

**DEVELOPMENT OF HEALTH
CRITERIA FOR SCHOOL SITE RISK
ASSESSMENT PURSUANT TO
HEALTH AND SAFETY CODE
SECTION 901(g):**

**PROPOSED CHILD-SPECIFIC
BENCHMARK CHANGE IN BLOOD
LEAD CONCENTRATION FOR
SCHOOL SITE RISK ASSESSMENT**

Final Draft Report
December 2006



**Integrated Risk Assessment Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency**

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Executive Summary

This document proposes a new child-specific health guidance value (HGV) for lead of 1 microgram lead per deciliter of blood ($\mu\text{g}/\text{dl}$). The Office of Environmental Health Hazard Assessment (OEHHA) is required to develop child-specific HGVs for use in health risk assessment at school sites pursuant to Health and Safety Code Section 901(g). In the case of lead, the HGV is termed a child-specific benchmark change in blood lead concentration (ΔPb_B). The ΔPb_B for lead is not an absolutely safe exposure level, since no safe level has been definitively established. One $\mu\text{g}/\text{dl}$ is a lower-bound estimate of an incremental increase in children's Pb_B that is estimated to decrease IQ by 1 point. It is based on an analysis of recent reports relating neurobehavioral deficits to Pb_B at concentrations lower than in previous reports. In developing the ΔPb_B , OEHHA recognized that the ideal would be no additional exposure to environmental lead. However, from a practical standpoint, a ΔPb_B of zero would not be useful. Changes in blood lead less than the adopted ΔPb_B are expected to cause no measurable adverse effect, although a very small adverse effect theoretically does occur at the ΔPb_B . Various exposure models can be used to estimate acceptable lead levels in soil and other media. The Department of Toxic Substances Control's Leadsread model predicts that a 1- $\mu\text{g}/\text{dl}$ increase in Pb_B corresponds to an increased daily intake of 6 μg of ingested soluble lead, or 5 μg of inhaled lead.

Introduction

Mandate and Methodology

Health and Safety Code (HSC) Section 901(g)¹, requires the Office of Environmental Health Hazard Assessment (OEHHA), in consultation with the appropriate entities within the California Environmental Protection Agency, to 1) identify chemical contaminants that are commonly found at school sites and determined by OEHHA to be of greatest concern based on criteria that identify child-specific exposure and child-specific physiological sensitivities, and 2) publish and make available to the public and other state and local environmental and public health agencies and school districts, child-specific numerical health guidance values (HGVs) for those chemical contaminants. HGVs established by this process are intended for use in assessing risk at proposed or existing California school sites, which may include pre-school and day-care children. They are not intended for use in clinical settings, or for population screening. HGVs are subject to review and refinement as the state of the science progresses.

Pursuant to HSC §901(g), in June 2002, OEHHA issued a report, "Development of Health Criteria for School Site Risk Assessment Pursuant to HSC Section 901(g): Identification of Potential Chemical Contaminants of Concern at California School Sites,"

¹ (g) On or before January 1, 2002, the office, in consultation with the appropriate entities within the California Environmental Protection Agency, shall identify those chemical contaminants commonly found at schoolsites and determined by the office to be of greatest concern based on criteria that identify child-specific exposures and child-specific physiological sensitivities. On or before December 31, 2002, and annually thereafter, the office shall publish and make available to the public and to other state and local environmental and public health agencies and school districts, numerical health guidance values for five of those chemical contaminants identified pursuant to this subdivision until the contaminants identified have been exhausted.

documenting the process by which OEHHA would identify chemicals meeting those two criteria and compiling a list of seventy-eight chemicals that met the two criteria. The report is available at http://www.oehha.ca.gov/public_info/public/kids/schoolsrisk.html. OEHHA has issued draft or final reports proposing HGVs for nickel, cadmium, chlordane, heptachlor, heptachlor epoxide, methoxychlor, manganese, atrazine, deltamethrin and pentachlorophenol, which are available at: http://www.oehha.ca.gov/public_info/public/kids/index.html.

Development of a HGV begins with the selection of high-priority chemicals from the compilations generated in Phase I, as described in the June 2002 report. Chemicals are high-priority if 1) they have been found at school sites in California, 2) they have possible adverse effects in organ systems that are still developing during childhood, 3) they have been identified as a concern by other OEHHA programs, 4) they are carcinogens and their existing RfD approximates the dose associated with a 10^{-4} lifetime cancer risk, and 5) appropriate quantitative health effects data are available. For the selected chemicals, OEHHA evaluates published studies to define a dose/response relationship for the kinds of effects to which children may be more sensitive, using these data to develop a HGV. HGVs are termed children's reference doses (chRD) if they are expressed as a dosage and children's reference concentrations (chRC) if they are expressed as a concentration in air. We have coined a new term "child-specific benchmark change in blood lead concentration" (ΔPb_B) for this HGV, since it is neither a dose nor a concentration in air.

Basis for Selection of Lead

Lead (Pb) meets both of the criteria for selection in HSC §901(g): it is commonly found at school sites and it is of concern based on criteria that identify child-specific exposure and child-specific physiological sensitivities. Lead is the third most frequently detected chemical at school sites having Preliminary Endangerment Assessments reviewed by the Department of Toxic Substances Control. A California Department of Health Services study found that soil lead concentrations at California public elementary schools ranged from non-detectable to a high of 6906 mg/kg. The report noted that six percent of the schools are likely to have bare soils with lead levels that exceed the USEPA reference value for bare soil in areas where children play (400 mg/kg). The Department of Health Services report is available at: <http://www.dhs.ca.gov/childlead/schools/opening.htm>. Young children are more sensitive to the effects of environmental lead than adults because they receive higher exposures in proportion to their smaller body size and they absorb a higher percentage of the lead they ingest (Rabinowitz et al., 1974, Ziegler et al., 1978). Fetuses, neonates, and children may also be more sensitive to the effects of Pb than adults because Pb affects the developing nervous system at levels that have not been shown to affect the mature nervous system (Needleman, 1982). Koller (2004) concluded that there is no margin of safety at existing exposures.

Occurrence, Use, Chemistry, and Environmental Fate

Lead, with an atomic number of 82, occurs in four stable isotopes: 204, 206, 207, and 208. Ratios of these isotopes have been used as "fingerprints" to help identify sources of environmental lead. Lead's density, malleability, ductility, resistance to corrosion, and poor electrical conductivity, make it useful in several industries (CARB, 1997). Environmental contamination with lead is most often the result of its use in storage batteries, ammunition, and ceramics, and its historical use in herbicides, gasoline, plumbing products, solder, and

paints. This “legacy” contamination remains a source of exposure. Pb concentrations in California soils analyzed by Bradford et al. (1996) ranged from 12 to 97 mg/kg.

Toxicology

Existing Health Criteria

The Centers for Disease Control (1991) determined that primary prevention activities in children should begin at 10 µg/dl, based on the body of evidence available at that time.

In 1996, FDA established a tolerable daily dietary lead intake of 6 µg for children under age 6 (<http://www.cfsan.fda.gov/~dms/fdalead.html>). A daily intake of 6 µg would be expected to increase Pb_B by approximately 1 µg/dl.

The Agency for Toxic Substances and Disease Registry (ATSDR) has not developed a Minimal Risk Level (MRL) for lead. The lowest effect levels reported by ATSDR (1997) are 6.5 µg/dl, based on lower scores on tests of cognitive function, 3 to 56 µg/dl, based on decreased aminolevulinic acid dehydratase, and 7.7 µg/dl, based on reduced growth.

The California Air Resources Board (CARB), (1997) identified lead as a toxic air contaminant based on its neurobehavioral effects in children and neonates, blood pressure effects in adults, and possible carcinogenicity. OEHHA, (1997b) estimated that each 1 µg/dl increase in Pb_B in children over 5 years of age would result in an average decline of 0.33 points of full-scale IQ.

OEHHA (1997a) published a public health goal (PHG) of 2 µg/L in drinking water, based on a “level of concern” of 28.6 µg/day, an uncertainty factor of 3, and a relative source contribution of 0.2 for water. The level of concern is based on CDC’s Pb_B benchmark of 10 µg/dl and a Pb_B/intake slope of 0.35 µg/dl per µg/day. The uncertainty factor is to account for uncertainty regarding the protectiveness of the level of concern. OEHHA (1997b) also established a No-Significant-Risk Level of 15 µg/day based on carcinogenic effects and a Maximum Allowable Dose Level of 0.5 µg/day for reproductive effects. The documents are available at: <http://www.oehha.ca.gov/prop65/pdf/June2004StatusRpt.pdf>

The U.S. Environmental Protection Agency has not developed a reference dose (RfD) or reference concentration (RfC) for lead (<http://www.epa.gov/iris/subst/0277.htm>). The National Ambient Air Quality Standard for Pb of 1.5 µg/m³ was set in 1978 (http://epa.gov/ttn/naaqs/standards/pb/data/npsaaqsl_fr.pdf). A more recent EPA draft review is available at <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=141779>.

General Toxicology

The database for lead contains abundant human toxicology information that is the basis for most lead health criteria. The exposure component of the database is usually expressed in terms of lead concentration in the blood [(Pb_B), usually reported in micrograms per deciliter (µg/dl)], teeth, or skeleton. Pb_B data do not distinguish between lead concentrations that result from exposure to organic versus inorganic lead. Although having a measure of internal dose is certainly advantageous, a single Pb_B measurement is a transient indicator of lead in one compartment of a dynamic system. Since lead has a half-life of about 35 days in the blood, it is not a good indicator of lead exposure that may have occurred years earlier (Needleman, 2004). On the other hand, skeletal lead persists for many years, thereby

providing a more integrated metric of exposure over time. Some recent studies have used X-ray fluorescence to non-invasively measure skeletal lead levels (e.g. Needleman et al, 1996, Bellinger et al, 1994, Needleman et al, 2002). Gulson, et al (1999) estimated that 30-50% of trabecular bone lead (0.9 to 2.7 $\mu\text{g}/\text{day}$) is mobilized during pregnancy. Since Pb freely crosses the placenta, this represents an added source of exposure to the fetus. Li, et al, (2000) found correlation coefficients of 0.714 and 0.353 between Pb_B and cord blood and milk, respectively.

Lead can affect the cardiovascular, gastrointestinal, hemolymphatic, urinary, immune, nervous, and reproductive systems, and can cause tumors in laboratory animals (ATSDR, 1997). Prenatal exposure to lead can cause reduced birth weight and premature births (Bellinger et al., 1991a). Prenatal or postnatal Pb exposure can adversely affect learning and behavior and may affect the endocrine and reproductive systems (California Air Resources Board, 1997). The minimum Pb_B causing neurobehavioral deficits is not well defined. As Pb_B in children and neonates continues to decline, our ability to study significant numbers of children with very low Pb_B , and therefore our ability to detect small differences in performance measures, continues to increase. Lidsky and Schneider (2003) concluded that the present 10- $\mu\text{g}/\text{dl}$ upper limit on acceptable Pb_B is too high.

OEHHA reviewed the toxicology of lead during the review of lead as a Toxic Air Contaminant, and during the development of the Public Health Goal for drinking water (OEHHA, 1997a, 1997b). This document is not intended as a general literature review; rather it is a brief overview of the relevant scientific literature appearing since the 1997 OEHHA reviews, focusing primarily on the non-carcinogenic effects of lead that occur at the lowest Pb_B and that may differentially affect children and neonates. Recent publications have reviewed the relevant literature (Needleman, 2004, Bernard, 2003, Lidsky and Schneider, 2003).

Neurological effects

Epidemiological studies in the 1970s and 1980s generally found maladaptive behavior, slower reaction times, decreased nerve conduction velocity, and reduced Intelligence Quotient (IQ) scores, and reading, spelling, and mathematics performance, in pre-school and school-age children with increasing blood or tooth lead levels (Banks et al., 1997). The investigators generally examined children with minimum Pb_B in the range of 5-9 $\mu\text{g}/\text{dl}$ and maximum Pb_B in the range of 32-60 $\mu\text{g}/\text{dl}$. Tooth lead levels generally ranged from minimums of 2-9 ppm to maximums of 24-32 ppm.

Five of six cohorts followed longitudinally in the late 1980s and early 1990s exhibited significant inverse relationships between Pb_B at birth to 5 years of age and one or more measures of linguistic ability, visual-spatial relations, sensory-motor co-ordination, memory, motor skills, verbal, perceptual, or quantitative skills, or various measures of achievement (Banks et al, 1997). Children in these cohorts generally had Pb_B ranging from 1-8 $\mu\text{g}/\text{dl}$ at the low end to 15 to 35 $\mu\text{g}/\text{dl}$ at the high end. In most cases, postnatal exposure had a stronger effect on outcomes than prenatal exposure. Some of these studies showed more pronounced effects of lead in lower socio-economic status (SES) children and/or in boys. None of the studies concluded that lead was the most important influence on cognitive development.

Effects on Cognition

Several more recent reports indicate that the effect of lead on cognitive abilities extends to Pb_B levels below 10 µg/dl, the concentration that has served as the “bright-line” for risk management for more than a decade. Schwartz (1994) analyzed data from eight longitudinal and cross-sectional studies of IQ published between 1981 and 1992 involving a total of 7700 school-age children. Mean Pb_B for children in these studies ranged from 6.5 to 21 µg/dl. A meta-analysis of these data resulted in a composite IQ/Pb_B slope of -0.26 (±0.04) IQ points per µg/dl. There was an apparent increase in slope with decreasing Pb_B. Schwartz concluded that the association between Pb_B and IQ continues at Pb_B below 5 µg/dl.

Bellinger et al. (1987) studied 249 infants using the adjusted Mental Development Index of the Bayley Scales of Infant Development (MDIA) administered at 6, 12, 18, and 24 months of age. From a cohort of ~2500 infants born between April and July 1979, 85, 88, and 76 infants were selected to represent <10th, ~50th, and >90th percentile exposures, respectively (see Table 1). After adjustment for 12 potential confounding variables, the children’s rankings on MDIA scores were inversely related to their rankings in cord blood Pb levels (i.e. higher Pb_B was associated with reduced development). The F statistic was significant at 12, 18, and 24 months (p<0.05) but not at 6 months (p=0.095). Actual MDIA scores were compared with expected scores based on 12 predictors of mental development, and the difference expressed as a deficit compared with expected values (Table 1).

Table 1 Mental Development Index scores versus Umbilical Cord Pb_B

Umbilical Cord Pb _B *	N	Mental Development Index scores (observed-expected)			
		6 months	12 months	18 months	24 months
<3 µg/dl, mean 1.8±0.6	85	1.72 ± 1.20	1.46 ± 1.46	2.12 ± 1.75	2.28 ± 1.58
6-7 µg/dl, mean 6.5±0.3	88	-0.06 ± 1.25	1.60 ± 1.38	1.22 ± 1.76	1.82 ± 1.60
>10 µg/dl, mean 14.6±3	76	-1.90 ± 1.20	-3.54 ± 1.54	-3.81 ± 1.97	-4.38 ± 1.76

* Although the low umbilical cord Pb_B group remained lowest in Pb_B at 6, 12, 18, and 24 months, the separation between the medium and high groups was not maintained.

Bellinger et al. (1991) assessed 169 of the original 249 children again at 57 months of age. They used Pb_B at 6, 12, 18, 24, and 57 months, and Pb_B integrated over various age spans as the independent variable and General Cognitive Index of the McCarthy Scales of Children’s Abilities (GCI) scores as the dependent variable. GCI is a composite score combining results on the verbal, perceptual-performance, quantitative, memory, and motor subscales. After adjustment for 13 potential confounding variables using a multiple regression model, GCI scores were inversely related to Pb_B, but the coefficient was statistically significant only for Pb_B at 24 months. When the children were grouped according to their Pb_B at birth, and at 6, 12, 18, 24, and 57 months of age (low: <3 µg/dl, medium: 3 – 9.9 µg/dl, and high: >10 µg/dl, GCI scores in the groups with low concurrent Pb_B exceeded the scores of the children in the medium Pb_B groups at the corresponding ages by 3.0 to 5.3 points.

Lanphear et al. (2000) assessed the relationship 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 using data from the Third National Health and Nutrition Examination Survey (NHANES III; available at <http://www.cdc.gov/nchs/about/major/nhanes/nh3data.htm>). Gender, race, poverty index, educational level of caregiver, serum ferritin and cotinine levels, tobacco-smoke exposure, and birth weight were all related to Pb_B. These variables, along with region of country, marital status of the head of household, and use of neonatal intensive care, were included as potential covariates in a multiple regression analysis relating Pb_B to performance on the four tests. The adjusted slopes for five Pb_B groupings are shown in Table 2. All regression coefficients were negative for all four tests; those shown in bold were statistically significant. The authors suggest that their results, along with the results of other studies, suggest that the “acceptable” blood lead should be ≤5 µg/dl.

Table 2: Adjusted Slopes of Composite Performance Scores versus Pb_B

Test	Block Design ¹		Digit Span ¹		Arithmetic ²		Reading ²	
	Slope	P	Slope	P	Slope	P	Slope	P
All	-0.1	.009	-0.05	0.04	-0.7	<0.001	-0.99	<0.001
<10 µg/dl	-0.13	0.03	-0.08	0.03	-0.89	<0.008	-1.44	<0.001
<7.5 µg/dl	-0.11	0.04	-0.09	0.11	-1.06	0.01	-1.53	<0.001
<5.0 µg/dl	-0.05	0.45	-0.09	0.2	-1.06	0.03	-1.56	<0.001
<2.5 µg/dl	-0.08	0.72	-0.25	0.17	-1.28	0.2	-1.71	0.07

¹ Standardized to a mean score of 10

² Standardized to a mean score of 100

Stone and Reynolds (2003) critiqued this work, citing shortcomings in the NHANESIII data, including potential inaccuracies in data collection, missing data, “odd distributions” of Pb_B data and cognitive and academic scores, and failure to include potentially important covariates. They question the representativeness of the sub-sample analyzed, judging it not applicable to the general population because of bias toward low SES. While this would be a concern if we were attempting to extrapolate the results to the entire US population, it does not affect this application, since the ΔPb_B must protect sensitive subgroups (CHSC). Their concerns do not negate the overall conclusions of Lanphear et al. (2000) that lead affects cognition in at least some segments of the population at Pb_B well below 10 µg/dL.

Wang et al. (2002) studied class rankings in 934 children in Taiwan with a mean age of 8.85 years and Pb_B levels ranging from 0.2 to 25.5 µg/dl (12 children exceeded 10 µg/dL Pb_B and one exceeded 15 µg/dL). Class rankings in Chinese, Mathematics, Natural Science, and History and Society were all inversely associated with Pb_B (p<0.01). In a multiple regression analysis, the fathers’ socioeconomic status and the mothers’ education were found to be significant predictors of the child’s achievement. After adjusting for these factors, concurrent

Pb_B was still a significant predictor of class rankings ($p < 0.05$). These three variables explained five to 14 percent of the overall variance in class rankings in the 4 areas of study. These relationships remained significant at Pb_B < 10 µg/dL

Stiles and Bellinger (1993) reported an average decline in WISC full-scale IQ of 0.58 points per µg/dl Pb_B (at 24 months of age) among 148 upper-SES 10-year-olds with mean Pb_B < 8 µg/dl.

Canfield et al. (2003a) studied the relationship between Pb_B at 6, 12, 18, 24, 36, 48, and 60 months of age and the composite scores of 172 children on the Stanford-Binet Intelligence Scale at the ages of 3 and 5 years. The authors found sex, birth weight, household income, Home Observation for Measurement of the Environment Inventory (HOME) score, and the mother's IQ, years of education, race, and tobacco use during pregnancy to be related to Pb_B and to composite Stanford-Binet scores. After adjustment for the above nine covariates, lifetime average Pb_B (LPb_B, calculated as the area under the Pb_B curve for all measurements to date) was significantly inversely related to IQ score, with no significant difference between the 3- and 5-year evaluations. Linear regression analysis predicted a reduction of 0.46 IQ points for each µg/dl increase in LPb_B (95% CI = -0.15 to -0.76). For the 101 children whose peak Pb_B was less than 10 µg/dl, the slope was -1.37 IQ point per µg/dl LPb_B (95% CI = -0.17 to -2.56). A polynomial model fit to the data for the full sample of children predicted a 7.4-point decline (95% C.I. = -3.2 to -12.9) in IQ corresponding to an increase in LPb_B from 1 to 10 µg/dl. Their results corroborate those of Lanphear et al. (2000), and support the view that adverse effects are associated with Pb_B below the current 10-µg/dl CDC level of concern.

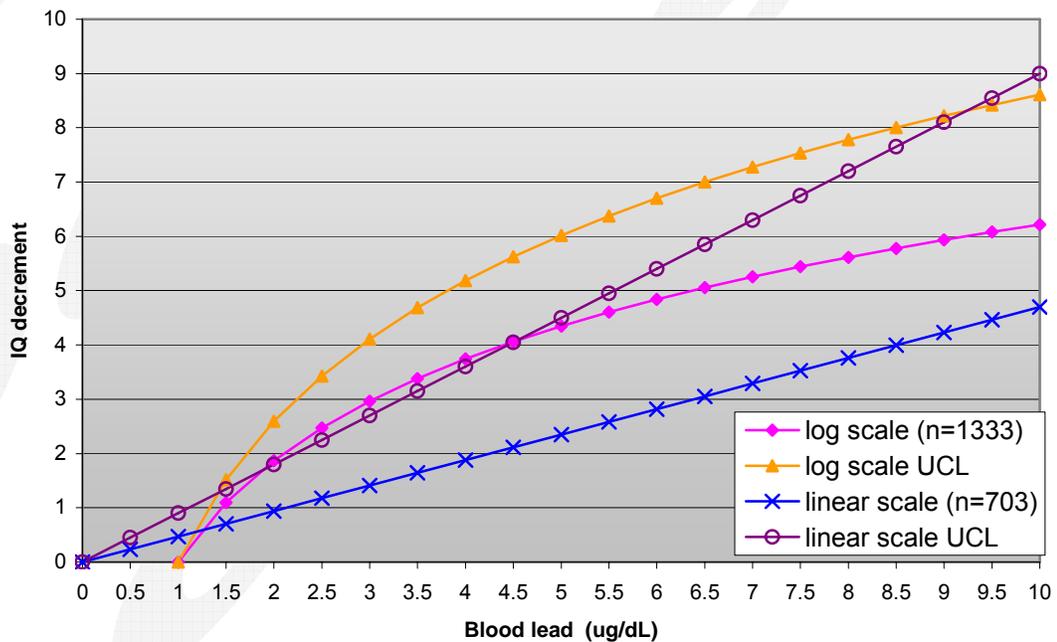
Several studies have yielded results that suggest interactions between Pb_B and other variables e.g. SES (Schneider, et al. 2001). Children of lower SES were more affected by increased Pb_B than were children of higher SES (Bellinger, 2000). This so-called protective effect of higher SES did not extend to children with the highest Pb_B.

Using the Fagan Test of Infant Intelligence (FTII), Emory et al. (2003) studied memory and cognitive functioning in 79 seven-month-old African-American infants in relation to their *in utero* Pb exposure, which ranged from 0.05 to 3.3 µg/dl. Infants with FTII novelty scores in the top five percent had a mean maternal Pb_B of 0.28 µg/dl, while those in the bottom five percent had a significantly higher mean maternal Pb_B of 1.18 µg/dl. Similarly, those in the top 15 percent had a mean maternal Pb_B of 0.44 µg/dl, while those in the bottom 15 percent had a significantly higher mean maternal Pb_B of 0.94 µg/dl. All upper quartile maternal Pb_B infants were in the low FTII group and vice versa (chi-square $P < 0.004$). The high and low maternal Pb_B groups did not differ significantly with respect to age at testing, gestational age, birth weight, or maternal education. These results suggest that there may be cognitive differences between 7-month-old infants with maternal Pb_B around 1 µg/dl and those with maternal Pb_B around 0.25 to 0.5 µg/dl.

Lanphear et al (2005) analyzed Pb_B and full-scale IQ data from 1,333 participants in seven international population-based longitudinal cohort studies. The children ranged in age at testing from 58 months to 10 years. The children 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. Exposure measures included 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. Concurrent Pb_B was found to be most strongly related to IQ, and was used as the exposure metric in all subsequent analyses. Cord Pb_B data were available for some of the subjects. Of the twelve variables included as covariates in the multivariate analysis, six terms significantly affected IQ: log of concurrent Pb_B , HOME score, birth weight, study site, and maternal IQ and education. 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 five percent change in the coefficient. After adjustment for the 5 covariates that significantly affected IQ, a log-linear model: [change in IQ (ΔIQ) = $\ln Pb_B * -2.7$ (95% CI, -3.74 to -1.66)] fit the data well. This model (depicted by the curved lines in figure 1) predicted a decline in IQ of 6.9 points (95% CI = 4.2-9.4) as Pb_B increased from 2.4 to 30 $\mu g/dl$ (the 5th and 95th percentiles, respectively). The model predicted a steeper decline in IQ of 3.9 points (95% CI = 2.4-5.3) as Pb_B increased from 2.4 to 10 $\mu g/dl$, while at higher Pb_B the declines were less: 1.9 (95% CI, 1.2-2.6), for 10-20 $\mu g/dL$; and 1.1 (95% CI, 0.7-1.5), for 20-30 $\mu g/dL$. The average linearized slopes over these ranges are shown in Table 4. Figure 4 in Lanphear et al (2005) suggests that a linear increase in either maximum or concurrent blood lead concentration associated with the mean change in IQ score could be estimated within the lower range of lead burden (i.e. < 10 $\mu g/dl$). One of the co-authors (Hornung, 2005) fit a linear model to the Pb_B and IQ data for 703 children with concurrent $Pb_B < 10 \mu g/dL$ using the same co-variates. That additional model (depicted by the straight lines in Figure 1) estimates a slope of -0.47 with a $UCL_{97.5}$ of -0.9 ($r^2 = 0.64$). Table 4 compares that slope with the other six-term linear models that were fit to data from children with lower burdens of lead:

Figure 1: IQ decrement as a Function of Blood Pb



When scores on the verbal and performance Wechsler scales were examined separately, the performance IQ / log Pb_B coefficient was very similar to the full-scale IQ (-2.73 versus 2.70) while the verbal scale showed a slightly lower slope (2.07), using the same 5 covariates.

After adjusting for concurrent Pb_B , cord Pb_B did not significantly influence IQ ($p=0.21$). Conversely, even with cord Pb_B included as a covariate, concurrent Pb_B was still significantly associated with IQ ($p=0.019$). Rothenberg and Rothenberg (2005) re-analyzed these data, concluding that the log-linear model provided a significantly better fit to the data than a linear-linear model, as illustrated in their Figure 1.

Behavioral and Motor Effects

To evaluate the association between body lead burden and social adjustment, 850 first-grade boys in a public school who scored in the upper 30 percent of the distribution on a self-reported antisocial behavior scale were matched with an equal number drawn by lot from the lower 70 percent of the distribution. From this sample, 301 students accepted the invitation to participate. Lead exposure was estimated using x-ray fluorescence spectroscopy of subjects' tibias at age 12 years. Child Behavior Checklist (CBCL), teachers' and parents' reports, and subjects' self-report of antisocial behavior and delinquency at 7 and 11 years of age were the measures of effect. At 7 years of age, lead levels were marginally associated with the teachers' aggression, delinquency, and externalizing scores after adjustment for covariates. At 11 years of age, parent- and teacher-reported somatic complaints, delinquent, aggressive, internalizing, and externalizing behavior, along with teacher-reported attention problems, social problems, and anxious/depressed behavior, were significantly associated with lead burden. High-lead subjects scored higher in self-reported delinquency at 11 years and had an increased risk of exceeding the clinical score ($T > 70$) for attention, aggression, and delinquency. The authors concluded that lead exposure is a risk factor for antisocial and delinquent behavior (Needleman et al., 1996).

Dietrich et al. (2001) found a significant 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. Nevin (2000) cites several studies showing associations between lead exposure and negative social outcomes such as involvement with the criminal justice system. Since he also cites several studies reporting inverse associations between IQ and negative social outcomes, it leaves open the question of whether these associations are the result of a direct effect of lead exposure on social outcomes or an indirect effect wherein lead affects IQ, which, in turn, affects social outcomes.

Dietrich et al. (1993) 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.

After controlling for potential confounders, Walkowiak et al (1998) found a significant inverse relationship between log Pb_B and attention span, WISC vocabulary, and WISC IQ in 384 German 6 year olds with mean $Pb_B = 4.7 \mu\text{g}/\text{dl}$, max = $17.4 \mu\text{g}/\text{dl}$. The Pb_B / attention span relationship remained even when WISC IQ was included as a co-variate.

Non-neurological effects

Although neurological effects are the best-studied effects of lead, other systems are also affected. Fels et al. (1998) found significant increases in abnormal values in various indicators of glomerular and proximal and distal renal tubular function in 62 (exposed) ten-year-old children living near lead-producing factories compared with 50 (control) children

living in the same province away from sources of environmental lead. At the time of the study, Pb_B in the controls averaged 3.9 µg/dl while exposed children averaged 13.3 µg/dl. Some of the exposed children previously had Pb_B up to 21 µg/dl.

Wu et al. (2003) used NHANES III data on self-reported attainment of menarche and physician-determined Tanner stage 2 pubic hair and breast development as indicators of sexual development in 8-16 year-old girls. After adjustment for age, race/ethnicity, income index, urban versus non-urban residence, family size, and body mass index, girls with Pb_B in the range of 2.1 to 4.9 µg/dl were 48 percent as likely (95% C.I. = 25-92%) to have attained stage 2 development of pubic hair as girls with Pb_B in the range of 0.7 to 2.0 µg/dl. They were 42 percent as likely (95% C.I. = 18-97%) to have attained menarche. Breast development was not significantly different between the groups (95% C.I. = 51-285%). Delayed sexual maturation was also seen in girls with Pb_B in the range of 5.0 to 21.7 µg/dl.

Selevan et al. (2003) also studied sexual maturation in girls based on NHANES III data. Data on Pb_B and at least one measure of pubertal development were available for 2299 of 2741 girls aged 8-18 years. Ethnic breakdown included 600 white, 805 African-American, 781 Mexican-American, and 113 belonging to other racial or ethnic groups. The latter were not analyzed due to low numbers, leaving 2186 in the analysis. Geometric mean Pb_B was <3 µg/dl for all 3 racial groups, with 99.7 percent of white girls, 98.4 percent of African-American girls, and 97.7 percent of Mexican-American girls having Pb_B <10µg/dl. Height, weight, and body mass index were included as covariates. As in the Wu et al. study, trained clinicians without knowledge of the girls' Pb_B status evaluated the Tanner stage of development. The age at menarche for girls 8-16 was obtained by interviewing the girls or a responsible adult. Ordinal logistic regression was used to estimate the mean age for attainment of each Tanner stage by Pb_B groups, after controlling for age, smoking, anemia, dietary calcium, iron, vitamin C, and total fat, rural versus urban residence, and family income. Results are summarized in Table 3.

Table 3: Odds ratio for girls with Pb_B = 3 µg/dl compared with girls with Pb_B = 1 µg/dl¹

	Non-Hispanic White	African-American	Mexican-American
Breast development	0.82 (0.47-1.42) ²	0.64 (0.42-0.97)	0.76 (0.63-0.91)
Pubic hair	0.75 (0.37-1.51)	0.62 (0.41-0.96)	0.70 (0.54-0.91)
Age at menarche	0.74 (0.55-1.002)	0.78 (0.63-0.98)	0.90 (0.73-1.11)

¹ Relative likelihood of having attained the indicator at the time of examination, fully age-adjusted

² (95% confidence interval) confidence intervals that do not include 1 indicate statistical significance

Two of the three indicators of sexual development were significantly related to Pb_B in Mexican-American girls and all three indicators of sexual development were significantly related to Pb_B in African-American girls. As shown by confidence intervals that include 1, non-Hispanic white girls' sexual development was not significantly related to their Pb_B. Both this study and that of Wu et al. (2003) reported that various markers of puberty were delayed in girls with Pb_B of around 3.0 to 3.5 µg/dl, compared with girls with Pb_B in the range of 0.7

to 2.0 µg/dl. These findings suggest another potential target for effects of lead at low levels in school-age children. Related changes have been observed in rats (Sant'Ana et al., 2001), (Der et al., 1974), (Grant et al., 1980), (Sokol and Berman, 1991).

Several studies in adults have shown adverse effects particularly involving the nervous, cardiovascular, and urinary systems. Using NHANESIII data, Nash et al.(2003) calculated odds ratios for diastolic hypertension by Pb_B quartile in peri- and post-menopausal women. They found statistically significant associations between Pb_B and blood pressure. For example, in post-menopausal women who had not been treated for hypertension, the odds ratio for diastolic hypertension was 4.6 (95% CI = 1.1-19.2) for women in the second quartile (Pb_B = 2.1-3.0 µg/dl) compared to those in the first quartile (Pb_B = 0.5-2.0 µg/dl). This result suggests the possibility of adverse effects in adults at Pb_B similar to those in children. However, children would still be more sensitive to environmental lead, since their exposures are higher on a body weight basis and they absorb a larger fraction of the lead they ingest. Thus, use of the proposed ΔPb_B in assessment of school sites is expected to result in protection of all age groups

Basis for the Benchmark Concentration for Blood Lead (ΔPb_B)

This section outlines the development of the ΔPb_B. The following section discusses the basis for the decisions that had to be made and the results of those decisions versus the alternatives.

Endpoint selection

Intellectual function as measured by full-scale Wechsler IQ was chosen as the endpoint on which to base the ΔPb_B. Intelligence testing for children was originally developed in France in 1905, and was translated into English and modified for American culture as the Stanford-Binet Intelligence Scale in 1916. This instrument was the dominant measure of children's intelligence in the first half of the 20th century. The United States military developed a separate but related instrument to measure the intelligence of recruits during World War I. Wechsler combined these two instruments into the Wechsler Intelligence Scale for Children (WISC) that evolved to the WISC-III for children 6-16 and the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-R) for children 3-7. The WISC-III and WPPSI-R include six subtests in each of the Verbal and Performance subdivisions. The Full-Scale Intelligence Quotient is a complex but consistent scoring of these subtests. Both tests have been extensively validated and shown to be reliable (Kaufman and Lichtenberger, 2000). IQ was chosen as the relevant toxicological indicator because it is a sensitive marker for neurodevelopmental effects of lead and it is the most widely measured neurodevelopmental endpoint, giving us many data sets to compare. It is also directly relevant to infants and school children.

Study selection

The Lanphear et al. (2005) pooled analysis was selected as the basis for the ΔPb_B for lead because it reports on a sensitive endpoint (full-scale Wechsler IQ) in 1,333 children participating in 7 recent longitudinal studies in 4 countries, using appropriate measures of exposure, and evaluating appropriate covariates. It involved a large number of pre-school to school-age children with relatively low Pb_B and therefore has sufficient statistical power to

define the relationship between blood lead and cognitive function at lower Pb_B levels within reasonably tight confidence limits.

IQ/Blood Lead Response Slope

The first decision was to use a response slope rather than a more traditional no-effect level with uncertainty factors approach. Based on the epidemiological studies discussed above, it is clear that an inverse relationship exists between Pb_B and cognitive function in children as measured by IQ. However, 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. OEHHA believes that this relationship is valid down to at least 1 $\mu\text{g}/\text{dl}$. It is possible that even lower Pb_B levels may adversely affect cognitive function, but a correlation between IQ and Pb_B in the range below 1 $\mu\text{g}/\text{dl}$ has not been determined because of inadequate data in that range. Since many children already have Pb_B in the range that is likely to adversely affect cognition, a response slope and benchmark response makes sense from a regulatory point of view and makes better use of all of the available data.

Lanphear et al. (2005) reported that the relationship between Pb_B and IQ was non-linear, with significant quadratic and cubic terms, after adjustment for five significant covariates. A log-linear function fit the data well. After adjustment for five significant covariates, log-linear regression analysis predicted an average reduction of 0.25 (95% CI = 0.15-0.34) IQ points for each $\mu\text{g}/\text{dl}$ increase in Pb_B over the range of 2.4 to 30 $\mu\text{g}/\text{dl}$ (Lanphear et al. 2005). However, it would be impractical to use the actual log-linear slope as the basis for the ΔPb_B . Since the slope of such a curve is different at every point on the curve, the user would have to know the pre-existing Pb_B of each child in order to calculate a benchmark dose for that child, assuming the same incremental decrease in IQ due to lead exposure at school was to be allowed in each child. In order to avoid that unworkable outcome, OEHHA identified two potential approaches: 1) calculate the average change in Pb_B over some range based on the log-linear function, or 2) a linear model based on 703 children with concurrent Pb_B up to 10 $\mu\text{g}/\text{dl}$. The slope for this subgroup was -0.47 (95% CI = -0.04 to -0.90) IQ points per $\mu\text{g}/\text{dl}$ (Hornung, 2005). The $UCL_{97.5}$ (the upper end of the 95% CI) on that slope (-0.9 points per $\mu\text{g}/\text{dl}$) was chosen as the basis for the ΔPb_B in order to account for variability and uncertainty in the data and to be reasonably certain that the result is not an underestimate of the true slope. OEHHA chose a model based on children in the lower half of the distribution because as population-wide Pb_B levels continue to decline, more and more children will fall into this range. Also, OEHHA's mandate is to protect sensitive children, and these data suggest that children at the lower end of the exposure spectrum may exhibit a greater change in IQ for a given change in Pb_B . Alternative choices and the effects of those choices are discussed below. Figure 1 compares the linear and log-linear models and their upper bounds.

Benchmark Response

U.S. EPA's web site (<http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20167>). describes several approaches to setting a benchmark response rate for continuous variables. Generally the methodology requires the most appropriate data set be used to develop the dose-response curve. A benchmark response value is chosen; U.S. EPA recommends that point be at a 10 percent response. From that value a one-way 95 percent lower confidence dose level is calculated as the point of departure. While that approach can work most of the time, it is

not useful in setting a maximum level of exposure to lead because; a) no threshold has been determined and b) a 10 percent change in IQ would not be considered by society to be a tolerable loss of cognitive function for school and pre-school children. In order to best use the available data, OEHHA chose to use a modification of the benchmark approach, using a change of 1 IQ point as the point of departure. A change of 1 IQ point would represent 0.067 standard deviations, since the distribution of IQ in the population is designed to be normal with a mean of 100 and a standard deviation of 15. This selection is discussed further below.

The ΔPb_B calculation was as follows:

$$\Delta Pb_B = \frac{-1 \text{ I.Q. point}}{-0.90 \text{ I.Q. points per } \mu\text{g/dl} * (UF = 1)} = 1.1 \mu\text{g/dl } Pb_B, \text{ rounded to } 1 \mu\text{g/dl}$$

An uncertainty factor (UF) of one is proposed because there is no interspecies or intraspecies extrapolation, since the data are based on sensitive humans, and the database was not considered deficient.

Comparison and Discussion of Alternative Choices

In developing this ΔPb_B , several choices had to be made, including which endpoint and study to use, which model from that study, which portion of the curve, and what level of predicted impairment to allow. Alternative choices and the effects of those choices are summarized in Table 4 and discussed below.

Table 4: Results of Alternative Choices

<u>Reference</u>	<u>Indicator</u>	<u>Slope</u>	ΔPb_B^1	<u>UCL</u> ²	ΔPb_B^1
Lanphear et al., 2005	Log-linear all children	-0.69	1.4	-0.96	1.0
	Log-linear, slope from 2.4 to 30 $\mu\text{g/dl}$	-0.25	4.0	-0.34	2.9
	Log-linear, slope from 2.4 to 10 $\mu\text{g/dl}$	-0.51	2.0	-0.70	1.4
	Linear concurrent $Pb_B < 10 \mu\text{g/dl}$	-0.47	2.1	-0.90	1.1
	Linear maximum $Pb_B < 10 \mu\text{g/dl}$	-0.74	1.4	-1.74	0.6
	Linear maximum $Pb_B < 7.5 \mu\text{g/dl}$	-2.94	0.3	-5.16	0.2
Canfield et al., 2003	Polynomial	-0.82	1.2	-1.43	0.7
	Linear: children w/ $Pb_B < 10$	-1.37	0.7	-2.56	0.4
	Linear: all children	-0.46	2.2	-0.76	1.3
Schwartz, 1994	Aggregate from 8 studies	-0.26	3.8		
Lanphear et al., 2000	Arithmetic	-0.89	1.1		
	Verbal	-1.44	0.7		
	Block design	-1.30	0.8		
	Digit span	-0.80	1.3		
Benchmark IQ decrement		5.0 pts	5.0		
		1.5 pts	1.7		
		1.0 pt	1.1		

¹Effect of this choice assuming that all other choices remain as recommended

² The upper end of a 95% confidence interval is the same as a 97.5% UCL

IQ/Blood Lead Response Slope

The use of a log function would result in a ΔPb_B that was different for each child, depending on where on the curve their background Pb_B fell. In order to avoid this unworkable situation, OEHHA identified two potential approaches: 1) calculate the average change in Pb_B over some range based on the log-linear function, or 2) the chosen linear model, i.e. a linear function fit to the data for the 703 children with concurrent $Pb_B < 10 \mu\text{g/dl}$ (Hornung, 2005). Either of these 2 approaches results in a slope that is the same when expressed to one significant figure. The upper bound on the slope is about twice the central estimate, leading to a ΔPb_B that is about half that based on the central estimate (see Table 4). The linear model is expected to over-predict the ΔIQ at higher Pb_B , so children with baseline $Pb_B > 10 \mu\text{g/dl}$ would experience a smaller ΔIQ than predicted by the model. OEHHA, (1997b) used a slope of -0.33 points of full-scale IQ for each $1 \mu\text{g/dl}$ increase in Pb_B in children over 5 years of age. The current “best estimate” of that slope is -0.47 points per $\mu\text{g/dl}$, with an upper bound of -0.9 points per $\mu\text{g/dl}$, the latter being the value that is proposed as the basis for the ΔPb_B . It is based on newer data, which have shown a slightly greater effect than earlier studies, particular at the lower end of the Pb_B range.

Benchmark Response

OEHHA chose a change of 1 IQ point as the benchmark response. Identifying a reasonable benchmark change in IQ involves balance. Ideally we would want to propose HGV that would cause no adverse effect in any child. However, that is impractical, since a no-effect level has not been identified, and even if one had been identified, many children would have pre-existing Pb_B values exceeding the no-effect level. Kauffman (2001) argues that fractional IQ points are meaningless, since the standard deviation on a single WISC test is about 3 points. Nation and Gleaves (2001) counter 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. Faced with that situation, OEHHA has identified a decrement one IQ point as a minimally significant change. A loss of one IQ point is clearly not a change that would be generally regarded as “clinical disease” nor would it cause affected individuals to seek medical care. Yet, in a population, an average decrement exceeding 1 IQ point may be biologically significant, and could be statistically significant as well, depending on the size of the population. Focusing on clinical versus epidemiological perspectives on neurobehavioral toxicity, Bellinger (2004) discusses the relevance of small changes in a continuous variable that indicates altered structure or function rather than clinical disease. He points out that a 1 point change in WISC full scale IQ, while within the standard error of an individual’s single measurement is still highly significant on a population basis, and that a small difference in population lead burden is associated with large differences in the number of children in the 2 tails of the IQ distribution.

Cumulative Exposure

Table 5 shows predicted incremental Pb_B increases and corresponding IQ decrements related to various environmental sources. These sources may be important in developing risk management strategies.

Table 5: Other Sources of Lead Exposure

Medium	Pb concentration	Corresponding increase in Pb _B (99 th percentile) ¹	Upper bound IQ decrement
Air ²	0.028 µg/m ³	0.11 µg/dl	0.1
Water ³	15 µg/L	2.9 µg/dl	2.7
Food ⁴	3.07 µg/kg	1.6 µg/dl	1.4
Candy ⁵	0.1 µg/g	1.6 µg/dl	1.4

¹ Based on the Leadsread model with default background levels of lead in environmental media

² The highest monthly average atmospheric concentrations measured by CARB in 1997 (data available at <http://www.arb.ca.gov/adam/toxics/statepages/pbstate.html>)

³ Based on the federal action level. (Most California water supplies are well below this level. However, drinking water samples from 200 randomly selected schools between 1995 and 1997 showed that 18% had lead concentrations exceeding the federal standard of 15 µg/L (<http://www.dhs.ca.gov/childlead/schools/execsum.htm>).

⁴ Based on FDA Total Diet Study (1999). Dietary concentrations in 2005 are probably lower.

⁵ Based on 100 grams daily consumption

Using the ΔPb_B

The ΔPb_B was developed for use in California Environmental Protection Agency school site evaluation programs. It differs from a typical chRD or chRC in three respects: a) it represents a concentration in a body fluid rather than a daily dosage or a concentration in an exposure medium like air, b) it is an incremental increase in Pb_B that would be associated with a minimal change in IQ in a population, and c) it is based on a modified benchmark dose method, not on a no-effect level. Since many children have Pb_B exceeding 1 µg/dl before any exposures occurring at school, the ΔPb_B is intended to be used as a *de minimus* increase in Pb_B resulting from exposure to environmental lead. The Centers for Disease Control's level of concern of 10 µg/dl remains as a separate consideration unaltered by this action.

OEHHA (2004) suggests using the California Department of Toxic Substances Control's Lead Risk Assessment Spreadsheet to estimate the increase in Pb_B resulting from environmental lead exposures, (available at <http://www.dtsc.ca.gov/AssessingRisk/leadsread.cfm>). Using this model, one could employ the "goal seek" function in Excel® to calculate the increase in soil Pb that would result in a predicted 1 µg/dl increase in Pb_B for appropriate population percentiles. U.S. EPA also has a model to estimate the increase in Pb_B resulting from environmental lead exposures. It is available at <http://www.epa.gov/superfund/programs/lead/products.htm>.

The ΔPb_B is intended to apply to pre-school infants and children, to students through high school, and to school staff. There is no well-established age limit for lead's neurodevelopmental effects. However, Chen et al. (2005) have shown that concurrent Pb_B in seven-year-olds continues to affect IQ beyond the effects of early exposure. Bellinger et al (1992) found a measurable relationship between Pb_B at 5 years of age and IQ at 10 years of

age. It appears that the upper end of the age range for neurodevelopmental effects overlaps the age of sexual maturity with the possibility of pregnancy, and the need to protect the fetus.

Temporal Pattern of Pb-induced Neurobehavioral Deficits

To determine the temporal pattern of the effect of postnatal Pb_B on the General Cognitive Index, Schnaas et al. (2000) used the McCarthy Scales, translated into Spanish, to test 112 children from the Mexico City Prospective Lead Study with complete evaluations from 36 to 60 months of age at 6-month intervals. They controlled for 5-min Apgar¹, birth weight, birth order, sex, socioeconomic level, maternal IQ, and maximum maternal education level in a repeated measures analysis of variance. They used the children's Pb_B measured every 6 months, and averaged over 6-18, 24-36, and 42-54 month periods as the exposure indicator. Average Pb_B for the 6-18 and 24-36 month intervals had an increasingly negative effect on GCI results at 36 to 48 months; the effect of early Pb_B leveled off then declined after 48 months. Pb_B at 42-54 months was significantly correlated with GCI at 54 months ($p = 0.04$) and at 60 months ($p = 0.06$).

Soong et al. (1999) studied a group of 28 exposed students at a kindergarten located next to a lead-recycling plant and an otherwise similar reference group of 28 students at a preschool 5 km away. The children who had attended the exposed preschool for 1-3 years (mean = 23 mo.) had a median Pb_B of 15.1 µg/dl. The exposed children had significantly ($p < 0.001$) lower IQ scores (median = 94.5) than the reference children (median = 101). The exposed students were then moved 2 km away from the recycling plant. When both groups were re-assessed 2 years later, the median Pb_B in the exposed and reference groups fell from 15.1 to 8.5 µg/dl and from 8.5 to 7.0 µg/dl, respectively. The follow-up median IQ scores were 107 and 109.5 respectively. The average increase was significant in the exposed group, but not in the reference group, indicating significant recovery in IQ scores as Pb_B fell by nearly 7 µg/dl.

Chen et al. (2005) 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. The relationship between Pb_B and IQ or MDI score was not affected by chelation treatment. Each Pb_B measurement and the average up to each age was a significant predictor of all concurrent and subsequent IQ or MDI scores. 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, suggesting that the damage is not purely a function of Pb_B up to 2 years of age; lead continues to be toxic in school-age children.

To test the hypothesis that long-term behavioral changes may result from sub-chronic Pb exposure, mice were given 5, 10, or 25 mg/kg Pb acetate intragastrically on postnatal days 6, 9, 12, 15, and 18. On postnatal day 38-42, when Pb_B was below 10 µg/dl the mice were individually tested in an unbaited tunnel maze. Locomotor activity, exploration, and experience-dependent changes in cul-de-sac entries were recorded. Exposed mice showed a dose-dependent increase in cul-de-sac entries. The results suggest that sub-chronic Pb exposure during development produced behavioral changes that lasted well beyond the exposure period, even though Pb_B declined to <10 µg/dl (Stewart et al., 1998).

Monkeys dosed with lead for their first post-natal year reached a Pb_B of 36 µg/dl. By age four, when their Pb_B was 5 µg/dl (controls were at 4 µg/dl), they were impaired in a

¹ See <http://www.childbirth.org/articles/apgar.html> for explanation

learning reversal task, indicating lack of full recovery from the effects of lead exposure during infancy (Banks et al., 1997).

Discussion

Association versus Causality

The existence of a relationship between Pb_B and various neurobehavioral indicators is well established in humans. Yet the nature of that relationship has been debated for decades. Many factors influence the intellectual abilities of children, including the IQ and socio-economic status (SES) of their parents and the quality and stability of the home environment (Wasserman, 2001, Nation, 2001). These and other determinants of intellectual development are often correlated with blood lead levels, creating a challenge to separate the effect of lead from the effects of the other variables. Several possible causal relationships are consistent with the observed correlations among neurobehavioral indicators, Pb_B , SES, and other potential risk factors (Hill, 1965). Figure 2 depicts these possibilities. Although there is no doubt that socio-demographic factors affect intellectual development directly, they may also affect exposure to lead, thereby confounding the association between lead exposure and neurological effects. If two or more independent variables (risk factors) are strongly correlated, it is difficult to know how much of the variation in the dependent variable (intellectual abilities) to allocate to each of the various risk factors (Needleman, 2001). If the incorrect relationship is inferred, then adjusting for covariates may result in the misattribution of the effects of Pb_B to other factors that are correlated with Pb_B .

Recent studies have employed multiple regression analysis to allocate the variation in intellectual abilities among the various risk factors. Multiple regression analysis may or may not correctly allocate variation in intellectual ability, since among strongly correlated risk factors one factor may be substituted for another with minimal impact on the goodness of fit. Although many parental and socio-economic factors may be related to blood lead and to intellectual abilities, in most cases, adding blood lead as an independent variable into a regression equation adds significant predictive ability to the equation (Canfield et al., 2003b). This result would not be expected if lead did not play an independent role in determining the intellectual abilities of children (Wasserman, 2001).

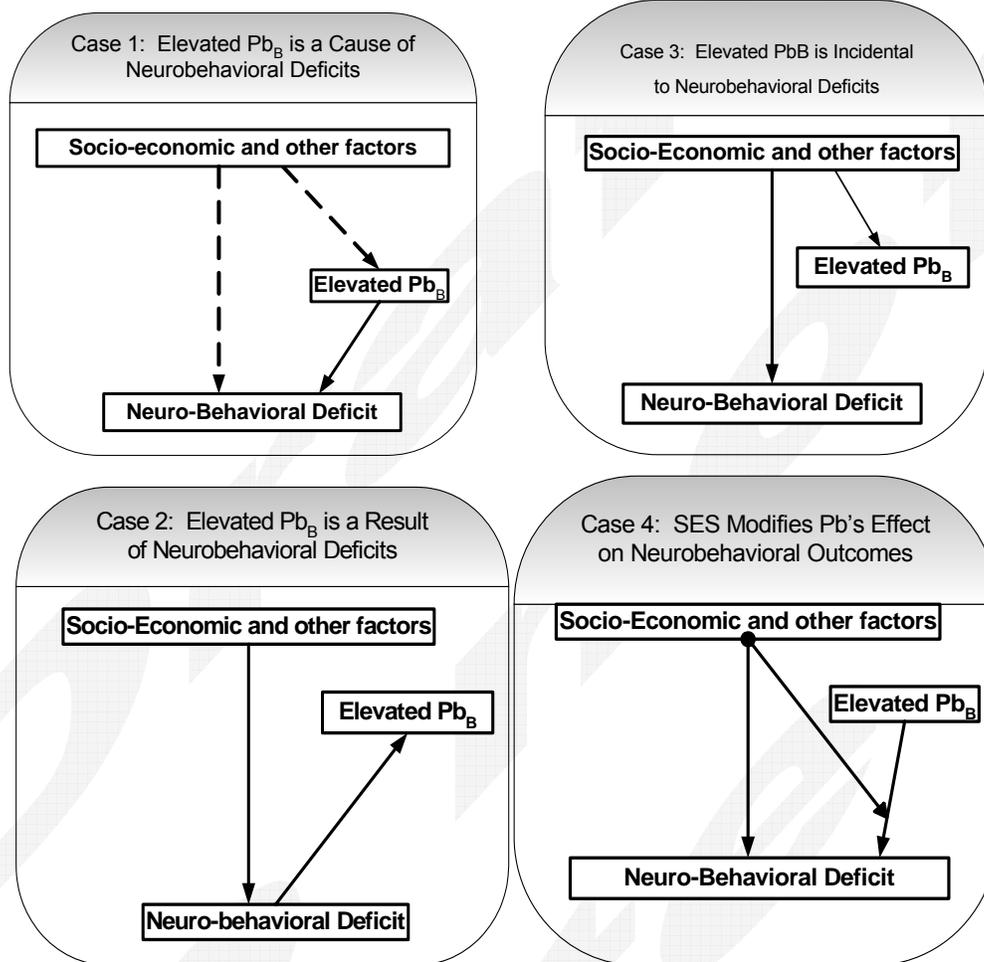


Figure 2: Postulated explanations for the observed correlations between neurobehavioral indicators, Pb_B, and SES and other potential risk factors. **Case 1:** Lead interferes with some aspect(s) of CNS functioning leading to neurobehavioral deficits. As indicated by the dashed arrows, lead may be an intermediate on the pathway from SES or other factors to intellectual deficits, and/or it may be one of multiple causes. **Case 2:** The altered behavior of neurologically challenged infants and children somehow increases their exposure to environmental lead (so-called “reverse causality”). **Case 3:** SES or other factors are confounders of the effect of lead exposure on neurobehavioral deficits. PbB is not causally related to lowered intellectual functioning, but is independently linked to a third factor or group of factors (e.g. SES), which is causally related to lowered intellectual functioning. **Case 4:** Lead interferes with some aspect(s) of CNS functioning leading to neurobehavioral deficits, and SES or other factors modify this effect.

One approach to sorting out these relationships is to study populations in which the factors under study are not correlated in the usual way. Factor-Litvak et al. (1999) conducted a prospective study comparing Yugoslavian children living near a smelter with a control group of similar age and parental education. This cohort was unusual in exhibiting a slight positive correlation between Pb_B and socio-economic status, in contrast to the more typical inverse relationship. Significant associations were found between Pb_B and height at 4 years and several behavioral problems at 3 years of age. Changes in cognitive indices associated with an increase in concurrent blood lead from 10 to 30 µg/dl are shown in Table 6. All adjusted slopes were significant at the 0.05 level (the 95% confidence intervals do not include zero). All slopes increased after adjustment for HOME score, ethnic group, maternal age,

birth weight, maternal Raven’s progressive index, maternal education, birth order or number of siblings, and hemoglobin levels (ages 2 and 4 only). This is important, because it indicates that in the unadjusted ratios the effect of lead was being partly offset by differences in these other variables, which were inversely related to lead. After adjustment, the effect of lead became stronger, supporting the position that it is the lead that is causing the deficit, not some other variable that is correlated with lead exposure.

Table 6: Changes in Cognitive Indices Associated with an Increase in Pb_B from 10 to 30 µg/dl

Endpoint		Unadjusted change	Adjusted ¹ change	
			Mean	Confidence interval
Bayley Mental Development Index (age 2)		-3.3	-5.3	-0.5 to -10.1
McCarthy Scales (age 4)	General Cognitive Index	-7.1	-9.4	-4.6 to -14.2
	Perceptual	-6.6	-7.1	-3.9 to -10.2
	Verbal	-0.8	-2.7	-0.1 to -5.4
	Quantitative	-5.5	-5.9	-2.3 to -9.6
	Memory	-1.0	-3.2	-0.5 to -5.8
	Motor	-2.6	-4.3	-0.3 to -8.3
Wechsler Scales (age 7)	Full Scale IQ ¹	-4.7	-9.0	-5.5 to -12.4
	Performance IQ ¹	-4.5	-9.4	-5.6 to -13.3
	Verbal IQ ¹	-3.7	-7.1	-3.7 to -10.5

¹ The six Verbal Scale tests use language-based items; the seven Performance Scales use visual-motor items that are less dependent on language. Five of the subtests in each scale produce scale-specific IQs, and the 10 subtest scores produce a Full Scale IQ (Factor-Litvak et al., 1999)

Similarly, Bellinger et al (1987) 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.

Neonatal behavioral evaluations can limit the influence of the post-natal environment on study outcomes, thereby helping to clarify the relationship between independent and dependent variables. Emory et al. (1999) examined 103 clinically healthy 1-2 day-old African-American infants using the Brazelton Neonatal Assessment Scale administered by trained examiners blinded to maternal Pb_B levels in the sixth and seventh gestational months, which were generally <10 µg/dl. Correlation and dose-effect trends reveal slightly poorer attention and motor control performance among offspring of mothers with higher Pb_B. When infants were divided into approximate terciles (Pb_B <1.1, 1.2 – 1.7, and >1.8 µg/dl), significant trends were found in Brazelton Scale scores on individual items relating to motor activity. Analysis of Variance (ANOVA) F-test one-tailed P values were <0.01 for both hand-to-mouth facility and general tonus. Post hoc analysis demonstrated significant

differences between the first tercile and the second and third terciles. These differences could not be attributed to birth weight or gestational age. Other variables, relating to autonomic sensitivity or emotional responses, were not significantly different between Pb_B groups. Although it is theoretically possible that heritable factors influenced both the maternal Pb_B levels and the observed developmental differences, the homogeneity of this study group makes it unlikely that SES, race, and demographic factors would be sufficient to explain the association between lead and neurological development.

The existence and the significance of an adverse effect of lead at blood concentrations below 10 µg/dl are not without controversy. Hebben (2001) identifies a number of limitations to our knowledge of the neurological effects of lead, and argues that lead has not been linked to several specific diagnoses such as ADHD or mental retardation. She also cautions about over-interpreting neuropsychological test results in individuals. Ernhart et al. (1989) 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.

Kauffman (2001a) identifies five methodological shortcomings of three widely cited meta-analyses from the early 1990s, urging greater caution in the interpretation of the lead/IQ data particularly at low exposure levels. Needleman and Bellinger (2001), and Nation and Gleaves (2001) have responded to Kauffman's points, pointing out, among other things, that given the limitations in the studies that Kauffman points out, the actual effect could be greater than the estimated effect. Kauffman (2001b), has, in turn, responded to Needleman and Bellinger and Nation and Gleaves. Since a point-by-point analysis of these alleged shortcomings is beyond the scope of this document, the reader is referred to these papers for further analyses of these methodological issues. OEHHA concludes that the preponderance of the evidence indicates that lead does affect neurological development at low body burdens and that reducing exposures is likely to benefit public health.

Additional evidence from studies in other species

The experimental evidence for causal effects of lead on neurobehavioral development supports the epidemiological evidence. Controlled laboratory animal studies can help clarify the role of various variables in neurobehavioral outcomes because it is possible to avoid confounding by limiting the variables to the one under study, i.e. lead. Positive results under such conditions would argue against the "reverse causality" or "incidental co-variation" hypotheses. Primates are particularly valuable as research subjects because they can be given learning tasks that are similar to those given to children. Several examples are given in the following paragraphs.

Monkeys dosed with lead from birth reached blood levels of 115 µg/dl in infancy, then leveled off to 35 µg/dl by a year of age. Despite the high Pb_B, the monkeys did not show signs of overt toxicosis, nor any increase in overall locomotor activity. Treated monkeys learned tasks more slowly than controls and responses to a fixed reinforcement schedule were

less stable. Monkeys treated only during infancy or only after infancy showed similar results when tested at ages 3 and 7-8 years (Banks et al., 1997).

Rats dosed with lead to reach blood levels of 19 or 39 $\mu\text{g}/\text{dl}$ showed impairment in serial reversal learning and fixed-interval responding tasks, and delayed spatial alternation, findings similar to those reported in monkeys (Banks et al., 1997).

Morgan et al. (2001) exposed rats to lead during gestation and lactation or during lactation alone. Maximum Pb_B of 158 $\mu\text{g}/\text{dl}$ was reached on postnatal day 24, declining to 12-16 $\mu\text{g}/\text{dl}$ on postnatal day 53. This treatment regimen caused impaired sustained attention and increased reactivity to errors, when cue duration and cue onset varied unpredictably between trials. The authors suggest that these changes may be related to the disruptive classroom behavior, low IQ scores and delinquency observed in lead-exposed children. Moreira et al., (2001) found hyperactivity, decreased exploratory behavior, and impairment of learning and memory in rats exposed during gestation and lactation with Pb_B of 21 ± 3 $\mu\text{g}/\text{dl}$.

Summary and Conclusions on Causality

Based on multiple lines of evidence, OEHHA concludes that lead is a causal factor in neuro-developmental deficits. Regression analysis of data from many epidemiologic studies has shown that lead exerts an independent effect on neurodevelopment and cognition, after adjustment for differences in other factors known to influence the same outcomes. Reverse causality is not a likely explanation, because differences can be found at birth. In two studies in which Pb_B was directly correlated with SES, the observed effect of lead on IQ tests was increased after adjustment for differences in SES. Finally, similar effects have been seen in controlled studies in several non-human species. Clearly, lead is only one of several risk factors for diminished intellectual capacity, and it may not be the most important. However, since our mandate is to protect school children from the effects of toxic chemicals, it is sufficient to show that low Pb_B concentrations play a direct role in the etiology of diminished intellectual capacity in affected children.

Mechanisms of lead toxicity

Chronic lead (Pb) exposure has been associated with cognitive impairments in children and laboratory animals, and these effects can be related to events at the cellular, sub-cellular, and biochemical levels. Many authors have studied the mechanisms of lead toxicity *in vivo* and *in vitro*, using concentrations approximating the range of blood levels seen in children. Children with Pb_B in the 7 to 59 µg/dl range showed concentration-related increases in latency of brain stem auditory evoked potentials. Rats showed increased latency of visual evoked potentials to visual stimuli at a Pb_B of 65 µg/dl. Similar increases were seen in lead-exposed monkeys. Spontaneous activity of cerebellar Purkinje cells is reduced in lead-treated cats and rats. This impairment persists long after tissue lead has returned to normal (Banks et al., 1997). The following is intended only as a brief overview of some cellular, sub-cellular, and biochemical changes associated with lead toxicity. Lidsky and Schneider (2003) reviewed many of these studies.

Effect	Reference
Lead disrupts Ca homeostasis and substitutes for Ca and/or Zn in a variety of enzymatic reactions & cellular processes.	Lidsky and Schneider, 2003 Bressler and Goldstein, 1991
Pb can pass readily through the blood-brain barrier. It is taken up by brain capillary endothelial cells via the Ca-ATPase pump.	Lidsky and Schneider, 2003
In vitro apoptosis of retinal cells due to cytochrome C-caspase activation effector protein path resulting in mitochondrial dysfunction.	He et al., 2000
Retinal damage in developing and adult rats at dosages similar to those causing visual deficits in monkeys and humans.	Fox DA, et al 1997
Pb enters astroglial cells by voltage-sensitive Ca channels	Kerper and Kinkle , 1997b
Pb accumulates in human mitochondria in vivo,	Anderson et al, 1996
Mitochondrial dysfunction leads to depression of heme synthesis and anemia. Resulting increase in aminolevulinic acid disrupts glutamate-mediated synaptic transmission causing neuron-killing excitotoxicity.	Beal et al, 1993 Anderson et al, 1996
Oxidative stress and lipid peroxidation leading to neuron death in prenatal, neonatal, juvenile, and adult rats	Shukla et al 1987 Antonio et al 1999 Villeda-Hernandez et al 2001
Affects energy metabolism in brain nerve endings in rats. Creatine phosphate, creatine kinase, O ₂ consumption and ATP are increased, Na-K-ATPase is decreased in brain synaptosomes.	Rafalowska et al, 1996 Struzynska et al, 1997
Pb substitutes for Ca in activating calmodulin <i>in vitro</i> ; higher concentration reduces calmodulin activity.	Kern and Audesirtk, 2000
Pb effects on calmodulin perturbs intracellular calcium homeostasis in rat neurons	Ferguson et al, 2000
Pb affects protein kinase C, which is involved in long-term potentiation	Bressler and Goldstein, 1991
Pb activates protein kinase C at lower concentrations than Ca	Bressler et al, 1999
Chronic exposure in rats reduces hippocampal protein kinase C expression, which could Impair synaptic activity, learning, & memory.	Nihei et al 2001
Pb suppresses activity-associated calcium-dependent neurotransmitter release	Lasley et al, 1999
Rats exposed from weaning to 3 months have fewer presynaptic vesicles & damaged mitochondria.	Jablonska et al 1994; 14: 701-9
Synaptosomal Na-K ATPase is increased by Pb exposure.	Regunathan and Sundaresan, 1985

Effect	Reference
Synaptosomal Ca-ATPase is inhibited <i>in vitro</i>	Bettaiya R, et al 1996
Pb disrupts synaptotaglin I <i>in vitro</i> , a protein in the synaptic terminal. This may lead to defective neurotransmitter release.	Bouton et al 2001
Pb-induced changes in post-synaptic neurotransmitter receptor density in young and adult rats may affect behavior.	McCoy L et al 1997 Lasley et al 2001
Pb increases threshold and decreases duration of long-term potentiation possibly due to diminished presynaptic glutamate release	Carpenter et al. (1994) Gilbert et al., 1999a
Chronic developmental Pb exposure disrupts hippocampal long-term potentiation in adult rats.	Gilbert et al 1996
Pb decreases total K ⁺ -stimulated hippocampal glutamate and gamma-amino butyric acid release. Calcium-mimetic induction of glutamate release at higher exposure levels	Lasley and Gilbert, 2002
Pb-treated adult rats retained a learned task less time than controls and had less hippocampal neural cell adhesion molecule polysialylation, a marker for synaptogenesis	Murphy and Regan, 1999
Pb blocks post-synaptic N-methyl D-aspartate (NMDA) receptors, involved in long-term potentiation. This could explain reduced learning ability associated with developmental Pb exposure).	Guilarte and McGlothlan, 1998
Pb exposures alter MK-801 binding, a marker of NMDA function.	Cory-Slechta et al. (1997)
Necrosis and apoptosis, in mesencephalic dopamine cells <i>in vitro</i> . Reduced dopamine uptake in remaining cells..	Scortegagna and Hanbauer, 1997
LTP is impaired in animals exposed to Pb for 30 days in the early postnatal period	Gilbert et al., 1999b
Delayed differentiation of glial progenitors <i>in vitro</i>	Deng et al 2001
Hypomyelination and demyelination <i>in vivo</i>	Coria et al 1984
Immature astroglia sequester lead preferentially <i>in vitro</i> . This may initially protect neurons but later astroglia release lead, resulting in prolonged exposure.	Lindahl et al 1999 Tiffany-Castiglioni et al 1989 Holtzman et al 1987
Astrocytes modulate synaptic activity by converting glutamate to glutamine. Glutamine synthetase activity is decreased in Pb-treated cultured astrocytes.	Norenberg and Martinez-Hernandez, 1979 Sierra and Tiffany-Castiglioni, 1991
Abnormal brain oligodendroglia and myelin <i>in vivo</i> at 38.2 µg/dl Pb (0.03 µg/g in brain)	Dabrowska-Bouta et al 1999
Decreased CNPase activity in young rats. CNPase is necessary for myelin synthesis during development.	Dabrowska-Bouta et al 2000
Delayed maturation of oligodendroglia.	Tiffany-Castiglioni et al 1989
Pb exerts toxic effects on Schwann cells in rats.	Dyck et al 1977

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Appendix A: Comments from Peer Reviewers and the Public

Review of Draft Report: Proposed Child-Specific Reference Concentration (chRC) for School Site Risk Assessment

Richard W. Hornung, DrPH

Oct 19, 2005

Thank you for the opportunity to review your draft report on lead hazards to California school children. As you know, I worked with Dr. Bruce Lanphear and the pooled analysis study team in producing our final models relating IQ to various blood lead indices. I am not an expert in the study of health effects attributable to lead exposure, and therefore I make no attempt to address your rather extensive review of the literature. I will primarily confine my comments to the interpretation of results from our analysis of the data from seven international cohorts and how those estimates are used to develop your child-specific reference concentration (chRC).

Major Points

Top of page 12, the report uses the published log-linear model to crudely estimate linear slopes for intervals 2.4 to 30 ug/dl and <1 to 10 ug/dl. These estimated slopes were apparently calculated by subtracting the estimated IQ decrement at the extremes of the interval and then dividing by the width of the interval. There are two problems with this approach. First, it assumes that a linear approximation in the interval is a good estimate of the linear dose-response over this range. It turns out that this approach produces rather poor estimates of the linear model fits in these two intervals. Since you had no access to the data for individual children in this study, this is an understandable approximation. Second, the estimates that you provided for the interval "<1 to 10 ug/dl" are incorrect using your algorithm. It appears that you calculated an average slope of 0.62 IQ points per ug/dl by: $[2.704 \ln(10) - 2.704 \ln(1)] / 10 = 0.62$. The interval width is actually equal to 9, so the estimated slope using your algorithm should be $6.22/9 = 0.69$ and the corresponding UCL would be 0.96 instead of 0.86.

In order to provide more accurate estimates for your eventual calculation of chRC, I ran a linear model using our pooled analysis data restricted to children with concurrent blood lead levels less than or equal to 10 ug/dl. There were 703 children in this analysis and the resulting slope = -0.47 with 95% CI = (-0.04 to -0.90). Similarly, if a linear model is fit to all children, the slope = -0.18 with 95% CI = (-0.10 to -0.28). Clearly, the latter model is a poor fit to the data over the full range of exposures, but it is substantially lower than your estimate of 0.25. For the interval at 10 ug/dl or below, the UCL = -0.90 is slightly larger than your estimate of -0.86 (calculated incorrectly), but smaller than the correct estimate of 0.96 using your

approximation. If you wish to use the actual estimates from our data, you may cite this as a personal communication from me.

Response: We have substituted the revised linear model for the original log/linear model

Page 13, the equation to calculate chRC is provided. Although I am not familiar with this calculation, the rationale for using $RSC = 0.5$ was not very well explained.

Response: We have augmented this discussion and omitted the RSC.

Page 13, last paragraph, the report mentions chRD instead of chRC. Are these two terms interchangeable? It would be better to remain consistent to avoid confusion.

Response: We have made this correction

Table 5, the last two rows under the Lanphear reference should be "Linear, children whose max PbB<10" or "max PbB<7.5". Also, similar to the previous comment, there is a column labeled "chRD" instead of "chRC".

Response: We have made this correction

Page 22, while I am not an expert on the lead health effects literature, the very short section on negative studies seems incomplete. It only contains one reference. One of the collaborators in our pooled study withdrew her name from the list of co-authors because she does not believe in low-level lead effects on IQ. Dr. Claire Ernhart and colleagues published a paper in 1989 in *Neurology and Teratology* 11:161-170 that concludes that decreases in child IQ are mostly attributable to confounders and not lead exposure. There may be other similar publications of which I am unaware.

Response: We have added the suggested reference along with a discussion of this report.

Minor Points

Page 6, first paragraph under Neurologic Effects, it is not clear what is meant by citing Pb_B studies ranging from 5-9 ug/dl "at the low end" to 32-60 ug/dl "at the high end". Does this mean that studies of low-exposed children ranged from 5-9 ug/dl and studies of high-exposed children ranged from 32-60 ug/dl? Similar statements are found in the next paragraph.

Response: We have attempted to clarify this point

Page 7, second paragraph, replace "class rankings in the 4 subjects" to "class rankings in the 4 areas of study" to avoid confusion.

Response: We have made this correction

In Table 3, and several other places in the report, remove the hyphen in the word "covariates".

Response: We have made this correction



Alan C. Lloyd, Ph.D.
Agency Secretary
Cal/EPA

Page 10, last paragraph, replace “were 48% as likely” with “were 48% more likely”.

Department of Toxic Substances Control



Arnold Schwarzenegger
Governor

Maureen F. Gorsen, Director
1001 I Street
Sacramento, California 95812-0806

Response: We do not agree with this suggestion
Top of page 11, there is no citation for Selevan, et al in the list of references.

Response: We have added this reference

Top of page 14, the report states that “sensitive children were studied” in the pooled analysis. To my knowledge no attempt was made to focus on sensitive children in any of the seven cohorts. This phrase should be removed. A more likely explanation for the higher than usual slope estimate is that we had large enough sample size to estimate effects at lower blood lead levels than had previously been possible in individual studies.

Response: We did not use the term “sensitive” in any sense other than that they had lower blood lead levels and because the slope is steeper in the lower blood lead levels those children are more “sensitive” in the sense that they will have a larger decrease in IQ for a given increase in Pb_B than other children. We will clarify the use of the term.

In summary, I found the draft report to be well done and clearly written. I hope my comments and additional estimates will help to improve an already well-crafted report.

**Human and Ecological Division
Department of Toxic Substances Control
February 6, 2006**

Review of “Development of Health Criteria for School Site Risk Assessment Pursuant to Health and Safety Code Section 901(g): Proposed Child-Specific Reference Concentration (chRC) for School Site Risk Assessment – Lead”, Internal Draft Report, June 2005, Integrated Risk Assessment Branch, CalEPA, Office of Environmental Health Hazard Assessment (OEHHA)

BACKGROUND

The OEHHA document proposes to adopt a children-specific reference concentration (chRC) for lead based on a recent international pooled analysis of the effect of lead on intellectual function of children (Lanphear *et al.*, 2005). The chRC is designed for use in the health risk assessment for children at lead contaminated school sites. OEHHA selected the neurodevelopmental effect for lead as the endpoint for chRC calculation because the effect is a sensitive marker and the most widely measured endpoint in human studies. Unlike traditional reference doses which specify an acceptable exposure level that will not cause adverse health effects in humans, the document describes the chRC for lead as an incremental increase in blood lead (Pb_B) that would be associated with a marginally detectable change in intelligence quotient (IQ) in children. The proposed chRC (a decline in one IQ point for an increase of 0.6 µg/dl lead in blood) is based on a decline in 0.86 IQ points per µg/dl Pb_B elevation and a relative source contribution (RSC) of 50% for lead intake from school exposure. The decline in 0.86 IQ point per µg/dl increase in blood lead is the 97.5% upper confidence limit of the mean obtained from the pooled analysis of seven longitudinal studies in four countries (Lanphear *et al.*, 2005).

COMMENTS

1. EPIDEMIOLOGICAL STUDY SELECTED AS THE BASIS FOR THE chRC.

a. EPIDEMIOLOGICAL STUDY DESIGN AND STATISTICAL ANALYSIS.

The study design and statistical analysis of the epidemiological studies discussed in the document were not reviewed in detail by HERD. *HERD recommends that this information be reviewed by individuals with expertise in epidemiology and statistical analysis of epidemiological studies. Specifically, review of the pooled analysis by Lanphear et al. (2005) is critical because this meta-analysis serves as the basis for the proposed chRC.*

We trust that the editors of the journal in which this article was published sent it to reviewers with appropriate expertise prior to publication. Also, some of the internal and external peer reviewers have expertise in statistical analysis and study design.

b. DATA MODELING, DATA QUALITY, AND STATISTICAL ANALYSIS:
Both the Lanphear et al. (2005) and Rothenberg and Rothenberg (2005) studies reveal a best log-linear fit for the pooled data, rather a linear fit. However, OEHHA assumes a linear relationship between IQ decline and blood lead increase for children with blood lead level at <1 to 10 µg/dl. This linear slope is used as the basis for determination of the lead chRC. HERD has the following comments:

- i. The wide variance in the slope of the curve between low blood lead levels and higher blood lead levels calls into question whether OEHHA's approach of estimating a linear slope is preferable to the current approach of setting a threshold blood level (probably lower than the current value of 10µg/dl recommended by CDC and USEPA). *At the least there should be a discussion in the document comparing the two approaches and their plusses and minuses.*

Discussion of the issue of estimating a linear slope versus the approach of setting a threshold blood level has been added. OEHHA identified no basis for estimating no-adverse-effect-level (NOAEL) in sensitive humans. OEHHA also has a stated preference for a benchmark dose approach over the NOAEL/UF approach.

- ii. Based on a good fit of the log-linear model for the pooled data, HERD believes that the derived linear slope results in an underestimation of the effect of lead for children with low blood lead level (close to detection limit). More importantly, this population group is considered as the most sensitive population based on the log-linear nature of the pooled data (as stated in the document). On the other hand, the linear relationship assumption causes an overestimation of the effect of lead at blood lead level close to 10 µg/dl. This blood lead level may represent the population group exposed to environmentally relevant concentrations of lead. *Therefore, HERD recommends including an uncertainty discussion and sensitivity analysis on the application of this linear slope at these data ranges and potentially to cases with blood lead levels exceeding 10 µg/dl.*

OEHHA agrees that the linear response slope chosen has a steeper slope than the log-linear model at higher blood lead levels and a less steep slope at lower blood lead levels. It would be impractical to use the actual log-linear slope as the basis for the ΔPb_B . Since the slope of such a curve is different at every point on the curve, the user would have to know the pre-existing Pb_B of each child in order to calculate a benchmark dose for that child, assuming the same incremental decrease in IQ due to lead exposure at school was to be allowed in each child. That being the case, OEHHA had two choices: 1) calculate the average change in Pb_B over some range based on the log-linear function, or 2) the chosen linear model (-0.47 (95% CI = -0.04 to -0.90) IQ points per µg/dl, $r^2 = 0.64$, Hornung, 2005), based on children with Pb_B up to 10 µg/dl (roughly the lower half of the distribution). The two slopes are similar at blood lead levels near the national average, and the resulting ΔPb_B resulting from the application of either model would be the same if given to one significant figure. OEHHA cautions against over-interpreting small differences in slopes between different studies and different analytical methods. For example, in Figure 3 of Lanphear et al., 2005, the difference in IQ between 5-10 ug/dl and 10-15 ug/dl is greater than the difference in IQ between 0-5 ug/dl and 5-10 ug/dl.

- iii. We were struck by Figure 1 in Rothenberg and Rothenberg (2005), which shows the large scatter in the blood lead vs. IQ data. The curvilinear slope decreases rapidly over the 1-10 $\mu\text{g}/\text{dl}$ blood lead concentration range. OEHHA chooses to approximate this curvilinear slope by a linear slope over the 1-10 $\mu\text{g}/\text{dl}$ concentration range and base its lead chRC on this slope. Thus a wide ranging scatter gram is condensed into a curvilinear slope which decreases rapidly over the 1 to 10 $\mu\text{g}/\text{dl}$ range. Then this varying slope is approximated by a linear slope on which the chRC is based. *Given all the approximations involved, HERD feels that a thorough review by experts as discussed above is essential prior to releasing the document for public review. Furthermore, inclusion of the linear regression coefficient for data within the 0-10 $\mu\text{g}/\text{dl}$ range is necessary for supporting the use of the linear slope.*

OEHHA has abandoned the original linear approximation of a log/linear response. In order to capture the apparently steeper response for children with lower Pb_B while avoiding that approximation, a linear regression equation has been fitted to the data for the 703 children in the study whose concurrent Pb_B did not exceed 10 $\mu\text{g}/\text{dl}$. The resulting slope is now the basis for the response slope used in calculating the benchmark ΔPb_B . OEHHA chose a model based on children in the lower half of the distribution because as population-wide Pb_B levels continue to decline, more and more children will fall into this range. Also, OEHHA's mandate is to protect sensitive children, and these data suggest that children at the lower end of the exposure spectrum sensitive may exhibit a greater Δ IQ for a given ΔPb_B .

- c. DATA QUALITY: Lanphear et al. (2005) reported a decline of 6.2 (3.8-8.6, 95% confidence interval) IQ points for blood lead levels increased from <1 to 10 $\mu\text{g}/\text{dl}$ based on a log-linear fit on the pooled data. Upon inspection of the data range for each individual longitudinal cohort, HERD finds that data from the Boston, Rochester, and Mexico studies heavily contributed to this data range. Although the Lanphear pooled analysis suggests a strong negative correlation between IQ score and concurrent blood lead level in children, the Boston study was based on blood lead data collected from children at 5 years of age and full-scale IQ score tests performed at 10 years of age. As stated above, data from the Boston study contributed significantly to the data within the 0-10 $\mu\text{g}/\text{dl}$ range. *HERD believes that it is important to include a discussion of this data limitation.*

The fact that a difference can still be 5 years later suggests that the effect persists for an extended period.

- d. FIGURE 1 (IQ DECREMENT VERSUS BLOOD LEAD). Figure 1 of the document does not correlate to the suggested slope, nor match with the reference (Lanphear et al., 2005). *Please edit the figure accordingly.*

The figure has been revised.

2. NON-THRESHOLD TOXICANT ASSUMPTION. The document states that the proposed chRC does not represent an absolutely safe exposure level since no safe level has been established, thereby implying that the toxicity of lead is associated with non-threshold effects. It is further noted in the document that the chRC is intended to be used as a *de minimus* increase in Pb_B resulting from lead exposure at a school site, which is in a sense

analogous to a source-specific incremental cancer risk. While the document discusses scientific studies supporting the assumption that the effect of Pb_B on measures of cognitive abilities extends below 10 $\mu\text{g}/\text{dl}$, the document does not include a discussion of the available scientific evidence supporting the assumption that lead is a non-threshold toxicant. *Because this assumption is a key element upon which the proposed chRC is based, HERD recommends that the document be revised to specifically address and include a discussion of the available information related to the assumption lead is a non-threshold toxicant.*

OEHHA's statement that no safe level has been established does not imply that OEHHA believes that the toxicity of lead is associated with non-threshold effects. In fact, the text on page 14 "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" suggests that the curve may flatten out at some point but we do not know where that point is. See also text on page 5: "The minimum Pb_B causing neurobehavioral deficits is not well defined." Again, this indicates the possibility of an as-yet-unidentified threshold.

3. ENDPOINT SELECTION. In this document IQ was selected as the measurement endpoint for lead toxicity because 1) it is a sensitive marker for neurodevelopmental effects of lead and 2) it is a widely measured neurodevelopmental endpoint providing many data sets. There is no discussion on the IQ tests themselves or what they mean. *To better support the use of the IQ as a measure of lead toxicity, HERD recommends that this section be expanded to include a general referenced discussion on the different types of IQ tests, the correlation between them, how they measure IQ, standard deviations, the strengths and limitations of IQ tests, and the functional effect of a decline of one or more IQ points.* OEHHA has added text to augment the discussion of IQ tests and what they mean.

4. NON-NEUROLOGICAL EFFECTS OF LEAD. The document discusses data suggesting potential adverse effects in adults at blood lead levels similar to those in children (i.e. less than 10 $\mu\text{g}/\text{dl}$). In particular, the document discusses adverse effects on the cardiovascular system (such as diastolic hypertension) in adults. HERD recommends that the document also include a discussion of the literature reporting that relatively small increases in blood lead appear to be associated with increased risks of both cardiovascular disease and mortality in men and women (Silbergeld et al, 2005). Data related to potential adverse effects of lead in adults is relevant for adult receptors at school site (e.g. teachers). The legislative mandate specifically refers to children. We have added text to explain how the child-based ΔPb_B offers similar protection to adults.

5. METHODOLOGY USED FOR THE REFERENCE CONCENTRATION DETERMINATION – RELATIVE SOURCE CONTRIBUTION.

- a. In the Executive Summary of the document, the chRC is stated to be one-half of a lower-bound estimate of an incremental increase in children's Pb_B that is estimated to decrease IQ by 1 point. The other one-half is assumed to come from air and drinking water. The document does not include a rationale or cite references supporting these relative source contribution (RSC) assumptions. Furthermore, the reference concentration calculation does not include contribution

from the intake of food and candy, which is the major source of blood lead according to the data shown in the Cumulative Exposure Section of the document. As a result, the relative source of contribution from school exposures, at the reference concentration level, is relatively small compared to all lead intake sources (~8.8% of the total). *The document should justify and compare the RSC assumptions from all of the potential sources, discuss the significance of blood lead increase contributed by school exposures under the reference concentration conditions, and discuss the cumulative impacts from all lead exposures. The document should also specifically state why only air and water were considered when estimating the RSC for lead.*

The relative source contribution has been eliminated.

- b. In the section which discusses “Calculation of the chRC ” (Page 15), the RSC is shown to be 0.5, which is based on assumed Pb_B increments of 0.5 from drinking water and 0.1 from air. Because units were not provided for the Pb_B increments from drinking water and air, the text could be interpreted such that the 0.5 and 0.1 values represent the RSCs for those media. *HERD recommends that the text be updated to clarify the units and specify the resulting assumed RSCs for drinking water and air.*

The relative source contribution has been eliminated.

- c. OEHHA derived the Public Health Goal (PHG) for lead in drinking water assuming an intake RSC of 0.2. In this document, the RSC for lead is 0.5 $\mu\text{g}/\text{dl}$ /1.2 $\mu\text{g}/\text{dl}$, or 0.42. HERD notes that the RSC variable is used in a different manner for the PHG and chRC calculations. Specifically, RSC for the PHG calculation relates to intake, while RSC for the chRC calculation relates to contribution to an increased blood lead level. *While the RSC variable is used in a somewhat different manner for the two calculations, HERD recommends that the document include a discussion as to whether these RSC assumptions are in general agreement in terms of the assumed contribution of lead from drinking water relative to other sources.*

The relative source contribution has been eliminated.

- d. The document recommends using the DTSC Leadsread Spreadsheet model that contains blood lead intake slopes of 0.16 $\mu\text{g}/\text{dl}$ per $\mu\text{g}/\text{day}$ for children and 0.04 $\mu\text{g}/\text{dl}$ per $\mu\text{g}/\text{day}$ for adult. However, OEHHA adopts the Centers for Disease Control (CDC) blood lead intake slope of 0.35 $\mu\text{g}/\text{dl}$ per $\mu\text{g}/\text{day}$ in its calculation of the PHG for lead. *Please clarify the discrepancy and discuss the significance of adopting these different intake slopes in risk determinations of lead exposure.*

The PHG for lead will soon be updated to include the current paradigm.

- e. In Table 6: Other Sources of Lead Exposures, the document estimates an upper limit of blood lead contribution of 2.9 $\mu\text{g}/\text{dl}$ from drinking water, which exceeds both the drinking water RSC assumption and the proposed reference concentration. *HERD recommends including a discussion of the cumulative impact of drinking water exposure and school exposure.*

The relative source contribution has been eliminated. The PHG for lead will soon be updated to include the current paradigm.

6. COMPARISON OF ALTERNATIVE CHOICES FOR THE chRC.

- a. HERD notes that in this section, chRC and chRD appear to have been used interchangeably. *The document should be updated to refer to the reference concentration as a chRC rather than a chRD.*

This has been corrected; a new term " ΔPb_B " has replaced "chRC".

- b. Table 5 presents slopes and "chRD" values determined based on selected studies on effects of lead in humans. Most of the slopes and hence the "chRDs" calculated are within one order of magnitude. As a result, these data support the strong correlation between blood lead levels and cognitive deficits in children with blood lead levels below 10 $\mu\text{g}/\text{dl}$. However, despite an assumed RSC of 0.5 used in the lead "chRD" equation, these alternative slopes and "chRDs" were determined based on a RSC of one. *To avoid confusion and enable a direct comparison between all the studies, HERD recommends using a consistent value of RSC in all the chRC calculations in the document.*

The relative source contribution has been eliminated.

- c. The document contains conflicting information as to whether the proposed decline in IQ of -0.86 point per $\mu\text{g}/\text{dl}$ increase in blood lead is the 97.5 upper confidence limit of the mean from the Lanphear study (2005), or the upper end of the 95% confidence interval (see pages 14 and 16). *Please clarify.*

They are the same thing. A 95% confidence interval leaves a 5% probability that the true slope is outside the interval, with a 2.5% probability in each tail, i.e. we can be 97.5% certain that the true slope is not greater than the UCL.

7. USE OF THE chRC. The document suggests that DTSC's Leadsread be used to calculate the increase in Pb_B resulting from environmental lead exposures and a specific example is included. The document indicates that assuming 100 mg/day soil ingestion for 5 days/week and 44 percent bioavailability of the lead species, Leadsread predicts that a soil concentration of 40 mg/kg at a school site would result in a 0.6 $\mu\text{g}/\text{dl}$ increase in the 99th percentile Pb_B . A soil concentration of 55 mg/kg would result in a 0.6 mg/dl increase in the 95th percentile Pb_B . *In order to avoid confusion as to whether these soil concentrations are appropriate for use in making risk management decisions, HERD recommends that the specific example be deleted from the document.*

The specific example has been deleted from the document. A reverence to EPA's IEUBK model has been added in response to other comments.

8. MECHANISMS OF LEAD TOXICITY:

- a. Chronic lead exposure has been associated with cognitive deficits observed in children and animals. The document discusses a biphasic effect of lead on

synaptic plasticity reported in animal studies. Gilbert and coworkers (1999) demonstrated an increase in long-term potentiation (LTP) induction threshold and a decrease in LTP duration in dentate gyrus of rats chronically exposed to lead. A decrease in pre-synaptic transmitter release at low doses of lead and an increase in glutamate release at high dose of lead to compensate for the LTP impairment were proposed as the mechanism of actions for the biphasic effect of lead on LTP. Recently, Lasley and Gilbert (2002) directly measured the effects of lead on hippocampal glutamate and gamma-aminobutyric acid (GABA) releases using an intracerebral dialysis technique. The results demonstrate multiple synaptic actions of lead with individual dose-effect curves of differential sensitivity to lead and calcium dependency. At low doses, lead diminishes calcium-dependent neurotransmitter release, probably through a partial agonistic action of lead on activation of protein kinase C (PKC) by calcium or binding of lead to the voltage-gated calcium channel. At high doses, the reversal of decrease in calcium-dependent component of release may be attributed to a mimicking action of lead on calcium, which directly induces exocytosis independent of calcium. *HERD recommends including the most current study in the section related to the mechanism of action of lead.*

The newer information has been added.

- b. The document relates the biphasic alteration in post-synaptic N-methyl-D-aspartate (NMDA) receptor density by lead exposure to the biphasic effect of lead on LTP (Lesley *et al.*, 2001), without including further details on the study. Although Lesley and coworkers (2001) reported a biphasic alteration in NMDA receptor density by lead exposure (which reflects an analogous relationship to that reported for hippocampal LTP impairment and glutamate release), the authors believed the upregulation of NMDA receptor at the intermediate dose of lead (not observed in low or high dose animals), may be a result of diminished glutamate release. They further concluded that the changes in NMDA receptor density are unlikely constituting a primary mechanism by which lead impairs hippocampal LTP induction. Instead, the nature of the receptor alternation may be dependent on exposure conditions or a secondary effect of lead on signal transduction pathways. *HERD recommends including this information in the discussion.*

The newer information has been added.

- c. The document suggests that lead may block the NMDA receptor at concentrations in the range that affect learning in children. However, Lesley and Gilbert (2000) reported that lead does not appear to inhibit NMDA receptor function at environmentally relevant exposure levels. Instead, they concluded that the biphasic reduction of neurotransmitter release by lead contributes significantly to the biphasic LTP impairment. *HERD recommends either providing additional support on the potential inhibitory action of lead at environmentally relevant exposure levels, or amending the discussion to eliminate this mechanism of action.*

The text has been amended to focus more on the mode of action at environmentally relevant exposure levels.

The document states that substitution of lead for calcium in proteins such as PKC can alter their enzymatic activity (Page 26, first paragraph). Results of *in vitro* studies demonstrate that lead stimulates PKC activity (in picomolar range) at a much higher potency than calcium, but with a much lower efficacy than calcium (Tomsig and Suszkiw, 1995). *HERD recommends amending the statement to indicate that at environmentally relevant levels, lead acts as a partial agonist for PKC and prevents maximal activation of the enzyme.* The proposed text, while more specific than the original OEHHA text, does not appear to conflict with it.



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SUBJECT: Comments on Proposed Child-Specific Reference Concentration for Lead

FROM: Susan Griffin, PhD, DABT
Toxicologist
USEPA, Region 8

TO: Jim Carlisle, D.V.M.
Chief, Applied Risk Assessment Section
California EPA

Thank you for the opportunity to review the 2005 draft document entitled *Proposed Child-Specific Reference Concentration (chRC) for School Site Risk Assessment (Lead)*. I agree with the conclusions of the General Toxicology section which state that adverse effects from lead exposure appear to occur at levels below the current 10 ug/dl regulatory level of concern. However, as with any non-threshold contaminant, it is a risk management or policy decision to determine at what point risk becomes unacceptable and regulatory action is required. Therefore, I will limit my comments to the toxicological aspects of this document. My specific comments are as follows:

1. Definition of Reference Concentration

Given the title of this document I was expecting the development of an acceptable level of lead in air, either directly or via a selected blood lead level of concern. It isn't until the end of the document that we find that this is not the case. Instead, we see the development of an incremental blood lead above background to be used as the basis for assessing risk or conducting remedial efforts. It would have been helpful to see this clarified in the very beginning of the document. The authors might even consider using another term, other than reference concentration, to prevent confusion.

Response: This has been corrected; a new term " ΔPb_B " has replaced "chRC".

2. General Toxicology

Page 10, Emory et al. (2003). The blood levels found in this study are unusually low. It would be helpful to add text explaining the analytical methods used to obtain such low detection levels.

Response: A sentence "The latter was measured using a modified atomic absorption method (described in the reference), and ranged from 0.05 to 3.3 $\mu\text{g}/\text{dl}$." has been added to the text to summarize the methodology description in the Emory et al. (2003) paper, which takes up more than a page.

- Page 11, Lanphear et al (2005). If the study included 1,333 participants total, then it would appear that the number of subjects in the individual categories in Table 3 is incorrect.

Response: I re-checked the numbers and believe they are correct. They are not additive.

- For standard intelligence tests for which there is a nationwide database, it would be useful to see how these control and tests subjects compared to the national norms.

Response: National norms should be close to the targeted mean (100 points) and standard deviation (15 points). I believe they are corrected for drift every few years.

I. Calculation of the Reference Concentration (pages 14-15)

- It is not clear to me where the 97.5% upper confidence limit on the slope was used. It appears that the 95% UCL was used in the equation on page 15 to estimate the reference concentration. Also, please define "RSC".

Response: The upper end of a 95% confidence interval (i.e. a 97.5% UCL) was used in all cases. Text has been added to clarify this. "RSC" stands for relative source contribution but has now been omitted

II. Using the Reference Concentration (pages 17-18)

This is the section which was most confusing to me. It is not clear at all how this Reference Concentration value is to be used. The text states that the 0.6 ug/dl value is to be used as a de minimus increment in blood lead above background. But what is background? Is it defined on a state-wide basis or school by school? How is it defined and what pathways are included in background?

Response: "Background Pb_B" means whatever blood lead level the child already has absent any school exposure. It is not meant to be a defined quantity. Reference to "background" has been deleted to avoid this confusion.

How firm is this 0.6 ug/dl increase? I'm sure you have noticed that it doesn't take much of an increase in soil or dust lead levels to go over this 0.6 ug/dl value. If this is implemented, California will be cleaning up lead in soil and dust at levels 10-30X lower than EPA. The regulatory implications of this document are immense and should be carefully considered by risk management.

The ΔPb_B has been changed from 0.6 to 1.1 (rounded to 1).

REVIEW OF OEHHA ASSESSMENT FOR LEAD

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August 31, 2006

Overview: This is in general a thoughtful, dependable and clear regulatory statement. There are some gaps in the scholarship. These are readily correctable, and will be cited below.

Response to specific questions:

1. Have important references been omitted? Has an appropriate report been chosen as the basis for developing a ΔPb_B ?
The pooled analysis directed by Bruce Lanphear is the most authoritative and convincing report on low level lead exposure. Because I designed the Boston study that was included in the pooled analysis, I was present at the meetings at which the data and analyses were presented. The methodology was sound; the statistical analysis was careful and exhaustive. This paper is a solid contribution that will stand for a long time.
No response
2. Does the re-analysis of the data in the Lanphear (2005) report provide a reasonable estimate of the slope relating changes in Pb_B to changes in full-scale IQ? Yes
No response
3. Is the incremental change in IQ chosen as the basis for the benchmark ΔPb_B defensible? I think that IQ is neither the most sensitive or important expression of lead toxicity, but it provides a convenient metric to use in finding a benchmark. Attention and social adjustment will, I believe, be recognized as the principal target, but are not as widely used, or as precisely scaled. For the purpose of defining a benchmark, IQ is satisfactory.
Additional discussion of behavioral problems has been added.
4. Have we explained what we did in a transparent manner? In particular, we endeavor to make all science policy choices explicit. Have we succeeded?
I believe you have.
No response
5. Is there any aspect that you feel that we have omitted or covered superficially?
I think that, as I have stated, social adjustment deserves fuller treatment. I think the treatment of negative studies needs revision, and will deal with it in greater depth below. Additional discussion of behavioral problems has been added. The discussion of negative studies has been revised

6. Anything else you would like to comment on.
I supply them in the line by line critique. .
No response

Detailed review of the draft

P2. The reference Needleman 1982 is out of date. Replace with:
Needleman HL (2004) Lead poisoning. Ann Rev Med 55: 209-22.
[The suggested reference has been added.](#)

P4. The Lidsky and Schneider paper is the strongest evidence for lead toxicity at extremely small doses. It should be elaborated as evidence that sensitive analytic methods discover toxic evidence at levels previously considered innocuous.
[The discussion of this reference has been expanded.](#)

P5. In general the draft has over reliance on $P < 0.05$ as a criterion for evidence. This is an antiquated and unreliable convention. RA Fisher, who established this standard in the 1920's, said "It is *convenient* to take this point [$p = .05$] as a limit in judging whether a deviation is to be considered significant or not." See: *Needleman HL, Bellinger DC (1989) Type II fallacies in the study of childhood exposure to lead at low dose: a critical and quantitative review. In: Lead Exposure and Child Development: An International Assessment. MA Smith, LD Grant, AI Sors, Eds. Boston, Kluwer Academic Publishers. 1989.* Effect size of the association is a more informative measure.

[We agree that effect size is a more informative measure than significance level. However, in some cases, we have little choice but to report the significance level of a finding as reported by the author \(along with the effect size\). Likewise, reporting a confidence interval around a slope or other statistic is not only standard practice, but necessary if the uncertainty contained within that confidence interval is to be incorporated into the final health guidance value, as we have done.](#)

P6. P2 "MDIA scores were opposite to their rankings..." Replace with "Inversely related"
[This change has been made](#)

P7 Schneider 2001 is not in bibliography. [Schneider 2001 has been added to the bibliography.](#)

P7. The behavioral effects of lead deserve more space. The studies of Dietrich et al support our findings, (*Dietrich KN, Ris MD, Succop PA, Berger O, Bornschein RL. (2001) Early exposure to lead and juvenile delinquency. Neurotox Teratol.23: 511-518.*)

[We agree and have added this reference and expanded the discussion of behavioral effects.](#)

Other useful papers showing an association between lead and crime:

Denno, DW (1990) Biology and Violence: From Birth to Adulthood. Cambridge University Press: New York/Cambridge.

Nevin R. How lead exposure relates to temporal changes in IQ, violent crime, and unwed pregnancy. Environ Res 2000;83:1-22

With regard to Nevin's paper, we agree with Julie Wakefield who, in the October 2002 issue of Environmental Health Perspectives, opines "...although Nevin's work is interesting and invites further study, it isn't nearly as solid scientifically as the case-control studies of Dietrich, Needleman, and others."

P12. I recommend the graph from Steve Rothenberg's paper (*Rothenberg SJ, Rothenberg JC. (2005) Testing the dose-response specification in epidemiology and public health and policy consequences for lead. Environ Health Perspect.;13:1190-5*) as the best visualization of the lead dose-response relationship.

We agree, and have added a reference to that paper.

P14. The discussion of causality should be tightened. First, causality is not subject to empirical proof. This was demonstrated by David Hume in the 18th century. The classic paper by Sir Austin Bradford Hill is still the best source for approaching this untidy subject. (*AB Hill The environment and disease: Association or causation? Proc royal Soc Med 58: 295-300, 1965.*) The discussion of confounding could be clearer.

We have attempted to clarify this discussion.

Preceding the 1999 study by Factor Litvak et al, we showed that control of social factors increased the effect size in our subjects. (*Bellinger D, Leviton A, Waternaux C, Needleman H, Rabinowitz M. Longitudinal analyses of prenatal and postnatal lead exposure and early cognitive development. NEJM 1987;316: 1037-1043.*)

We have added the reference and attempted to clarify the discussion of confounding.

P16, Identify the source of the data for Table 6.

The reference for the data in Table 6 has been moved from the title to the footnote.

P17. The section on animal studies is scanty and misses the important studies of Rice et al, and Cory Slechta et al. (*Rice DC (1993) Lead-induced changes in learning: Evidence for behavioral mechanisms from experimental animal studies. Neurotoxicol 14: 167-178.*) (*Cory-Slechta DA, Weiss B, Cox c. (1985) Performance and exposure indices of rats exposed to low concentrations of lead. Toxicol Appl Pharmacol 78: 291-299.*)

A definitive review of effects in non-human species is beyond the scope of this document. The purpose of including a small number of studies in species other than humans was to support the assertion that the association between lead exposure and various adverse effects in humans is a causal association, not an artifact caused by some unrecognized source of confounding.

P17 Morgan is cited but is not in references.

This has been corrected.

P18. The paper of Soong et al examined such a small sample that it does not deserve citation. 28 subjects is inadequate to provide a dependable judgment.

The paper was included because it is a longitudinal study showing a rather remarkable change in blood lead levels in a relatively short time following removal of the principal

source of exposure. The gain in IQ associated with this drop in blood lead (effect size) was sufficient to attain statistical significance despite the relatively small numbers.

P19, The mechanisms section is selective, and does not attend to such important aspects as genotoxicity, e.g., (*Brown RS, Hingerty BE, Dewan JC, Klug A. Pb(II)-catalysed cleavage of the sugar-phosphate backbone of yeast tRNAPhe--implications for lead toxicity and self-splicing RNA. Nature. 303:543-6.*), This paper by a Nobel Laureate, is strong evidence against any threshold for lead toxicity. Other important targets are the heme pathway and synaptogenesis. (Averill, D; Needleman, HL (1980) Neonatal Lead Exposure Retards Cortical Synaptogenesis in the Rat. In: HL Needleman (Ed.) Low Level Lead Exposure: The clinical implications of current research. (pp 201-210) New York: Raven Press.)

The mechanisms section is intended as a brief overview of some of the principal mechanisms of lead toxicity. It is not intended to definitively cover all of the mechanisms of lead toxicity, but rather focuses on neurological endpoint since neurological effects are the basis for developing a health guidance value is.

We have extensively revised this section, adding several references but abbreviating the discussion of each to provide greater breadth and less depth.

P20 The section on two reports that do not corroborate the effects of lead is scanty and flawed. I have only the abstract of the Minder paper, and am not impressed. If you send me a full copy, I will critique it. The Ernhart paper does not qualify as legitimate evidence for no effect. Half of the mothers in her study were alcohol abusers, and the statistical power, according to the graph in her paper was 0.4. Ernhart was one of the earliest to report an effect of lead on children's IQ. (Perino J and Ernhart CE (1974) The relation of subclinical lead level to cognitive and sensorimotor impairment in black preschoolers. *J Learning Disabilities* 7:26-30.) She later stated that any effect of lead, if it existed, was minimal. She became a paid consultant to the International Lead Zinc Research Organization, and testified on their behalf against the reduction of lead in gasoline, considered by many to be the most important public health action of the late 20th century. In the Lanphear pooled study, her data was included, and showed a lead effect. After participating in the discussions, and after the manuscript was completed and submitted, she asked that her name be withdrawn as a coauthor. I think it is fair to say that she is not taken seriously by informed scientists in the lead field.

We agree and have removed reference to the Minder paper, and extensively revised the discussion of negative arguments.