{TWA Pb (blood)} = \frac{\sum\left(\frac{Pb_i + Pb_{i+1}}{2}\right) \times (t_i - t_{i+1})}{\Sigma(t_i - t_{i+1})}$$

where Pb is the blood lead concentration of the ith time ordered sample and t is the time (date) the sample was taken.

For the glass factory workers, the single blood lead measurement was also assumed to reflect average exposure.

NEUROBEHAVIOURAL CORE TEST BATTERY (NCTB)

The purpose of the WHO neurobehavioural core test battery[19] is to measure a broad range of neurobehavioural functions in four domains: psychomotor speed and dexterity, memory, mood, and visual-spatial ability. The tests took about 50 minutes a subject with mostly pencil and paper, and were given face to face by a trained and experienced physician-interviewer in a room free from noise and distraction. All tests had previously been translated from English to Venezuelan Spanish, pilot tested, and revised, when necessary.[21]

The occupational and medical questionnaire covered work history, including previous exposures to neurotoxic substances; medical conditions and medications; lifestyle exposures to neurotoxins (tobacco, alcohol, hobbies); and 21 symptoms associated with neurotoxins or exposure to lead.[19,22]

Profile of mood states

The profile of mood states questionnaire is one in which the subject rates himself on a scale from one to five about feelings experienced during the previous seven days.[23] This includes 65 items and provides a six point mood profile: tension, depression, anger, vigour, fatigue, and confusion. The profile of mood states was a sensitive indicator of neurotoxicity in a previous study of smelter workers exposed to lead,[2–3] and Venezuelan workers exposed to mixtures of organic solvents.[21]

Simple reaction time

Simple reaction time measures simple visual reaction time. The subject responds to a red light stimulus presented at delays from one to 10 seconds in a 2 cm window of a reaction timer by immediately depressing a small button with his index finger. The mean simple reaction time (ms) of 64 trials is the response variable. Slowed simple reaction time has been reported among smelter workers[6,7,13] and workers manufacturing ethyl lead.[17]

Digit span

Digit span, from the Wechsler adult intelligence scale,[24] measures short term memory and attention. The tester recites groups of three, four, five, six, progressively up to eight numbers, and the subject is instructed to repeat the sequences in the correct order. The maximum number of digits repeated correctly in either one of two trials is the response variable. Digit span forwards and digit span backwards were separate response variables, and probably measure different aspects of the function domain of memory.[25] Versions of this test have detected behavioural impairments in workers exposed to lead.[4 5 10]

Santa Ana manual dexterity test

The Santa Ana manual dexterity test measures manual dexterity.[26] The subject must rotate pegs through 180°. The pegs are arranged in four rows of 12 pegs on a rectangular board. The number of pegs rotated in 30 s is the response variable. The test was repeated for both the preferred and non-preferred hand. Several studies of lead workers found impairments on versions of this test.[5 10]

Digit symbol

Digit symbol measures perceptual speed.[24] The subject is presented with a key at the top of the page with numbers one to nine displayed with their respective matching symbols. Below are blank blocks with digits above. The subject must copy the appropriate matching symbol for each digit based on the key at the top of the page. The number of correct symbols drawn in the 90 second test period is the response variable. Versions of this test have detected behavioural impairments in foundry workers[16] and workers manufacturing ethyl lead.[13]

Benton visual retention

Benton visual retention measures visual memory.[27] The subject is shown a drawing for 10 seconds composed of geometric figures. After the drawing is removed, the subject is shown four similar looking drawings, only one of which is a true replica of the original. The subject must identify the correct drawing. The number correct in 10 trials is the response variable. Versions of this test were positively associated with poorer performance among smelter[6] and ethyl lead workers.[13]

Pursuit aiming

Pursuit aiming measures fine motor control and perceptual speed.[26] With a pencil, the subject is instructed to dot the centre of circles, as quickly and as accurately as possible. The circles, 2 mm in diameter, are arrayed on a paper sheet in 30 columns by 40 rows. Excluding outliers, the number of dotted circles in two 30 s trials is the response variable. This test has not usually been in test batteries applied to workers exposed to lead.

STATISTICAL METHODS

To test the hypothesis of an association between exposure to lead and performance for each neurobehavioural test variable, multivariate models were constructed that incorporated age and education as mandatory covariates and one of the four exposure variables as an index of exposure. Models with additional, albeit weaker, or uncertain covariates (alcohol consumption, medical conditions possibly affecting performance, and previous job involving solvent exposure) were also constructed to determine whether exposure coefficients changed in magnitude or direction. Because the results differed little with either modelling strategy, models with the expanded variable list only are presented. Alternative statistical models with multivariate analysis of covariance (MANCOVA), in which continuous variables of exposure to lead had been categorised, gave nearly identical results.

In analyses of dichotomous exposure variables, analysis of covariance was used that gave results essentially the same as simple t tests. In analyses with blood lead concentration, multiple linear regressions models were used. These included an additional indicator variable for location (smelter).

All 2 × 2 interactions between exposure and covariates were examined in models. The few significant but isolated interactions found between exposure and age on the neurobehavioural function tests were plotted.

For the analysis of the symptoms that occurred in the year before testing, prevalence ratios were derived from 2 × 2 tables to provide a measure of the association between exposure to lead in dichotomous groups and presence or absence of symptoms. The 95% Confidence intervals (95% CIs) were based on normal approximations.

All levels of significance testing were set with a one sided α of 0·05, given the weight of the scientific literature about adverse (rather than beneficial) effects. Two subjects with extreme results that probably

Table 1 Characteristics of exposed and non-exposed workers

Item	Exposed	Non-exposed
Population (n)	100	> 300
Eligible (n (%))	43 (100)	55 (100)
Participants (n (%))	43 (100)	47 (85)
Age (mean (SD))	34 (9)	35 (11)
Age (n (%)):		
25–34	26 (61)	23 (49)
35–44	10 (23)	16 (34)
45–67	7 (16)	8 (17)
Education (mean (SD) y)	7 (3)	8 (3)
Education (n (%)):		
Primary	21 (49)	15 (32)
Secondary	19 (44)	30 (64)
Some college	3 (7)	2 (4)
Job duration (y):		
Mean (SD)	4 (2)	5 (6)
Range	0·4–7	0·3–26
Past job exposure to solvents (n (%))	15 (36)	30 (64)
Alcohol consumption (n (%)):		
Frequency (sittings):		
< 1/month	10 (23)	7 (15)
l/month-l/week	17 (40)	23 (49)
1–3/week	16 (37)	17 (36)
Intensity (drinks/sitting):		
None	0 (0)	1 (2)
1–6	11 (26)	13 (28)
7–12	12 (28)	23 (50)
≥ 13	19 (45)	10 (21)
Cigarette smoking (n (%)):		
Never	18 (42)	22 (47)
Current	21 (49)	15 (32)
Former	4 (9)	10 (21)
Previous medical conditions* (n (%))	28 (65)	32 (66)

*Includes hand fractures (23 reports), whiplash (19), current medicine takers (16), loss of consciousness (16), migraine headaches (10), wrist conditions (8), arthritis (5), anaemia (3), emotional illness (3), Bell's palsy (1), and seizures (1). Missing data were excluded in calculations of percentages.

Table 2 Distribution of blood lead concentration

Item	*Current*	*Peak*	*TWA*
Concentration (μmol/l):			
Range	0·43–3·24	0·43–5·47	0·43–3·63
Mean (SD):	1·40 (0·77)	1·79 (1·30)	1·50 (1·26)
Exposed	2·03 (0·58)	2·85 (0·97)	2·27 (0·58)
Non-exposed	0·73 (0·29)	0·73 (0·29)	0·73 (0·29)
Distribution of concentration (n (%)):			
<0·48	3 (4)	3 (4)	3 (4)
0·48–1·19	37 (44)	34 (41)	33 (39)
1·20–1·89	17 (20)	11 (13)	19 (23)
1·90–2·89	22 (26)	15 (18)	23 (27)
2·90–3·86	5 (6)	15 (18)	6 (7)
≥3·87	0 (0)	6 (7)	0 (0)

Missing data were excluded in calculations of percentages.

arose from current medical conditions (arthritis), were excluded. Blood lead concentrations were unavailable for seven workers at the glass factory. Although multiple comparisons were unavoidable, the results were interpreted in the context of overall patterns with biological coherence, rather than single isolated significant associations.

Results

RESPONSE AND CHARACTERISTICS OF SUBJECTS

All 43 (100%) of the eligible long term smelter workers and 47 (85%) of 55 glass factory workers participated (table 1). The exposed group was on average slightly younger, slightly less educated, had proportionately fewer men with a history of occupational solvent exposure, but proportionately more men who were heavy drinkers and current cigarette smokers. The pattern of taking medicine, and medical conditions, temporary mental or physical conditions, and sleep the night before testing was similar in both the exposed and non-exposed groups.

Table 3 Correlation coefficients (Pearson r) between blood lead concentration and covariates

	Blood lead concentration		
Item	*Current*	*Peak*	*TWA*
Peak lead concentration	0·84**	—	—
TWA concentration	0·95**	0·94**	—
Age	−0·04	0·11	0·02
Education	0·003	−0·11	−0·03
Alcohol (drinks/sitting)	0·12	0·09	0·10
Alcohol (sittings/week)	−0·16	−0·06	−0·09

**P < 0·01.

Table 4 Neurobehavioural function in workers exposed and non-exposed to lead

	Exposed	*Non-exposed*		
Test	*mean (SD)**	*mean (SD)*	*P value*	*Effect† (%)*
Profile of mood states:‡				
Tension-anxiety	11·5 (6)	10·6 (6)	0·24	8 ↓
Hostility	8·0 (8)	6·7 (7)	0·20	19 ↓
Fatigue	5·4 (5)	4·9 (4)	0·34	10 ↓
Depression	7·3 (8)	6·0 (6)	0·20	22 ↓
Vigour	19·1 (4)	19·0 (4)	0·42	1 ↓
Confusion	6·1 (5)	5·6 (4)	0·27	9 ↓
Simple reaction time (ms)	291 (59)	313 (66)	0·06	7 ↑
Digit symbol (n correct)	38·0 (12)	37·1 (14)	0·33	2 ↑
Digit span (digits recalled):				
Forward	5·2 (2)	5·2 (2)	0·19	0 =
Backward	4·0 (2)	4·3 (2)	0·47	7 ↓
Santa Ana peg board (n completed):				
Preferred hand	41·6 (6)	42·6 (7)	0·20	2 ↓
Non-preferred hand	36·9 (6)	37·4 (7)	0·18	1 ↓
Benton (n correct)	7·2 (2)	6·8 (2)	0·19	6 ↑
Pursuit aiming (n completed)	136 (42)	144 (50)	0·36	6 ↓

*Analysis of covariance, means adjusted for age, education, alcohol intake, previous occupational exposure to solvents, medical conditions.
†Effect in percentage difference (exposed-non-exposed)/non-exposed ↓ indicates poorer performance in exposed group.
‡Profile of mood states scale: 1 (best) to 20 (worst).

EXPOSURE AND POTENTIAL CONFOUNDING

The mean (range) current blood lead concentrations were 1·40 (0·43 to 3·24) μmol/l (9–67 μg/dl) (table 2). Similarly, peak concentration ranged from 0·43 to 5·47 μmol/l (9–113 μg/dl) and nearly a quarter of the men registered a peak concentration above 2·90 μmol/l (60 μg/dl). The TWAs were intermediate between current and peak.

Correlations between the quantitative variables of exposure to lead (including both smelter and glass factory workers) and the covariates of age, education, and alcohol consumption (table 3) indicate that younger workers tended to have higher current blood lead concentrations, but that older workers tended towards higher peak concentrations and higher TWAs. Workers with higher levels of education tended to have lower peak or TWA lead concentrations. Alcohol consumption was inconsistently associated with exposure. More highly exposed workers (whether classified by current, peak, or TWA concentration) tended to drink less often (fewer sittings), but with greater intensity (more drinks a sitting) than workers with less exposure.

Whether current dichotomous or quantitative exposure classifications to lead were used, the distribution of covariates indicated potentially competitive confounding tendencies, which, although weak, generally would mask (negative confounding) neurobehavioural effects related to exposure.

NEUROBEHAVIOURAL TESTS

Overall, in 10 of 14 subtests (table 4), the exposed group had poorer performance than the non-exposed, but none of the observed differences reached significance. Likewise, of 14 subtests, poorer performance was associated with increasing blood lead concentration in 11 for current blood lead concentration, 10 for peak, and 12 for TWA, (table 5).

Poorer scores on the profile of mood states were consistently associated with exposure to lead, whether defined as dichotomous categories (table 4) or blood lead concentrations (table 5). The difference between exposed and non-exposed workers ranged from 2% to 22% (table 4) with hostility and depression scores most pronounced. Dose-related (fig) and significantly poorer (table 5) mood states were found for tension-anxiety (current), hostility (current, TWA), and depression (current, peak, and TWA).

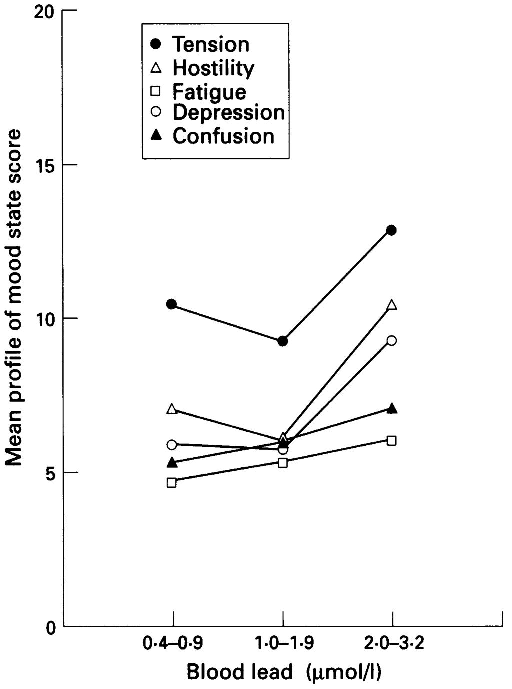
Simple reaction time was slower among lead workers for current lead and TWA concentration, but the reverse was true for dichotomous and peak exposure variables (tables 4 and 5). Performance on the digit-symbol test was consistently associated with higher exposure to lead but not significantly

Table 5 Multiple linear regression of neurobehavioural function in workers and lead exposure indices

	Current	Peak	TWA
Test	Coefficient (P value)*	Coefficient (P value)	Coefficient (P value)
Profile of mood states:			
Tension-anxiety	0·17 (0·009) ↓	0·05 (0·12) ↓	0·10 (0·06) ↓
Hostility	0·20 (0·01) ↓	0·09 (0·06) ↓	0·15 (0·04) ↓
Fatigue	0·09 (0·07) ↓	0·03 (0·19) ↓	0·05 (0·19) ↓
Depression	0·22 (0·003) ↓	0·14 (0·003) ↓	0·21 (0·004) ↓
Vigour	0·03 (0·25) ↓	−0·003 (0·44) ↑	0·005 (0·45) ↓
Confusion	0·07 (0·10) ↓	0·03 (0·20) ↓	0·05 (0·18) ↓
Simple reaction time (ms)	0·34 (0·32) ↓	−0·08 (0·44) ↑	0·53 (0·23) ↓
Digit symbol (n correct)	0·05 (0·35) ↓	0·03 (0·36) ↓	0·03 (0·40) ↓
Digit span (digits recalled):			
Forward	0·0004 (0·49) ↑	−0·004 (0·38) ↓	−0·005 (0·40) ↓
Backward	−0·02 (0·10) ↓	0·004 (0·35) ↑	−0·006 (0·36) ↓
Santa Ana peg board (n completed):			
Preferred	−0·05 (0·25) ↓	−0·02 (0·30) ↓	−0·007 (0·46) ↓
Non-preferred	−0·04 (0·29) ↓	0·03 (0·23) ↑	0·07 (0·18) ↑
Benton (n correct)	0·001 (0·48) ↑	−0·002 (0·42) ↓	−0·007 (0·46) ↓
Pursuit aiming (n completed)	0·12 (0·41) ↑	−0·006 (0·49) ↓	0·07 (0·18) ↑

*Multiple linear regression including the covariates of age, education, alcohol intake, previous occupational exposure to solvents, medical conditions, and location (glass factory *v* smelter) P values are one sided.

Subtests of profile of mood states as a function of current blood lead category: 0·4–0·9 μmol/l (n = 35), 1·0–1·9 μmol/l (n = 23), 2·0–3·24 μmol/l (n = 25).



so. Smaller digit span (forward or backward) was not consistently or significantly associated with increasing indices of exposure to lead. Fewer pegs turned with the preferred hand in the Santa Ana pegboard was associated with exposure to lead, but this was not found for the non-preferred hand (table 5). No consistent or significant association between performance and lead exposure index was found in either the Benton or pursuit aiming subtests (tables 4 and 5).

PREVALENCE OF SUBJECTIVE SYMPTOMS

The frequency of symptoms suggestive of central and peripheral nervous system problems was consistently higher among the exposed group (table 6). Significantly increased relative risks were found for difficulties in concentration (RR = 1·8), often being angry or upset without reason (RR = 2·2), and feeling abnormally tired (RR = 2·2). Although the prevalence of gastrointestinal and other symptoms was higher among exposed workers, only joint pain (RR = 1·8) reached significance.

Table 6 Annual period prevalence of symptoms among lead smelter workers by exposure category

	Exposed	Non-exposed	
Symptom	n (%)	n (%)	RR (95% CI)
Central nervous system:			
Said to be forgetful by friends or family	20 (47)	14 (30)	1·5 (0·9– 2·7)
Often forget to do important activities	16 (37)	12 (26)	1·5 (0·8– 2·7)
Difficulties concentrating	21 (49)	13 (28)	1·8 (1·0– 3·1)
Often angry or upset without reason	20 (47)	10 (21)	2·2 (1·2– 4·1)
Often downcast or sad without reason	20 (47)	10 (21)	1·6 (0·8– 3·3)
Difficulties in making decisions	11 (27)	10 (21)	1·2 (0·6– 2·6)
Feeling abnormally tired	12 (28)	6 (13)	2·2 (0·9– 5·3)
Sensation of falling on arising or walking	10 (23)	7 (15)	1·6 (0·7– 3·7)
Peripheral nervous system:			
Pins and needles in arms	17 (40)	12 (26)	1·6 (0·8– 2·8)
Pins and needles in legs	14 (33)	14 (30)	1·1 (0·6– 2·0)
Loss of strength in arms	11 (26)	8 (17)	1·5 (0·7– 3·4)
Loss of strength in legs	10 (23)	10 (21)	1·1 (0·5– 2·4)
Difficulties in clasping buttons	3 (7)	1 (2)	3·3 (0·4–30)
Gastrointestinal:			
Metallic taste in mouth	10 (23)	12 (26)	0·9 (0·4– 1·9)
Joint pain	20 (47)	12 (26)	1·8 (1·0– 3·3)
Colic or cramp	14 (33)	11 (33)	1·4 (0·7– 2·7)
Diarrhoea	3 (7)	2 (4)	1·6 (0·3– 9·4)
Constipation	9 (21)	5 (11)	2·0 (0·7– 5·4)
Loss of appetite	9 (21)	6 (13)	1·6 (0·6– 4·2)
Other:			
Pressure in chest	14 (33)	11 (23)	1·4 (0·7– 2·7)
Difficulty in falling asleep	18 (42)	12 (26)	1·6 (0·9– 3·0)

Missing data were excluded in calculations of percentages.

Discussion

The central findings of this study are altered mood states related to blood lead concentrations that reflected current, peak, and TWAs. Other aspects of performance such as memory (digit span, Benton), perceptual speed (digit-symbol), reaction time, and manual dexterity (Santa Ana pegboard) generally tended to be poorer with increasing exposure, but the magnitude of the effect was small.

This study has several strengths and limitations. Because participation was very high, non-response bias was not a concern. Because significant layoffs of long term smelter workers occurred shortly before the study began, concerns may be raised whether the surviving population was truly representative. Although data are not available to assess this, it seems unlikely that a less productive and less healthy group would have been retained.

A non-exposed control group within the lead smelter was not available because of widely shared exposures from job rotation. Moreover, new workers were disproportionately younger and management did not support inclusion of new workers in the study. A nearby glass plant drawing from the same general worker population was selected as a source of the non-exposed group. Further, a plant indicator variable was included in all statistical analyses with blood lead concentration to pick up potential association related to population selection or test administration at the two different sites. Quantitative effects of exposure persisted despite the inclusion of this site variable in the analyses of mood states.

An important strength of this study was the availability of current and historical measurements of blood lead concentration so that dose-response relations could be evaluated. The range (0·43–3·24 μmol/l) and duration (mean of four years) of current exposure to lead were low compared with similar studies. The small effects found were consistent with what would be expected at the low end of the dose-response curve.

This study was limited to detect small differences because of the relatively small sample size. Power calculations of subtests of the NCTB based on previous studies in Venezuelan industrial workers indicate that in comparisons of 50 exposed and 50 non-exposed workers, only simple reaction time would be able to detect a 10% difference in means with 80% power with 95% CI (a = 0·05, one sided).

The smelter workers and glass factory workers seemed to be comparable in basic demography, and were selected to reflect comparable intellectual and work demands. Potentially confounding variables of age, education, alcohol consumption, past occupational exposure to solvents, medical conditions, and site were included in multivariate models. Models adjusted for age and education, and models with 2 × 2 interaction terms only yielded small differences compared with main effects models with the expanded set of covariates. The covariates consistently predicted neurobehavioural performance as expected: poorer performance associated with increasing age, decreasing education, increasing alcohol consumption, and previous jobs exposed to solvents. This also supports the validity of the models themselves. Symptoms of depression and of spontaneous anger and upset that were significantly increased (table 6) reinforce the findings of the altered mood scales (hostility and depression). This internal consistency lends support to the strength of the findings.

Internal consistency was also found between the measures of lead exposure. Coefficients and P values of multiple linear regression models were usually of the same sign and magnitude no matter which exposure indices were used: current, peak, or TWA, although the current concentration was more strongly and more often significantly associated with altered mood states. Cumulative exposure (the sum of the products of concentration and time—the numerator of the equation for TWA) has been used in several studies as an additional exposure index.[13 16] With cumulative exposure to lead (μmol/l × years), visual (Benton: $\beta = -0{\cdot}003$, P = 0·01), auditory memory (digit span: $\beta = -0{\cdot}002$, P = 0·06) and manual dexterity (Santa Ana pegboard: $\beta = -0{\cdot}01$, P = 0·01) also showed significant dose-response relations of poorer performance. Age and cumulative exposure were strongly and positively associated (Pearson r = 0·42), raising the possibility of confounding by age. This seemed to be confirmed by analyses of covariance (not presented) in which significant associations for Benton, digit span, or Santa Ana were diminished among cumulative exposure categories (high, medium, or low), after adjustment for age as well as the other covariates.

Another source of potential bias was that neither the subjects nor the interviewer were blinded to exposure status. Although this may be thought to have skewed results in exposed *v* non-exposed comparisons, it is less likely to be an explanation of dose-response.

The results of this study bear close resemblance to those of Baker *et al*,[2] except that the overall exposure effect occurred at a slightly lower average exposure (1·40 *v* 1·60 μmol/l). Most previous studies did not include profile of mood states or similar checklists, but, of those that did,[1 2 7] the results are consistent: moods indicative of depression, anger, hostility, fatigue, or confusion were more pronounced among exposed workers.

Several workers have suggested that a threshold for adult neurobehavioural effects found by psychometric testing is associated with blood lead concentrations of between 1·93–2·41 μmol/l (40–50 μg/dl). Studies for which this is most obvious relied on Wechsler adult intelligence subtests (block design, digit span, digit-symbol), simple or choice reaction time tests, or newer tests based on information processing theory.[15 17] These studies also often reported considerably slower peripheral nerve conduction among exposed workers. Our findings and those of others[1 2 7] suggest that altered mood measured by profiles of mood states and similar tests may be among the earliest psychometrically detectable changes due to low exposure to lead.

To our knowledge, this is the first study in South America that used the WHO neurobehavioural core test battery to confirm adverse effects of a low occupational exposure to lead. The findings support efforts to reduce lead exposures to the lowest possible level and to follow-up workers exposed to lead over a longer period to evaluate the degree to which improved performance results from reduced exposures.

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1 Baker EL, White RF, Pothier L, Berkey CS, Dinse GE, Travers PH, *et al*. Occupational lead neurotoxicity: improvement in behavioural effects after reduction in exposure. *Br J Ind Med* 1985;**42**:507–16.
2 Baker EL, Feldman RG, White RF, Harley JP, Niles CA, Dinse GE, Berkey CS. Occupational lead neurotoxicity: a behavioural and electrophysiological evaluation. *Br J Ind Med* 1984;**41**:352–61.
3 Campara P, D'Andrea F, Micciolo R, Savonitto C, Tansella M, Zimmermann-Tansella C. Psychological performance of workers with blood-lead concentration below the current threshold limit value. *Int Arch Occup Environ Health* 1984;**53**:233–46.
4 Grandjean P, Arnvig E, Beckmann J. Psychological dysfunctions in lead-exposed workers: relation to biological parameters of exposure. *Scand J Work Environ Health* 1978;**4**:295–303.
5 Hanninen H, Hernberg S, Mantere P, Vesanto R, Jalkanen M. Psychological performance of subjects with low exposure to lead. *J Occup Med* 1978;**20**:683–9.
6 Hogstedt C, Hane M, Agrell A, Bodin L. Neuropsychological test results and symptoms among workers with well-defined long-term exposure to lead. *Br J Ind Med* 1983;**40**:99–105.
7 Johnson B, Burg JR, Xinteras C, Handke JL. A neurobehavioral examination of workers from a primary nonferrous smelter. *Neurotoxicology* 1980;**1**:561–81.
8 Kirby H, Nielsen CJ, Nielsen VK, Gyntelberg F. Subjective symptoms after long term lead exposure in secondary lead smelting workers. *Br J Ind Med* 1983; **40**:314–7.
9 Zimmerman-Tansella C, Campara P, D'Andrea F, Saronitto C, Tansella M. Psychological and physical complaints of subjects with low exposure to lead. *Hum Toxicol* 1983;**2**:615–23.
10 Mantere P, Hanninen H, Hernberg S, Lukkonen R. A prospective follow-up study on psychological effects in workers exposed to low levels of lead. *Scand J Work Environ Health* 1984;**10**:43–50.
11 Repko JD, Morgan BB, Nicholson J. *Behavioral effects of occupational exposure to lead*. Cincinnati: National Institute for Occupational Safety and Health, 1975. (USDHEW (NIOSH) Publ No 75–184.)
12 Repko JD, Corum CR, Jones PD, Garcia LS. *The effects of inorganic lead on behavioral and neurologic function*. Cincinnati: National Institute for Occupational Safety and Health, 1978.
13 Schwartz BS, Bolla KI, Stewart W, Ford DP, Agnew J, Frumkin H. Decrements in neurobehavioral performance associated with mixed exposure to organic and inorganic lead. *Am J Epidemiol* 1993;**137**:1006–21.
14 Stollery BT, Broadbent DE, Banks HA, Lee WR. Short term prospective study of cognitive functioning in lead workers. *Br J Ind Med* 1991;**48**:739–49.
15 Stollery BT, Banks HA, Broadbent DE, Lee WR. Cognitive functioning in lead workers. *Br J Ind Med* 1989;**46**:698–707.
16 Valciukas JA, Lilis R, Eisinger J, Blumberg WE, Fischbein A, Selikoff IJ. Behavioral indicators of lead neurotoxicity: results of a clinical field survey. *Int Arch Occup Environ Health* 1978;**41**:217–36.
17 Williamson AM, Teo RKC. Neurobehavioural effects of occupational exposure to lead. *Br J Ind Med* 1986;**43**: 374–80.
18 American Conference of Governmental and Industrial Hygienists. *Threshold limit values and biological exposure indices for 1990–1991*. Cincinnati: ACGIH, 1991.
19 World Health Organisation. *Operational guide for the WHO neurobehavioral core test battery*; and WHO. *Field evaluation of WHO neurobehavioral core test battery*. Geneva: WHO, 1986.
20 Anger WK, Cassito MG, Liang You-Xin, *et al*. Comparison of performance from three continents on the WHO-recommended neurobehavioral core test battery. *Environmental Res* 1993;**62**:125–47.
21 Escalona E, Yanes L, Feo O, Maizlish N. Neurobehavioral evaluation of Venezuelan workers exposed to organic solvent mixtures. *Am J Ind Med* 1995;**27**:15–27.
22 Letz R. The neurobehavioral evaluation system: an international effort. In: Johnson BL, Anger WK, Durao A, Xinteras C, eds. *Advances in neurobehavioral toxicology*. Chelsea, MI: Lewis, 1990:189–201.
23 McNair DM, Lorr M, Dropleman LF. *EITS Manual-Profile of mood states*. San Diego: Educational Testing Service, 1971.
24 Wechsler D. *The measurement and appraisal of adult intelligence*. Baltimore: Williams and Wilkins. 1958.
25 Lezak MD. *Neuropsychological assessment, 2nd ed*. New York: Oxford University Press, 1983.
26 Fleishman EA. Dimensional analysis of psychomotor abilities. *Journal of Experimental Psychology* 1954;**48**: 437–54.
27 Benton A. *The revised visual retention test*. Ames, Iowa: State University of Iowa, 1963.

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