Occupational exposure to lead and neuropsychological dysfunction

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Abstract

Objective—To evaluate the neuropsychological effects of current low level and previous higher levels of exposure to lead and evaluate the relation between effects of lead and bone lead.

Methods—A neuropsychological test battery was given to 54 storage battery workers with well documented long term exposure to lead. The effect was studied in two subgroups: those whose blood lead had never exceeded 2.4 $\mu\text{mol/l}$ (the low BPb_{Max} group, n=26), and those with higher exposure about 10 years earlier (the high BPb_{Max} group, n=28). In both groups, the recent exposure had been low. Correlations between the test scores and the indices of both long term and recent exposure—including the content of lead in the tibial and calcaneal bone—and covariance analyses were used to assess the exposure-effect relation. Age, sex, and education were controlled in these analyses.

Results—Analyses within the low BPb_{Max} group showed a decrement in visuospatial and visuomotor function (block design, memory for design, Santa Ana dexterity), attention (digit symbol, digit span), and verbal comprehension (similarities) associated with exposure to lead and also an increased reporting of subjective symptoms. The performance of the high BPb_{Max} group was worse than that of the low BPb_{Max} group for digit symbol, memory for design, and embedded figures, but there was no reporting of symptoms related to exposure, probably due to selection in this group. No relation was found between the output variables and the tibial lead concentration. The calcaneal lead concentrations were related to the symptoms in the low BPb_{Max} group.

Conclusions—Neuropsychological decrements found in subjects with high past and low present exposure indicate that blood lead concentrations rising to 2.5–4.9 $\mu\text{mol/l}$ cause a risk of long lasting or even permanent impairment of central nervous system function. Milder and narrower effects are associated with lower exposures; their reversibility and time course remain to be investigated. History of blood lead gives a more accurate prediction of the neuropsychological effects of lead than do measurements of bone lead.

Keywords: blood lead; bone lead; exposure history; neuropsychological testing

Research on the neuropsychological effects of occupational exposure to lead started about 20 years ago. At that time three independent studies compared the results of workers exposed to lead in various neuropsychological tests with those of a control group. The studies also examined the dose-effect correlations within the exposed group.^{1–3} The results strongly suggested a mild to moderate neuropsychological dysfunction caused by exposure to lead. Several subsequent studies that used more or less similar approaches have, in general, supported this conclusion,^{4–11} but at least one recent study has yielded a negative result.¹²

Although most studies report adverse effects due to exposure to lead, the neuropsychological functions affected differ as does the concentration of lead in blood (BPb) that does not cause detectable effects. These differences can be due to differences in the outcome variables used (the selection of the test), or in the exposure variables available and used, or to unknown confounding factors in the groups studied. Moreover, the effects found can also depend on variation in the exposure histories, such as period of exposure, and pattern of BPb during that period. The neuropsychological effects associated with a long and intensive exposure may not only differ quantitatively from early effects but also qualitatively.

In this study we have made a separate evaluation of the continuing effects of previous higher exposures on the one hand and of the effects associated with current low levels of exposure on the other. Also we have considered the question of the relevance of bone lead measures as a marker of cumulative dose of tissue lead versus histories of BPb with regard to the neuropsychological outcome. Care was taken to obtain reliable and thorough documentation of the exposure histories of the people studied. As to the methods, our choice favoured classic procedures which best permit comparison with results from previous studies. Results dealing with the biological measures of exposure to lead and the neurophysiological study findings, have been reported in another paper.¹³

Methods

SUBJECTS AND THEIR EXPOSURE

In a previous study, the content of lead in tibial bone was studied among 87 workers from two small lead acid battery factories.¹⁴ For the present study, 30 of these workers with a low

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Table 1 Characteristics of the subjects in two groups with lower and higher BPb_{Max}

	$BPb_{Max} \leq 2.4 \mu\text{mol/l}$ (n=26, 22M, 7F)		$BPb_{Max} > 2.4 \mu\text{mol/l}$ (n=28, 21M, 7F)		p Value*
	Mean	SD	Mean	SD	
Age, (y)	41.7	9.3	46.6	6.2	0.046
Education, (y)	8.4	1.7	7.6	1.0	0.024
Exposure, (y)	12.3	6.7	20.5	6.9	0.000
Tibial lead, (mg/kg)	19.8	13.7	35.3	16.6	0.001
Calcaneal lead, (mg/kg)	78.6	62.4	100.4	43.1	0.282
BPb_{Int} ($\mu\text{mol/l}\cdot\text{y}$)	15.7	9.5	39.2	18.5	0.000
BPb_{Max3} ($\mu\text{mol/l}$)	1.9	0.4	3.3	0.7	0.000
BPb_{Ave3} ($\mu\text{mol/l}$)	1.4	0.3	1.9	0.4	0.000
BPb_{Int3} ($\mu\text{mol/l}\cdot\text{y}$)	3.7	1.3	4.6	1.2	0.034
BPb_{Max3} ($\mu\text{mol/l}$)	1.6	0.5	1.9	0.5	0.030
BPb_{Ave3} ($\mu\text{mol/l}$)	1.3	0.4	1.6	0.4	0.074

*Student's *t* test.

There were up to 2 pieces of missing data for each variable.

 BPb_{Int} =time integrated BPb during working life; BPb_{Max} =maximal recorded BPb during working life; BPb_{Ave} =average BPb during working life; BPb_{Int3} , BPb_{Max3} , BPb_{Ave3} =corresponding measures for the past three years; M=male; F=female.

tibial lead content and 30 with a high concentration were invited to participate, and all accepted the invitation. Both plants were situated in a suburb of Helsinki and had similar working conditions. Absence of any central nervous system illness or handicap, excessive alcohol consumption, and previous neurotoxic exposures was verified by both a questionnaire and a neurological interview.

The sample was homogeneous in respect to ethnic background, native language, socio-economic group, and type of job. For 55 people the education consisted of the customary comprehensive school of six to nine years with or without one or two additional years in a vocational school. Five people had more education and were excluded from the analyses. One was excluded because of missing data on some variables. The remaining group consisted of 43 men and 11 women. The mean age was 43 years for the men and 48 years for the women, and the mean duration of exposure was 15 years for the men and 17 years for the women.

Exposure assessment was based on statutory, regular BPb measures covering the total exposure period. The variables chosen to reflect long term exposure were the following: (1) the time weighted average BPb (BPb_{Ave}), (2) the highest ever measured BPb (BPb_{Max}), and (3) the cumulative dose of BPb integrated over the entire exposure history (BPb_{Int}). Corresponding variables were used to describe the average, maximal, and time integrated cumulative BPb for the past three years (BPb_{Ave3} , BPb_{Max3} , BPb_{Int3}). Calcaneal lead, tibial lead, and the duration of exposure in years were additional

exposure variables. More information about these variables is given elsewhere.¹³

Among the people studied, BPb values $>2.4 \mu\text{mol/l}$ (the statutory limit in Finland since June 1985) had been common in the past, but non-existent during recent years. For 26 subjects (the low BPb_{Max} group) the BPb had never exceeded $2.4 \mu\text{mol/l}$. For 28 subjects (the high BPb_{Max} group) higher values had been documented in the past.

NEUROPSYCHOLOGICAL TESTS

Reaction speed was measured by visual and auditory simple reaction time (RT) tasks. In both tasks the stimuli were presented at random intervals (3–10 s) for six minutes. For the speed of visuomotor function the Santa Ana dexterity test with the preferred and non-preferred hand (Santa Ana 1 and Santa Ana 2, respectively), and the digit symbol test from the Wechsler adult intelligence scale (WAIS) were used. Santa Ana is a pure test for visuomotor function or dexterity,¹⁵ whereas the digit symbol test has a notable cognitive component and is often used as a test for attention.¹⁶

The tests used for visual and visuospatial function were block design from WAIS, Valciukas' embedded figures test,³ the memory for design test,¹⁵ and the retention task of digit symbol. These tests tap different aspects of visuospatial function. Block design and memory for design are visuoconstructive tasks and require the analysis and reconstruction of abstract visual patterns, but memory for design also taps visual memory.¹⁵ Embedded figures measures visuo-perceptual function and

Table 2 Correlations of the exposure indices for the low BPb_{Max} group ($BPb_{Max} < 2.4 \mu\text{mol/l}$; $100 \times r$, $n = 24-6$, only correlations of ≥ 0.20 are indicated)

	Age	Exposure duration	Tibial lead	Calcaneal lead	BPb_{Int}	BPb_{Max}	BPb_{Ave}	BPb_{Int3}	BPb_{Max3}
Exposure duration	65***	—	—	—	—	—	—	—	—
Tibial lead	24	46*	—	—	—	—	—	—	—
Calcaneal lead	—	—	40†	—	—	—	—	—	—
BPb_{Int}	52**	92***	51*	—	—	—	—	—	—
BPb_{Max}	21	—	40*	46*	37†	—	—	—	—
BPb_{Ave}	—	—	21	54***	20	85***	—	—	—
BPb_{Int3}	—25	—	—	46*	—	55**	80***	—	—
BPb_{Max3}	—39†	—39†	—	66***	—	59**	87***	84***	—
BPb_{Ave3}	—36†	—33†	—	54**	—	57**	88***	90***	96***

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; † $p < 0.1$. BPb_{Int} =time integrated BPb during work life; BPb_{Max} =maximal recorded BPb during working life; BPb_{Ave} =average BPb during working life; BPb_{Int3} , BPb_{Max3} , BPb_{Ave3} =corresponding measures for the past three years.

Table 3 Correlations of the exposure indices for the high BPb_{Max} group (BPb_{Max} > 2.4 µmol/l; 100 × r, n = 26–8, only correlations ≥ 0.20 have been indicated)

	Age	Exposure duration	Tibial lead	Calcaneal lead	BPb _{Int}	BPb _{Max}	BPb _{Ave}	BPb _{Int3}	BPb _{Max3}
Exposure duration	48*	—	—	—	—	—	—	—	—
Tibial lead	31	50**	—	—	—	—	—	—	—
Calcaneal lead	—	26	40*	—	—	—	—	—	—
BPb _{Int}	30	89***	56**	48*	—	—	—	—	—
BPb _{Max}	—	30	43*	62***	47*	—	—	—	—
BPb _{Ave}	-25	23	37†	54**	43*	57**	—	—	—
BPb _{Int3}	-40*	-28	—	31	—	—	75***	—	—
BPb _{Max3}	-46*	-41*	—	30	—	26	50**	85***	—
BPb _{Ave3}	-46*	-33†	—	32	—	24	67***	98***	93***

*p<0.05; **p<0.01; ***p<0.001; †p<0.1.

BPb_{Int}=time integrated BPb during working life; BPb_{Max}=maximal recorded BPb during working life; BPb_{Ave}=average BPb during working life; BPb_{Int3}, BPb_{Max3}, BPb_{Ave3}=corresponding measures for the past three years.

requires recognition of familiar objects that are superimposed on the visual field.³ Digit symbol retention requires the subject to reproduce correct symbols in the right places immediately after the digit symbol task. It is a test for incidental visual learning.

Similarities from the WAIS and a Finnish synonyms test¹⁵ were used for verbal comprehension. Similarities were orally given and orally answered. Synonyms is a paper and pencil test. Verbal (auditory) memory was assessed by digit span and the associative learning test. Digit span was given and scored according to the WAIS-R manual. In the data analyses the total score was used. Besides being a test for immediate auditory memory, it is also considered to be a measure of attention. Associative learning was a modification of the Wechsler associative learning test, containing five easy and five difficult items. The scoring was done according to the manual of the Wechsler memory scale.

The presentation order of the 12 tests was designed to give variety to the testing session and to keep the fatigue effect at a minimum. Two psychologists alternated as examiners. The tests were given in a strictly standardised manner and without knowledge of the blood or bone lead concentrations of the subjects. The scoring was carried out independently by the two psychologists. In the rare cases of initial discrepancy, a consensus was easily reached.

SUBJECTIVE SYMPTOMS AND MOODS

During the bone lead measurements the subjects filled out two questionnaires on subjective effects—that is, a symptom ques-

tionnaire with 31 items and three response alternatives and the Finnish version of the profile of mood states (POMS). The symptom questionnaire asked about symptoms experienced during the past year. The following six symptom scales were included: sleep disturbances, fatigue, memory problems, emotional lability, somatic complaints, and sensory and motor symptoms. The POMS inquired about feelings and moods during the past seven days. The scales yielded by our POMS version were tension, anger, depression, fatigue, vigour, memory problems, and helplessness.

STATISTICAL ANALYSES

Analysis was with SAS statistical software. The association between the exposure and outcome variables was studied by partial correlations and by two covariate analyses. Correlations between the exposure and outcome variables were calculated for both the total group and the low and high BPb_{Max} groups separately. Age, sex, and education were controlled in these analyses. All correlations were Pearson's correlations. The general linear model procedure was used in the covariate analyses. The first analysis aimed at identifying the effects due to past high exposure. It also compared the variances in the low and high BPb_{Max} groups. The second analysis was done to identify the effects of the recent low level exposure. The second analysis was performed within the low BPb_{Max} group, which was divided into two parts by the median BPb_{Ave3} (1.37 µmol/l) of the group. The potential confounders age, sex, and education were stepwise inclusions in the model, according to the backward selection

Table 4 Partial correlations of the psychological test scores with the exposure variables in the total group (100 × r, n = 51–4, age, sex, and education are controlled for, and only correlations of ≥ 0.20 are given)

Test	Tibial lead	Calcaneal lead	BPb _{Int}	BPb _{Max}	BPb _{Ave}	BPb _{Int3}	BPb _{Max3}
Visual RT	—	—	—	—	—	—	—
Auditive RT	—	—	—	—	—	—	23
Santa Ana 1	—	—	—	—	-36*	-32*	-25†
Santa Ana 2	—	—	—	—	-27†	-20	-22
Digit symbol	—	—	-32*	-33*	-35*	-32*	-23
Block design	—	—	-21	-29*	—	—	—
Embedded figures	—	-31*	-36*	-28*	-27°	—	—
Memory for design	—	-23	-29*	-29*	—	—	—
Digit symbol (retention)	—	—	-27†	-27†	-20	—	—
Digit span	—	—	-20	—	—	—	—
Associative learning	—	—	—	—	—	—	-23
Similarities	—	-20	-31*	-30*	-23	—	—
Synonyms	-20	-20	-25†	-23	—	—	—

*p<0.05; **p<0.01; †p<0.1.

BPb_{Int}=time integrated BPb during working life; BPb_{Max}=maximal recorded BPb during working life; BPb_{Ave}=average BPb during working life; BPb_{Int3}, BPb_{Max3}, BPb_{Ave3}=measures for the past three years. For reaction time positive correlations reflect association of weak performance with increasing lead burden; for the other variables negative correlations reflect the same association.

Table 5 Partial correlations of the psychological test scores with the exposure variables for the low BPb_{Max} group (100 × r, n = 24–6, age, sex, and education are controlled for, only correlations of ≥ 0.20 are given)

Test	Tibial lead	Calcaneal lead	BPb _{Int}	BPb _{Max}	BPb _{Ave}	BPb _{Int3}	BPb _{Max3}
Visual RT	—	—	—	—	29	—	—
Auditive RT	—	—	—	—	—	–26	—
Santa Ana 1	—	—	—	—	–36†	–38†	–40†
Santa Ana 2	—	—	—	–30	–26	–20	–29
Digit symbol	—	—	—	–28	–35	–43*	–34
Block design	—	–20	–31	–31	–55**	–58**	–48*
Embedded figures	—	–30	—	–43*	—	—	–20
Memory for design	–23	–20	–28	—	–35	–41*	–35
Digit symbol (retention)	22	33	—	–26	—	–29	—
Digit span	—	—	–26	—	—	–45*	–25
Associative learning	—	—	—	—	—	—	–24
Similarities	–25	—	–22	–35†	–43*	–24	–40†
Synonyms	–23	—	–26	—	—	—	—

*p<0.05; **p<0.01; †p<0.1.

BPb_{Int}=time integrated BPb during working life; BPb_{Max}=maximal recorded BPb during working life; BPb_{Ave}=average BPb during working life; BPb_{Int3}, BPb_{Max3}, BPb_{Ave3}=corresponding measures for the past three years. For reaction time positive correlations reflect association of weak performance with increasing lead burden; for the other variables negative correlations reflect the same association.

method. Two sided analyses were applied throughout.

Results

Table 1 shows the characteristics of the low and high BPb_{Max} groups. The low BPb_{Max} group was younger and had a shorter exposure time. The means of the exposure indices indicated a rather stable exposure throughout the work history of this group. Although the BPb_{Max} values had been higher in the past, the time weighted average for the total exposure period was very close to that of the past three years (1.4 v 1.3 µmol/l). In the high BPb_{Max} group the level of exposure had been reduced, but the recent BPbs were still higher than those in the low BPb_{Max} group. However, the difference in the recent exposure between the groups was small when compared with the long term exposure indices and the content of lead in tibial bone. The difference in the calcaneal lead concentrations was not significant between the groups.

Age and duration of exposure showed negative correlations with recent exposure (tables 2 and 3). Unexpectedly, BPb_{Ave} (for the total period of exposure) was closely related to all the indices of recent exposure but less strongly to total exposure. In the following discussion, BPb_{Ave} is therefore considered as a variable of recent exposure. Because of the close association between BPb_{Int} and exposure years BPb_{Int}

was excluded from the subsequent analyses. In the low BPb_{Max} group all the BPb variables (except BPb_{Int}) strongly correlated with each other. Tibial lead was related to BPb_{Int} (but not to BPb_{Int3}), and calcaneal lead was associated with the other BPb variables, particularly the highest BPb measured during the past few years. In the high BPb_{Max} group, the BPb_{Int3}, BPb_{Max3} and BPb_{Ave} were interrelated. In this group, both bone lead measures were more closely related to the variables reflecting total exposure than to those reflecting recent exposure. Because of the high mutual correlations of the recent exposure indices, including the actual BPb, in both groups, BPb_{Ave3} was excluded from the subsequent analyses. The internal correlations of the exposure indices in the total group have been given elsewhere.¹³

PARTIAL CORRELATIONS BETWEEN EXPOSURE AND THE OUTCOME VARIABLES

In the total group digit symbol, block design, embedded figures, memory for design, and similarities were related to the long term exposure indices (table 4). Digit symbol correlated also with the recent exposure, whereas the Santa Ana variables correlated only with recent exposure. The only significant correlation of the bone lead variables was that between calcaneal lead and embedded figures. The low correlations of the bone lead measures were,

Table 6 Partial correlations of the psychological test scores with the exposure variables for the high BPb_{Max} group (100 × r, n = 26–8, age, sex, and education are controlled for, only correlations of ≥ 0.20 are given)

Test	Tibial lead	Calcaneal lead	BPb _{Int}	BPb _{Max}	BPb _{Ave}	BPb _{Int3}	BPb _{Max3}
Visual RT	—	—	—	—	—	—	—
Auditive RT	—	—	—	—	—	38†	31
Santa Ana 1	25	—	—	—	–32	–31	—
Santa Ana 2	—	—	—	—	–29	–22	—
Digit symbol	25	–34†	—	—	—	—	—
Block design	—	—	–23	–34†	—	35†	30
Embedded figures	–21	–32	–46*	–29	–24	—	—
Memory for design	—	–20	–27	–23	26	28	22
Digit symbol (retention)	–25	–36†	–41†	–41*	–25	—	—
Digit span	—	—	—	—	—	—	—
Associative learning	–21	—	–35†	–35†	—	—	–29
Similarities	–20	—	–24	–24	—	—	—
Synonyms	–21	–36†	–27	–31	—	20	—

*p<0.05; †p<0.1.

BPb_{Int}=time integrated BPb during working life; BPb_{Max}=maximal recorded BPb during working life; BPb_{Ave}=average BPb during working life; BPb_{Int3}, BPb_{Max3}, BPb_{Ave3}=corresponding measures for the past three years. For reaction time positive correlations reflect association of weak performance with increasing lead burden; for the other variables negative correlations reflect the same association.

Table 7 Partial correlations of the symptom and mood scales with the exposure variables in the low BPb_{Max} group (100 × r, n = 24–6, age, sex, and education controlled for, only correlations of ≥ 0.20 are given, and scales with no correlation > 0.30 are not included)

	Tibial lead	Calcaneal lead	BPb _{Int}	BPb _{Max}	BPb _{Ave}	BPb _{Int3}	BPb _{Max3}
Symptom scale:							
Sleep disturbances	—	50*	—	35†	22	20	27
Fatigue	—	32	—	46*	39†	34	37†
Emotion lability	—	21	—	33	20	—	—
POMS scale:							
Tension	—	39†	23	46*	36†	24	29
Fatigue	20	36†	—	24	—	—	20
Memory disturbances	—	—	27	33	26	—	—
Depression	—	42†	—	49*	33	—	—
Anger	—	—	27	33	22	—	—
Helplessness	34	49*	45*	58**	53**	36†	33

*p<0.05; **p<0.01; †p<0.1.

BPb_{Int}=time integrated BPb during working life; BPb_{Max}=maximal recorded BPb during working life; BPb_{Ave}=average BPb during working life; BPb_{Int3}, BPb_{Max3}, BPb_{Ave3}=corresponding measures for the past three years.

however, in the expected direction, as were all of the low correlations in table 4.

The subjective symptoms and moods did not show a significant relation with exposure in the total group, except for correlations of sleep disturbances and the POMS helplessness scale with calcaneal lead. A marginal correlation was found between the POMS memory scale and BPb_{Int} (table of correlations not included.)

The partial correlations calculated for the two subgroups differed from those in the total group and from each other. In the low BPb_{Max} group, block design, digit symbol, digit span, similarities, and marginally, Santa Ana 1 and memory for design were associated with the indices of recent exposure (table 5). Embedded figures was associated with BPb_{Max}. The correlations of the bone lead measures were not significant and were even in the opposite direction for digit symbol retention.

In the high BPb_{Max} group, embedded figures, digit symbol retention, and marginally, block design and associative learning correlated with BPb_{Int} or with BPb_{Max} or with both (table 6). None of the correlations of the tests with recent exposure were significant (those of block design and memory for design in reversed direction). Calcaneal lead had a marginally significant association with digit symbol, digit symbol retention, and synonyms.

Correlations of the exposure indices with the symptom and mood scales showed an even more obvious difference between the two subgroups. In the low BPb_{Max} group several symptoms and moods were associated with exposure (table 7). The POMS helplessness scale had a significant correlation with the integrated, maximal, and average BPb and with calcaneal

lead. Other scales correlating with these exposure indices, although in a less systematic way, were sleep disturbances and symptoms of fatigue, and the POMS scales for tension and depression. In the high BPb_{Max} group no association of exposure with symptoms or moods was found (table 8). All the correlations were low (and those with BPb_{Ave} and BPb_{Int3} were negative).

COVARIANCE ANALYSES

The covariance analysis within the low BPb_{Max} group showed a significant effect for BPb_{Ave} (a weaker effect in the subgroup with a BPb_{Ave} above the group median) for the block design test (p=0.03), for the symptoms of fatigue (p=0.02), and for the POMS tension scale (p=0.04). A marginal effect was found for the POMS scales of helplessness (p=0.07) and depression (p=0.09).

Of the covariates, age had a significant or nearly significant effect on the visual retention time, Santa Ana 1 and 2, digit symbol, associative learning, and synonyms. Sex accounted for performance in the Santa Ana, associative learning, and similarities tests. Education had an effect on block design and associative learning. None of the symptom scales showed any effect of the potential confounders. For the POMS scales, there was an age effect on the memory scale and an effect of education on fatigue.

The covariance analysis between the low and high BPb_{Max} groups showed or suggested an effect of BPb_{Max} on digit symbol (p=0.01), embedded figures (p=0.04), and memory for design (p=0.08). The POMS scale of fatigue also showed an effect (p=0.03), but it was the

Table 8 Partial correlations of the symptom and mood scales with the exposure variables in the high BPb_{Max} group (100 × r, n = 26–8, age, sex, and education are controlled for, only correlations ≥ 0.20 are given, and scales with no correlation > 0.30 are not included)

	Tibial lead	Calcaneal lead	BPb _{Int}	BPb _{Max}	BPb _{Ave}	BPb _{Int3}	BPb _{Max3}
Symptom scale:							
Memory disturbances	—	—	—	—	—	—	31
Somatic	—	32	—	—	–23	–20	—
POMS scale:							
Memory disturbances	—	32	34†	—	—	—	—
Depression	—	—	—	—	–35†	–21	20
Anger	—	—	—	—	–27	–31	—

†p<0.1.

BPb_{Int}=time integrated BPb during working life; BPb_{Max}=maximal recorded BPb during working life; BPb_{Ave}=average BPb during working life; BPb_{Int3}, BPb_{Max3}, BPb_{Ave3}=corresponding measures for the past three years.

Table 9 Prevalence of subjects with low scores in at least four tests in the subjects divided in two groups based on different variables of exposure

Exposure indicator	Cut off value	Group with low variable value		Group with high variable value		p Value*
		Total group n	Subjects with ≥ 4 low test scores n (%)	Total group n	Subjects with ≥ 4 low test scores n (%)	
Exposure time	<20 years	46	7 (15)	9	5 (56)	0.13
BPb _{int}	<40 $\mu\text{mol/l} \times \text{y}$	43	7 (16)	12	5 (42)	0.28
BPb _{Max}	<3.3 $\mu\text{mol/l}$	42	6 (14)	14	6 (43)	0.17
Tibial lead	<38 mg/kg	39	6 (15)	16	6 (38)	0.29
Calcaneal lead	<120 mg/kg	39	6 (15)	16	6 (38)	0.29

*Fishers exact test.

BPb_{int}=time integrated BPb concentration; BPb_{Max}=maximal BPb concentration.

For all the exposure indicators, the division into two groups was based on the 80th percentile of the total population studied (60 people).

opposite of what was expected in that the group with a high BPb_{Max}, which reported fewer feelings of fatigue than the group with a low BPb_{Max}.

Of the covariates, the effect of age was significant or nearly significant for visual reaction time, Santa Ana 1 and 2, digit symbol, digit symbol retention, digit span, and memory problems in the POMS. Sex had an effect on visual and auditive reaction times, and on associative learning. An effect of education was found for digit symbol, similarities, and synonyms, and on scales for sensory and motor symptoms, somatic symptoms, and fatigue (POMS).

SUBJECTS WITH EXTENSIVE NEUROPSYCHOLOGICAL DYSFUNCTION

Finally, the prevalence of subjects with low test scores for several tests was examined. A low score was defined as a score corresponding to about the lowest 10 to 12 percentiles of the normal working populations. Twelve subjects—four in the low BPb_{Max} group (15%) and eight in the high BPb_{Max} group (29%)—had four to seven low scores, a result suggesting more extensive neuropsychological dysfunction. The prevalence of extensive dysfunction showed a relation to the long term history of lead exposure, high BPb, and high bone lead concentrations. The relation was marginally significant for the duration of exposure and BPb_{Max} (table 9).

Discussion

The participants in this study had been working in lead acid battery production from one to >30 years. During this period the exposure had been drastically reduced. In our sample, the portion of subjects with BPb_{Max} >2.4 $\mu\text{mol/l}$ was 64% for those with >15 years of exposure, whereas the respective proportion was 17% for those who had entered the job during the past 15 years, and 0% for those who had entered it during the past five years. Our data analysis aimed at a separate evaluation of the effects caused by the recent low level of exposure and those associated with the high BPb in the past. Thus the sample was divided into two subgroups: those with past BPb values >2.4 $\mu\text{mol/l}$, and those with no maximal BPb at that level. The applied exposure indices included the maximal, cumulative, and time weighted average BPb with reference to the

total period of exposure and to exposure during the past three years, plus current contents of lead in tibial and calcaneal bones.

Separate analyses of the relations between these exposure indices in the two subgroups aided the interpretation of the exposure-effect relations found in the two groups. When these relations were analysed, age, sex, and education were controlled. The effects of the low recent exposure and those of high past exposure were inferred from the exposure-effect correlations found in the total group, as well as from the correlations found within the respective subgroup and from the two covariance analyses conducted.

RECENT LOW EXPOSURES

The effects occurring at BPb_{Max} $\leq 2.4 \mu\text{mol/l}$, and associated with recent exposure, seemed to involve visuospatial and visuomotor function (block design, and more marginally, memory for design and Santa Ana), attention (digit symbol and digit span), and verbal comprehension (similarities). There was also an effect on the embedded figures test in this group; it was related to the BPb_{Max} of the total period of exposure. The effects caused by low exposure also included depressive symptoms and feelings. They also correlated with total rather than with very recent exposure. Our findings tally with previous results. In the first Finnish study on lead acid battery workers with present and past BPb <3.4 $\mu\text{mol/l}$, Santa Ana, block design, memory drawings, and digit span tests displayed an association with the BPb.² In a two year follow up of new lead acid battery workers, a subtle effect on block design and Santa Ana was detected at BPb <2.2 $\mu\text{mol/l}$.¹⁷ Valciukas *et al*³ found effects of lead on the digit symbol, block design, and embedded figures test in a group with present and past BPb ranging to 3.8 $\mu\text{mol/l}$. At a somewhat higher level of exposure, Grandjean *et al*¹ found an effect on digit symbol, several visuospatial tests, digit span, and similarities, as well as on other tests of verbal comprehension and verbal memory. Previous higher levels of exposure were not excluded in these two studies.^{1,3} The same applies to most of the recent studies on low exposures to lead.

In the present study, the most pronounced effect on subjective wellbeing was shown by our helplessness scale, which corresponds roughly to the confusion scale of the original POMS. Other symptoms and moods related to lead

included tension, depression, fatigue, and sleep disturbances. A previous study by Hänninen *et al* showed a lead related increase of symptoms indicative of fatigue, emotional lability, tension, and difficulties in coping with the environment, among workers with present and past BPb <3.4 $\mu\text{mol/l}$.¹⁸ A corresponding pattern of subjective response has also been found among workers exposed to lead with higher BPb.^{4 6 18 19}

PREVIOUS HIGH EXPOSURES

In the total group, decrements in the digit symbol test, visuospatial tests, and similarities tests were associated with long and high past exposures. The variance analysis further affirmed that people with BPb >2.4 $\mu\text{mol/l}$ in their exposure history, even years ago, still had inferior visuospatial and visuoconstructive performances when compared with those whose BPb had always remained below that concentration. Also within the high BPb_{Max} group, performance tended to decrease with increasing BPb_{Int} and increasing BPb_{Max}, even though few of these associations reached significance. The high previous exposure did not show any effect on the subjective wellbeing of our high BPb_{Max} group. This result does not fit our expectation, nor does it agree with the results of previous studies.^{4 6 18 19} We assume that it reflects selection in this group. Most of the workers who had started lead battery work >15 years ago had indeed already stopped. The adverse effects of lead, and in particular those on subjective wellbeing, probably contributed to the decision to change jobs, and in some cases, led to early retirement so that only the most resilient workers were still in that job. The performance effects indicated by our statistical analyses have probably also been attenuated by this selection. Another type of confounding by selection may have contributed to the lack of association between the exposure indices and symptoms in this group as well as to the low and partly even reversed association found between recent exposure and visuospatial performance. Internal correlation of the exposure indices and age showed that the subjects with a long period of exposure have been working at lower exposures during the recent years than those with a shorter period of exposure. We assume that the serious concern of factory management and healthcare personnel for the health of the workers has led to the transfer of subjects with high long term exposure, and perhaps with some difficulties in coping with their job, to tasks with less exposure.

Our results do not allow any conclusive description of the late effect of past high exposure. In all, it seems to be rather diffuse and rather widespread. The core effect is on tests involving the encoding of complex visually presented material, but verbal functions (similarities, associative learning) and the digit symbol performance seem also to be affected. It is interesting that short term exposure is associated with an even more pronounced effect on the visuoconstructive function (embedded figures) than on visuoconstructive tasks (block design, memory for design). An effect on visuoconstructive function rather than on visuo-

constructive performance has previously been documented by Campara *et al*⁶ at BPb ranging from 2.2 to 2.9 $\mu\text{mol/l}$, and by Araki *et al*⁷ in a group in which the current BPb ranged up to 3.1 $\mu\text{mol/l}$. Effects on verbal comprehension or verbal memory have earlier been documented in several studies in which the actual or maximal BPb exceeded 3 $\mu\text{mol/l}$.^{1 4 6 11} Verbal tests, notably the so called vocabulary tests, are generally considered to be measures of acquired knowledge, and as such are resistant to impairment during adulthood. However, this view may be an oversimplification because cognitive processes contributing to verbal performance other than verbal knowledge,^{20 21} and can indeed be vulnerable and sensitive to certain neurotoxic effects. The digit symbol performance, again, is known to be sensitive to different kinds of brain dysfunction.¹⁶

At the individual level, one third of the high BPb_{Max} group showed a wide, although not necessarily grave, neuropsychological impairment, whereas about half of the group still had intact, in some cases even good, test results. Whether their condition had improved during the six to 15 years in reduced exposure cannot be evaluated from the available data. The two year follow up study by Baker *et al*²² indicated some improvement in the subjective wellbeing after exposure was reduced, but no significant improvement in the neuropsychological functions.

BONE LEAD MEASURES AS INDICES OF EXPOSURE

Lead both accumulates in the calcaneus and is eliminated from it more rapidly than for the tibia. Correspondingly, tibial lead correlated only with the long term exposure in the low BPb_{Max} group, and calcaneal lead was a better indicator of recent exposure. Neither of the bone lead measures had any significant association with the test performances of this group, but calcaneal lead was related to the results of the symptom and mood scales. In the high BPb_{Max} group with a longer exposure history and higher BPb values in the past, the calcaneal lead concentration had decreased to about the same level as seen in the low BPb_{Max} group, but it was still associated with the duration and intensity of past exposure and tended to correlate with the test performances associated with high past exposure. In all, the content of lead in bone seems not to reflect the effect on brain function as well as the history of BPb.

RISKS CAUSED BY LOWER AND HIGHER EXPOSURES

For the people whose BPb had never exceeded 2.4 $\mu\text{mol/l}$, we found significant deterioration of neuropsychological performance related to lead, similar to that found in previous studies. Our data do not allow a definition of the lowest BPb that cause a hazard to central nervous system function. A BPb_{Ave3} cut off point of 1.37 $\mu\text{mol/l}$ was used in the variance analysis. In our data this concentration corresponds with PBb_{Max} of about 1.50 $\mu\text{mol/l}$. This value is near the limit suggested earlier by Mantere *et al*.¹⁷

Low limit values for occupational exposure to lead are based on two arguments: (a) that even the mild effects found at low BPb can

essentially lower the ability to cope with the demands of everyday life, at least for subjects with restricted adaptive resources, and (b) that early mild effects can be taken as warning signals that indicate incipient changes in the function of the nervous system, likely to accelerate along with cumulative dose of lead.¹⁷ This argument has recently been questioned because of insufficient documentation of any association between long term exposure and neuropsychological functioning.²³ This subject matter has, indeed, been neglected in existing research on adult exposure to lead.

A dose-effect relation has been recently reported between cumulative exposure and neuropsychological performance in lead smelter workers with high past and low recent exposure.¹¹ A similar relation was found in the present study. Our results indicate that long term exposure with previous BPb >2.4 µmol/l, causes a risk for a long lasting, or even permanent, impairment in central nervous system functions. In older subjects the effect may accelerate along with the incipient aging process. Whether the effects due to long term exposure at more moderate levels of exposure are more reversible remains to be investigated in future studies.

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