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# A blood lead benchmark for assessing risks from childhood lead exposure

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Lead exposure is an insidious problem, causing subtle effects in children at low exposure levels where clinical signs are not apparent. Although a target blood lead concentration ($Pb_B$) of ten micrograms per deciliter (10 $\mu$g/dL) has been used as the basis for environmental decision-making in California for nearly two decades, recent epidemiologic evidence suggests a relationship between cognitive deficits and $Pb_B$ at concentrations <10 $\mu$g/dL. Based on a published meta-analysis of children's IQ scores and their blood lead concentrations, we developed a new blood lead benchmark: an incremental increase in blood lead concentration ($\Delta Pb_B$) of 1 $\mu$g/dL, an increase that we estimate could decrease the IQ score in an average school child in California by up to one point. Although there is no evidence to date for a threshold for the neurobehavioral effects of lead, a one-point IQ decrement was chosen to represent a *de minimus* change. To safeguard the intellectual potential of all children, additional efforts to reduce or eliminate multiple-source exposures to lead are warranted.

**Keywords:** Lead, toxicity, children, behavior, neurodevelopment, cognition, IQ, slope, risk assessment.

## Introduction

The purpose of this article is to document the development of a numerical blood lead benchmark intended to protect the health of school children. The California Health and Safety Code requires the California Office of Environmental Health Hazard Assessment (OEHHA) to identify chemical contaminants that are found at existing or proposed school sites and are of special concern for children, and to publish numerical health standards or benchmarks for those contaminants for use in assessing risk at California school sites. The benchmark is intended for use in environmental programs, not for application to individuals in clinical settings or for population screening.

Exposure to lead (Pb) is of particular concern for school-age children. They receive higher exposures in proportion to their smaller body size and absorb a higher percentage of the lead they ingest.[1,2] They are more sensitive to the effects of environmental lead than adults because Pb affects the developing nervous system at levels that have not been shown to affect the mature nervous system.[3] Koller et al.[4] concluded that there is no margin of safety at existing exposures. OEHHA's benchmark change in $Pb_B$ does not imply or depend on a threshold. It is intended to be applied at the population level. Because an upper age limit for neurobehavioral and other health effects is not well defined, and because of the possibility of pregnancy in older girls, we suggest that this benchmark be applied to all pre-school and school children.

Historical use of lead in herbicides, gasoline, plumbing products, solder, and paints has contaminated the environment, and, since elemental lead does not degrade, this "legacy" contamination remains a source of exposure, especially in older housing.[5] Additionally, cultural practices by different ethnic groups, including the use of lead-glazed pottery for food preparation and storage, lead-based home remedies, and consumption of lead-contaminated Mexican candies, increase lead exposures.[6–10] Recent immigrants had higher average $Pb_B$ than non-immigrants.[11] Lead's uses in paint on imported toys, in storage batteries and ammunition, and as a plastic stabilizer could also result in human exposure.[12]

### *Toxic effects of lead and existing health criteria*

Most lead health criteria are based on epidemiological data. Exposures are usually expressed in terms of lead concentration in the teeth, skeleton, or blood ($Pb_B$). $Pb_B$ is usually reported in micrograms per deciliter ($\mu$g/dL). Since lead has a half-life of about 35 days in the blood, $Pb_B$ is

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a limited indicator of past lead exposure.[13] On the other hand, skeletal lead persists for many years, providing a more integrated metric of exposure over time. Some recent studies have used X-ray fluorescence as a noninvasive measure of skeletal lead levels.[14–16] An estimated 30–50% (0.9 to 2.7 $\mu$g/day) of trabecular bone lead is mobilized during pregnancy.[17] Since lead freely crosses the placenta, this represents an added source of exposure to the fetus.[18]

Lead can affect the cardiovascular, gastrointestinal, hemolymphatic, urinary, immune, nervous, and reproductive systems, and can cause tumors in laboratory animals.[19] Prenatal exposure to lead can cause reduced birth weight and premature births.[20] Prenatal or postnatal Pb exposure can adversely affect learning and behavior, and may affect the endocrine and reproductive systems.[21] Several recent articles indicate that the effect of lead on cognitive abilities extends to $Pb_B$ levels below 10 $\mu$g/dL.[13,22–24] Neurobehavioral effects and other health effects have been recently reviewed.[12,19] This review focuses primarily on the neurodevelopmental effects of Pb, which occur at the lowest measured $Pb_B$ and to which children and neonates are especially sensitive.

The Food and Drug Administration's tolerable daily dietary lead intake is 6 $\mu$g for children under age 6.[25] The Agency for Toxic Substances and Disease Registry[19] documented several adverse effects at $Pb_B$ <10 $\mu$g/dL, but did not develop a minimal risk level (MRL) for lead, because a clear threshold for some toxic effects has not been identified. The U.S. Environmental Protection Agency has not developed a reference dose or reference concentration for lead.[26] The National Ambient Air Quality Standard for lead is 0.15 $\mu$g/m$^3$.[27] U.S. EPA[28] defines a dust-lead hazard as surface dust in a residential dwelling or child-occupied facility that contains $\geq$40 $\mu$g Pb/ft$^2$ on floors or 250 $\mu$g/ft$^2$ on interior window sills based on wipe samples.

CDC's Advisory Committee on Childhood Lead Poisoning Prevention convened a work group to review published evidence relating children's $Pb_B$ to cognitive function and other health measures.[29,30] The work group concluded that even though the available evidence had important limitations, the overall weight of the evidence supported the conclusions that (1) the observed associations between $Pb_B$ <10 $\mu$g/dL and cognitive function are caused, at least in part, by lead toxicity, (2) there is an inverse association between $Pb_B$ <10 $\mu$g/dL and the cognitive function of children, and (3) the dose-response curve is steeper at lower $Pb_B$, with no evidence for a threshold. In the majority of the studies, the inverse relationship between $Pb_B$ and measures of cognitive function was attenuated but not eliminated with adjustment for potential confounders.[29]

### *Basis for the benchmark blood lead concentration ($\Delta Pb_B$)*

Lanphear et al.[31] analyzed $Pb_B$ and full-scale Wechsler IQ data from 1,333 participants in seven population-based longitudinal cohort studies from 4 countries. Linear relationships between $Pb_B$ and IQ for each of the seven cohorts are shown in Fig. 1. The children, ranging in age at testing from 58 months to 10 years, were administered a version of the Wechsler Intelligence Scales for Children-Revised, Wechsler Intelligence Scales for Children-III, Wechsler Preschool and Primary Scales of Intelligence (WPPSI), or Wechsler Intelligence Scales for Children, Spanish Version under uniform conditions within each study. Four measures of exposure–concurrent $Pb_B$, lifetime average $Pb_B$, maximum $Pb_B$ at any time prior to testing, and mean $Pb_B$ from 6 to 24 months of age, were tested for strength of relationship to outcome.

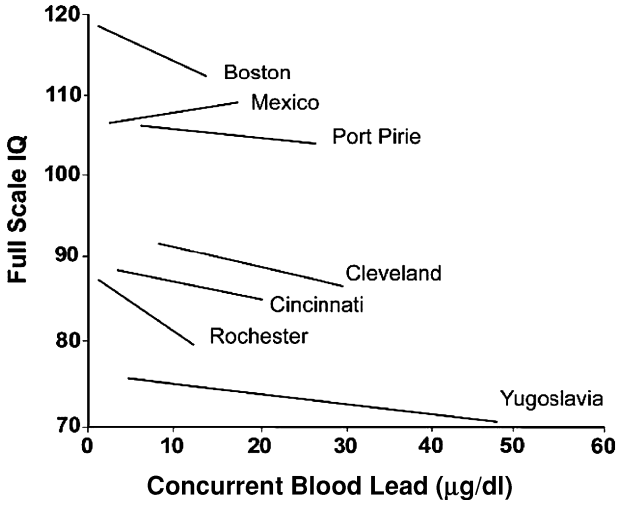


**Fig. 1.** Linear Models for the Pooled Analysis Cohort Studies. All were adjusted for maternal IQ, HOME score, maternal education, and birth weight. The range of data shown for each study represents the 5th to 95th percentile of the blood lead level at the time of IQ testing. Source: Lanphear et al.[31] as reproduced in[12]

Concurrent $Pb_B$ was most strongly related to IQ and was used as the exposure metric in subsequent analyses. Of the 12 variables included as covariates in the multivariate analysis, 6 significantly affected IQ: log of concurrent $Pb_B$, birth weight, maternal IQ, maternal education, study site, and home inventory for measurement of the environment (HOME) inventory score. The HOME score is an index that reflects the quantity and quality of stimulation in the home.[32] Six additional terms (sex, birth order, maternal age and marital status, prenatal smoking and alcohol use) were not used in the final model because each resulted in less than a 5% change in the blood lead coefficient. After adjustment for the 5 covariates that significantly affected IQ, the log-linear model depicted in equation 1 provided a good fit to the data:

$$\Delta IQ = \ln Pb_B \times -2.7 \quad (1)$$

where $\Delta$IQ = change in IQ and the confidence interval (CI) for $\beta$ is [−3.74 to −1.66].

(All CIs in this paper are at $\alpha$ =0.05 and are given in brackets.)

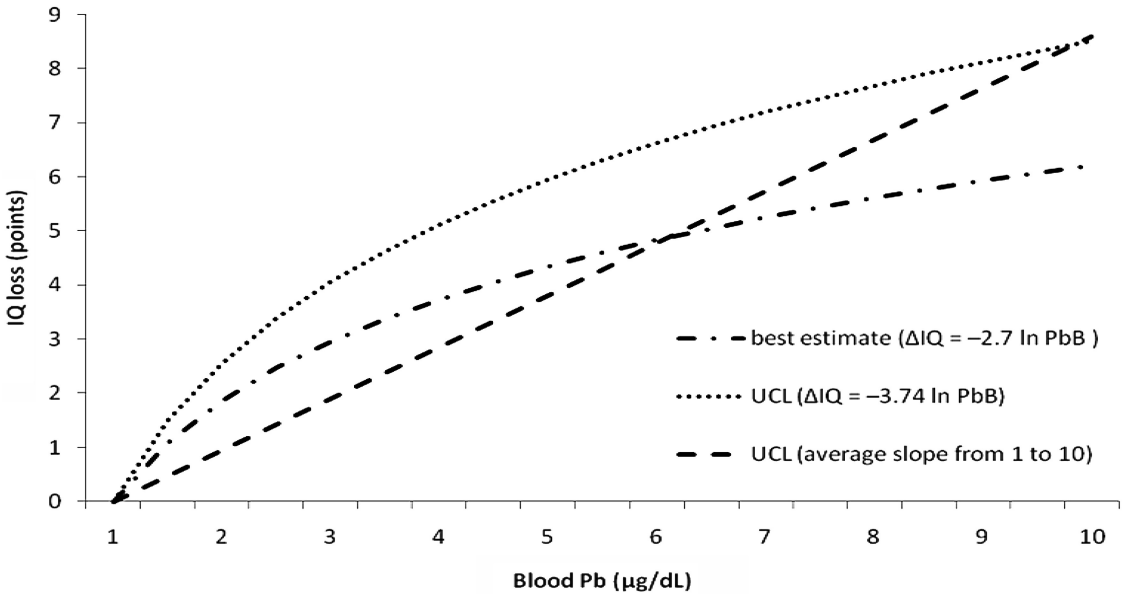


**Fig. 2.** Modeling IQ loss versus blood lead level. The dotted/dashed line depicts the best-fit log-linear model based on Lanphear et al. [31], where $\Delta$IQ = change in IQ. The dotted line represents the corresponding upper 97.5% confidence limit (UCL) on the log-linear function, and the dashed line depicts the average slope of the UCL over the $Pb_B$ range of 1 to 10 $\mu$g/dL.

This model (Fig. 2) predicts a decline of 6.9 [4.2 to 9.4] IQ points for a $Pb_B$ increase from 2.4 to 30 $\mu$g/dL and a decline of 6.2 [2.4 to 8.6] points for a $Pb_B$ increase from 1 to 10 $\mu$g/dL. When scores on the verbal and performance Wechsler scales were examined separately using the same five covariates, the coefficient for performance IQ was very similar to the full-scale IQ ($-2.73$ versus $-2.70$) while the verbal scale showed a slightly lower coefficient ($-2.07$). Even with umbilical cord $Pb_B$ (available for a subset of the subjects) included as a covariate, concurrent $Pb_B$ was still significantly associated with IQ ($P = 0.019$). A re-analysis of the Lanphear et al. data concluded that the log-linear model fits the data significantly better than a simple linear model.[33]

The lack of an identified threshold dictated that we use a response slope rather than a no-effect level with uncertainty factors. Based on the available epidemiological studies, it is clear that an inverse relationship exists between $Pb_B$ and cognitive function in children as measured by IQ; this relationship appears to be valid down to at least 1 $\mu$g/dL. A point at which the dose-response curve flattens out— i.e., where further reductions in $Pb_B$ yield no further improvement in intellectual functioning – has not been identified. While it is possible that even lower $Pb_B$ levels may adversely affect cognitive function, a correlation between IQ and $Pb_B$ in the range below 1 $\mu$g/dL has not been determined because of inadequate data in that range. Calculation of a response slope and makes optimum use of all of the available dose-response data. A benchmark dose can then be applied to children who already have $Pb_B$ in the range that is likely to affect cognition.

According to the log-linear function of Lanphear et al.[31], the average IQ decrement per $\mu$g/dL increase in $Pb_B$ over the $Pb_B$ range of 1 to 10 $\mu$g/dL is -0.69 IQ points per $\mu$g/dL, with an upper 97.5% confidence limit (UCL) of $-0.96$ IQ points per $\mu$g/dL. The UCL, depicted as a dashed line in Fig. 2, was chosen as the basis for the $\Delta$ $Pb_B$ in order to account for variability and uncertainty in the data and to avoid underestimating the true slope. The latter is close to the median of the estimated slopes for blood-Pb levels $<10$ $\mu$g/dL presented in Table 8–7 from EPA.[12] We selected the lower part of the distribution because most children in California fall into this range. Although this slope averaging will underestimate the slope at the low end and overestimate the slope at the high end, we made this choice because it would be impractical to use the variable slope of the log-linear function as the basis for the $\Delta$ $Pb_B$. Since the slope of such a curve is different at every point on the curve, a separate $\Delta Pb_B$ would be needed for each child, depending on his or her pre-existing $Pb_B$.

Finally, a benchmark response of one IQ point was selected. Kauffman[34] argued that fractional IQ points are meaningless, since the standard deviation on a single WISC test is about 3 points. Nation and Gleaves[35] countered that unless measurement error is non-random, the standard error on a single test does not matter, since errors will be in both directions and any differences between groups will be measurable on a population basis. Focusing on clinical versus epidemiological perspectives on neurobehavioral toxicity, Bellinger[36] discussed the relevance of small changes in a continuous variable that indicates altered structure or function rather than clinical disease. He pointed out that

while a one-point change in WISC full-scale IQ is within the standard error of an individual measurement and would not be regarded as clinical disease or cause affected individuals to seek medical care, it is still highly significant on a population basis, since a small difference in population lead burden is associated with large differences in the number of children in the two tails of the IQ distribution. Rogan and Ware[37] noted

> "Although critics question the importance of small decrements in the IQs of individual children, these measures are blunt instruments for detecting subtle changes in brain function; any detectable effect occurring from a widespread exposure is cause for concern. Relatively small changes in the mean IQ of a large number of children will dramatically increase the proportion of the population below any fixed level of concern such as an IQ of 80 and decrease the proportion above any 'gifted' level, such as 120."

Weighing these arguments, we identified a decrement of one IQ point as a *de minimus* change, concluding that at present, the effect of changes less than 1 $\mu$g/dL are too uncertain to use as the basis for regulatory action. Given the selected slope and benchmark response, the $\Delta$ $Pb_B$ was calculated as shown in equation 2:

$$\Delta Pb_B = \frac{-1\ I.Q.\text{ point}}{-0.96\ I.Q.\text{ points } per\ \mu g/dL} = 1.0\ \ \mu g/dL \quad (2)$$

Strengths of the Lanphear et al.[31] study include the following: it evaluated a relevant indicator of cognitive ability, it employed appropriate measures of exposure, it evaluated appropriate covariates, and it involved a sufficient number of pre-school and school-age children with $Pb_B \leq 10$ $\mu$g/dL to give it sufficient statistical power to describe the relationship between blood lead and cognitive function in this range. Limitations of this study include a limited ability to discern the shape of the dose-response curve at the lowest blood lead levels due to inherent variability in responses and the potential for measurement error in both independent and dependent variables as well as in some covariates due to methodological differences among the different cohort studies. In this as in any observational study, residual confounding cannot be ruled out.[38]

### *Risk management*

Various exposure models, e.g., the California Department of Toxic Substances Control's Lead Risk Assessment Spreadsheet[39] or EPA's Integrated Exposure Uptake Biokinetic Model for Lead in Children,[40] can be used to estimate a distribution of $Pb_B$ values for a specified daily lead intake from a variety of environmental sources. As an example of how these models and the new benchmark could be used to evaluate the effect of an identified exposure, the DTSC Lead Risk Assessment Spreadsheet predicts that daily consumption of 1 ounce of candy containing 0.1 $\mu$g of lead per gram would increase a 95th percentile child's blood lead level by about 1 $\mu$g/dL.

### *Supporting data*

Numerous reports (see Table 1) support the overall conclusion that the inverse relationship between $Pb_B$ levels and cognitive performance and other neurological and behavioral indicators extends to $Pb_B$ below 10 $\mu$g/dL. Jusko et al.[23] compared covariate-adjusted performance and full-scale WPPSI-R IQ scores in 174 6-year-olds with four indices of $Pb_B$. Full-scale IQ decrements of children with lifetime average, concurrent, infancy average, or peak $Pb_B$ between 5 and 9.9 $\mu$g/dL were 4.9, 3.7, 5.4, and 5.6 points, respectively, compared with children with $Pb_B$ below 5 $\mu$g/dL. Corresponding performance IQ decrements were 4.9, 5.5, 5.2, and 5.9 points, respectively. Bellinger et al.[41] found inverse relationships between cord blood Pb and infant Mental Development Index scores after adjusting for 12 potential confounding variables. The inverse relationship between $Pb_B$ at 24 months and cognitive ability was still apparent in a subset of the original cohort at age 5.[42] Stiles and Bellinger[43] reported an average decline in WISC full-scale IQ of 0.58 points per $\mu$g/dL $Pb_B$ (at 24 months of age) among 148 upper-SES 10-year-olds with mean $Pb_B$ <8 $\mu$g/dL.

After controlling for potential confounders, Walkowiak et al.[44] found a significant inverse relationship between log $Pb_B$ and attention span, WISC vocabulary, and WISC IQ in 384 6-year-old German children with a mean $Pb_B$ of 4.7 $\mu$g/dL. The $Pb_B$/attention span relationship remained even when WISC IQ was included as a covariate. Schwartz[45] analyzed data from eight longitudinal and cross-sectional studies of IQ published between 1981 and 1992, involving 7700 school-age children with mean $Pb_B$ levels ranging from 6.5 to 21 $\mu$g/dL. He derived a composite IQ/$Pb_B$ slope of -0.26 ($\pm$0.04) IQ points per g/dL, and concluded that the association between $Pb_B$ and IQ continues at $Pb_B$ < 5 $\mu$g/dL and that the slope is apparently steeper at lower $Pb_B$ levels.

Using data from the Third National Health and Nutrition Examination Survey, Lanphear et al.[46] found inverse relationships between $Pb_B$ and age-adjusted performance on tests of arithmetic and reading skills, nonverbal reasoning, and short-term memory among 4853 children ranging from 6 to 16 years of age. Concurrent $Pb_B$ was a significant predictor of class rankings in Chinese, Mathematics, Natural Science, and History & Society in 934 Taiwanese children (average age = 9 years) with $Pb_B$ levels ranging from 0.2 to 25.5 $\mu$g/dL. The relationships remained significant at $Pb_B$ < 10 $\mu$g/dL.[47] Using the Fagan Test of Infant Intelligence (FTII), Emory et al.,[48] found an inverse relationship between *in utero* Pb exposure and memory and cognitive functioning in 79 seven-month-old African-American infants.

**Table 1.** Summary of studies with quantitative relationships for IQ and blood lead.*

| *Reference* | *Study location* | *n* | *Age of children* | *Model used* | *Slope and 95% CI (IQ points/μg/dL)–$Pb_B$ 10th to 90th percentile* | *Slope and 95% CI (IQ points/μg/dL)–$Pb_B$ 10th percentile to 10 μg/dL* |
|---|---|---|---|---|---|---|
| Bellinger and Needleman[71]*a* | Boston, Massachusetts | 148 | 10 years | Linear | 0.6 (1.0, 0.2) | 1.6 (2.9, 0.2) |
| Canfield et al.[49] | Rochester, New York | 154 | 5 years | Linear | 0.6 (1.0, 0.2) | 1.8 (3.0, 0.6) |
| Dietrich et al.[72] | Cincinnati, Ohio | 148 | 6 years 6 months | Linear | 0.3 (0.6, 0.1) | NA |
| Kordas et al.[73] | Torreón, Mexico | 589 | 6–8 years | Linear | 0.2 (0.4, 0.1) | 0.4 (1.2, 0.4) |
| Lanphear et al.[31]*b* | International pooled analysis | 1,333 | 58 months to 10 years | Linear | NA | 0.8 (1.7, 0.1) |
| Téllez-Rojo et al.[74] | Mexico City, Mexico | 294 | 24 months | Linear | NA | 1.0 (1.8, 0.3) |
| Wasserman et al.[75]*a* | Kosovo, Yugoslavia | 258 | 7 years | Linear | 0.2 (0.3, 0.2) | NA |
| Al-Saleh et al.[76]*c* | Riyadh, Saudi Arabia | 533 | 6–12 years | Log-linear | 0.7 (1.2, 0.1) | 0.8 (1.4, 0.2) |
| Baghurst et al.[77]*a* | Port Pirie, South Australia | 494 | 7 years | Log-linear | 0.2 (0.4, 0.1) | NA |
| Lanphear et al.[31]*b* | International pooled analysis | 1,333 | 4 years 10 months to 10 years | Log-linear | 0.2 (0.3, 0.2) | 0.4 (0.6, 0.3) |
| Schnaas et al.[78] | Mexico City, Mexico | 150 | 6–10 years | Log-linear | 0.4 (0.6, 0.1) | NA |
| Téllez-Rojo et al.[74] | Mexico City, Mexico | 294 | 24 months | Log-linear | NA | 0.9 (1.4, 0.5) |

*Source: U.S. Environmental Protection Agency.[27]

[a]Slope estimates are the relationship between IQ and concurrent blood lead levels, except Bellinger & Needleman,[71] used 24-month blood lead levels; Baghurst et al.[77] used lifetime average blood lead levels; and Wasserman et al.[75] used lifetime cumulative blood lead levels.

[b]The pooled analysis by Lanphear et al.[31] included data from seven individual studies, including Baghurst et al.,[77] Bellinger et al.,[79] Canfield et al.,[49] Dietrich et al.,[72] and Wasserman et al.[75]

[c]In Al-Saleh et al.,[76] 69% (n = 368) of the children had blood lead levels <10 μg/dL. The estimated slope for blood lead levels <10 μg/dL is based on the model for the entire sample population.

Canfield et al.[49] evaluated composite scores of 172 children on the Stanford-Binet Intelligence Scale administered at the ages of 3 and 5 years. Lifetime average $Pb_B$, calculated as the area under the $Pb_B$ curve for all measurements to date, was inversely related to IQ score after adjustment for 9 covariates, at both evaluations. Linear regression analysis predicted a reduction of 0.46 [−0.15, −0.76] IQ points for each $\mu$g/dL increase in average $Pb_B$. For 101 children whose peak $Pb_B$ was less than 10 $\mu$g/dL, the slope was steeper, at −1.37 [−0.17, −2.56] IQ point per $\mu$g/dL.

The IQ scores of 28 kindergarten students recovered significantly 2 years after they were moved away from a lead-recycling plant and their median $Pb_B$ fell from 15.1 to 8.5 $\mu$g/dL[50]. Schnaas et al.[51] found that the negative effect of post-natal $Pb_B$ on cognitive performance peaked 1–3 years after the $Pb_B$, becoming less apparent after that. Chen et al.[52] studied the relationship between $Pb_B$ at 2, 5, and 7 years as well as average and peak $Pb_B$ on MDI or IQ scores at 2, 5, and 7 years in 780 children enrolled in a chelation study. In a multivariate analysis using concurrent and prior $Pb_B$ values as independent variables, concurrent $Pb_B$ was always more predictive than prior $Pb_B$.

Further evidence for a causal role for lead comes from cohorts in which potential confounding factors are inversely correlated with lead exposure. Factor-Litvak et al.[53] compared Yugoslavian children living near a smelter with a control group of similar age and parental education. Lead exposure was slightly positively correlated with SES in this group, but negatively associated with multiple measures of cognitive development. The association between lead and measures of cognitive ability became more negative after adjustment for HOME score, ethnic group, maternal age, birth weight, maternal Raven's progressive index, maternal education, and birth order or number of siblings. Similarly, Bellinger et al.[42] studied children whose economic status was positively correlated with blood lead. They found that adjusting for 12 potential confounders increased the magnitude and significance of the effect of prenatal lead exposure on mental development. The fact that adjustment for these confounders strengthened the negative association between lead exposure and the outcomes of interest when SES was positively associated with lead exposure supports the position that the lead is causally related to the deficit in mental development.

Neonatal behavioral evaluations can avoid influences of the post-natal environment on study outcomes. Emory et al.[54] examined 103 clinically healthy one- to two-day-old African-American infants using the Brazelton Neonatal Assessment Scale. Maternal $Pb_B$ levels in the sixth and seventh gestational months were generally $<10$ $\mu$g/dL. Offspring of mothers with higher $Pb_B$ had slightly poorer attention and motor control performance. Significant trends were found in individual Brazelton Scale scores relating to hand-to-mouth facility and general tonus. Differences between the first tercile and the second and third terciles of $Pb_B$ could not be attributed to birth weight or gestational age. Dietrich et al.[55] found neonatal $Pb_B$ to be inversely correlated with fine motor function, upper limb speed, and dexterity in 6-year-olds. Postnatal exposure was inversely correlated with bilateral coordination, upper limb speed, dexterity, and visual-motor functioning.

Behavioral endpoints have also been related to lead exposures. Needleman et al.[15] reported an association between lead measured in subjects' tibias using x-ray fluorescence spectroscopy and antisocial and delinquent behavior at 7 and 11 years of age. Dietrich et al.[56] found a relationship between low-level prenatal and postnatal Pb exposure and behavioral problems in adolescents after adjusting for birth weight, HOME scores, socioeconomic status, and parental IQ. A prospective study by Wright et al.[57] showed increasing risk of total arrests and arrests for violent offenses with increasing $Pb_B$ during gestation and childhood. Nevin[58,59] used temporal trend data from several countries to show associations between exposure indices such as lead use and preschool $Pb_B$ and negative outcomes such as decreasing IQ scores, unwed pregnancy, and involvement with the criminal justice systems.

Some studies have not shown a significant inverse relationship between $Pb_B$ and IQ. Ernhart et al.[60] used WPPSI scores to prospectively examine the relationship between neuropsychological deficits and low-level lead exposure from before birth up to age 58 months. Most $Pb_B$ measures were statistically significantly correlated with WPPSI scores. However, after adjustment for confounding variables, relationships of prenatal and preschool lead exposure to intellectual development were attenuated, inconsistent in direction, and not statistically significant. The authors concluded that the relationship between $Pb_B$ and cognitive development was largely a reflection of the dependence of each on the quality of the caretaking environment.

## Discussion and conclusions

Although the existence of a causal relationship between $Pb_B$ above 10 $\mu$g/dL and various neurobehavioral indicators in humans is well established, several recent studies indicate that the effect of lead on cognitive abilities extends to $Pb_B$ levels below 10 $\mu$g/dL e.g.,[13,22–24,61]. These and other epidemiologic analyses have concluded that lead exerts an independent effect on neurodevelopment and cognition at these levels, after adjustment for differences in other factors known to influence the same outcomes. These studies have typically employed multiple regression analysis to analyze the variation in intellectual abilities among children with average $Pb_B$ levels $<10$ $\mu$g/dL. In most cases, adding blood lead as an independent variable into these regression equations adds significant predictive ability to the equation.[62] This result would not be expected if lead did not independently affect the intellectual abilities of children at these lower blood levels.

The existence and significance of adverse effects of lead at blood concentrations < 10 $\mu$g/dL are not without controversy. Numerous articles and letters to the editor have questioned or defended various reports. For example, Ernhart[63] expressed concern that a single study site was driving the Lanphear et al.[31] results, that the HOME score was not always measured with the IQ test, and that the early blood Pb results were based on capillary finger stick samples rather than venous blood Pb samples. Lanphear et al.[64] agreed that using an early measure of the HOME inventory in the Rochester cohort was a potential limitation, but also noted that excluding this cohort from the pooled analysis changed the coefficient by less than 3%.

Kauffman[34] identified methodological shortcomings of three widely cited meta-analyses from the early 1990s, including uncontrolled confounding and/or poor measurement of confounders, failure to control for multiple comparisons, poor measurement of IQ, and comparison of extreme values. He urged greater caution in the interpretation of the lead/IQ data particularly at low exposure levels, contending that even if lead does cause IQ loss, the relationship cannot be extrapolated to a minute amount of lead in the blood. He also urged better control of confounders in future studies. Five authors or teams were invited to respond. Hebben[65] supported Kauffman, identifying a number of limitations to knowledge of the neurological effects of lead, arguing that lead has not been linked to several specific diagnoses such as ADHD or mental retardation. She also cautioned about over-interpreting neuropsychological test results in individuals. Needleman and Bellinger,[66] and Nation and Gleaves[35] argued that the limitations discussed by Kauffman could have introduced bias in either direction. Kauffman,[67] in turn, responded to the commenters, conceding some points and reinforcing others, while offering several suggestions for future researchers. More recent studies do not suffer to the same degree from some of his concerns about the slopes being driven by individuals with high $Pb_B$, or about the need to extrapolate to low blood lead levels, since they have significant numbers of children with $Pb_B$ <10 $\mu$g/dL and the trends remain significant when the analysis is limited to the children with $Pb_B$ <10 $\mu$g/dL.

Even though the trend is not uniformly expressed in all cohorts that have been studied, the preponderance of evidence indicates that lead is a causal or contributing factor in neuro-developmental deficits at blood lead levels below 10 $\mu$g/dL. Clearly, other factors including parental education, parental care, and many others affect the cognitive development of young children.[4] However, the conclusion that lead exposure accounts for a small but significant diminution of intellectual potential implies that removal or reduction of the lead exposure will result in a reduction in this undesirable outcome.[68] The geometric mean of $Pb_B$ in U.S. 1 to 5 year-olds has been reduced to 1.9 $\mu$g/dL,[69] but this is still elevated compared to levels in pre-industrial humans, estimated to be 0.016 $\mu$g/dL.[70] Thus, to safeguard the intellectual potential of all children, additional efforts to reduce or eliminate multiple-source exposures to lead are warranted. The pooled analysis of Lanphear et al.,[31] supported by evidence from several other epidemiological investigations and laboratory studies, provides a strong basis for a 1 $\mu$g/dL benchmark incremental increase in blood lead for risk assessment of children's exposures to lead through various media and for localized exposure scenarios such as at existing or proposed California school sites.

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