Review

Lead Toxicity: Does the Critical Level of Lead Resulting in Adverse Effects Differ between Adults and Children?

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Department of Environmental Health Sciences, Akita University School of Medicine—Objectives:

Lead is a toxic element causing a variety of adverse effects such as encephalopathy, peripheral neuropathy, anemia, and renal failure in humans, although it is used in the manufacture of batteries, paints, metal products, and ceramic glazes¹, ²). Children are particularly susceptible to chronic exposure to lead at a low level, with slowed cognitive development, reduced growth and other effects reported¹–³) . While there has been much debate over subtle neuropsychological effects in children with blood lead (BPb) levels of less than 10 µg/dl³–⁶), the Scientific Committee on Neurotoxicology and Psychophysiology and the Scientific Committee on the Toxicology of Metals of the International Commission on Occupational Health (ICOH) abruptly declared that the action level for children, which triggers community prevention efforts to reduce exposure sources, should be immediately reduced to a BPb level of 5 µg/dl in nations worldwide⁷). This might be due to concern about the vulnerability of the immature brain and blood-brain barrier in young children, but whether such a low level of lead affects only child health, and not adult health, is not well understood.

According to a report by Araki et al.⁸ who reviewed 102 cross-sectional studies of workers occupationally exposed to lead, reduction in the peripheral nerve conduction velocity (NCV), together with adverse effects on the event-related potential (P300) latency, postural balance, and electrocardiographic R-R interval variability (CVRR), occurred at a mean BPb level as low as 30–40 µg/dl. Effects on latencies of the short-latency somatosensory, visual, and brainstem auditory evoked potentials started at BPb levels of 40–50 µg/dl.

Management should take evidence-based preventive action against subclinical lead poisoning in workers, as well as in children.

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International review bodies have also estimated that the threshold BPb levels for reduction in NCV and impaired sensory motor function were between 30 and 40 µg/dl in lead workers. The American Conference of Governmental Industrial Hygienists recommends that the biological exposure index for lead be 30 µg/dl. These values were obtained from the lowest dose producing adverse effects (i.e., the lowest mean BPb level among lead-exposed populations with significant impairment), termed the lowest-observed-adverse-effect level (LOAEL). Concerning the estimation of the critical level, a more desirable method uses the highest reported dose or exposure level for which no toxicity was observed, i.e., the no-observed-adverse-effect level (NOAEL). However, the NOAEL has many weak points, e.g., not adequately reflecting the shape of the dose response and not appropriately accounting for study size. Instead of the NOAEL or LOAEL approach, the benchmark dose (BMD) approach, providing a point of departure for low level extrapolation, has been applied in environmental health sciences. The BMD is a level of (or exposure to) a chemical substance that corresponds to a prescribed increase in response (called the benchmark response, BMR) of a health effect, and a lower statistical bound on the critical level of BPb actually differs between adults and children. The three underlying questions of this study are: a) What is the critical organ of lead in humans? b) At what level can the adverse effect be associated with the BPb? c) Is there a method other than the BMD approach for estimation of the critical dose? In the process of data synthesis, we apply the BMD approach to previous studies. For this purpose, the sample number-weighted mean (BMDLmean) was calculated, under the assumption of homoscedasticity, by using the Statistical Package for the Biosciences (SPBS V9.54) to derive continuous data of the endpoint. The cutoff value (C) is defined so that the risk in an unexposed subject is P0 and it depends on the confounders used. The cutoff value in subjects with all confounder values equal to 0 can be calculated with use of the following equation: P0 = 1 − Φ((C − β0)/σ), where Φ and σ indicate the normal cumulative distribution function and the standard deviation (SD) of the endpoint in the unexposed population, respectively. We used P0 of 5% and BMR of 5% as mentioned above, and the cutoff value for an average subject was computed by using the normalized value (i.e., |Xi − Xmean|/SD) for each confounder (X). The BMD calculation, along with hockey stick regression analysis, i.e., a regression model using segmented curves, was performed using the Statistical Package for the Biosciences (SPBS V9.54). To employ information about the BMDL in a risk-based probabilistic assessment of lead, it is necessary to derive a summary expression of BMDLs obtained from the selected studies. For this purpose, the sample number-weighted mean (BMDLmean) was calculated, under the assumption of homoscedasticity, by using the BMDL and sample size (n) of each study; i.e., BMDLmean = Σ(ni × BMDLs)/Σn.

Data Sources and Extraction

Although 25 reports addressing “BMD,” “lead,” and “humans,” published in English up to April 2008, were chosen from PubMed of the U.S. National Library of Medicine, only five of them proved to be relevant to lead toxicity. On the other hand, since we could find only two reports about lead neurotoxicity involving BMD calculations, other studies with figures illustrating significant relationships between lead and neurophysiologic parameters were also collected. Then, the paired data of the BPb level and outcome variable in each subject were scored using Paint software (Microsoft Co., U.S.A.) after scanning the figure. Finally, four more studies were selected and therefore publication bias cannot be avoided in this case.

The BMD is defined as the BPb level that results in an increased probability of an abnormal value of an outcome variable by a BMR, i.e., from P0 to P0 + BMR at the BMD, where the P0 and BMR represent an abnormal probability of the endpoint in unexposed subjects and an excess risk in exposed subjects, respectively. The BMD level (BMDL) is calculated as the statistical 95% confidence limit of the BMD but the method of BMD and cutoff value calculation differs among studies. When the threshold of daily ethanol intake affecting blood pressure was calculated with data from 1,100 Japanese salesmen using the BMD method and multivariate logistic regression model, the BMDL and BMD, set at P0 of 0.05 and BMR of 0.05, corresponded to the NOAEL and LOAEL, respectively.

Concerning the BMD calculation used in this study, the BMD method is a hybrid approach and needs an abnormal response level to interpret continuous data of the endpoint. The cutoff value (C) is defined so that the risk in an unexposed subject is P0 and it depends on the confounders used. The cutoff value in subjects with all confounder values equal to 0 can be calculated with use of the following equation: P0 = 1 − Φ((C − β0)/σ), where Φ and σ indicate the normal cumulative distribution function and the standard deviation (SD) of the endpoint in the unexposed population, respectively. We used P0 of 5% and BMR of 5% as mentioned above, and the cutoff value for an average subject was computed by using the normalized value (i.e., |Xi − Xmean|/SD) for each confounder (X). The BMD calculation, along with hockey stick regression analysis, i.e., a regression model using segmented curves, was performed using the Statistical Package for the Biosciences (SPBS V9.54).

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Data Synthesis

Overview of studies addressing BMDL of lead in workers

The critical level of the relationship between the BPb and δ-aminolevulinic acid (ALA) levels was investigated in 186 lead workers with BPb levels of 2.1–62.9 µg/dl, aged 18–62 yr. The BMDLs of BPb calculated from the workers, after controlling for age, were 14.3 µg/dl for ALA in plasma (ALA-P), 15.3 µg/dl for ALA in blood, and 2.6 µg/dl for ALA dehydratase (ALAD) activity in red blood cells (RBCs). Likewise, the BMDLs in 154 of
the above workers, who had BPb levels of less than 40 µg/dl, were 2.9 µg/dl, 3.5 µg/dl, and 2.3 µg/dl in that order. The cutoff value (11.3 µg/l) of ALA-P of these 154 workers, defined as the 95th percentile (i.e., the upper normal limit) in a hypothetically unexposed population, was closer to the upper normal limit (12.5 µg/l) in unexposed adults than the cutoff value (17.9 µg/l) of the 186 workers. When the BPb exceeds approximately 40 µg/dl, the ALA-P level has been hypothesized to be extremely elevated, probably due to increased activity of ALA synthase. Likewise, the data obtained from two reports, shown in Fig. 1, reveal significant relationships between the BPb and ALAD-related indicators in 195 lead workers. In applying the hockey stick regression model to the log-transformed data, the ALAD activity decreases exponentially but the model does not always fit all of the workers with BPb levels of more than 30–40 µg/dl, implying the validity of the above hypothesis. The critical level of BPb causing increased levels of ALA, therefore, is probably below 5 µg/dl in adults.

The critical level of lead inducing anemia, characterized by reduced levels of hemoglobin (Hb), hematocrit (Hct), and RBC count, was examined in 388 lead workers with BPb levels of 1–115 µg/dl (age, 18–67 yr) . The BMDL of BPb affecting hematopoietic parameters was calculated to be 19.4–29.6 µg/dl, after controlling for age and work status (i.e., day or shift work). The cutoff values resulting from the BMD calculations were 13.7 g/dl for Hb, 40.0% for Hct, and 425 × 10⁴/µl for RBC.

Evidence that lead-exposed workers have poorer postural stability than unexposed controls has been identified by many researchers. Likewise, all postural sway parameters, except for sagittal sway with eyes open, in 121 lead workers with BPb levels of 6–89 (mean 40) µg/dl were significantly larger than those in 60 unexposed controls, and the BPb level in the former group was significantly related to sagittal sway at 1–2 Hz and 2–4 Hz with eyes open, and sagittal and transversal sway at 1–2 Hz and 2–4 Hz with eyes closed, after adjustment for age, height, and smoking and drinking habits. From the data, the BMDL of BPb causing increased sway in the lead workers was estimated to be between 12.1 and 16.9 µg/dl (mean 14.3 µg/dl).

Lead-exposed workers with BPb levels of 21–86 (median 55.5) µg/dl showed significantly high serum prolactin (PRL) levels as compared to controls unexposed to neurotoxic chemicals. Based on the logistic function describing the dose-response curve between the BPb level and the probability of increased serum PRL, Mutti and Smargiassi evaluated the BMDL of BPb. Among the lead workers, the calculated BMD for BPb was 21.7 µg/dl, with the corresponding BMDL being 11.2 µg/dl. In some reports not using the BMD approach, altered serum levels of pituitary hormones such as follicle stimulating hormone, luteinizing hormone, and thyroid stimulating hormone have been observed in workers with BPb levels of more than 30–40 µg/dl.

Lin and Tai-Yi explored the biologic exposure limit for renal dysfunction caused by lead. The relationships between the BPb concentration and the urinary excretion of total protein, β₂-microglobulin (β₂-MG), and N-acetyl-β-D-glucosaminidase (NAG) were studied in 135 lead workers with a mean BPb level of 42.2 µg/dl (age, 28.7 ± 6.6 yr) and 143 unexposed workers with a mean BPb level of 11.9 µg/dl (27.0 ± 8.5 yr). The BMDLs of BPb for renal dysfunction were 25.3–40.2 µg/dl, but no confounders such as age or smoking habit were included in the quantal linear logistic regression model for the BMD calculation. The cutoff values of urinary total

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**Fig. 1.** Dose-dependent relations of δ-aminolevulinic acid dehydratase (ALAD) activity in red blood cells and δ-aminolevulinic acid level in plasma (ALA-P) to blood lead in 195 lead workers obtained from two studies. The line represents a hockey stick regression curve.
protein, β₂-MG and NAG activity were 66.55 mg/g creatinine (Cre), 145.55 µg/g Cre, and 17.47 U/g Cre, respectively. In light of these findings, the authors suggested that urinary NAG could serve as a sensitive indicator for detecting early renal impairment, as indicated by some researchers. In other research, a significant positive association between the BPb level and concurrent concentration of serum creatinine has been observed among adults whose BPb levels had never exceeded 10 µg/dl throughout the study period.

The reported BMD and BMDL of lead affecting different target organs in lead workers are summarized in Table 1. As a threshold analysis other than the BMD approach, Chuang et al. applied hockey stick regression to data from 217 workers at a lead battery factory and suggested that lead might cause sensory neuropathy, assessed by the vibration perception threshold, with an effect threshold corresponding to a 5-yr mean BPb level of 31 µg/dl. When Bonde et al. determined semen volume and sperm concentration in 362 lead-exposed workers with BPb levels of 4.6–64.5 (mean 31.0) µg/dl and 141 referent workers with BPb levels <19.8 (mean 4.4) µg/dl, it was revealed that the median sperm concentration was reduced by 49% in workers with BPb levels above 50 µg/dl, and threshold slope least square regression identified a BPb level of 44 µg/dl.

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<th>Table 1. Benchmark doses (BMDs) and BMD levels (BMDLs, 95% lower confidence limits of BMD) of lead affecting several target organs in lead workers</th>
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<td>a ALA, δ-aminolevulinic acid; ALAAD, ALA dehydratase. b range of the BMDL or BMD calculated from six sway parameters.</td>
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<tr>
<th>Table 2. Benchmark doses (BMDs) and BMD levels (BMDLs, 95% lower confidence limits of BMD) of lead calculated from previous neurophysiological studies of workers</th>
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<td>Median MCV</td>
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<td>CCVF</td>
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<td>a MCV, maximal motor nerve conduction velocity; CVRR, electrocardiographic R-R interval variability; CCVHF, parasympathetic component of CVRR; CCVF, sympathetic component of CVRR.</td>
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A large number of researchers have examined NCVs in lead-exposed workers, but most of the reports have no figure illustrating the significant dose-effect relation to BPb. Araki and Honma observed significant correlations between the BPb level and maximal motor nerve conduction velocities (MCVs) in lead workers, aged 21–60 yr, with BPb levels of 2–73 (mean 29) µg/dl. From the scored data after scanning the figure with data unadjusted for age or drinking habit, we calculated the BMDL of BPb to be 7.5 µg/dl for the median MCV and 8.2 µg/dl for the posterior tibial MCV (Table 2).

Similarly, Seppäläinen et al. pointed to a significant relationship between the current BPb and median MCV for 78 workers occupationally exposed to lead and 34 referents; the BMDL of BPb affecting the MCV was 8.4 µg/dl. Figure 2 demonstrates the dose-effect relations of lead in the process of BMD calculations. The cutoff value of MCV was computed to be 55.1 m/s, which almost corresponded to the lower normal limit. Still, when the maximal BPb level recorded in the past was used as an exposure indicator, the BMD and BMDL of BPb affecting the sensory nerve conduction velocity of the median nerve were calculated to be 23.9 and 16.6 µg/dl.
respectively, two times higher than those from the current BPb.

By measuring P300, the effect of lead and zinc on cognitive function was assessed in 22 gunmetal foundry workers with BPb levels of 12–59 (mean 33.4) µg/dl and 14 unexposed controls with BPb levels of 8–18 (mean 12.6) µg/dl. The BMDL of BPb was calculated to be 6.1 µg/dl after adjusting for age, zinc concentration in plasma, cigarette smoking, and alcohol consumption (Fig. 2 and Table 2). Likewise, Hirata et al., using visually-evoked P300, observed impaired cognitive function in lead workers with a mean BPb level of 58.6 (range, 33 to 106) µg/dl, but the BMDL could not be calculated because of the small sample number.

With respect to the autonomic nervous effect of lead, three studies observed significant differences between exposed and unexposed groups, and one report found no association between exposure and R-R interval variations. The autonomic nervous function in 36 lead workers aged 21–35 yr and 15 textile workers aged 22–29 yr was assessed by the CVR with the two components (CCV HF and CCV LF). The exposed group had BPb levels of 25.8–79.3 (mean 55.6) µg/dl, and the unexposed group had BPb levels of 4.7–8.6 (mean 6.3) µg/dl. All subjects were female, and had rarely smoked. The BMDLs of BPb affecting age-adjusted autonomic nervous parameters were between 10.3 and 15.4 µg/dl, as shown in Table 2. The BMDL for the parasympathetic component of the CVR (i.e., CCV HF) was somewhat higher than those for two other parameters, which might be due to the fact that the CCV HF can be readily affected by various environmental and occupational factors other than lead.

Interpretation of BMDLs in lead workers

As shown in Fig. 3, the BMDL and BMD of BPb for neurotoxicity in industrial workers, including neuroendocrine and neuromotor functions, were between 6.1 and 14.3 µg/dl and between 11.3 and 23.6 µg/dl, respectively, and we calculated the sample number-weighted mean to be 10.7 µg/dl for BMDL and 17.5 µg/dl for BMD. As the sample size grows smaller, the BMDL becomes smaller. As a result, the true critical level for each outcome variable used in this study is thought to lie somewhere between the calculated BMDL and BMD.

The NOAEL and LOAEL, on the contrary, would become higher in this case. Also, the BMD and BMDL computed from data without possible confounders such as age tend to be smaller than those calculated from data with such confounders. Taken together, neurotoxic effects in lead workers appear to be associated with BPb levels of less than 18 µg/dl despite uncertainties in the estimation process.

The BMDL and BMD of lead for the reduced NCV differed between the current and maximum BPb levels, as noted above. Whether the changes in the outcome variables are associated with current measures of exposure or measures of cumulative exposure remains to be elucidated. However, Araki et al. have provided evidence on the reversibility of NCVs in lead-exposed workers; that is, a relatively short-term change of the BPb level was negatively correlated with alterations in NCVs. Likewise, when visual evoked potential (VEP) latency was measured in gunmetal workers twice at a 12-mo interval, the N2 latency (i.e., conduction time from the retina to the visual cortex) in the second examination returned to the “normal” level and the yearly alteration in the N2 latency of VEP was positively correlated with the corresponding change in the erythrocyte lead level. Also, partial correlation analyses adjusting for age found that the wave I latency of brainstem auditory evoked potentials was associated with the current BPb (r=0.13, p<0.01) and working-lifetime weighted average BPb (r=0.11, p<0.05) in 359 lead smelter workers, suggesting that current lead exposure preferentially affects conduction in the distal auditory nerve. For the threshold assessment of lead neurotoxicity in workers, thus, it appears to be desirable to use the current BPb level, but not the maximum or working-lifetime weighted average BPb level of the past.

The BMDL of BPb for inhibited ALAD activity is considered to be less than 3 µg/dl, implying that ALAD activity changes almost parallel to the BPb level when the lead exposure level is relatively low. As a consequence, increased ALA in the blood follows inhibited ALAD activity immediately. In contrast, anemia, defined as a reduction of Hb, Hct or RBC, has not been found at BPb levels below 20 µg/dl. The start point for the analytical identification process (i.e., the BMDL of BPb for anemia) was estimated to be around 20 µg/dl in adults. The difference in BMDL between inhibition of heme synthesis and anemia due to lead may be explained by the rate-limiting activity of ALA synthase with feedback inhibited by heme.

Renal damage such as enzmyuria and proteinuria in lead-exposed workers seems to be initiated at BPb levels between 25 and 40 µg/dl, although the overall dose-effect pattern suggested increasing severity of nephrotoxicity with increasing BPb, with effects on glomerular filtration evident at BPb levels below 20 µg/dl. This BMDL for the kidney is somewhat higher than for other target organs. There are two possible explanations of the higher BMD and BMDL of BPb for nephrotoxicity. Some biomarkers of renal tubular function such as β-2-MG and NAG may be highly sensitive, but not specific to lead toxicity; for this reason, they may be confounded even by low-level exposure to cadmium or mercury, but such combined effects have not been demonstrated. Also, renal cells may have higher regeneration ability than those of the
of the relationship was a BPb level of 30 \( \mu g/dl \), and regression analyses were applied to the data, the threshold level lead toxicity.

Considering these data, ALAD-related indicators appear more sensitive to lead than other indicators (Tables 1 and 2). Still, the former indicators cannot be exactly regarded as evidence of harmful effects, because ALAD-related changes at low levels of lead have been seen in adults without occupational exposure and the lead-induced inhibition of ALAD seems to be reversible even in rats. Therefore, the critical organ of lead toxicity in adults is thought to be the nervous system, when the issue of lead carcinogenicity is excluded.

Recent perspective on lead toxicity in children

Children typically engage in hand-to-mouth activities that result in greater ingestion of lead than adults normally experience, and they are more vulnerable to lead exposure in several respects. Therefore, most of the epidemiological studies on the adverse effects of lead have been focused on children. For example, a relationship was observed between the NAG activity in urine and BPb (34.2±22.4 \( \mu g/dl \)) in 151 children aged 3–6 yr, as demonstrated by a 14% increase of NAG per \( \mu g/dl \) BPb. Still, such studies have rarely noted a threshold value of lead.

By applying logistic regression analyses to data of both BPb and Hct obtained from 579 children aged 1 to 5 yr, Schwartz et al. reported that the probability of anemia (Hct <35%) in one-year-old children was 0% at BPb levels below 20 \( \mu g/dl \), 2% at levels between 20 and 39 \( \mu g/dl \), 18% at levels between 40 and 60 \( \mu g/dl \), and 40% at BPb levels above 60 \( \mu g/dl \). The authors concluded that BPb levels close to the recommended limit value of 25 \( \mu g/dl \) were associated with dose-related depression of Hct in young children.

Schwartz et al. demonstrated a negative correlation between the BPb level and MCV in asymptomatic 5- to 9-yr-old children living near a lead smelter, and they looked for a threshold BPb level for reduced MCV. The children had BPb levels of 13–97 \( \mu g/dl \). When three regression analyses were applied to the data, the threshold of the relationship was a BPb level of 30 \( \mu g/dl \) in the hockey stick regression, 20 \( \mu g/dl \) in the logistic regression, and 25–30 \( \mu g/dl \) in the quadratic regression. However, none of age, sex, socioeconomic status and duration of residence near the smelter significantly modified the relationship. The authors concluded that measurement of MCV was an insensitive screen for low-level lead toxicity.

By the end of 2002, the majority of human data indicated that there were persistent and deleterious effects of BPb levels above 10 \( \mu g/dl \) on children’s brain function, including lowered intelligence, behavioral problems and diminished school performance; whereas, German researchers, who evaluated 24 selected publications in a meta-analysis, concluded that neurobehavioral deficits due to lead exposure in adults were associated with average BPb levels between 37 and 52 \( \mu g/dl \). Therefore, Canfield et al. reported that BPb levels, even those below 10 \( \mu g/dl \), were inversely associated with children’s intelligence quotient (IQ) scores at 3 and 5 yr of age, and that associated declines in IQ were greater at these levels than at higher levels. Using international pooled data, Lanphear et al. concluded that environmental lead exposure of children who had maximal BPb levels <7.5 \( \mu g/dl \) was associated with intellectual deficits.

Surkan et al. observed that 6- to 10-yr-old children with concurrent BPb levels of 5–10 \( \mu g/dl \) scored 7.8±2.4 (SD) and 6.9±2.2 points lower on reading and math composite scores of the Wechsler Individual Achievement Test, respectively, compared to age-matched children with concurrent BPb levels of 1–2 \( \mu g/dl \). Also, Jusko et al. found significant differences in full-scale IQ and performance IQ between 6-yr-old children with infant BPb levels of less than 5 \( \mu g/dl \) and of 5–9.9 \( \mu g/dl \), although no significant difference in any IQs was seen between those with peak BPb levels of less than 5 \( \mu g/dl \) and of 5–9.9 \( \mu g/dl \).

Summarizing these findings, the critical organ of lead toxicity in children is also thought to be the central nervous system. The main sources of lead exposure in American children were floor lead loading, poor housing conditions, paint chip ingestion, and soil ingestion, and the mean BPb level from infants to schoolchildren decreased gradually. Neurological disorders may not arise if the timing between the most susceptible period of the brain and the peak exposure of lead are subtly different. In this sense, the findings of Jusko et al. would be implicative for the assessment of lead neurotoxicity in children because the exposure level at less than 2 yr of age has been suggested to be of great importance.

Conclusions

Lead toxicity in adults

An International Workshop on Neurotoxic Metals convened by two Scientific Committees of the ICOH reached the following conclusion in 2006: "For industrial workers, the standard for BPb should be reduced immediately to 30 \( \mu g/dl \) in nations worldwide. Additional consideration should be given to further reducing this standard to 20 \( \mu g/dl \) and below in the years ahead. This reduction in exposure standard will reduce the incidence of subclinical neurotoxicity and other toxic effects during the working life and responds to new documentation presented at the Workshop that long-term lead exposure..."
increases the risk of dementia in later life.” The present review of lead toxicity in workers suggests that the critical organ is the nervous system, and the critical level of BPb is estimated to be between 10.7 and 17.5 μg/dl, although the critical level for higher central or peripheral neuropathy might differ from those for damage to the autonomic nervous system, hypothalamus or cerebellum (Fig. 3). The neurotoxic effects of lead exposure at such levels seem to be reversible98–100 but cognitive function can progressively decline due to past occupational exposure93, 94. Accordingly, we should not disregard asymptomatic neurotoxic effects of low-level exposure to lead in workers.

**Lead toxicity in children**

Notably, the BPb levels at which lead-associated intellectual deficits occur in children are as low as the critical levels of BPb both for suppressed ALAD activity and for elevated ALA in workers. For this reason, preventive actions against lead poisoning have been taken in the U.S.A.95–97. Bergomi et al. have observed that total and verbal IQ scores on the Wechsler Intelligence Scale for children were significantly correlated with ALAD values among schoolchildren with a mean BPb level of 11 μg/dl98. Although we cannot obtain direct evidence on the effect of ALA on the human brain, there are some animal experiments suggesting ALA-induced effects on the brain99–102. For instance, it has been indicated that ALA inhibits glutamate uptake in differentiated astrocyte cultures by selectively affecting the GLT-1 subtype of glutamate transporter101, and that ALA can generate free radicals102. Also, previous studies have shown that ALA is generated even in the brain103, 104. We may therefore hypothesize that lead impairs children’s intelligence and neurobehavioral performance, possibly due to increased ALA in the brain, despite the presence of at least one animal experiment reporting that lead-induced cell death in the hippocampus in vivo may be partly due to apoptosis105. However, this raises some questions: a) Can ALA at a low level truly damage the immature brain in infants? b) When does the blood-brain barrier in children begin to play an active role in preventing lead neurotoxicity? c) When is the critical window for lead exposure affecting the brain in children? Solutions to these problems require further research.

In humans, maternal transfer of lead through the placenta (geometric mean of cord blood-to-maternal blood ratio, 0.76) is not so high as that of methylmercury (geometric mean, 1.64)106, although it is possible that fetal lead exposure has an adverse effect on neurodevelopment83. Also, lead has a low transfer coefficient from maternal blood to breast milk (estimated ratio range, 0.01–0.97)107. Apart from human studies, lead exposure during early stages of the rat brain development has been suggested to decrease protein kinase C (PKC) activities and also to reduce PKC isoforms including PKC-γ and ε which are reported to have roles in memory formation and long-term potentiation108. Since early exposure to lead at the developmental stage, as well as to methylmercury and arsenic109–113, can produce lifelong loss of intelligence and permanent disruption of behavior114, special attention should be directed to food and water safety for younger children and mothers.

**Methods for estimation of critical dose**

Nowadays, critical levels of hazardous chemical substances in workers are being revised on the basis of data resulting from the BMD, but not the LOAEL, approach16. The hockey stick regression method, as well as the BMD approach16–18, may be useful as methods for estimation of the critical level, and they would be rather complementary in regard to the presence or absence of a threshold value. The hockey stick model can treat a log-transformed outcome variable, as shown in Fig. 1, but can also provide a 95% lower confidence limit28, regrettably, none of the studies cited in the present review calculated this50, 75. Also, a model of multivariate regression could control for possible confounders such as age, inasmuch as the polynomial regression models are frequently used when the linear regression model does not fit well28. Additional study is necessary to clarify the association between the estimator (and 95% lower confidence limit), assessed by the hockey stick regression method, and LOAEL (or NOAEL) in human data.

**Conclusions**

The critical organ of lead resulting in harmful effects other than carcinogenesis must be the nervous system in humans. The critical level of BPb for neurotoxicity in adults is considerably lower than the levels previously estimated using the LOAEL approach, although it seems somewhat higher than in children. Each national institute for risk management should take evidence-based preventive action against subclinical lead intoxication in adults, as well as in children.

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