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No cognitive deficits in men formerly exposed to lead

Robert Winker[1*], **Alfred Barth**[2*], **Elisabeth Ponocny-Seliger**[3], **Alexander Pilger, Wolf Osterode**[1], and **Hugo W. Rüdiger**[1]

[1] Division of Occupational Medicine, Medical University of Vienna, Vienna, Austria
[2] Institute of Management Science, Division Ergonomics and Organisation, Vienna University of Technology, Vienna, Austria
[3] Empirical Research & Statistical Consulting, Vienna, Austria

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Keine kognitiven Defizite in ehemals bleiexponierten Arbeitnehmern

Zusammenfassung. *Ziel:* Das Ziel der gegenwärtigen Studie war es, kognitive Langzeitfolgen von Bleiexposition innerhalb gültiger Grenzwerte nach Expositionsende zu untersuchen. Deshalb wurden exekutive Funktionen, Aufmerksamkeit, visuelles räumliches Denken, einfache und komplexe Reaktionszeit in früher exponierten Bleiarbeitern untersucht.

Methodik: Die Studiengruppe umfasste 48 männliche Arbeiter, die früher berufsbedingt bleiexponiert waren, mit einem mittleren aktuellen Blutblei von 5,4 μg/100 ml, sowie 48 gematchte Kontrollen (PbB: 4,7 μg/100 ml), welche aus einem Pool von 61 männlichen Stahlarbeitern gebildet wurden. Die Kontroll- und Studiengruppe wurden hinsichtlich Alter, Bildungsjahre, verbaler Intelligenz und der Einnahme alkoholischer Getränke paralellisiert. Folgende neuropsychologische Tests wurden durchgeführt: Modified Wisconsin Card Sorting Test, Block Design Test, visuelles räumliches Denken, einfache Reaktionszeit, komplexe Reaktion und der Zahl-Symbol Substitutionstest. Die Bleibelastung wurde anhand von aktuellen und kumulativen Parametern beurteilt.

Resultate: Bei allen neurobiologischen Parametern zeigten sich keine signifikanten Unterschiede zwischen den Gruppen. Negative Korrelationen wurden zwischen aktuellen Blutblei und Block Design Test, visuell räumlichen Denkens und Zahl-Symbol Substitutionstest gefunden. Hohe kumulative Exposition (IBL > 5000 und Dauer der Exposition länger als 5 Jahre) korrelierte nur mit falschen Reaktionen beim komplexen Reaktionstest.

Schlussfolgerungen: Die Ergebnisse unserer Studie weisen darauf hin, dass kognitive Defizite von niedriger Bleiexposition reversibel sind. Unsere Ergebnisse sind auf langjährige niedrige Bleiexposition limitiert (alle aktuellen Blutblei-Werte waren immer unter 55 μg/100 ml). Eine Extrapolation der Ergebnisse auf höher exponierte Arbeiter ist daher nicht möglich.

* Contributed equally to this study. Supported by the General Austrian Accident Insurance Institution.

Summary. *Objectives:* The objective of the study was to investigate long-term cognitive effects resulting from low-to-moderate lead exposure below current threshold values. Executive functions, attention, visuospatial and visuomotor functioning in workers formerly exposed to lead were investigated.

Methods: 48 men formerly exposed to lead and with a mean current blood level (PbB) of 5.4 μg Pb/100 ml were investigated, together with 48 matched controls (PbB: 4.7 μg Pb/100 ml) out of a pool of 61 males. The two groups were matched for age, years spent in education, verbal intelligence and gram alcohol consumption per week. The following neuropsychological tests were used: modified Wisconsin card sorting test, block design test, visual recognition test, simple reaction time, choice reaction and digit symbol substitution. Lead exposure was assessed using both current and cumulative measurements.

Results: There were no significant differences in cognitive parameters between the two groups. When analyzing dose-response relationships, negative correlations were found between PbB and performance in the block design test, and between PbB and scores in the visual recognition and digit symbol substitution tests. High cumulative exposure (IBL > 5000 and duration of exposure > 5 years) correlated only with wrong reactions in the choice reaction test.

Conclusions: The results of our study indicate that cognitive deficits resulting from low-level exposure to lead are reversible. The study was limited to low-level long-term exposure (all PbB values were always below 55 μg Pb/100 ml), and extrapolation of these results to persons heavily exposed to lead is not possible.

Key words: Blood lead, neurobehavioral function, glutamatergic neurotransmission system, cumulative blood lead, neuropsychological tests.

Introduction

Lead is widely used industrially and excessive exposure may therefore occur in a broad range of occupations [1]. With progress in production techniques, innovation in operation processes and improvement of occupational health, overt lead poisoning has been controlled [2]. However, the insidious effects of low-level and long-term lead exposure have become the focus of clinical research. Many human and experimental studies during past decades have demonstrated adverse effects on the central nervous system (CNS) after chronic exposure to inorganic lead [3–5]. Neuropsychological symptoms and cognitive deficits have been the main manifestations of milder adverse effects, and although several studies have demonstrated the neuropsychological effects of current lead exposure [6–11] only a few studies have examined cognitive abilities after long-term exposure has ceased [12, 13]. Results from the two latter studies are controversial, and it remains unclear whether reduced cognitive abilities from chronic low-level lead exposure are reversible or not [11].

We recently showed that impairments of certain cognitive abilities, mainly involving executive functions (Wisconsin test, visual recognition test) and visuospatial abilities (block design test), correlate significantly with current blood lead levels (PbB) but not with cumulative exposure indices (integrated blood lead, IBL) [10]. We interpreted these findings as indicating that neurobehavioral effects of lead exposure might be acute and reversible.

In general we can differentiate between two approaches to investigate reversibility. Doubtless the best way is a longitudinal design where individuals are tested twice, during and after lead exposure. Alternatively, formerly exposed persons can be compared with never-exposed controls (cross-sectional design), although this approach does not allow investigation of reversibility of lead effects on cognitive function direct. Nevertheless, a negative finding (i.e. no differences between persons formerly and never exposed) would show that there are no long-term effects of lead on cognitive functions. Assuming that formerly exposed persons had cognitive deficits during their current exposure, a negative finding would additionally support the reversibility hypothesis.

In this study we used the cross-sectional design and investigated cognitive abilities in a group of men formerly exposed to lead and in a control group never exposed to lead.

Methods

Study participants

The study group was composed of 48 male workers who had been occupationally exposed to lead in a storage-battery plant in the past: mean (SD) duration since last exposure 5.2 (3.5) years; age 39.6 (8.8) years, duration of exposure 10.6 (7.1) years (Tables 1 and 2). A control group was matched pairwise (concept of test-twins) from a pool of 61 male workers employed at a steel production plant who had never been exposed to lead and who had participated in an earlier study at the Medical University of Vienna [10] and been tested under exactly the same conditions and with the same tests. The groups were matched according to four variables that were possible sources of error: age, years spent in education, verbal intelligence [14] and number of alcoholic drinks/gram alcohol consumption per week. A control was considered a perfect test-twin when its parallel variables were within one standard deviation (SD) of the group under study. Where more than one control could be considered a suitable test-twin, one was cho-

Table 1. Characteristics of workers formerly exposed to lead and controls never exposed

Item	Formerly exposed	Controls	P
Subjects (n)	48	48	
Age in years			
Mean (SD)	39.6 (8.8)	39.9 (8.8)	0.241
Range	26–59	24–64	
Verbal Intelligence Score			
Mean (SD)	25.9 (3.9)	25.9 (5.8)	0.940
Range	17–35	10–34	
Education			
Basic school only (%)	10.4	8.3	0.710
Apprenticeship (%)	89.6	91.7	
Mean years (SD)	10.9 (1.2)	10.6 (1.5)	0.317
Range	8–12	8–12	
Alcoholic drinks per week			
Mean (SD)	3.9 (3.9)	4.3 (4.1)	0.288
Range	0–15	0–15	
Grams of alcohol/week			
Mean (SD)	58.2 (57.2)	63.5 (59.0)	0.270
Range	0–216	0–216	
Smoking status			
Never smokers (n)	8	7	0.729
Past smokers (n)	8	13	
Current smokers (n)	32	28	

SD standard deviation.

Table 2. Measurements of lead exposure

Item	Formerly lead-exposed		Controls	
	Mean (SD)	Range	Mean (SD)	Range
PbB (µg Pb/100 ml)	5.4 (2.7)	1.6–14.5	4.7 (2.5)	1.6–12.6
IBL (µg Pb/100 ml × months)	4153.3 (3690.3)	237.6–14233.2	–	–
DE (years)	10.6 (7.1)	1–29	–	–
Years since last exposure	5.3 (3.5)	1–15.5		

PbB current blood lead level; *IBL* time-integrated blood lead; *DE* duration of exposure.

sen randomly (random generator), with each control being used only once (Table 1).

Details of recruitment into the study have been described previously [10]. The study protocol included medical examination, detailed anamnesis, lead exposure and neuropsychological assessment. Exclusion criteria were (a) present acute exposure, (b) present or past exposure to neurotoxic substances in the control group, (c) not having German as the native language, (d) diseases that markedly affect CNS functions, including cerebrovascular stroke, severe brain trauma in the past, brain tumor, Alzheimer's disease, epileptic disease, multiple sclerosis, Parkinson's disease, and diagnosed chronic alcoholism, (e) intake of medication which could affect the CNS. For all men in the study group, occupational lead exposure had ceased at least one year before the study began. One steel production worker was excluded from the control pool because of exposure to organic solvents and lead from paint in his leisure time during the previous two years, and two storage-battery workers were excluded from the study pool because German was not their native language. Two steel production workers and one storage-battery worker were excluded because of CNS disease (stroke and chronic alcoholism with signs of nerve damage). The cut-off amount for large-scale alcohol consumption (over 280 g per week) was only exceeded in one case, which was excluded; the range for the remaining cases was 0–216 g per week.

All participants were examined by a neurologist and no study participant exhibited symptoms of a systemic illness that might affect CNS functions. The study was approved by the ethics committee of the University of Vienna and all participants gave written informed consent before entering the study.

Exposure to lead

Exposure was assessed using the following parameters:

(1) Current blood level of lead (PbB) was defined as the blood lead at the time of testing. PbB was determined using a standard method in atomic absorption spectrometry [15, 16]. Venous blood samples were collected on the day of testing.

(2) Time-integrated blood level of lead (IBL) was based on multiple PbB concentrations, determined every 3 months, during the previous 9 years. The IBL was calculated as a measurement of cumulative exposure based on Haber's law. Thus, IBL was the sum of the products of interval PbB and the time intervals between the samples (µg Pb/100 ml × months). For all persons who had been exposed for longer than 9 years, we calculated mean IBL per year, which was added to the 9-year IBL.

(3) Duration of exposure was used as a cumulative measurement.

Neuropsychological tests

Control data from the original control cohort were used for the analysis, in order to exclude learning effects. All participants exposed to lead were tested with the same neuropsychological test battery as was used in the earlier study [10]. The battery included the following functional domains: visual recognition, simple reaction time, choice reaction and verbal intelligence.

Visual recognition test [17]: measures working memory. Different objects are presented continuously, and for each object the subjects decide whether they are seeing it for the first time or not. This test is a self-paced task.

Simple reaction time [18]: measures visual reaction time. Subjects respond to a yellow light stimulus by immediately pressing a small button with their index finger.

Choice reaction [19]: measures ability to respond to complex stimuli. Subjects press different buttons, and the numbers of correct, wrong and missed responses are recorded.

Verbal intelligence [14]: measured by a synonyms task that gives a measure of acquired linguistic knowledge. Subjects are given a list of 38 words, each with 6 alternatives, and are asked to determine the one correct alternative word. The score is the number of correct answers.

All participants also underwent the modified Wisconsin card sorting test, digit symbol substitution and the block design test.

Modified Wisconsin card sorting test [20]: a self-paced task that measures concept formation and planning abilities. Subjects are asked to sort 48 cards on the basis of three possible categories (color, number and shape). Whatever category is chosen first is designated "correct" by the examiner. After six consecutive correct responses, subjects are told that the rule has changed and are instructed to find another sorting principle. Four performance categories are recorded: the number of categories completed, the total number of errors, the number of perseverative errors (these measure the inability to "shift cognitive set"), and the number of times the sorting principle is forgotten. The performance measurements are dependent on each other.

Digit symbol substitution [21]: measures attention, visual scanning and visuomotor speed. Subjects are asked to replace a series of numbers with symbols according to a specified code in a 90-s test.

Block design test [21]: measures visuospatial abilities. Subjects are asked to reproduce a series of geometric designs using red and white blocks. This test is a speed task.

Table 3. Neurobehavioral performance I

Item	Formerly lead-exposed Mean (SD)	Controls Mean (SD)	P
Block design	29.3 (8.2)	28.5 (10.5)	0.157
Visual recognition (number of correct answers)	79.6 (10.2)	80.9 (10.3)	0.604
Simple reaction test (ms)	292.3 (53.2)	279.8 (44.6)	0.698
Digit symbol substitution (number of substituted digits)	46.7 (10.1)	49.0 (12.3)	0.695
Choice reaction			
Correct (*n*)	230.6 (31.3)	228.6 (35.7)	0.108
Wrong (*n*)	12.9 (6.7)	12.3 (8.9)	0.344
Missed (*n*)	16.2 (8.8)	16.4 (7.7)	0.777

Statistical analysis

Data were analyzed using SPSS 11.0 for Windows (SPSS Inc., Chicago, IL, 1989–99). Group differences were examined by means of two-tailed t-tests for paired samples or Wilcoxon matched-pairs signed-ranks tests, depending on normal distribution of the differences. Group mean test scores were also examined, stratified by exposure groups. Generally all tests were performed at an error level of 5%; because of multiple univariate testing, the Bonferroni-Holm correction algorithm of the error I level was applied to retain the global error level at 5%. The current sample size was sufficient to prove clinically relevant effect sizes (Cohen's $d \geq 0.58$) at a power of 80%.

Results

Table 2 gives the measurements of biological monitoring of exposed persons and never-exposed controls. PbB of the exposed workers (range 1.6–14.5 µg PbB/100 ml) did not differ significantly ($p = 0.14$) from that of the controls (range 1.6–12.6 µg PbB/100 ml).

Differences between exposed and non-exposed workers

No significant differences could be found in any of the neuropsychological variables (Tables 3 and 4). When test results were compared stratified by exposure groups (high exposure group: IBL > 4500, n = 14 paired samples; low exposure: IBL < 4500, n = 34 paired samples) there were still no differences between the two groups (data not shown).

Dose-response relationship

To investigate the relationship between exposure and neuropsychological variables, correlations between all variables and all exposure measurements were analyzed. Cumulative parameters were not available for the controls, therefore we based correlations on the exposed group (n = 48) only. Correlations with PbB were based on the whole study group (n = 109) in order to maintain precious information. Cognitive performance and cumulative exposure were influenced by age, therefore correlations were corrected for age by partial correlation. Significant negative correlations were found between PbB and the number of correct responses in the block design test, the accuracy of the visual recognition test, and the digit symbol substitution score (Table 5). IBL and duration of exposure correlated only with wrong reactions in the choice reaction test.

Table 4. Neurobehavioral performance II

Modified Wisconsin Test	Formerly lead-exposed Mean (SD)	Controls Mean (SD)	P
Categories	5.2 (0.9)	5.0 (1.2)	0.199
Total errors	8.8 (5.6)	9.9 (6.7)	0.284
Perseverations	2.2 (2.0)	1.7 (2.3)	0.314
Loss of sorting principles	1.9 (1.5)	1.9 (1.8)	0.855

Discussion

In this study we investigated cognitive abilities in men formerly exposed to lead and in controls who had never been exposed. The objective was to determine whether exposure has negative long-term effects on cognitive functions, even after exposure has ceased. We also attempted to investigate the issue of reversibility of lead effects on cognitive function. The main result was that we found no differences in cognitive abilities between the men who had been exposed to lead and the controls, even when test results were stratified by exposure groups. From this we can draw two conclusions. Firstly, this indicates that there are no long-term neurobehavioral effects under occupational exposure limits after exposure has ceased. Secondly, to a certain extent these findings support the hypothesis of reversibility, but note that this argument is based on a specific premise, i.e. that current lead exposure does actually diminish cognitive abilities. Obviously we have no direct evidence that the group who had been exposed did indeed suffer neurobehavioral deficits during exposure, but many studies in the literature have demonstrated the negative impact of lead within a similar exposure range to that of our study group [6, 22–24]. A recent meta-analysis has also shown the negative effect on cognitive function [25]. In our earlier study we confirmed impaired executive function and visuospatial abilities in men currently exposed at a mean PbB of 30.8 µg Pb/100 ml and with a mean IBL of 4613.5 [10]. This exposure measurement is nearly the same as in the formerly exposed men in our present study (mean IBL = 4153.3), thus we can assume that these men also suffered from deficits during exposure. Our present findings are therefore evidence that cognitive

Table 5. Correlations between lead exposure and neuropsychological performance

	Block design	Visual recogn.	Simple React. time	Digit Symbol subst.	Choice reaction			Modified Wisconsin Test			
					Correct	Wrong	Missed	Categories	Errors	Perseverations	Loss of cat.
PbB	–0.28**	–0.21*	–0.07	–0.26**	–0.17	0.01	0.05	–0.10	0.14	0.01	0.09
IBL	–0.15[c]	–0.03[c]	–0.06[c]	0.01[c]	0.02[c]	0.28*[c]	–0.06[c]	–0.06[c]	–0.03[c]	0.09[c]	0.18[c]
DE	–0.13[c]	–0.09[c]	–0.22[c]	0.07[c]	–0.06[c]	0.29*[c]	–0.02[c]	0.07[c]	–0.03[c]	0.09[c]	0.11[c]

* $P < 0.05$ (one-tailed significance); ** $P < 0.01$ (one-tailed significance). *PbB* current blood lead level, based on n = 109; *IBL* time-integrated blood lead, based on n = 48; *DE* duration of exposure, corrected for age.

deficits caused by low-level exposure to lead are probably reversible. Nevertheless, there is a conflict between our results and those of a previous study by Schwartz et al. [12], where similar methods allow direct comparisons. Their results indicate that lead-exposed workers show a progressive decline in cognitive function years after exposure has ceased, but instead of using IBL or time-weighted average of lead to assess exposure, tibia lead levels were measured. Tibia lead can be used for estimation of previous lead exposure when other data are lacking [26], and the association with IBL is more significant than with other cumulative indices [27]. However, we consider the IBL to be a better predictor than tibia lead of actual occupational lead exposure in the past, since the IBL is based on the gold standard for biological monitoring, the PbB [27]. The different study results from Schwartz et al. might partly be explained by the older age of the study group (mean ages 39 and 55 years, respectively) and their additional exposure to organic lead. However, in a second study Schwartz et al. [28] concluded that lead has an acute effect as a function of recent dose and a chronic effect on cognitive decline as a function of cumulative dose. However, they defined longitudinal effects as dose differences between two time-points, thus the effect of the actual doses may be obscured. In addition, their regression models are prone to colinearity, because of the obvious dependency of blood and tibia lead levels, making proper comparisons between the effect coefficients impossible. Further, the actual dose is confounded with learning effects, which are not taken into account in the models, presumably also reducing the effect estimators.

The results of Yokayama et al. [13] also indicate that effects of lead on psychological performance are reversible, but only 17 persons were included in their study and the group size must be considered insufficient to generate a conclusion.

In our study, PbB did not differ significantly between formerly exposed men and the controls, although the level was slightly higher in the exposed group. Lead accumulates in the skeleton with a half-life between six and ten years [29–31] and provides an ongoing contribution to PbB after exposure has ceased [29], therefore we had expected to find higher levels in the men formerly exposed.

The fact that small but significant dose-response relationships between lower performance scores (block design, visual recognition, digit symbol substitution) and measurements of PbB were found supports the hypothesis of acute effects of lead exposure. These relationships are similar to those previously reported by us [10]. However, a significant small relationship was also found between the wrong reactions in the choice reaction test and both measurements of cumulative exposure (IBL and duration of exposure, Table 5). Interestingly, these associations were stronger in a sub-group with high cumulative exposure: when analyzing only the men with an IBL above 5000 and duration of exposure longer than 5 years, significances were even more pronounced. In contrast, when analyzing men with an IBL below 5000 and duration of exposure less than 5 years, associations were no longer significant. On one hand, these findings suggest that heavy exposure to lead may cause cognitive deficits which may partly persist, which is in agreement with Haenninen et al. [11]; on the other hand, we conclude from the present results that cognitive deficits caused by low-level exposure are reversible.

Our findings are subject to several limitations. Firstly, as already stated, our study design does not allow investigation of reversibility of toxic effects on cognitive function directly. We only found indirect indications, which support the assumption of reversibility. Future research on this topic requires the use of a longitudinal study design.

Secondly, data on PbB concentration were only available for nine years. Therefore, for all persons with a longer history of exposure, we had to calculate a mean IBL per year, which was then added to the nine-year IBL. However, exposures in the past were in general higher and therefore the mean IBL is probably too low and underestimates the cumulative exposure.

Thirdly, our study was limited to low-level long-term lead exposure (all PbB values were always below 55 µg Pb/100 ml and therefore at all times below the Austrian occupational exposure limit of 70 µg Pb/100 ml). Extrapolation of the results to groups with higher exposure is therefore not possible, and further investigation is necessary to confirm or disprove these findings in persons heavily exposed to lead.

Our findings highlight the importance of continued efforts to maintain low occupational exposure limits for lead, since no negative effect would be expected for workers after exposure has ceased, especially when the duration of exposure was short. Generally, western European countries have been successful in those efforts, but in other countries exposure conditions may still be unacceptable.

In conclusion, our data provide evidence that cognitive deficits resulting from low-level lead exposure do not interact with the normal aging process and are reversible. However, our study was limited to low-level long-term lead exposure (all PbB values were always below 55 µg Pb/100 ml). Extrapolation of the results to groups with higher levels of exposure is therefore not possible, and further investigation is necessary to confirm or disprove these findings in persons exposed to higher levels of lead.

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Correspondence: Robert Winker, MD, Division of Occupational Medicine, Medical University of Vienna, Währinger Gürtel 18–20, 1090 Vienna, Austria,
E-mail: robert.winker@medunivie.ac.at