

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

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

Final Report
April 2007



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

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Executive Summary

This document establishes a new child-specific health guidance value (HGV) for lead, for use in health risk assessment at school sites pursuant to Health and Safety Code Section 901(g). This HGV is a benchmark incremental change in blood lead concentration (ΔPb_B) of 1 microgram lead per deciliter ($\mu\text{g}/\text{dl}$) of blood. More specifically, this HGV identifies lead exposures from a specific location that cause a rise in a child's blood lead level by more than 1 $\mu\text{g}/\text{dl}$ as significant for purposes of risk assessment. A change in blood lead of 1 $\mu\text{g}/\text{dl}$ does not represent an absolutely safe exposure level, since no safe level has been definitively established. One $\mu\text{g}/\text{dl}$ is the estimated incremental increase in children's Pb_B that would reduce IQ by up to 1 point.

Since 1991, the U.S. Centers for Disease Control has recommended that primary prevention activities in children should begin when blood lead levels exceed 10 $\mu\text{g}/\text{dl}$. At that time, it was not clear whether the effects trend extended to blood Pb levels below 10 $\mu\text{g}/\text{dl}$. Numerous epidemiology studies and meta-analyses over the past three decades have firmly established that there is an inverse relationship between blood lead concentrations in infants and children and several health and developmental indicators. As a consequence of declining blood lead concentrations in children in several countries, the more recent of these studies have included significant numbers of children with Pb_B levels less than 10 $\mu\text{g}/\text{dl}$. It is becoming increasingly clear that the inverse relationship between blood lead concentrations and these health and developmental effects extends well below 10 $\mu\text{g}/\text{dl}$. Since a clear no-effect concentration has not been established, our assessment used a dose-response slope characterizing the relationship between Pb_B and full-scale IQ scores rather than a more traditional no-effect level with uncertainty factors. As a basis on which to develop such a dose-response slope, we selected a pooled analysis of seven epidemiology studies conducted in four countries. This study 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. U.S. EPA (2006) also selected this study for their pilot risk assessment. We used the upper confidence limit on the slope to estimate an incremental increase in Pb_B that would cause a decrease in IQ of up to one point. 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 .

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.

Various exposure models such as U.S. EPA's IEUBK model or the California Department of Toxic Substances Control's Leadsread model can be used to relate environmental lead levels to blood lead levels in exposed infants and children. These models can be used to estimate acceptable lead levels in soil and other media to be compared with measured concentrations in the environment at existing or proposed school sites. The 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) §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), OEHHA issued a report 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 (OEHHA, 2002). 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.

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.

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 (DHS) 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) (DHS, 1998). 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 agricultural soils in California 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 blood lead levels exceed 10 µg/dl, based on the body of evidence available at that time.

FDA’s tolerable daily dietary lead intake is 6 µg for children under age 6 (FDA, 1996)). 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 accounts for uncertainty regarding the protectiveness of the level of concern. The PHG is currently under review and the review will consider the information in this document. OEHHA (1997b) also established a Proposition 65 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 U.S. Environmental Protection Agency has not developed a reference dose (RfD) or reference concentration (RfC) for lead (U.S.EPA, 2004). The National Ambient Air Quality Standard for Pb is 1.5 µg/m³ (U.S.EPA,1978). A more recent EPA draft review is available (U.S.EPA, 2006)

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 teeth, skeleton, or most frequently, blood (Pb_B), usually reported in micrograms per deciliter (µg/dl). 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 30-50percent of trabecular bone lead (0.9 to 2.7 µg/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-µg/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 $\mu\text{g}/\text{dl}$, 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 $\mu\text{g}/\text{dl}$. A meta-analysis of these data resulted in a composite IQ/ Pb_B slope of -0.26 (± 0.04) IQ points per $\mu\text{g}/\text{dl}$. Schwartz concluded that the association between Pb_B and IQ continues at Pb_B below 5 $\mu\text{g}/\text{dl}$ and that the slope is apparently steeper at lower Pb_B levels.

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).

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

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.

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). 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.

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.

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

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 of age. 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 (Δ IQ) = ln Pb_B x -2.7 (95% CI, -3.74 to -1.66)] fit the data well. This model (depicted in Figure 1) predicted a decline in IQ of 6.9 points (95% CI = 4.2 to 9.4) as Pb_B increased from 2.4 to 30 µg/dl (the 5th and 95th percentiles). The model predicted a steeper decline in IQ of 6.2 points (95% CI = 2.4 to 8.6) as Pb_B increased from <1 to 10 µg/dl, while at higher Pb_B the declines were less: 1.9 (95% CI, 1.2 to 2.6), for 10 to 20 µg/dL; and 1.1 (95% CI, 0.7 to 1.5), for 20 to 30 µg/dL.

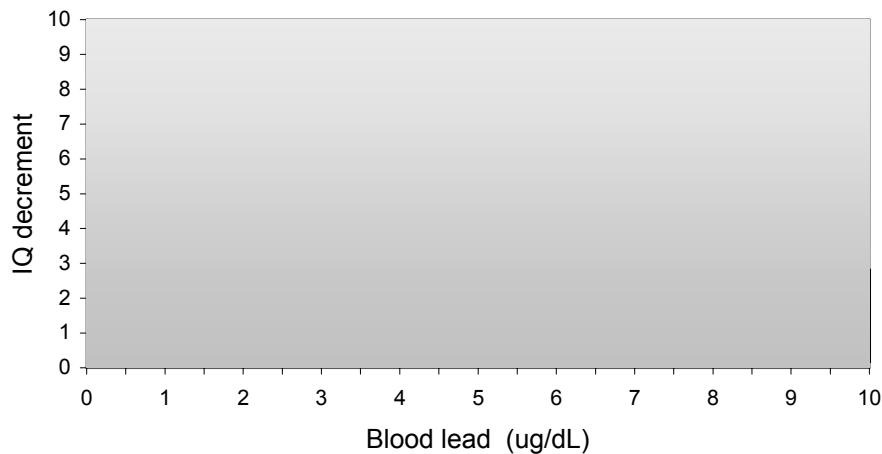
When scores on the verbal and performance Wechsler scales were examined separately, the performance IQ / log Pb_B coefficient was very similar to the full-scale IQ (-2.73 versus -2.70) while the verbal scale showed a slightly lower slope (-2.07), using the same 5 covariates. After adjusting for concurrent 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 the Lanphear et al data, concluding that the log-linear model provided a significantly better fit to the data than a linear-linear model. A linear model fit to the Pb_B and IQ data for 703 children with concurrent Pb_B ≤10 µg/dL using the same co-variables yielded a slope of -0.47 (r² = 0.64) Hornung (2005). The UCL_{97.5} on the slope (-0.9) was similar to the UCL on the average change over the same range predicted by the best-fit log-linear model. Table 4 compares linear and non-linear models that were fit to the data.

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

Figure 1: IQ decrement as a Function of Blood Pb



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 $Pb_B = 4.7 \mu\text{g/dl}$, max = $17.4 \mu\text{g/dl}$. 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. = 25-92percent) 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. = 18-97percent) to have attained menarche. Breast development was not significantly different between the groups (95% C.I. = 51-285percent). 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)
P u b i c h a i r	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 $\mu\text{g}/\text{dl}$, compared with girls with Pb_B in the range of 0.7 to 2.0 $\mu\text{g}/\text{dl}$. 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 ($Pb_B = 2.1\text{-}3.0$ $\mu\text{g}/\text{dl}$) compared to those in the first quartile ($Pb_B = 0.5\text{-}2.0$ $\mu\text{g}/\text{dl}$). 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. U.S. EPA (2006) also selected this study for their pilot risk assessment.

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. 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 [$\Delta\text{IQ} = \ln Pb_B \times -2.7$ (95% CI, -3.74 to -1.66)] fit the data well. 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 the allowable blood lead increment for that child that would correspond to any given incremental decrease in IQ due to lead exposure at school. In order to avoid that unworkable outcome, OEHHA calculated the average IQ/ Pb_B slope over the Pb_B range of <1 to 10 $\mu\text{g}/\text{dl}$ based on the above log-linear function. The average slope over this range was -0.69 (95% CI = -0.42 to -0.96) IQ points per $\mu\text{g}/\text{dl}$. The upper end of the 95% CI on that slope (-0.96 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 to use the average slope over the lower part 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.

Benchmark Response

U.S. EPA (2007) 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:

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

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	1.0		

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 calculated the average change in Pb_B over the lower part of the Pb_B range based on the log-linear function. The upper bound on the slope is about 1.4 times the central estimate, leading to a ΔPb_B that is about 72 percent of that based on the central estimate (see Table 4). Using the average change over the lower end of the range will over-predict the ΔIQ at higher Pb_B , so children with baseline $\text{Pb}_B > 10 \mu\text{g}/\text{dl}$ may experience a smaller ΔIQ than predicted by the model. U.S. EPA (2006) noted that their overall confidence in being able to characterize the shape of the concentration-response functions diminishes significantly below $2.4 \mu\text{g}/\text{dl}$. OEHHA agrees with this view, but believes that the use of the UCL on the average slope is likely to cover any changes in the slope below $2.4 \mu\text{g}/\text{dl}$. Hornung (2005) fit a linear function to the IQ data for 703 children with concurrent $\text{Pb}_B \leq 10 \mu\text{g}/\text{dl}$. The UCL on the slope of that model was about 6 percent less than the slope we chose.

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 the California Air Resources Board (CARB, 1997)

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 18percent 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 (2007) Lead Risk Assessment Spreadsheet to estimate the increase in Pb_B resulting from environmental lead exposures. 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 (2007b) also has a model to estimate the increase in Pb_B resulting from environmental lead exposures.

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 pre-school 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 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

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

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).

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 $\mu\text{g}/\text{dl}$ 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.

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.

Figure 2

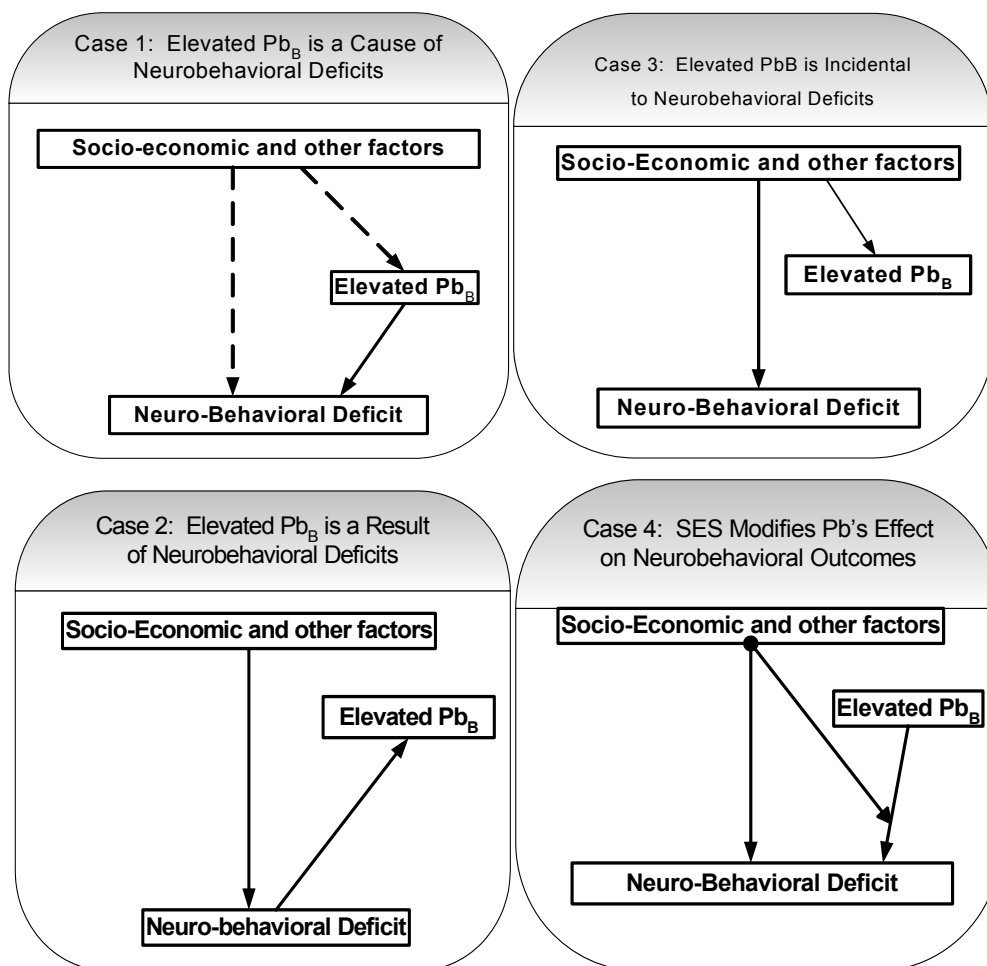


Figure 2: Postulated explanations for the observed correlations between neurobehavioral indicators, Pb_B, and SES and other potential risk factors. **Case 1:** Lead interferes with some aspect(s) of CNS functioning leading to neurobehavioral deficits. As indicated by the dashed arrows, lead may be an 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. Pb_B 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.

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)

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 $\mu\text{g}/\text{dl}$ in infancy, then leveled off to 35 $\mu\text{g}/\text{dl}$ 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 $\mu\text{g}/\text{dl}$ 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 $\mu\text{g}/\text{dl}$. 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).

Table 7 is a brief overview of some cellular, sub-cellular, and biochemical changes associated with lead toxicity. Lidsky and Schneider (2003) reviewed many of these studies.

Conclusion

This document proposes a benchmark incremental change in blood lead of 1 $\mu\text{g}/\text{dl}$ as a new child-specific health guidance value for lead for use in health risk assessment at school sites pursuant to Health and Safety Code § 901(g). The benchmark incremental change in blood lead ΔPb_B for lead is not an absolutely safe exposure level, since no safe level has been definitively established. Rather, it 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. 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 . While the ideal would be no additional exposure to environmental lead, a ΔPb_B of zero would not be useful, since it would require zero exposure, which is not achievable in practical terms.

Table 7: Cellular, Sub-Cellular, and Biochemical Changes Associated with Lead Toxicity

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
Synaptosomal Ca-ATPase is inhibited <i>in vitro</i>	Bettaiya R, et al 1996
Pb disrupts synaptotagin 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

Effect	Reference
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 McGlothan, 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 $\mu\text{g}/\text{dl}$ and <1 to 10 $\mu\text{g}/\text{dl}$. 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 $\mu\text{g}/\text{dl}$ " are incorrect using your algorithm. It appears that you calculated an average slope of 0.62 IQ points per $\mu\text{g}/\text{dl}$ 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 $\mu\text{g}/\text{dl}$. 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 $\mu\text{g}/\text{dl}$ 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.

OEHHA Response: We have corrected the interval width for calculating the average change over the Pb_B range of <1 to 10 $\mu\text{g}/\text{dl}$, changing this ratio from -0.96 to -0.86. We note that the revised linear model based on 703 children with concurrent $Pb_B \leq 10 \mu\text{g}/\text{dl}$ gives a UCL slope of -0.9. To one significant figure this is the same as the corrected slope of -0.86 based on the original log/linear model. Although the comment questions whether a linear approximation in the interval is a good estimate of the linear dose-response over this range, it is in fact only about 6percent different and leads to a delta Pb_B that is the same to one significant figure.

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.

OEHHA 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.

OEHHA Response: We have made this correction

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

OEHHA 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.

OEHHA 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 $\mu\text{g}/\text{dl}$ "at the low end" to 32-60 $\mu\text{g}/\text{dl}$ "at the high end". Does this mean that studies of low-exposed children

ranged from 5-9 µg/dl and studies of high-exposed children ranged from 32-60 µg/dl? Similar statements are found in the next paragraph.

OEHHA 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.

OEHHA Response: We have made this correction

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

OEHHA Response: We have made this correction

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

Response: We believe that to follow this suggestion would change the intended meaning. If the basis for comparison is a likelihood of 1.0, then “48% as likely” would mean 0.48, whereas “48% more likely” would mean 1.48.

Top of page 11, there is no citation for Selevan, et al in the list of references.

OEHHA 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.

OEHHA 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.



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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.*

OEHHA response: Some of the internal and external peer reviewers are experts in statistical analysis and study design. Furthermore, the analysis was published in a refereed journal .

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 10 µg/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.*

OEHHA response: 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 response: 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 calculated the average change in IQ Pb_B over the Pb_B range from <1 to $10 \mu\text{g}/\text{dl}$, based on the log-linear function. 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 $5\text{-}10 \mu\text{g}/\text{dl}$ and $10\text{-}15 \mu\text{g}/\text{dl}$ is greater than the difference in IQ between $0\text{-}5 \mu\text{g}/\text{dl}$ and $5\text{-}10 \mu\text{g}/\text{dl}$.

- 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 $1\text{-}10 \mu\text{g}/\text{dl}$ blood lead concentration range. OEHHA chooses to approximate this curvilinear slope by a linear slope over the $1\text{-}10 \mu\text{g}/\text{dl}$ 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 $0\text{-}10 \mu\text{g}/\text{dl}$ range is necessary for supporting the use of the linear slope.*

OEHHA response: OEHHA chose to focus on the average $\Delta \text{IQ} / \Delta Pb_B$ ratio over 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 ΔIQ for a given ΔPb_B .

Hornung, one of the co-authors of the Lanphear, 2005 report (see comments above) fit a linear model to the data for children with Pb_B up to $10 \mu\text{g}/\text{dl}$ (roughly the lower half of the distribution). The resulting slope (-0.47 (95% CI = -0.04 to -0.90) IQ points per $\mu\text{g}/\text{dl}$, $r^2 = 0.64$,) is similar to the average change in IQ based on the log-linear model. The ΔPb_B resulting from the application of either model would be the same if given to one significant figure.

- c. **DATA QUALITY:** Lanphear et al. (2005) reported a decline of 6.2 ($3.8\text{-}8.6$, 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 $0\text{-}10 \mu\text{g}/\text{dl}$ range. *HERD believes that it is important to include a discussion of this data limitation.*

OEHHA response: 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.*

OEHHA response: 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 µg/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 response: 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. OEHHA's position is that a threshold has not been identified. [See 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*". See also text on page 5: "The minimum Pb_B causing neurobehavioral deficits is not well defined."]

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 response: 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 µg/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).

OEHHA response: 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 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.*
- 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.*

OEHHA response: The relative source contribution has been eliminated but can be added on a program-specific basis.

- 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 $\mu g/dl/1.2 \mu g/dl$, 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.*

OEHHA response: The relative source contribution has been eliminated but can be added on a program-specific basis.

- d. The document recommends using the DTSC Leadsread Spreadsheet model that contains blood lead intake slopes of 0.16 µg/dl per µg/day for children and 0.04 µg/dl per µg/day for adult. However, OEHHA adopts the Centers for Disease Control (CDC) blood lead intake slope of 0.35 µg/dl per µg/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.*

OEHHA response: 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 µg/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.*

OEHHA response: 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.*

OEHHA response: 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 µg/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.*

OEHHA response: The relative source contribution has been eliminated from this calculation.

- 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.*

OEHHA response: 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.*

OEHHA response: The specific example has been deleted from the document. A reference 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.*

OEHHA response: 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 alteration may be dependent on exposure conditions or a secondary effect of lead on signal transduction pathways. *HERD recommends including this information in the discussion.*

OEHHA response: 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.*

OEHHA response: 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 picromolar 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.*

OEHHA response: 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
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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 µg/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.

OEHHA 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.

OEHHA 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 µg/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.

OEHHA response: The numbers in the various categories are not additive. We re-checked the numbers and they are correct.

- 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.

OEHHA response: National norms should be close to the targeted mean (100 points) and standard deviation (15 points). 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”.

OEHHA 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 µg/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?

OEHHA response: 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 µg/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 µg/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.

OEHHA response: The ΔPb_B has been changed from 0.6 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.
OEHHA response: 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.

OEHHA response: 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.

OEHHA response: 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.

OEHHA response: 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 [$p = 0.05$] 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.

OEHHA response: 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"

OEHHA response: This change has been made

P7 Schneider 2001 is not in bibliography.

OEHHA response: 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.*)

OEHHA response: 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

OEHHA response: 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.

OEHHA response: 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.

OEHHA response: 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, Wateraux C, Needleman H, Rabinowitz M. *Longitudinal analyses of prenatal and postnatal lead exposure and early cognitive development*. *NEJM* 1987;316: 1037-1043.)

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

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

OEHHA response: 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.)

OEHHA response: 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.

OEHHA response: 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.

OEHHA response: 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 statistically 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.)

OEHHA response: 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.

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

**Comments on December 2006 Draft Proposed Health Criteria
For Lead in School Site Risk Assessments
Issued by California Environmental Protection Agency**

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OEHHA responses are indicated by red font.

Summary OEHHA response:

The comments are rather general and somewhat philosophical. A general theme is that more and better data would be desirable. We agree, but on the other hand, the database for lead is probably the most complete of any chemical that we currently regulate. Another theme is that the supralinearity of the dose-response curve is unproven. Again, we agree, but nothing in the proposed ΔPb_B depends on an assumption of supralinearity of the dose-response curve. In fact, we have used a linear approximation of the log-linear response curve of Lanphear et al (2005). Most of the comments do not offer specific remedies to the perceived problems with the analysis. However, two specific suggestions are offered:

1. Use the best estimate of the slope of the dose-response relationship, rather than the upper confidence limit on the slope.
OEHHA response: OEHHA followed EPA benchmark dose methodology, which recommends using a lower confidence limit on the benchmark dose. This is equivalent to using an upper confidence limit on the slope.
2. Use the log-linear dose-response relationship published by Lanphear et al (2005), rather than the unpublished linear response by Hornung (2005).
OEHHA response: This suggestion was followed and the document was changed accordingly.

Executive Summary

On behalf of the Association of Battery Recyclers, Gradient Corporation has prepared these comments on the December 2006 draft document *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* (the draft lead health criterion document) issued by the California Environmental Protection Agency's (CalEPA) Office of Environmental Health Hazard Assessment (OEHHA; CalEPA, 2006). In this draft document, OEHHA has identified a health criterion for assessing potential health risks posed by lead exposures at schools, *i.e.*, OEHHA has defined a child-specific benchmark change in blood lead concentration (ΔPb_B) as an increase in blood lead concentrations of 1 $\mu\text{g}/\text{dL}$ and has equated that increase with a 1 point decrement in IQ. OEHHA has specified that this risk level will be assessed on an incremental basis in determining whether a specific school location presents health risks of concern. As a result, it appears that the proposed approach will focus on whether the lead exposures associated with the school result in the specified change in blood lead concentration (*i.e.*, an incremental change from background exposures in the absence of school-related exposures) rather than assessing the absolute blood lead concentration of exposed individuals or populations.

\This review of OEHHA's draft lead health criterion document raises the following specific concerns:

- The proposed lead health criterion (ΔPb_B) is based on a relationship between blood lead concentrations and IQ effects that is derived from a database with significant scientific limitations, *e.g.*, in the number of directly relevant studies that are available and in the interpretation of the available data.
- Concerns exist regarding the application of the available data to quantify the dose-response relationship between low-level lead exposures and adverse neurological effects in young children (including the specific study [Lanphear *et al.*, 2005] and approaches that OEHHA has used to derive the ΔPb_B), the role of mathematical and statistical factors (rather than biologically-based effects) in the observed results, and the potential for errors or mischaracterizations in the use of the data.
- The proposed lead health criterion incorporates a number of highly conservative elements, which result in a criterion value that significantly overstates the health impacts suggested by the best estimates derived from the available data by the study authors.
- These factors combine to raise questions regarding the validity of the proposed approach and its effectiveness in targeting limited public health resources towards meaningful efforts to reduce lead exposures, improve health, and yield observable results.

Because of the significant limitations in the available data, the choice of a specific value to use as the benchmark health criterion is, to a large extent, arbitrary and subject to substantial uncertainty regarding the biological, public health, and practical significance of the proposed value. Moreover, in describing the basis for the proposed health criterion, OEHHA acknowledges that some values for ΔPbB (e.g., zero) "would not be useful" from a "practical standpoint" and that changes in blood lead concentrations that are less than the benchmark value "are expected to cause no measurable adverse effect" although theoretical effects may occur (CalEPA, 2006). In light of the limitations and uncertainties that exist in the available data regarding health effects of low-level lead exposures, it is not clear that the selected value will, in fact, be any more useful than a value of zero for guiding risk management decisions, or that changes in blood lead concentrations that are at or somewhat greater than the benchmark level would yield measurable adverse effects.

OEHHA response: *We believe that the selected value will, in fact, be more useful than a value of zero for guiding risk management decisions. The proposed benchmark would lead to a finite clean-up or screening level that is greater than naturally occurring background under any reasonable scenario. On the other hand, a value of zero would lead to a clean-up or screening level of zero (which for practical purposes means the detection limit), obviously less than naturally occurring background. The adopted approach is protective of public health and can guide others to reduce exposures to lead.*

As a result of these concerns, questions exist regarding the utility of the proposed approach in effectively prioritizing and managing lead-related health risks and improving public health overall. In particular, it appears that the proposed approach would associate "elevated" risk levels with quite small (and potentially unmeasurable) changes in. For example, using the ΔPbB and OEHHA's LeadSpread model, it appears that a school yard could be targeted for remediation based on a concentration of lead in soil that is only 27 mg/kg greater than the soil concentration in the surrounding area.

OEHHA response: *Environmental concentrations that may be associated with the ΔPbB are easily measurable. Using typical school parameters, 182 mg/kg soil lead would increase the PbB in a 95th percentile child by 1 $\mu\text{g}/\text{dl}$. And 131 mg/kg soil lead would increase the PbB in a 99th percentile child by 1 $\mu\text{g}/\text{dl}$.*

Given the typical degree of heterogeneity in lead concentrations in soil, it is doubtful that a 27 mg/kg difference in average lead concentrations in soil from two locations could even be identified. Thus, it is unclear whether the proposed approach will be useful in helping to identify important contributors to current lead exposures or meaningful actions that can be undertaken to improve public health. The incremental approach proposed by OEHHA also raises concerns regarding the effectiveness of the proposed methodology for targeting important priorities and/or useful measures for improving public health. While it is recognized that the approach is designed to specifically look at exposures associated with schools, it is unclear how the use of an incremental approach to assess potential lead exposures will effectively address potential differences in exposure and risk for individual children (i.e., children with different baseline lead exposure levels).

OEHHA response: *(The proposed benchmark does not differentiate between children with high background exposure and those with low background exposure).*

In addition, as noted by one US EPA reviewer of an earlier draft of the proposed approach (CalEPA, 2006, p. 44), it appears that the proposed approach will lead California to impose substantially more stringent cleanup requirements than will be required by regulatory agencies in other states. Such an approach has the potential to arbitrarily discriminate against businesses in California while providing negligible, if any, additional benefit to public health.

OEHHA response: *The comments do not show how the proposed standard will discriminate against businesses in California, and provide no evidence to show that the benefits thereof are “negligible, if any”.*

Although OEHHA's analyses are designed to present a risk assessment basis for identifying a health criterion to be used in assessing potential health risks posed by schools, the significant limitations in the available scientific data have necessitated the incorporation of a number of "risk management" decisions within the proposed approach. As a result, OEHHA should carefully assess the implications of the proposed approach for its overall effectiveness in improving public health and the likelihood that it will yield any meaningful or measurable changes in lead exposures and effects. In particular, OEHHA should evaluate whether implementation of the proposed approach at California's schools will most effectively identify actions that will result in overall improvements in public health or whether the proposed approach will instead divert health improvement efforts and resources from more significant problems.

OEHHA response: *The comments do not identify a more cost-effective alternative for improvement of public health. Furthermore, the legislation is quite specific in who and what it targets.*

1 Overview

On behalf of the Association of Battery Recyclers, Gradient Corporation has prepared these comments on the December 2006 draft document *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* (the draft lead health criterion document) issued by the California Environmental Protection Agency's (CalEPA) Office of Environmental Health Hazard Assessment (OEHHA; CalEPA, 2006). In this draft document, OEHHA has identified a health criterion for assessing potential health risks posed by lead exposures at schools. The proposed approach for assessing lead health risks includes two key components. First, OEHHA has identified a minimal risk level (or "minimally significant change") that will serve as the benchmark for assessing whether a specific school location presents health risks of concern. OEHHA defines this risk level as an increase in blood lead concentrations of 1 µg/dL and has equated that increase with a 1 point decrement in IQ. OEHHA abbreviates this child-specific benchmark change in blood lead concentration as ΔPb_B. Second, OEHHA has specified that this risk level will be assessed on an incremental basis in determining whether a specific school location presents health risks of concern. As a result, it appears that the proposed approach will focus on whether the lead exposures associated with the school result in the specified change in blood lead concentration (*i.e.*, an incremental change from background exposures in the absence of school-related exposures) rather than assessing the absolute blood lead concentration of exposed individuals or populations.

OEHHA response: *The assumption is correct, although CDC's 10 µg/dL level of concern remains in place as a benchmark for absolute blood lead concentrations. There is a very good reason for this approach. While the exact numerical relationship and whether that relationship is the same or different at different exposure levels is arguable, there is substantial evidence that, within the relevant range of exposures, an increase in environmental lead is associated with an increase in blood lead, which is, in turn associated with cognitive and other impairments. There is no known threshold below which this relationship does not exist.*

These comments address selected issues raised in the draft lead health criterion document regarding the health effects of lead exposures. Because OEHHA has emphasized issues associated with the potential neurotoxic effects of low-level lead exposures on fetuses and young children when developing the draft health criterion, these comments also focus on these issues. In particular, these comments address both statistical and biological issues associated with dose-response relationships for low-level lead exposures (as reflected in blood lead concentrations that are less than 10 µg/dL), the degree to which the draft lead health criterion document has adequately characterized and interpreted the available data, and factors influencing the application and health policy implications of the proposed approach. The proposed approach developed by OEHHA relies heavily on a study conducted by Lanphear *et al.* (2005), so these comments also specifically address issues associated with this paper and similar studies.

OEHHA response: *The proposed approach developed by OEHHA does indeed rely heavily on the study conducted by Lanphear et al. (2005); however, a number of published studies could have been used without major changes in the resulting benchmark.*

Because the proposed approach emphasizes potential health effects that may be associated with extremely low-level lead exposures (*i.e.*, including exposure levels that may approach 0 µg/dL), in applying such an approach it is especially important to consider the health significance of potential effects associated with low-level exposures as well as the degree to which such effects are likely to reflect actual health effects caused by lead exposures rather than apparent effects reflecting methodological or analytical factors. In conducting such evaluations, it is important to

take into account the full suite of available information. For example, the results of epidemiological studies should be assessed within the contexts of statistical uncertainties and the biological plausibility of the observed epidemiological results. Moreover, it should be recognized that researchers have only recently turned their attention to specifically examining potential health effects associated with low-level lead exposures (*i.e.*, exposures that result in blood lead concentrations that are less than 10 µg/dL) and that only a modest number of studies are available that have focused on this exposure range or provided any level of detail regarding potential impacts of exposures in this range.

OEHHA response: *Adverse effects at Pb_B less than 10 ug/dl have been known or suspected for two decades. While more data is always desirable to have, the number of available studies to evaluate the developmental neurotoxicity of lead at relevant exposure levels is substantially greater than for most, if not all chemicals for which health criteria have been developed. Absolute certainty has never been a prerequisite for establishing a standard.*

Therefore, substantial additional work is necessary to obtain a sound understanding of the nature of the effects that may be associated with lead exposures in this range, the quantitative dose-response relationships and biological mechanisms of action that underlie any such effects, and the clinical significance and potential persistence of any observed effects. In addition, OEHHA should ensure that the data that are presented to support or suggest potential health effects associated with low-level lead exposures actually reflect populations that have experienced consistently low-level exposures.

OEHHA response: *Blood lead data were available for the test subjects from a young age (in some cases even at birth). After examining multiple exposure indices, Lanphear et al. (2005) found that concurrent Pb_B was the best predictor of IQ. This would not be the case if the observed effects were the result of earlier higher exposures.*

Any regulatory or policy decisions that are based on the available data must reflect the limitations in the information that is currently available regarding the potential impacts associated with low-level lead exposures. Regulatory decision-makers must also evaluate the degree to which the available data indicate that proposed approaches for addressing low-level lead exposures would result in measurable changes in lead exposures and effects.

OEHHA response: *We believe we have made a strong case that changes in Pb_B exceeding the proposed ΔPb_B would result in measurable lead-induced effects. The idea of this environmental regulatory action is to prevent measurable lead-induced effects. This is consistent with most regulatory standards.*

In addition, decision-makers should assess whether proposed approaches would affect exposure sources that contribute significantly to current lead exposures and would effectively target available public health resources on important contributors to health risk.

OEHHA response: *The legislature did not instruct us to focus our efforts on whatever source(s) of lead exposure might be the greatest contributors to impaired neurodevelopment in children.*

This review of OEHHA's draft lead health criterion document raises the following specific concerns:

- The proposed lead health criterion (ΔPb_B) is based on a relationship between blood lead concentrations and IQ effects that is derived from a database with significant scientific limitations, *e.g.*, in the number of directly relevant studies that are available and in the interpretation of the available data.
- Concerns exist regarding the application of the available data to quantify the dose-response relationship between low-level lead exposures and adverse neurological effects in young children (including the specific study [Lanphear *et*

al., 2005] and approaches that OEHHA has used to derive the ΔPb_B), the role of mathematical and statistical factors (rather than biologically-based effects) in the observed results, and the potential for errors or mischaracterizations in the use of the data.

- The proposed lead health criterion incorporates a number of highly conservative elements, which result in a criterion value that significantly overstates the health impacts suggested by the best estimates derived from the available data by the study authors.
- These factors combine to raise questions regarding the validity of the proposed approach and its effectiveness in targeting public health resources towards meaningful efforts to reduce lead exposures, improve health, and yield observable results.

The remaining sections of this document present a more detailed discussion of these comments. Section 2 addresses scientific issues associated with potential neurological effects of low-level lead exposures (including statistical and biological issues associated with dose-response relationships), while Section 3 discusses various factors influencing application and interpretation of the proposed approach. Conclusions regarding the public health implications of the proposed approach are provided in Section 4. Additional detail regarding the issues addressed in Section 2 is provided in the Attachment to these comments.

2 Limitations in the Scientific Database for Potential Health Effects Associated with Low-Level Lead Exposures

Several features of typical methods for characterizing lead exposures and health risks influence scientific evaluations of lead health effects as well as regulatory and policy approaches for managing lead exposures. In contrast with toxicological evaluations of many other chemicals, health effects studies of lead have typically focused on biomonitoring data rather than intake (*e.g.*, from ingestion or inhalation) as the primary means of characterizing lead exposure. Blood lead concentrations are the type of biomarker most commonly used to quantify lead exposures in scientific studies, and are frequently used as benchmarks for assessing regulatory exposure levels of concern, as reflected in the health criterion approach proposed by OEHHA.

The nature of typical lead health effects studies also yields the potential for a number of factors to be present that can influence interpretation or add uncertainty to the study results. For example, the types of health effects commonly under study for lead exposures are frequently associated with a number of other potentially causative or contributing factors, some of which may be more important contributors to the health effect of interest than lead exposures. As a result, ensuring that confounding factors have been adequately accounted for plays a critical role in evaluating the results for lead health effects studies.

OEHHA response: *We agree that confounding factors should be controlled for. This is discussed extensively in the document.*

Standard epidemiological issues such as study size, appropriateness of control populations, and adequacy of the characterization of exposure levels also play important roles in evaluating the results of lead health effects studies.

OEHHA response: *We agree.*

In 1991, the Centers for Disease Control selected 10 $\mu\text{g}/\text{dL}$ as a benchmark blood lead concentration for use in blood lead screening programs (CDC, 1991). This value was the lowest of a range of benchmark values that were established for varying levels of intervention to address lead exposures. The benchmark values were set based on the scientific information available at

the time, as well as practical considerations when applying benchmark levels in settings such as blood lead screening programs. Subsequent research and evaluations of available data have examined whether blood lead concentrations that are less than the 10 µg/dL benchmark are associated with adverse effects. In addition, such analyses have explored the magnitude of potential impacts occurring at low-level lead exposures.

OEHHA response: *We agree.*

One issue that has generated a great deal of interest is the suggestion in several recent studies that, at low-level lead exposures, the lead dose-response relationship for neurobehavioral impacts in young children is supralinear (*e.g.*, Canfield *et al.*, 2003; Lanphear *et al.*, 2005). As noted above, such studies (especially the Lanphear study) played a pivotal role in OEHHA's development of the lead health criterion (*i.e.*, the ΔPb_B). The supralinearity theory suggests that, at low dose levels, the slope of the negative relationship between lead exposures and neurobehavioral impacts is steeper than that observed at higher doses, *i.e.*, that the neurological decrements are greater for a given increase in blood lead concentration. As recognized in the draft lead health criterion document, however, "The existence and the significance of an adverse effect of lead at blood concentrations below 10 µg/dl are not without controversy" (CalEPA, 2006, p. 20). Moreover, in the recently issued Air Quality Criteria Document for lead (US EPA, 2006a), the U.S. Environmental Protection Agency (US EPA) concluded that "A biological mechanism for a steeper slope at lower than at higher blood levels has not been identified" (p. 8-66) and that the steepness of the dose-response curves "at the lower blood Pb levels...may be an artifact of the model chosen" (p. 8-78). A similar conclusion was reached by a Work Group of the Centers for Disease Control in a recent review of available data regarding potential health effects associated with low-level exposures to lead (ACCLPP, 2004).

OEHHA response: *OEHHA does not assume that the dose-response curve is supralinear. The proposed criterion relies on the average loss of IQ between the two ends of a range that we consider to be a relevant range for school children.*

The following subsections of these comments present critical information that must be addressed when evaluating the quantitative dose-response relationship for low-level lead exposures and assessing potential health effects associated with low-level lead exposures. Specifically, Section 2.1 reviews issues associated with interpretation of the dose-response relationship for lead exposures and neurobehavioral effects in young children and fetuses. This section includes information regarding the likely role of statistical and mathematical considerations in generating the supralinear dose-response curves observed in some epidemiological studies (Section 2.1.1), a critique of OEHHA's use of Lanphear *et al.* (2005) as the basis for the proposed lead health criterion (Section 2.1.2), and the lack of a biological basis to support the supralinearity theory (Section 2.1.3). Section 2.2 discusses additional factors influencing evaluation of effects associated with low-level lead exposures, including limitations in the availability and interpretation of low-level lead exposure data (Section 2.2.1), issues associated with the use of large public health databases to address etiology (Section 2.2.2), and the adequacy of efforts to address residual confounding when interpreting study results (Section 2.2.3).

2.1 Issues Associated with Interpretation of the Dose-Response Relationship for Lead Exposures and Neurobehavioral Effects in Young Children and Fetuses

Both technical and regulatory evaluations of the potential health effects associated with lead exposures (including the evaluations presented in the draft lead health criterion document) have focused extensively on potential neurobehavioral effects in young children and fetuses, particularly the dose-response relationship for low-level lead exposures. This section addresses critical factors that must be incorporated into evaluations of the potential neurobehavioral health effects associated with low-level lead exposures including statistical and mathematical factors

and the availability of supporting biological data. This section also discusses specific concerns with the Lanphear *et al.* (2005) study, which forms the primary basis for OEHHA's proposed lead health criterion.

2.1.1 Statistical Issues Influencing the Dose-Response Relationship for Lead

As noted above, several recent studies have suggested that a supralinear dose-response relationship exists between blood lead concentrations and neurobehavioral or cognitive effects (*e.g.*, as measured by IQ or equivalent test scores). Some of these studies were reviewed in the draft lead health criterion document; however, the draft document does not include a recent evaluation of these studies that explored the impacts of mathematical requirements on the dose-response relationships between typical measures of lead exposures and measures of neurobehavioral effects (Bowers and Beck, 2006). The Bowers and Beck analysis examined the nature of the mathematical relationship between a lognormally distributed independent variable (*e.g.*, a measure of environmental lead exposure such as blood lead concentrations) and a normally distributed dependent variable (*e.g.*, a measure of lead health effect such as IQ score). In this analysis, Bowers and Beck concluded that the supralinear dose-response curves that have been reported in recent epidemiological studies may, in fact, reflect a statistically-required consequence of comparing such distributions. As illustrated in Bowers and Beck (2006), when assuming an inverse relationship between a lognormally distributed independent variable (*e.g.*, blood lead concentrations) and a normally distributed dependent variable (*e.g.*, IQ), a graph showing the relationship between the two variables will naturally possess a supralinear shape. This analysis also indicates that the observed supralinear shape of the dose-response curve would not necessarily change when addressing potential confounding factors that might influence the relationship between lead exposures and adverse health effects, if the confounders are also normally distributed (*e.g.*, mother's IQ). Thus, these researchers observe that the finding of a supralinear dose-response curve for low-level lead exposures and effects measures such as IQ is not unexpected in light of statistical considerations and may arise primarily or solely due to statistical effects rather than actual biological effects associated with lead exposure. Bowers and Beck describe three of the recent studies that discuss observations of a supralinear or nonlinear dose-response relationship between blood lead concentrations and IQ or other cognitive test scores, *i.e.*, Schwartz (1994), Canfield *et al.* (2003), and Lanphear *et al.* (2005). Based on a review of these studies as discussed in the draft lead health criterion document, OEHHA chose the Lanphear *et al.* (2005) pooled analysis as the basis for the proposed lead health criterion (ΔPbB) stating that "these data [from the Lanphear study] suggest that children at the lower end of the exposure spectrum may exhibit a greater change in IQ for a given change in PbB " (CalEPA, 2006, p. 12).

Since the Bowers and Beck analysis was prepared, several additional publications have been identified that either suggest that the presented data support a supralinear dose-response curve for low-level lead effects on cognitive function or have been interpreted by others as illustrating such an effect. These publications include Dudek and Merez (1997); Nevin (2000); Bellinger and Needleman (2003), who update the analysis presented in Bellinger *et al.* (1992); Wasserman *et al.* (2003); Chiodo *et al.* (2004); Jusko *et al.* (2005), who respond to comments and confirm the conclusions of Canfield *et al.* (2003); Kordas *et al.* (2005); and Schnaas *et al.* (2005). The evidence presented in these publications suggesting supralinearity in the dose-response relationship between low-level blood lead concentrations and cognitive function is briefly discussed in the Attachment to these comments. In general, the observations described in these publications are consistent with the analysis presented by Bowers and Beck (2006), thus providing no evidence for a biological basis for the supralinearity in the dose-response slopes and reinforcing the need for further evaluation of the epidemiology studies and the plausibility of the underlying biological mechanisms that could give rise to such observations.

Several concerns have been raised regarding the Bowers and Beck (2006) analysis since its publication (Bergdahl, 2006; 2007; Hornung *et al.*, 2006; Jusko *et al.*, 2006; Svendsgaard *et al.*, 2007). Specific issues raised by these commenters include questions regarding certain assumptions and procedures used in the Bowers and Beck analysis (*e.g.*, how the theoretical distributions of lead exposure and effects were compared with each other and appropriate distribution assumptions for IQ data) and questions regarding interpretation of the conclusions based on the analysis. Bowers and Beck have addressed these concerns in detail and concluded that none of the questions raised modifies the main point of their analysis, *i.e.*, "...that there are instances where the statistical constraints imposed by the distributional properties of blood lead concentration data and IQ data do form the basis of the shape of the dose-response relationship, and one should not automatically eliminate this possibility in the interpretation of non-linear dose-response relationships that are found" (Bowers and Beck, 2007).

The statistical analysis presented by Bowers and Beck demonstrates that the reported findings of supralinear dose-response curves for low-level lead exposures should be interpreted cautiously, especially with respect to their significance regarding health effects. As recommended in Bowers and Beck (2006), the datasets from the underlying epidemiological studies should be carefully evaluated to determine the role of mathematical requirements in the observed dose-response relationships. In particular, the findings of studies reporting supralinear dose-response curves for the effects of low-level lead exposures should be examined to determine whether the magnitude of the observed slope in these studies is more or less than would be expected based on the distributions of the dose and response data. Moreover, such findings should be carefully reviewed in light of available biological data (*e.g.*, from *in vitro* and animal studies) to evaluate the potential biological basis for any observed relationship and its biological plausibility. Such an evaluation was recently undertaken by a work group of the Centers for Disease Control (ACCLPP, 2004). The results of their evaluation, as well as other information regarding the biological plausibility of a supralinear dose-response curve for low-level lead exposures, are presented in Section 2.1.2 of these comments. These types of evaluations should be reflected in the draft lead health criterion document as well as in evaluations of the implications of the epidemiological studies for establishing regulatory and policy goals.

The analysis presented by Bowers and Beck notes that similar findings are expected and observed in other data sets for environmental contaminants that are associated with adverse neurological effects. For example, as illustrated by Bowers and Beck, review of data regarding lognormally distributed cord blood mercury concentrations and normally distributed cognitive test scores yielded a similar dose-response slope for low-level mercury exposures that was consistent with statistical predictions (NRC, 2000). Again, these data merit additional analysis to evaluate the relative roles of statistical requirements and biological factors in determining the observed dose-response relationship.

OEHHA response: *OEHHA believes that while the existence of a relationship between internal dose and response in the low-dose region is well established, the precise shape of the dose-response curve in the low-dose region is uncertain (hence the use of the UCL on the slope). However, the change in the slope of the concentration-response curve as a function of Pb_B is observable visually as well as by a number of statistical procedures. It is not dependent on the constraints of a particular model.*

2.1.2 Concerns with the Interpretation and Application of the Results from the Lanphear Study

Since the publication of Bowers and Beck (2006), additional concerns regarding the validity of the conclusions presented in the Lanphear *et al.* (2005) study have been raised in the

scientific literature (Ernhart, 2006; Lanphear *et al.*, 2006). Moreover, as discussed below, errors have been identified within the Lanphear publication. Because OEHHA has relied so heavily on this study for the proposed lead health criterion, these errors are of significant concern. As described below, concerns are also raised by OEHHA's interpretation, presentation, and application of the Lanphear data.

For example, Lanphear *et al.* (2005) contains typographical errors in its Table 4, which presents the dose-response slopes and blood lead concentration ranges of the population for which the slopes were derived (i.e., rows were transposed in one column). The US EPA recently posted a corrected version of this table (US EPA, 2006b). The corrected table contains the correct 5th and 95th percentile blood lead levels associated with the four blood lead concentration metrics examined in the study (i.e., early childhood, peak, lifetime average, and concurrent values). However, close examination of the corrected table indicates that errors remain. For example, the column that reports the IQ deficit calculated to occur between the 5th and 95th percentile blood lead concentration levels cannot be reproduced from the blood lead – IQ slopes and the blood lead ranges. OEHHA should ascertain whether any references that it has made to the information contained in this table in Lanphear *et al.* – or any calculations or conclusions that it has based on these data – are correct.

OEHHA response: *We agree that the original Table 4 (Lanphear et al. 2005) contained errors that have been corrected subsequently, and that the revised values in column 4 apparently require corresponding changes in the last column. However, these corrections do not affect the OEHHA analysis, since the preferred model used in that analysis gives the IQ deficits noted in the text (e.g. a 6.2 point decline between 1 µg/dl and 10 µg/dl).*

In developing the proposed lead health criterion, OEHHA has also extended its interpretation of the data beyond the range that can reasonably be supported by available information. For example, in recent analyses presented in the Staff Paper prepared in support of the National Ambient Air Quality Standard (NAAQS) for lead, the US EPA took a measured approach in estimating IQ deficits based on the Lanphear *et al.* analysis (US EPA, 2006b). Although concluding that no threshold blood lead level has been identified below which effects are not found, the US EPA also recognized that the range of blood lead concentrations for populations that have been studied effectively provide a limit, below which effects cannot be quantitatively estimated. As a result, the US EPA chose not to estimate the magnitude of IQ deficits below the 5th percentile of the population analyzed by Lanphear *et al.* For the concurrent blood lead metric, the 5th percentile corresponds to a blood lead concentrations of 2.4 µg/dL. By contrast, OEHHA has estimated IQ deficits for blood lead concentrations that are less than 2.4 µg/dL – ranging from 2.2 IQ points (between blood lead concentrations of 0 and 2.4 µg/dL based on an upper estimate of the dose-response slope in the linear model) to 3.3 IQ points (between blood lead concentrations of 1 and 2.4 µg/dL based on the upper estimate of the slope in the log-linear model; see Figure 1, p. 8; CalEPA, 2006). These estimates have no basis in the Lanphear *et al.* analyses and should not be presented as if they have been derived from that study. Furthermore, the IQ effects of lead have not been studied in any populations with blood lead levels that are less than 2.4 µg/dL.

Another deficiency in OEHHA's quantitative analysis of the Lanphear data is that it chooses to rely on an estimate of the blood lead – IQ dose-response slope that is based on unpublished work by Hornung, reported as a personal communication in 2005. This foundation for OEHHA's analysis is inappropriate as this work is not available for review by the scientific community or the public. Figure 1 shows that the upper estimate of the linear dose-response slope provided by Hornung (0.9) over-estimates the IQ effect compared to either the central estimate or the upper estimate of the log-linear model at blood lead concentrations greater than approximately 4 µg/dL. Specifically, Lanphear *et al.* estimate an IQ deficit of 3.9 IQ points between blood lead

concentrations of 2.4 and 10 $\mu\text{g}/\text{dL}$, with an upper confidence estimate of 5.3 IQ points. By contrast, OEHHA's use of the Hornung linear slope estimate gives an IQ deficit over this blood lead concentration range of 6.8 IQ points, or 28% higher than the upper estimate provided by the authors of the original study. When OEHHA rounds the linear slope estimate of 0.9 up to 1.0, this approximation yields an IQ deficit over this blood lead concentration range of 7.6 IQ points, or 43% higher than the upper estimate provided by the authors of the original study. Note that OEHHA's estimate of the blood lead - IQ slope is based on an upper confidence level of the estimated slope, which is then further rounded up from 0.9 to 1.0, a value that is greater than any estimate of the actual upper confidence limit.

OEHHA response: *This has been corrected. In the revised analysis, OEHHA uses the predicted difference in IQ between Pb_B levels of 1 and 10 $\mu\text{g}/\text{dL}$, the same slope metric used by EPA (US EPA, 2006b).*

OEHHA is also unclear in the information it presents regarding its interpretation and application of the Lanphear data. For example, Table 4 on page 13 of the draft lead health criterion document (which presents alternative values that OEHHA reviewed in developing the proposed health criterion) is confusing because it presents slope estimates derived for full scale IQ loss as well as for various other cognitive test results, and for different ages of children. These various presentations of the dose-response slope are not comparable. The cognitive tests scores are not all on the same scale (*e.g.*, the mean block design score of the data set analyzed in the Lanphear *et al.* [2000] study was reported as 9.5, compared to mean IQ scores that are generally in a range of 90 to 100 for these studies). Furthermore, as described by Lanphear *et al.* (2005), blood lead – IQ dose-response slope estimates differ for different ages of children, which likely is, in part, a function of the change in blood lead concentration that occurs with age. In addition, this table should include the sample size analyzed in each study to provide the reader with further information about the certainty of the slope estimates. For example, it should be made clear that the six estimates from Lanphear *et al.* (2005) are not all for the same population. While there were more than 1,300 children in the full data set, the sixth slope estimate “linear maximum $\text{Pb}_B < 7.5 \mu\text{g}/\text{dL}$ ” is based on a sample size of only 103 children. Smaller sample sizes lend additional uncertainty to the slope estimates, and this uncertainty should be reflected in the data presentation. OEHHA should clearly label the entries in this table, including sample size, age of children, and mean estimate of cognitive endpoint for each estimate of the dose-response relationship.

OEHHA response: *The purpose of Table 4 is to compare and contrast alternatives to the benchmark we proposed. We chose not to use these alternative approaches because they were not as strong as the proposed approach. To discuss their limitations would serve no real purpose and might be confusing to readers. Had several commenters found the information in Table 4 incomplete and/or difficult to understand, we would consider adding more information. However, this is the only comment on that issue, and we are reluctant to add an in-depth discussion of approaches not used in the final proposal and risk confusing other readers..*

One additional uncertainty relates to OEHHA's use of the upper confidence limits on the dose-response slopes rather than the best estimate of the slopes. The upper confidence limits are related to the r^2 , which describes the amount of correlation between blood lead concentration and IQ seen in each analysis. A poor correlation gives a low r^2 , which in turn gives less confidence on the estimated slope and, therefore, a higher upper confidence limit on the slope. As a result, the highest estimates of the upper confidence limit on the dose-response slopes come from studies with the poorest correlations between blood lead concentration and IQ. It would be more appropriate for OEHHA to use the best estimate of the dose-response slope as derived from these studies, preferably from a study where the r^2 is high.

OEHHA response: *There is abundant and long-standing precedent for including uncertainty in the assessment by such methods as uncertainty factors and confidence limits. As shown in the following table, the chosen ratio of the UCL to the best estimate of the slope is near the lowest of all those considered. The only lower ratios are for the log-linear slope representing children from 2.4 to 30 ug/dl, which was not chosen because it is heavily influenced by the children with PbB >10, which are not the primary group targeted for protection. The log-linear slope representing children from 2.4 to 10 ug/dl, has a slightly lower UCL/slope ratio, but using it would not change the ΔPb_B expressed to one significant figure.*

Reference	Indicator	Slope	ΔPb_B	UCL ²	ΔPb_B	UCL/slope
Lanphear et al., 2005	Log-linear average slope from 1-10	-0.69	1.4	-0.96	1.0	1.39
	Log-linear, slope from 2.4 to 30 $\mu\text{g/dl}$	-0.25	4	-0.34	2.9	1.36
	Log-linear, slope from 2.4 to 10 $\mu\text{g/dl}$	-0.51	2	-0.7	1.4	1.37
	Linear concurrent $Pb_B < 10 \mu\text{g/dl}$	-0.47	2.1	-0.9	1.1	1.91
	Linear maximum $Pb_B < 10 \mu\text{g/dl}$	-0.74	1.4	-1.74	0.6	2.35
	Linear maximum $Pb_B < 7.5 \mu\text{g/dl}$	-2.94	0.3	-5.16	0.2	1.76
Canfield et al., 2003	Polynomial	-0.82	1.2	-1.43	0.7	1.74
	Linear: children w/ $Pb_B < 10$	-1.37	0.7	-2.56	0.4	1.87
	Linear: all children	-0.46	2.2	-0.76	1.3	1.65

These errors and deficiencies in OEHHA's interpretation and presentation of the Lanphear data and associated analyses, as well as the ongoing scientific debate regarding the potential effects associated with low-level lead exposures, again illustrate the significant uncertainties that have yet to be resolved in the current understanding of this topic.

2.1.3 Lack of Biological Data to Support a Supralinear Dose-Response Curve for Lead at Low Doses

In addition to the uncertainties raised regarding the results of the epidemiological studies by the statistical issues discussed in Section 2.1.1, review of information from other types of studies (*e.g.*, *in vitro* and animal studies) also raises questions regarding the biological basis for a supralinear dose-response curve for lead effects at low-dose exposures. As recognized in US EPA (2006a, pp. 8-66), "A biological mechanism for a steeper slope at lower than at higher blood lead levels has not been identified." As noted in a review of available data by a CDC Work Group (ACCLPP, 2004) and by others (*e.g.*, Bellinger, 2004), the available epidemiological data should be reviewed in the context of results from animal and *in vitro* studies. Such data can provide useful supplemental information regarding causation or mechanisms of action for dose-response relationships suggested by epidemiological findings. Indeed, OEHHA (CalEPA, 2006) cites experimental evidence to support a causal relationship between lead exposure and neurodevelopmental effects, but the available experimental evidence falls short in many ways as described below and in the Attachment (*e.g.*, because low-dose exposures are not specifically addressed in these studies or the study results provide no direct support for a supralinear dose-response relationship at the study exposure levels).

OEHHA response: *The proposed criterion is based on the change in IQ as Pb_B increases from 1 to 10 $\mu\text{g/dl}$. Although it is based on the log-linear curve of Lanphear et al (2005) OEHHA's view is that the exact shape of the curve in this region is uncertain, and that individual children may have different IQ/ Pb_B slopes depending on their baseline Pb_B and other factors.*

Based on a review of available animal and *in vitro* data, the CDC Work Group concluded that the mechanisms of action for some types of adverse health effects of lead are relatively well-characterized (e.g., impacts on anemia). For other, more complex effects such as neurobehavioral effects, the specific pathways by which lead may exert toxic effects are less clear. In particular, the Work Group observed that, while available information from *in vitro* studies provides some insights into biochemical or physiological changes associated with lead exposures, the precise mechanism by which these changes may mediate certain effects observed in human epidemiological studies remains speculative. They also noted that difficulties exist in extrapolating results observed in *in vitro* test systems to predict effects in intact laboratory animals or in humans. As an example, the Work Group noted a study in which lead interfered with protein kinase C function in cultured choroid plexus endothelial cells, but not in such cells in an intact animal (Zhao *et al.*, 1998, as cited in ACCLPP, 2004). Moreover, the Work Group noted that most of the available animal studies of lead exposures involved blood lead concentrations that were greater than 10 µg/dL. Thus, they provided little information regarding responses at lower levels of lead exposure.

Overall, the Work Group determined that "firm conclusions concerning relations of health status of children to blood lead levels in the range < 10 µg/dL cannot be drawn from these [*in vitro* and experimental animal] studies because of limitations of extrapolating from *in vitro* systems to intact animals and from animals to humans and because of the limited amount of data available from studies of animals dosed to produce a range of blood lead levels less than 10 µg/dL. Data from primates, which can most readily be extrapolated to humans, are especially limited."

Moreover, despite a thorough review of the available scientific literature, the Work Group stated that it "is unaware of directly relevant animal or *in vitro* studies that demonstrate a steeper slope for adverse effects of lead exposure at lower blood lead levels than observed at higher levels." In a review of lead toxicity, Bellinger (2004) also concluded that "[t]he precise shape of the dose-effect relationship in the lower portion of the exposure remains uncertain" and that "a convincing mechanism has not been proposed" to account for a steeper dose-response slope for low-level lead exposures.

OEHHA response: We agree.

Proponents of the supralinearity theory have cited several animal and *in vitro* studies to support their hypothesis; however, review of the specific studies cited does not change the conclusions reached by the CDC Work Group and others cited above. While some of the references cited by the researchers provide theoretical explanations for how lead might induce adverse health effects at low dose levels, the associations remain speculative. Moreover, the cited studies generally do not directly address the issue of whether such effects have a steeper dose-response curve or occur to a greater extent at lower dose levels. In addition, some of the cited studies also support suggestions that low-level lead exposures may have a hormetic effect (*i.e.*, could produce beneficial effects at low doses) and, thus, could be associated with a sublinear dose-response relationship. Additional information regarding these studies is provided in the Attachment to these comments.

The available *in vitro* results are subject to the uncertainties associated with piecing together the results of such studies of individual components to gain insights into the mechanisms by which potentially toxic agents may exert adverse effects in humans and other receptor organisms. The results discussed in the Attachment illustrate, however, that mechanistic information that is comparable to that being presented in support of the supralinear dose-response curve hypothesis is available to suggest that biologically-based alternatives may exist. To provide a balanced perspective, the draft lead health criterion document should include information on these observations, as well as information regarding the limitations of the available *in vitro* and animal study data to support a biological basis for a supralinear dose-response curve for low-level lead exposures.

OEHHA response: *The OEHHA analysis does not rely on in vitro or animal data to support any particular dose-response curve.*

2.2 Other Factors Influencing Interpretation of the Dose-Response Relationship for Lead

2.2.1 Limitations in the Availability and Interpretation of Low-level Lead Exposure Data

In discussing the available data for evaluating low-level lead exposures, OEHHA (CalEPA, 2006) observes that "The minimum PbB [blood lead concentration] causing neurobehavioral deficits is not well defined" (p. 4) and that "...a point at which the dose-response curve flattens out – *i.e.*, where further reductions in PbB yield no further improvement in intellectual functioning – has not been identified" (p. 12). OEHHA has hypothesized that an inverse relationship between blood lead concentrations and cognitive function in children exists at blood lead concentrations at least as low as 1 µg/dL; however, the body of evidence regarding potential health effects associated with low-level lead exposures is relatively limited and the draft lead health criterion document suggests the existence of a greater level of scientific resolution regarding these issues than is actually the case.

As recognized by a number of authors (*e.g.*, Chiodo *et al.*, 2004; Canfield *et al.*, 2004), researchers have only recently turned their attention to specifically examining potential effects associated with low-level lead exposures (*i.e.*, as reflected in blood lead concentrations less than 10 µg/dL). Despite increasing interest in the potential impacts of such low-level lead exposures, only a modest number of studies are currently available that have focused on this exposure range or provided any level of detail regarding potential impacts of exposures in this range. As illustrated in Section 2.1, substantial work is necessary to obtain a sound understanding of the nature of the effects that may be associated with lead exposures in this range, the quantitative dose-response relationships and biological mechanisms of action that underlie any effects, and the potential persistence and clinical significance of any observed effects. In light of the limitations in the existing information, the use of such data to support regulatory or policy decisions (especially within quantitative risk assessment frameworks) is fraught with challenges and any decisions made based on such data would consequently be subject to considerable uncertainty. In assessing the available data regarding potential health effects associated with low-level lead exposures, the degree to which available studies have assessed children who have only experienced low-level exposures should be noted (*i.e.*, studies should be carefully reviewed to ensure that the study population did not experience significantly greater exposure levels at some point in the past).

OEHHA response: *Two aspects of the Lanphear et al (2005) study would argue against the possibility that it was earlier, higher lead exposures that caused the intellectual impairment: 1) Full-scale IQ was more strongly related to concurrent blood lead than to early childhood blood lead (or any of the other blood lead indices) and 2) the relationship between concurrent blood lead and IQ remained significant when cord blood lead was included as a co-variate.*

Specifically, the draft lead health criterion document characterizes several recent reports as reflecting the effects on cognitive abilities of blood lead concentrations that are less than 10 µg/dL (*e.g.*, in the *Effects on Cognition* section beginning on p. 5); however, the cited studies includes studies of children whose abilities were assessed during later childhood. For example, Lanphear *et al.* (2000) evaluated children between the ages of 6 and 16 years old, while Wang *et al.* (2002) studied children with a mean age of 8.85 years old. Because blood lead concentrations typically peak around the age of 2 to 3 years old, the children in these studies are likely to have had greater blood lead concentrations at earlier ages, and the effects observed in these studies

cannot reliably be directly attributed to the absolute blood lead concentrations reported. The availability of studies demonstrating consistently low-level lead exposures is more limited and this factor should be acknowledged. This same concern arises in some of the other lead health effects data that OEHHA discusses in the draft lead health criterion document. To better reflect the available data, the draft lead health criterion document should clearly and systematically identify and acknowledge the available data that specifically address low-level lead exposures, including information regarding the actual exposure levels that were associated with the specific types of health effects that are discussed. Moreover, OEHHA should clarify which types of effects have been observed in populations whose blood lead concentrations have consistently been less than 10 µg/dl and which types of effects have been observed in populations who may have been exposed to higher levels at some point in their exposure history. In addition, conclusions regarding the lead exposure levels that have been associated with various effects should more accurately reflect the extent of the supporting data that are actually available.

2.2.2 Limitations Related to Use of Population Study Data

A number of available lead studies rely on extensive national databases such as those compiled *via* the National Health and Nutrition Examination Survey (NHANES). NHANES is a periodic survey conducted by the National Center for Health Statistics of the CDC and is designed to collect data on the health and nutritional status of the civilian, non-institutionalized US population. This database offers the potential for quick, relatively inexpensive studies that can be useful for exploratory analyses (Wartenberg and Buckler, 2001). Several of the studies that OEHHA has reviewed in developing the proposed lead health criterion are based on analyses of NHANES data (CalEPA, 2006). Such studies include Lanphear *et al.* (2000), which used data from NHANES III to assess the relationship between blood lead concentrations and age-adjusted performance on tests of arithmetic and reading skills, nonverbal reasoning, and short-term memory. The results of these analyses led these authors to express concern regarding potential adverse health effects of low-level lead exposures (*i.e.*, for blood lead concentrations between 5 and 10 µg/dL). Several studies of other health endpoints that are discussed by OEHHA also relied upon NHANES data (*e.g.*, Nash *et al.*, 2003; Selevan *et al.*, 2003; and Wu *et al.*, 2003). While databases such as those compiled in the NHANES surveys can provide a useful basis for exploratory analyses, some researchers have identified limitations that should be recognized when interpreting and applying the results obtained from such studies. For example, Wartenberg and Buckler (2001) discuss the use of large public health databases to address existing public health concerns and investigate the etiology of various health conditions. They emphasize that the utility of the results and their relevance for generalization outside of the study population should be addressed "openly and explicitly." One concern they raise is whether the appropriate exposure and outcome of concern have been captured in a single database or in complementary databases. An important aspect of this concern is whether or not a temporal relationship exists between the measured exposure and the measured outcome and, if the exposure and outcome data reflect different datasets, whether the temporal relationship between the datasets has been accurately identified.

Stone and Reynolds (2003) specifically address whether NHANES III data can be used to help resolve the controversy over low-level lead exposures and neuropsychological development in children. In attempting to replicate and extend the findings of Lanphear *et al.* (2000), Stone and Reynolds identified "serious shortcomings in the NHANES III data that center around missing data, odd distributions of blood lead levels as well as cognitive and academic scores, and potential inaccuracies in the data collection itself." They also questioned the degree to which the results could be generalized outside of the sample population from which the data were obtained.

OEHHA acknowledges the Stone and Reynolds criticisms, but then dismisses them stating that the bias of the results toward low SES is consistent with its mission to protect sensitive subgroups (CalEPA, 2006). However, this response only addresses one of several of the concerns raised by Stone and Reynolds, the sum of which leads Stone and Reynolds to conclude that "Neither policy nor scientific problems related to cognitive and other neurodevelopmental problems should be considered using the NHANES III Youth dataset."

OEHHA response: *Lanphear et al (2000) is a supporting study. We have not relied heavily on the NHANES data for this analysis.*

2.2.3 Adequacy with which Residual Confounding has been Addressed

Another important factor in interpreting the effects of lead health studies is the adequacy with which confounding of observed effects by other potential causal factors has been addressed. For example, among the sources of uncertainty affecting the strength and significance of the CDC Work Group's conclusions regarding the interpretation of health data for low-level lead exposures is "the potential for residual confounding by social factors" (ACCLPP, 2004). As recognized by the Work Group, social factors such as socio-economic status are strongly related to lead exposures and cognitive function, and distinguishing between the effects of lead and social factors has been difficult to achieve in most studies. If controls on confounding are insufficient, then erroneous conclusions can result. In assessing the potential impact of residual confounding on estimates of the impact of lead exposures on cognitive function, the Work Group estimated that such confounding could be responsible for an impact of 1.0 IQ point per $\mu\text{g}/\text{dL}$ change in blood lead level – a value that is equal to the proposed lead health criterion identified by OEHHA. As noted by the Work Group, this analysis highlights "the need for caution in interpreting the absolute value of the estimated effect sizes." The Work Group also presented a hypothetical example illustrating how residual confounding, if not adequately accounted for, could yield an apparent supralinear dose-response relationship between lead exposures and measured cognitive effects.

OEHHA response: *This issue is extensively discussed in the document. It should be pointed out that failure to correctly account for confounding can alter the beta term in either direction, and it is no more likely to inflate beta than it is to underestimate it. The latter can occur if a social factor is strongly related to IQ, leading to attribution of a significant share of the variability in IQ to that factor, when in fact that relationship is mediated by the factor's effect on lead exposure. The document includes discussion of at least two studies in which the social factors referred to by the ACCLP do not co-vary with lead exposure; yet the effect of lead on IQ is undiminished in these studies.*

The importance of ensuring that confounding factors are appropriately controlled in the data analyses was also illustrated in a 2004 analysis that constructed a hypothetical study specifically to explore the impacts of confounding (Mink *et al.*, 2004). The hypothetical study examined the association between exposures to a potentially neurotoxic substance and neurobehavioral effects in young children using two tests of cognitive function and intelligence. The three confounders that were explored in the analysis were maternal intelligence, home environment, and socioeconomic status. To explore these issues, the researchers constructed a hypothetical data set of test results and population characteristics for the three confounders of interest. They then analyzed the data controlling for one, two, or all three of the confounding factors. These researchers found that, if confounding was not adequately controlled for in the analyses, relatively small differences between the "exposed" and "unexposed" groups (with respect to the confounding variables) could yield spurious observed differences in the test scores, *i.e.*, the results would erroneously suggest that the exposure had affected the test scores. The magnitude

of difference in the test scores (*i.e.*, 3-10 point differences in the cognitive test scores) was in the range that has been suggested to have meaningful impacts on populations in some studies (*e.g.*, Pocock *et al.*, 1994, as cited in Mink *et al.*, 2004).

OEHHA response: *The comment does not cite particular sources of confounding that have not been addressed.*

The methods used to control the confounding also affected the results. This study provides further support for the importance of adequate evaluation and control of confounding factors when interpreting study results. Additional context for interpreting the significance of small changes in test scores is provided by observations that the standard measurement error for IQ test scores spans a several point range. For example, the 90-95 percent confidence interval for IQ scores from the Weschler's Intelligence test has been estimated as encompassing +/- 6 points (Kaufman, 2001).

OEHHA response: *The significance of the results of a single test varying within the confidence interval versus a difference of that same magnitude in a population is discussed in the document. Suffice it to say here that there is no reason to believe that such variability would be non-random.*

It has been suggested that analyses of the role of confounding factors should also consider the potential that confounding factors may serve as proxies for the exposure of interest (at least in part), rather than simply replacing the exposure of interest as a causal factor (*e.g.*, Bellinger, 2000; 2004). These reviews acknowledge, however, that a thorough evaluation of such issues would require more detailed analyses of potential confounding factors. Methods for characterizing the confounding factor would need to be developed that would allow those aspects of the confounder that contribute to exposure potential to be evaluated separately from those that do not affect exposure. This observation further highlights the challenges inherent in discriminating among effects associated with lead exposures and those associated with other factors, particularly when using currently available data.

OEHHA response: *We agree that confounding factors may serve as proxies for the exposure of interest. This effect would tend to diminish the effect of the exposure of interest, since the effect is partially attributed to a confounder which is a proxy for the exposure. Thus, where multivariate regression has been used, the true effect of lead may be stronger than that attributed to lead by the model.*

Other researchers have also noted that substantially lower test scores are frequently observed in many of the populations examined in studies of lead impacts on the cognitive development of young children relative to typical scores observed in more advantaged populations of children (*e.g.*, Angle, 2002). These researchers suggest that such findings both call into question the "precision and significance" of small-scale differences in test scores as well as highlight the substantial role of socioeconomic factors in cognitive development. Similarly, researchers examining results from the Cincinnati prospective lead study noted that their "results underscore the complexity of models of neurobehavioral development, and the modest predictive power of any one determinant" (Ris *et al.*, 2004). OEHHA should recognize such factors in assessing the potential efficacy of proposed approaches for assessing and managing potential health risks associated with low-level lead exposures.

OEHHA response: *OEHHA acknowledges that substantially lower test scores are frequently observed in many of the populations examined in studies of lead impacts on the cognitive development of young children relative to typical scores observed in more advantaged populations of children. However, similar results have been found in populations from all socio-economic strata and in various racial and ethnic groups. OEHHA acknowledges that the differences in cognitive development attributable to lead exposure are not precise, but we contend that they are significant.*

3 Factors Influencing Application of the Proposed Approach

3.1 Quantitative Implications of the Proposed Approach

Although the draft lead health criterion document does not provide a detailed discussion of how the proposed criterion will be applied to assess potential health risks at specific school locations, the draft document suggests that a lead exposure assessment model such as California's LeadSpread could be used in applying the approach. To assess the quantitative implications of the proposed approach, the LeadSpread model and the associated "default" values provided in the model were examined (CalEPA, 2007). Specifically, for each of the three main environmental media (*i.e.*, air, soil/dust, and water), all other initial default values were held constant while the concentration of one of the environmental media was changed until the blood lead concentration at a specific percentile of the population distribution increased by 1 µg/dL. This procedure was applied for each of the three media and for each of three percentile values (*i.e.*, 50th, 95th, and 99th percentiles). The results of this evaluation are summarized in Table 1.

Table 1

Results of LeadSpread Evaluation of Potential Implications of Proposed Approach

Environmental Medium	Initial Default Concentration	Concentration required to increase default blood lead concentration at listed percentile by 1 µg/dL		
		50 th	95 th	99 th
Air (µg/m ³)	0.028	0.75	0.38	0.28
Soil/dust (mg/kg)	146	225	180	173
Water (µg/L)	15	30	22	20

Note: Default blood lead concentrations for young children: 3.3 µg/dL (50th percentile), 7.2 µg/dL (95th percentile), 10 µg/dL (99th percentile).

As can be seen, these results suggest that – under some conditions – exceedances of the proposed benchmark health criterion could be associated with relatively small (and potentially unmeasurable) changes in environmental concentrations of lead. The results for air indicate that exceedances of the proposed benchmark health criterion are unlikely to be identified based on site-specific concentrations of lead in this medium. Specifically, even at the 99th percentile (where the smallest medium concentration changes are required to result in a 1 µg/dL change in blood lead concentration), the air concentration would have to increase by an order of magnitude (from 0.028 µg/m³ to 0.28 µg/m³) to result in a 1 µg/dL increase in blood lead concentration. Because the "default" value presented in the LeadSpread model is characterized as the highest monthly average reported for any California monitoring site (based on 1997 data collected by the California Air Resources Board), it is unlikely that increases in the air concentration alone would cause the incremental change in blood lead concentration to exceed the benchmark.

OEHHA response: *We agree that the model indicates that blood lead is relatively insensitive to small changes in atmospheric lead and that atmospheric lead will rarely be a limiting issue at school sites. This approach would be the starting point for other programs to address media-specific concerns of exposure and uptake.*

By contrast, however, small changes in the soil/dust concentrations would yield exceedances of the benchmark. For example, at the 99th percentile, an increase of only 27 mg/kg in the soil/dust concentration (from 146 mg/kg to 173 mg/kg) would increase the blood lead concentration by 1 µg/dL. Thus, it appears that a schoolyard with a lead concentration in soil that is estimated to be

27 mg/kg higher than the lead concentration in soil in the surrounding community could be targeted for remediation. Given the typical degree of heterogeneity in lead concentrations in soil, it is doubtful that a 27 mg/kg difference in average lead concentrations in soil from two locations could even be identified. As discussed in more detail below, this type of finding raises questions regarding whether the proposed approach will effectively identify actual health risks associated with lead exposures, will be consistent with approaches used in other lead regulatory programs, and will target meaningful health protection measures.

OEHHA response: *Since the calculations are not shown in the table, we cannot determine how those estimates were obtained. However, assuming that children are at school 5 days per week and that they ingest ½ of their daily soil and breathe ½ of their daily air while at school, 182 mg/kg soil lead would increase the PbB in a 95th percentile child by 1 µg/dl. And 131 mg/kg soil lead would increase the PbB in a 99th percentile child by 1 µg/dl.*

3.2 Factors Influencing Interpretation of Results

As noted above, the small changes in certain environmental media concentrations that are required to result in exceedances of the benchmark health criterion raise questions regarding the practical and policy implications of the proposed approach. Such concerns are not unique to the health criterion approach recently proposed by OEHHA for use in school risk assessments, but instead are an integral part of evaluations of any approach for evaluating potential health risks associated with low-level lead exposures. For example, as noted above, in 2004, a Work Group of the Centers for Disease Control (CDC) reviewed and reaffirmed the 10 µg/dL benchmark lead exposure level that CDC recommends for use in screening programs designed to identify young children who may require interventions to reduce lead exposures. This Work Group review focused on the available data regarding potential adverse health effects associated with low-level lead exposures (ACCLPP, 2004; CDC, 2004). The focus of these efforts was on cognitive function; however, other health endpoints were evaluated as well. This analysis included a comprehensive review of the available scientific data, methodological considerations, and the practical implications of interpretations of the available data. The findings of the CDC Work Group, together with analyses by others, provide useful context for efforts to quantify the dose-response relationship for low-level lead exposures. In particular, the Work Group's findings note the general limitations in the available data as well as specific limitations in the ability to draw quantitative conclusions regarding the potential impacts of low-level lead exposures.

Based on a comprehensive review of the available information, the Work Group concluded that the available data "[support] an inverse association between blood lead levels in the range less than 10 µg/dL and the cognitive function of children" (ACCLPP, 2004). The Work Group noted, however, that "In reaching this conclusion, the [Work Group] is mindful of limitations in the available evidence base." They noted that few studies had directly examined the effects of blood lead concentrations that are less than 10 µg/dL, and that many of the available studies of blood lead concentrations in this range had limited or no information regarding blood lead concentrations or important confounding factors at earlier stages of life. The Work Group also concluded that the data regarding other health effects were substantially more limited and variable, although the data were "consistent" with an association between low-level lead exposures and adverse health impacts.

The Work Group's conclusions were also tempered by recognition of the substantial uncertainties that exist in the available data set, including uncertainties regarding whether the observed associations are causal. The equivocal nature of the available data is reflected in the qualified nature of the conclusion drawn by the Work Group regarding the causal nature of the association between low level lead exposure and effects on cognitive function (ACCLPP, 2004), *i.e.*, that "the

weight of the available evidence favors, and does not refute, the interpretation that these associations are, at least in part, causal." Most importantly for evaluations of the potential shape of the low-level lead dose-response curve, the Work Group also noted that "the possibility of residual confounding and other factors leaves considerable uncertainty as to the absolute size of the effect and shape of the dose response relationship at blood lead levels < 10 µg/dL." For other health effects, the Work Group concluded that the currently available data are too limited to support any firm conclusion regarding a causal relationship. As indicated in the current set of comments, although additional studies and data analyses have been published since the Work Group completed its evaluations of these issues, the more recently available information does not warrant any substantive modification to the conclusions drawn by the Work Group regarding the significance of the health effects associated with low-level lead exposures or the uncertainties inherent in the available data.

OEHHA response: *OEHHA agrees that "the weight of the available evidence favors, and does not refute, the interpretation that these associations are, at least in part, causal" and that "the possibility of residual confounding and other factors leaves considerable uncertainty as to the absolute size of the effect and shape of the dose response relationship at blood lead levels < 10 µg/dL." We do not contend that the absolute size of the effect and shape of the dose response relationship are known precisely, hence the use of a confidence interval.*

In determining appropriate blood lead concentrations for use in childhood blood lead screening programs, CDC also recognized the importance of practical considerations (CDC, 2004). Specifically, when discussing its decision not to reduce the blood lead level of concern in children's lead exposure screening programs to a value less than 10 µg/dL, CDC noted that it is not currently possible to routinely and reliably determine whether a child's blood lead concentration is actually less than 10 µg/dL due to limitations in the accuracy of available sample collection and laboratory testing methods. CDC also noted that no effective response measures are available to reduce blood lead levels for children at levels less than 10 µg/dL or to reduce, with any degree of certainty, risks for adverse health effects in such children. As a third factor, CDC noted that the uncertainties regarding the degree of health risk associated with blood lead levels less than 10 µg/dL also made the choice of any such reduced target blood lead concentration inherently "arbitrary" and associated with "uncertain benefits." As noted in the Work Group report (ACCLPP, 2004), relative to the uncertainties in the interpretation of the available epidemiological studies noted above, "Even greater uncertainty attends the use of associations observed in the relevant population studies for interpretations of [blood lead levels] measured in individual children at a single point in time." Thus, in the face of considerable uncertainties and in the absence of reliable methods to determine exposure levels or to implement meaningful health interventions, CDC decided not to reduce the blood lead level of concern in children's screening programs to a level less than 10 µg/dL.

OEHHA response: *As stated in the document, the proposed ΔPb_B is not intended for use in clinical settings, or for population screening. Thus the inability "to routinely and reliably determine whether a child's blood lead concentration is actually less than 10 µg/dL due to limitations in the accuracy of available sample collection and laboratory testing methods" and the lack of "effective response measures ... to reduce blood lead levels for children at levels less than 10 µg/dL" are irrelevant. OEHHA developed a health-protective approach which is preventive in nature. Factors such as detection limits, costs, interventions etc. are to be addressed by various risk management programs.*

Similar practical and policy considerations surround development and implementation of the lead health criterion approach that OEHHA has proposed. For example, in determining this approach, OEHHA should carefully evaluate and acknowledge the limitations in the available database documenting health effects associated with low-level lead exposures, particularly when attempting to derive quantitative risk assessment interpretations of the available data. Moreover,

OEHHA should address the implications of implementation of the proposed approach, *e.g.*, by assessing the potential effectiveness of the proposed approach for identifying meaningful opportunities for addressing potential lead exposures of health concern and for improving overall public health. As noted in the previous sections, a number of factors suggest that the proposed approach is likely to yield a limited ability to observe actual changes in lead exposure levels (*i.e.*, blood lead concentrations) or IQ levels resulting from risk management decisions made based on the proposed approach.

OEHHA response: *OEHHA agrees that the improvement in blood lead levels and cognitive development may not be measurable, short of conducting new epidemiological studies large enough to be able to detect small differences. The same concern can be levied against regulating carcinogens at a risk level of 10^{-6} or even 10^{-5} . Yet most people would not accept the approach of regulating toxic chemicals only at levels where their effects are overt and obvious.*

When assessing the implications of the proposed approach, OEHHA should also recognize the relative roles of lead exposures and other influences on children's neurocognitive development. As recognized by OEHHA as well as a number of other studies, "lead is only one of several risk factors for diminished intellectual capacity, and it may not be the most important" (CalEPA, 2006, p. 21). Other factors such as parental factors, social factors, and other aspects of a child's history and development have been identified as significant determinants of children's cognitive development (Calderon *et al.*, 2001; Dickens and Flynn, 2001; Kaufman, 2001; Khan and Faraone, 2006; Wasserman and Factor-Litvak, 2001; Weiss, 2000). Based on a review of recent data regarding low-level lead exposures and children's intellectual development, Koller *et al.* (2004) conclude that "from a public health perspective, exposure to lead should be seen within the many other risk factors impacting on normal childhood development." Moreover, these researchers note that "Current lead exposure accounts for a very small amount of variance in cognitive ability (1-4%), where as social and parenting factors account for 40% or more." Similar findings have been reported by other researchers (*e.g.*, Ris *et al.*, 2004; Wasserman *et al.*, 2000; Wasserman and Factor-Litvak, 2001). These types of findings should be acknowledged when determining the likely impacts of the proposed lead health criterion on children's cognitive development.

OEHHA response: *OEHHA acknowledges in the document that "lead is only one of several risk factors for diminished intellectual capacity, and it may not be the most important.*

4 Conclusions Regarding Public Health Implications of Proposed Approach

As reflected in these comments, the proposed lead health criterion developed by OEHHA is based on a technical foundation that contains numerous limitations, especially for use in deriving quantitative estimates of potential health risks associated with low-level lead exposures. Most importantly, because of the significant limitations in the available data, the choice of a specific value to use as the benchmark health criterion is, to a large extent, arbitrary. For example, in describing the basis for the proposed health criterion, OEHHA states that a value of zero for the ΔPb_B "would not be useful" from a "practical standpoint" and that changes in blood lead concentrations that are less than the benchmark value "are expected to cause no measurable adverse effect" although theoretical effects may occur (CalEPA, 2006). Moreover, as described in these comments, the specific value proposed by OEHHA incorporates a number of highly conservative assumptions that increase the uncertainty surrounding the proposed value regarding its biological, public health, and practical significance. In light of the limitations and uncertainties

that exist in the available data regarding health effects of low-level lead exposures, it is not clear that the selected value will, in fact, be any more useful than a value of zero for guiding risk management decisions, or that changes in blood lead concentrations that are at or somewhat greater than the benchmark level would yield measurable adverse effects.

OEHHA response: *A blood lead increment of zero would require that lead exposures at school sites also be zero. The proposed increment of 1 µg/dl would require that residual lead at school site be at a measurable and manageable level.*

As a result of these concerns, questions exist regarding the utility of the proposed approach in effectively prioritizing and managing lead-related health risks and improving public health overall. As described above, it appears that the proposed approach would associate "elevated" risk levels with quite small (and potentially unmeasurable) changes in environmental concentrations. Thus, it is unclear whether the proposed approach will be useful in helping to identify important sources of lead exposure or meaningful actions that can be undertaken to improve public health. The incremental approach proposed by OEHHA also raises concerns regarding the effectiveness of the proposed methodology for targeting important priorities and/or useful measures for improving public health. While it is recognized that the approach is designed to specifically look at exposures associated with schools, it is unclear how the use of an incremental approach to assess potential lead exposures will effectively address potential differences in exposure and risk for individual children (*i.e.*, children with different baseline lead exposure levels).

OEHHA response: *OEHHA acknowledges that there are likely to be differences in exposure and risk for individual children with different baseline lead exposure levels. Other programs (e.g. the Childhood Lead Poisoning Prevention branch of the California Department of Health Services) address other aspects of childhood lead exposure.*

In addition, as noted by one US EPA reviewer of an earlier draft of the proposed approach (CalEPA, 2006, p. 44), it appears that the proposed approach will lead California to impose substantially different cleanup requirements than other regulatory agencies. Such an approach has the potential to arbitrarily discriminate against businesses in California while providing negligible, if any, additional benefit to public health.

OEHHA response: *It is not the role of OEHHA to determine health benefit versus economic benefit. That is a risk management function left to the regulatory agencies.*

Although OEHHA's analyses are designed to present a risk assessment basis for identifying a health criterion to be used in assessing potential health risks posed by schools, the significant limitations in the available scientific data have necessitated the incorporation of a number of "risk management" decisions within the proposed approach. As a result, OEHHA should carefully assess the implications of the proposed approach for its overall effectiveness in improving public health. In particular, OEHHA should evaluate whether implementation of the proposed approach at California's schools will most effectively identify actions that will result in overall improvements in public health or whether the proposed approach will instead divert health improvement efforts and resources from more significant problems.

OEHHA response: *The authorizing legislation does not provide for the cost/benefit analysis that is implied by this comment.*

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Attachment: Additional Documentation of Limitations in Available Data Regarding Health Effects Associated with Low-Level Lead Exposures

Additional Documentation of Critique of Studies Cited to Support Supralinearity Theory

As noted in Section 2.1.1 of the main text of these comments, a number of studies have been identified that suggest a supralinear dose-response relationship for low-level lead exposures. A careful review of these studies indicates, however, that the observations reported in these studies are consistent with the analysis presented by Bowers and Beck (2006). For example, in one of the recently issued reports, Kordas *et al.* (2005) examined the relationship between blood lead concentrations and several cognitive test scores in approximately 600 Mexican first graders residing near a metal foundry. These researchers report that they observed a supralinear relationship with lead exposures for several of the cognitive measures examined. The figures presented in this report are very similar to those shown in Canfield *et al.* (2003), and are consistent with the statistical analysis described by Bowers and Beck. Similarly, in another recently issued study conducted in Mexico, Schnaas *et al.* (2005) compared the results of IQ tests administered to eight year-old children with third trimester maternal blood lead concentration data that had previously been collected from the children's mothers. Again, the authors observed the expected supralinear dose-response slope between blood lead concentrations and IQ measurements, and their curve is also consistent with the statistical analysis described by Bowers and Beck. Thus, in both cases, the supralinear nature of the observed dose-response relationships is expected based on the statistical parameters of the data sets alone, and provides no new information concerning the relative impact of low-level vs. higher-level lead exposures on cognitive abilities.

The Bellinger and Needleman (2003) analysis also appears to result in a dose-response observation that is consistent with the statistical analysis presented by Bowers and Beck; however, the lack of summary statistics for the blood lead data sets preclude reproducing the curve to confirm this observation. Specifically, as stated in the article, this publication describes a larger IQ deficit (per $\mu\text{g}/\text{dL}$) at blood lead concentrations that are less than $10 \mu\text{g}/\text{dL}$ than is observed for blood lead concentrations that are greater than $10 \mu\text{g}/\text{dL}$. This observation is based on a study of approximately 200 children who participated in a long-term prospective study in Boston, using IQ test results obtained when the children were 10 years old and blood lead concentrations obtained when the children were 24 months old. In an earlier analysis of these data, Bellinger *et al.* (1992) estimated that each $\mu\text{g}/\text{dL}$ increase in blood lead concentrations in this cohort yielded a 0.58-point decrement in IQ scores. In the 2003 reanalysis (which includes only those children who had blood lead concentrations that were less than $10 \mu\text{g}/\text{dL}$), Bellinger and Needleman estimated that each $\mu\text{g}/\text{dL}$ increase in blood lead concentration resulted in a 1.56-point decrement in IQ scores. Bellinger and Needleman noted that this result is "puzzling" and could reflect residual confounding; however, the ratio of slopes observed in the two analyses (*i.e.*, including only children with blood lead concentrations less than $10 \mu\text{g}/\text{dL}$ and including children with blood lead concentrations greater than $10 \mu\text{g}/\text{dL}$ as well; $1.56 / 0.58 = 2.7$) is consistent with both the extent of nonlinearity observed in other studies and the theoretical relationship expected based on the statistical analysis presented by Bowers and Beck. Therefore, this analysis again does not support a biological interpretation of increased damage at blood lead concentrations that are less than $10 \mu\text{g}/\text{dL}$.

Wasserman *et al.* (2003) report measurements of both blood lead and bone lead concentrations for their study population, and describe regression analyses of both measures against IQ. Based on the data collected in this study, both bone lead and blood lead concentrations are lognormally distributed, and both display a greater decrement in IQ at the low end of the lead exposure range. These findings are consistent with those noted in other publications. Although this study is the first to suggest a supralinear dose-response slope between bone lead concentrations and IQ, this result is not surprising because the same statistical requirements are placed on regressions

involving bone lead concentrations as apply when evaluating blood lead concentrations, because both exposure measures are lognormally distributed. Thus, this finding is again consistent with the statistical analysis presented by Bowers and Beck.

Two of the other studies present some information that again is consistent with the statistical analyses discussed by Bowers and Beck, but also provide some indications of possible departures from the expected dose-response relationships that may warrant additional exploration. For example, in a study of 247 children from Detroit, Chiodo *et al.* (2004) examined the relationship between blood lead concentrations and IQ as well as other cognitive test score results. The authors concluded that the dose-response relationship reflected in their data was linear; however, this "linear" relationship is shown on a log-linear plot of IQ scores and blood lead concentrations. In other words, the results of this study are consistent with those of other studies demonstrating a supralinear slope. The linear nature of the relationship shown on the log-linear plots is consistent with the statistical analysis presented by Bowers and Beck and therefore is not indicative of a biological interpretation of increased damage at low-level lead exposures. However, the authors also note that they observed a nonlinear relationship for three of their analyses (involving attention and color-naming). If observed in other studies, this type of observation (which is not consistent with the dose-response curve predicted by the statistical analyses) should be further explored to determine whether there is a potential causal basis or biological mechanism of action associated with this observation. In this instance, the nonlinear portion of the curve is formed on the basis of very few data points (*i.e.*, as few as 10) and does not appear to be significant at this point.

A study by Dudek and Merez (1997) of approximately 400 school-age children also yields some findings that require further analysis and discussion in the context of the statistical analyses discussed by Bowers and Beck. This publication has been cited (*e.g.*, by Nevin, 2000) as being consistent with other studies suggesting an increasing slope at low blood lead concentrations in the dose-response relationship between blood lead concentrations and measures of cognitive function; however, this paper appears to have been misinterpreted by Nevin (2000). Dudek and Merez examine IQ measurements in subsets of the study population based on 5 µg/dL blood lead concentration increments, noting that the steepest decline in IQ measurements is observed when the IQ results for the subset with blood lead concentrations between 5 and 10 µg/dL are compared with the IQ results for the subset with blood lead concentrations between 10 and 15 µg/dL. However, the paper shows a more shallow decline both at blood lead concentrations that are greater than 15 µg/dL and less than 5 µg/dL, suggesting that the dose-response relationship is sigmoidal or sublinear at blood lead concentrations that are less than 10 µg/dL. Since the study subgroup that had blood lead concentrations less than 5 µg/dL was at the tail of the distribution of blood lead concentrations and thus is expected to be rather small, a conclusion about the significance of this observation would not be warranted at this time.

The final additional publication that was identified as potentially providing support for a supralinear dose-response curve for the effects of low-level lead exposures on cognitive function contains a number of errors in the underlying data analysis that undermine the conclusions reached by this researcher (Nevin, 2000). Specifically, Nevin performed an analysis based on declines in blood lead concentrations for children between the ages of 1 and 6 years old using data from the National Health and Nutrition Examination Survey (*i.e.*, NHANES II [1976-1980] and III [1988-1991]) and increases in cognitive test score data for 9- and 10-year old children from 1984 and 1992. He compared the resulting slopes relating blood lead concentrations and cognitive function scores generated from these data sets to the slopes observed in published epidemiology studies (*e.g.*, Schwartz, 1994). Nevin observed that the slopes were consistent and concluded that the increase in cognitive test scores reflected in these data sets could be ascribed to concomitant declines in blood lead concentrations; however, this conclusion is in error for at least two reasons. First, the blood lead concentration declines occurred over an approximately 12-year time period, while the test score data sets correspond to an 8-year time period. Thus, the children

represented by the test score data sets would not have experienced the full decline in blood lead concentrations observed between the times when the NHANES II and III data were collected. Second, as several authors have noted (*e.g.* Lanphear *et al.*, 2005, Chen *et al.*, 2005), the slope of the relationship between blood lead concentrations and cognitive function scores depends on the age of the child at the time of the blood lead test, and steepens with age as blood lead concentrations decrease. Nevin has not corrected for this factor, and calculates expected IQ changes using slopes assessed for older children (*e.g.*, slopes for 6- to 15-year old children presented in Dudek and Merez, 1997) by applying them to blood lead data for younger children (*i.e.*, ages 1-5 years old) in the NHANES study.

This approach also overestimates the change in cognitive test scores that can be ascribed to lead exposure. As a result, less than half (and possibly no more than one quarter) of the IQ change between the test scores from 1984 and 1992 can be related to changes in blood lead concentrations on the basis of published studies, leaving the other half with no explanation. The nonlinearity Nevin observes at the high and low end of the distribution of cognitive test scores remains in both the half that can be "explained" by blood lead concentrations and the half that has no explanation. This analysis provides no evidence for any biological interpretation of a supralinear dose-response relationship between blood lead concentrations and cognitive function.

In summary, review of these additional publications suggests that the statistical interpretation of the supralinear dose-response relationship between blood lead concentrations and cognitive test scores is equally applicable to these articles. None of the studies described here provide evidence for an increased effect of lead on cognitive abilities at low-level exposures *vs.* high-level exposures. Both Dudek and Merez (1997) and Chiodo *et al.* (2004) show some evidence of a departure in the dose-response relationship between blood lead concentrations and cognitive function from that expected based on the statistical nature of the distributions; however, the possible departures shown by these two studies are in opposite directions. In one case, the departure suggests an increasing effect of blood lead concentrations on cognitive function in the low blood lead concentration region (Chiodo *et al.*, 2004). In the other case, the departure suggests a decreasing effect of blood lead concentrations on cognitive function in the low blood lead concentration region (Dudek and Merez, 1997). In both cases, there are too few data points in the region where the departures begin to appear to substantiate the trends; however, these are the types of observations which (if confirmed in studies of sufficient power) would yield relevant information about the effects of low-level lead exposures on cognitive abilities.

Additional Documentation of Limitations in the Biological Basis for a Supralinear Dose-Response Relationship for Low-Level Lead Exposures

As noted in Section 2.1.3 of the main text of these comments, although several animal and *in vitro* studies have been cited to support the supralinearity hypothesis, these studies provide no direct evidence of a biological basis for such a dose-response relationship for low-level lead exposures. For example, based on observations in an *in vitro* study of cultured human skin cells (Bae *et al.*, 2001), Canfield *et al.* (2003) suggest that exposures to heavy metals may stimulate cellular defense mechanisms, reducing the damage associated with additional exposures. Lanphear *et al.* (2005) also mention the existence of mechanistic data from several cell culture and biochemical studies as offering a potential explanation for increased lead-associated deficits at lower lead exposures (*e.g.*, Lidsky and Schneider, 2003; Markovac and Goldstein, 1988; Schneider *et al.*, 2003). Lanphear *et al.* (2005) recognize, however, that "it is not yet possible to link any particular mechanism with the deficits observed in [their] analysis [of seven epidemiological cohort studies]." Although these authors briefly mention the possibility that existing mechanistic studies may provide a biological basis for a supralinear dose-response curve, they provide little detailed support for this hypothesis. Moreover, review of the cited studies yields little specific information that is directly relevant for assessing the potential mechanism by which low-level lead exposures might be associated with neurobehavioral effects.

As recognized by the CDC Work Group, of especial concern when attempting to apply the results of such studies to understand observations in epidemiological studies is the relevance of the study results for evaluating the types of effects observed in the epidemiological studies. In general, evaluations of the implications of results from *in vitro* test systems (e.g., cell culture studies) must assess the degree to which the observed effect may occur in intact organisms, including humans (e.g., whether a similar response would occur). Moreover, such evaluations must also review the relevance of the studied effect for the effect of interest in the overall analyses. Such extrapolations are particularly difficult when attempting to use *in vitro* findings of a limited number of indicators within a simplified biological system to draw conclusions regarding complex responses in humans (e.g., effects on behavior or learning). For example, the Bae *et al.* (2001) *in vitro* study cited by Canfield *et al.* (2003) examined the acute cytotoxicity of 4 heavy metals (individually and when combined) on four strains of human skin cells in a laboratory cell culture system. Although the study noted that skin cells were a relevant cell type for two of the metals studied (*i.e.*, arsenic and chromium) because of their potential to cause skin lesions or sensitization in exposed humans, no such toxicological rationale was provided in the study documentation for including the other two metals (*i.e.*, lead and cadmium) in this test system. Instead, the other two metals appear to have been included in the study because they are commonly found at contaminated sites. Thus, when attempting to apply these results to provide a basis for a supralinear dose-response curve for neurobehavioral effects of low-level lead exposures, one must first consider whether the cultured skin cells are reacting similarly to how skin cells (and other cells) in lead-exposed humans might react. Then, the evaluation must assess whether the responses in skin cells are relevant for assessing potential responses of cells that mediate the neurobehavioral effects of interest in the epidemiological studies. In addition, as observed in the Bae study, the observed results were dependent on the cell strain as well as the specific dose of metal or metal mixture that the cells were exposed to, adding another layer of complexity to evaluations of the relevance of the *in vitro* results to observations in exposed humans.

Several of the other studies cited by the proponents of the supralinearity theory also are *in vitro* studies or theoretical reviews of available data that provide interesting bases for deriving theories regarding mechanisms of action or for identifying future research needs, but which do not directly characterize the potential existence, nature, or magnitude of the quantitative dose-response curve for low-level lead exposures, including whether such a curve is supralinear. For example, the Markovac and Goldstein (1988) paper cited by Lanphear *et al.* (2005) examines a possible biochemical mechanism by which low-level exposures to lead may result in adverse health effects. Specifically, using an *in vitro* biochemistry approach based on enzyme extracts from rat brain tissue, these researchers studied levels of protein kinase C (a regulatory enzyme in the body) and how lead may mimic calcium in regulating the function of this enzyme and its subsequent impact on proteins that regulate cell growth and differentiation in the body. The Schneider *et al.* (2003) study cited by Lanphear *et al.* (2005) used fetal rat neurons in culture to evaluate the effects of lead exposure on cell survival and growth. Inhibitory effects on neurite growth were observed at lower exposure levels than were necessary to affect neuron survival. These researchers speculate that lead may modulate neurite growth through mechanisms by which lead mimics calcium in a variety of physiological functions or by directly interacting with cytoskeletal proteins. The difficulties inherent in interpreting *in vitro* results were directly acknowledged in the Schneider *et al.* (2003) study, which noted that other cell culture studies had observed promotion of neurite growth in the presence of lead and observed that these results were "difficult to compare with the present findings due to differences in the type of cells...and culture conditions utilized."

The third paper cited by Lanphear *et al.* (2005) presents a review of potential mechanisms by which lead may induce neurotoxicity in children (Lidsky and Schneider, 2003). Again, these researchers suggest that some of lead's mechanisms of action may be related to its ability to

substitute for calcium in cellular processes. In general, the studies cited to support the supralinearity theory provide possible mechanisms for lead effects, but do not address the specific questions raised by the supralinearity theory. For example, the papers by Markovac and Goldstein (1988) and Schneider *et al.* (2003) provide the basis for hypotheses of possible mechanisms of low-dose lead effects; however, they do not specifically address the issue of supralinearity (*i.e.*, whether adverse effects occur to a greater extent at lower doses than higher doses or why such a response might be observed).

Animal studies also have the potential to provide alternative insights into potential mechanisms of action for lead toxicity; however, results from such studies also must be interpreted in light of their relevance to effects observed in humans. As noted by Bellinger (2004), animal models "are of relatively little help, however, in evaluating lead's effects on the ability to manipulate symbolic or abstract systems...that have no compelling nonhuman analogues." The Bellinger review also notes that scientists have yet to develop "a unifying model of the mechanisms of lead neurotoxicity."

The understanding of the potential dose-response relationship between lead exposure and neurotoxic effects may be at least partially obscured by differences in lead exposure levels among various sites in the body and uncertainties regarding which biomarker levels and which specific time frames of exposure are best correlated with health impacts. For example, although most studies of the health effects of lead have used whole blood lead concentrations as a biomarker for lead exposure, the actual dose that is experienced by the central nervous system in mediating neurotoxic effects may be quite different (*e.g.*, Lidsky and Schneider, 2003). Moreover, differences in the half-life of lead in whole blood *vs.* that in other organs add another layer of complexity to evaluations of potential lead effects. Other factors such as dietary habits and rates of deposition in bones and soft tissue may also vary greatly between subjects and may affect whole blood lead measurements (*e.g.*, Manton *et al.*, 2001; Leggett, 1993). These types of considerations reflect yet another aspect of uncertainty in the underlying biological mechanisms by which lead may generate neurotoxic effects that warrants additional research and must be adequately addressed when interpreting currently available data to support regulatory and policy assessments.

The importance of putting dose-response models in a biological context when conducting risk analyses also played an important role in assessing the potential neurobehavioral effects of methylmercury exposures. In evaluating the available data, the National Research Council (NRC, 2000) recognized that use of different dose-response models (*e.g.*, linear, square-root, and log models) could yield widely varying estimates of the potential toxicity of methylmercury, especially when observed results were used to extrapolate potential effects that might occur at lower dose levels. As a result, the NRC concluded that the dose-response modeling choice "cannot be based on statistical grounds alone" and that biological plausibility should be evaluated in determining an appropriate dose-response model. After a thorough review of the available data, the NRC concluded that a linear model that excluded the possibility of a supralinear dose-response curve at low doses made "the most sense" for modeling the toxicity of methylmercury. One factor influencing this decision was the relative absence of actual exposure levels and effect observations at low doses. US EPA (2007) agreed with this analysis and adopted this approach in its Integrated Risk Information System (IRIS) listing for methylmercury. For example, in deriving a reference dose for methylmercury, US EPA noted that "[t]here is no identified mechanism by which methylmercury would produce a supralinear response; therefore the [selected dose-response model] was thought to have more biological plausibility compared with other models." As an additional element of assessing the biological plausibility of a supralinear dose-response curve for low-dose lead exposures, it should be noted that some biological information suggests that low-level lead exposures could have a hormetic effect, *i.e.*, could produce beneficial effects at low doses. For example, a comprehensive review of available data regarding potential hormetic effects of metals (Calabrese and Baldwin, 2003) found hormetic responses in a wide variety of

non-essential metals and in a wide variety of species. Specifically, they found a number of studies indicating that low-level lead concentrations can induce protective mechanisms (*e.g.*, increased levels of glutathione, a tripeptide that plays a role in protecting various target organs from metal toxicity). For example, Legare *et al.* (1993) observed this type of response in a cell culture study using astroglial cells, a type of cell of the central nervous system. In another example, Iavicoli *et al.* (2003) looked at the effects of low doses of dietary lead on the production of red blood cells in mice. Pregnant mice were dosed during gestation and lactation, and litters were dosed until postnatal day 90, when animals were sacrificed. The researchers found that doses of lead providing exposure considered to be less than normal background (less than 2.0 µg/dL) led to enhanced red blood cell production, even though higher lead exposures yielded decreases in red blood cell production. Such effects would yield a sublinear dose-response relationship at low dose levels rather than a supralinear response. Toxic effects in such cells are thought to be mediated by effects on cellular metabolism and function.

A potential hormetic effect was also mentioned in the study cited by Canfield *et al.* (2003) as providing potential support for a mechanistic basis for a supralinear dose-response curve. Specifically, Bae *et al.* (2001) noted that growth stimulation was observed in certain of the cell lines that they tested when they used the lowest tested concentrations of the metal mixtures. This response was observed only when the cells were exposed to the metal mixtures, not to individual metals. These researchers suggested that this response might be due to hormesis. Thus, illustrating the uncertainties currently inherent in determining the dose-response curve for low-dose lead exposures and potential underlying mechanisms of action, the same research used to suggest a possible mechanism for a supralinear dose-response curve also provides information that suggests a possible mechanism for a sublinear dose-response curve.

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May 25, 2006
David Siegel, Ph.D.
Chief, Integrated Risk Assessment Branch
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Dear Dr. Siegel,

The Human and Ecological Risk Division (HERD) of the Department of Toxic Substances Control has completed the review of the OEHHA Response to DTSC/HERD Comments on the draft document:

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).

Since the conclusions of the document may have large impacts on DTSC projects and because there is national attention about the issue of blood thresholds for lead in children, HERD strongly recommends that this document go out for additional peer review by experts in the area of meta-analysis, psychometrics, and IQ testing. This peer review should include peer review by University of California, Center for Disease Control (CDC), and USEPA Headquarters.

The HERD comments on the OEHHA Response to Comments are attached to this letter. If you have any questions concerning these comments, please contact Dr. Michael Wade at 916-255-6653 or Dr. Deborah Oudiz at 916-255-6647.

Sincerely,

Stephen M. DiZio, Ph.D.
Chief, Human and Ecological Risk Division

DTSC/HERD Response to Comments OEHHA Child Specific Reference Concentration Lead May 25, 2006

DTSC/HERD Reply
to OEHHA Responses to Comments on
“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), February 6, 2006
May 25, 2006

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 $\mu\text{g}/\text{dl}$ lead in blood) is based on a decline in 0.86 IQ points per $\mu\text{g}/\text{dl}$ 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 $\mu\text{g}/\text{dl}$ 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.*

Response: The study design and statistical analysis of the epidemiological studies discussed in the document were reviewed by individuals with expertise in epidemiology and statistical analysis of epidemiological studies. 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.

HERD REPLY TO RESPONSE: HERD appreciates that the document was reviewed by individuals with expertise in epidemiology and statistical analysis, and that the paper selected as the basis of the chRC (Lanphear et al., 2005) was published in a peer reviewed journal. Nonetheless, responses to the 2005 Lanphear study raised methodological issues that need to be addressed if this study is to be used as the basis of the chRC (Eskenazi, B et al., Environ Health Perspect. 2005 October; 113(10): 1419–1429; Ernhart, CB, Environ Health Perspect. 2006 February; 114(2): A85–A86; Lanphear, BP et al., Environ Health Perspect. 2006 February; 114(2): A86–A87). HERD continues to recommend that the document be sent out for a peer review by individuals with expertise in the application of meta-analysis in psychometric studies.

OEHHA Response: OEHHA obtained additional peer review. The Centers for Disease Control (CDC), and USEPA Headquarters declined to comment

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 than 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.*

Response: OEHHA has a stated preference for a benchmark dose approach over the NOAEL/UF approach. Furthermore, OEHHA identified no basis for estimating no-adverse-effect-level in sensitive humans. The absence of an identified NOAEL is discussed in the document.

HERD REPLY TO RESPONSE: We believe that there is significant scientific evidence correlating blood lead concentrations at or above 10 ug/dl and cognitive deficits observed in children. However, the wide dispersion of data reported in Rothenberg and Rothenberg (2005), especially at low blood lead levels (<10 ug/dl) makes it impossible to differentiate the neurotoxic effect of lead on IQ test

results and the normal distribution of IQ score in the population. The OEHHA document indicates that it is impossible to identify a NOAEL. We find it highly uncertain to linearly fit the low blood lead data (<10 ug/dl). In order to address this uncertainty and support the use of the linear fit model, HERD believes that it is essential to present the linear regression coefficients for several data ranges of blood lead concentrations (e.g. <1 to 7.5 ug/dl, <1 to 10 ug/dl, ≥7.5 ug/dl, and ≥10ug/dl).

OEHHA Response: The slopes, along with confidence intervals, are given in the document (see page 9).

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.*

Response: 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. 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 allowable increase in Pb_B would be different for each child, depending on his or her pre-existing Pb_B , 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, 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 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 ΔIQ between the 5-10 ug/dl group and the 10-15 ug/dl group is greater than the ΔIQ between the 0-5 ug/dl group and the 5-10 ug/dl group.

HERD REPLY TO RESPONSE: We understand the problems in applying the log-linear model to risk assessment. However, based on the nature/property of the data, the linear fit model can oversimplify the effects of children exposure to lead. The two proposed options (calculating an average slope from the log-linear

model, or linear fit of the data) are both based on an assumption of a linear correlation between concurrent blood lead concentration and IQ decrement observed in the studies. In the absence of a clear linear correlation between the concurrent blood lead concentration and the IQ decrement observed in children (at <10 ug/dl blood lead), HERD is of the opinion that it is inappropriate to use the data for linear modeling or to obtain an average slope using the log-linear model.

In order to determine whether the lead-associated IQ decrement was greater at lower blood lead concentrations, Lanphear and coworkers performed the linear fit on the data and compared the blood lead coefficients for the concurrent blood lead index at two different cut-points. The authors concluded that the coefficient for children with maximal blood lead levels <7.5 ug/dl was significantly greater than the coefficient for children with blood lead level ≥ 7.5 ug/dl (Figure 4 of Lanphear et al., 2005), whereas the coefficient for children with maximal blood lead <10 ug/dl was not significantly greater than the coefficient for children with maximal blood lead ≥ 10 ug/dl.

OEHHA Response: The coefficient for children with maximal blood lead <10 ug/dl was -0.8; the coefficient for children with maximal blood lead ≥ 10 ug/dl was -0.13, a > 6-fold difference ($p=0.1$). The linear slope relating IQ to Pb_B for children with concurrent $Pb_B > 10$ ug/dL blood was significant (95% confidence interval does not include 0).

OEHHA did not present a rationale for choosing 10 μ g/dl as the cut-point for their linear model.

OEHHA Response: The revised document presents a rationale for choosing 10 μ g/dl as the cut-point for their linear model on page 11-12. More importantly, we do not concur with the interpretation of Figure 4 stated in the OEHHA document (page 8). According to the text, Lanphear and coworkers did not indicate that the 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. From our review of the article, we believe that Figure 4 was used to illustrate the cut-point applied in above analysis.

OEHHA Response: The article clearly states (page 898, middle column) that the results using 10 as a cut-point are consistent with the results using 7.5 as a cut-point. Basing our slope on the latter would have meant basing it on about 1/7 as many data-points and would have resulted in a UCL about 5-fold higher. The interpretation of Figure 4 on page 8 of an earlier OEHHA draft document has been eliminated. However, we note that in Figure 1, the cubic spline function shows the bi-phasic nature of the IQ/blood lead relationship even more clearly than the more-constrained log function.

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 μ g/dl blood lead concentration range. OEHHA chooses to approximate this curvilinear slope by a linear slope over the 1-10 μ g/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 µg/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 µg/dl range is necessary for supporting the use of the linear slope.*

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Response: OEHHA is aware that there is a good deal of scatter in the data. This reflects the fact that many factors besides lead exposure affect children's intellectual development. The document states on page 6 that none of the studies concluded that lead was the most important influence on cognitive development. The multifactorial nature of neurobehavioral development is further discussed on page 16. In order to capture the apparent steeper response for children with lower Pb_B while avoiding the above-mentioned 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 µg/dl, and the resulting slope used as in calculating the benchmark change in

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blood lead concentration. A regression coefficient is not immediately available for these regressions, but we do know that the coefficient was statistically significant. 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 change in IQ for a given change in Pb_B. As previously stated, we believe that the document has been sufficiently reviewed by experts.

HERD REPLY TO RESPONSE: Please refer to our responses to Parts i and ii of this section.

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 µg/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 µg/dl range. *HERD believes that it is important to include a discussion of this data limitation.*

Response: The fact that a difference can still be detected 5 years later suggests that the effect persists for an extended period. Had there been concurrent measurement of Pb_B and IQ in the Boston study, the association between the two may have been stronger and the slope (for that study) slightly steeper. It is unlikely that the composite slope for the seven studies would have changed significantly.

HERD REPLY TO RESPONSE: We agree with OEHHA that an effect which can still be detected five years later suggests the persistence of the chemical and its toxicity. However, our comment was related to concerns that concurrent blood lead concentrations not were collected in the Boston study. Blood lead concentrations can be affected by recent exposures and homeostasis of bone lead. The presence of a five year gap between the blood lead measurements and the IQ test results can introduce significant uncertainty to the correlation between IQ decrement and concurrent blood lead concentration. HERD believes that the uncertainty should be addressed, especially because OEHHA is trying to quantify the correlation (slope) between IQ decrement and concurrent blood lead concentrations.

OEHHA Response: While we agree that concurrent measurement of Pb_B and IQ would have been optimal, it is highly unlikely that the Pb_B levels of this cohort increased during the interval between the last Pb_B measurement and the IQ testing. Not only is Pb_B declining in the general population over time, but also most children show declining Pb_B with increasing age. Further, the model was not highly dependent on any single cohort; eliminating the cohorts one at a time from the analysis resulted in a range of estimated slope values from -2.36 to -2.94.

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.*

Response: The figure has been revised.

HERD REPLY TO RESPONSE: The figure included in the March 2006 draft version of the document has been updated.

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.*

Response: OEHHA's statement that no safe level has been established does not imply that OEHHA believes that the toxicity of lead is a non-threshold phenomenon. 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.

HERD REPLY TO RESPONSE: HERD agrees that the discussion referenced in the Response indirectly suggests the possibility of an as-yet-unidentified threshold. However, in the absence of an identified no-adverse effect level, the proposed use of a slope approach may appear to imply an assumption of non-threshold effects. As commented earlier by HERD, the June 2005 draft version of the OEHHA document stated that this proposed approach is "in a sense analogous to a source-specific incremental cancer risk." In the absence of sufficient data to clearly indicate that a threshold does not exist, HERD concurs with the deletion of the comparison of the proposed blood lead concentration change approach to the use of cancer slope factors in the revised document.

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.

Response: OEHHA has added some discussion of test methods (see page 12).

HERD REPLY TO RESPONSE: HERD appreciates the brief history of IQ testing presented on page 12 of the revised document. However, HERD's original concerns regarding the lack of basic information on IQ testing remains. The concept of IQ, as well as the many tools to measure the concept, has been questioned by researchers over the years. Issues such as the use of verbal vs. non-verbal IQ tests, cultural bias, age of testing, are just a few that have received long consideration in the scientific and psychometric communities (Blinkhorn, S, Nature 2005 November, **438**, 31-32; Furnham, A et al., Inter J of Selection & Assessment 2005 March, **13**:11-24; Benson, E, Monitor on Psych. 2003 February, **34**:48). HERD continues to recommend that this section be revised to include a discussion on the use of IQ testing, the strengths and limitations of the tests, and the functional effects of a decline of one or more IQ points.

OEHHA Response: The discussion of the effect of a 1-point decline in IQ both in an individual and as a population-wide average is expanded in the revised document.

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 µg/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).

Response: The legislative mandate specifically refers to children. Consideration of teachers and other adults at schools is focused on protecting fetuses and nursing infants. OEHHA is not aware of any evidence suggesting that adults are more sensitive than children, infants, and fetuses. Thus any risk-based decisions at school sites that results in the protection of children, infants, and fetuses will also protect adults.

HERD REPLY TO RESPONSE: As indicated in our initial comment, it has been reported in the literature that small increases in blood lead can result in adverse effects in adults. It is HERD's opinion that this literature relevant to the document.

OEHHA Response: The legislation requiring this analysis directs OEHHA to analyze effects that are greater in children than in adults. We have included sufficient data concerning effect levels in adults to illustrate this difference.

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.*

Response: The relative source contribution has been eliminated.

HERD REPLY TO RESPONSE: The March 2006 draft version of the document has been updated in this regard.

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.*

Response: The relative source contribution has been eliminated.

HERD REPLY TO RESPONSE: The March 2006 draft version of the document has been updated in this regard.

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.*

Response: The relative source contribution has been eliminated.

HERD REPLY TO RESPONSE: The March 2006 draft version of the document has been updated in this regard.

d. The document recommends using the DTSC Leadsread Spreadsheet model that contains blood lead intake slopes of 0.16 µg/dl per µg/day for children and 0.04 µg/dl per µg/day for adult. However, OEHHA adopts the Centers for Disease Control (CDC) blood lead intake slope of 0.35 µg/dl per µg/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.*

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

HERD REPLY TO RESPONSE: Because the noted discrepancy will exist in the meantime (i.e. until the PHG for lead is updated), HERD recommends that this issue be addressed in the document. Minimally, the discrepancy should be acknowledged with an indication that the PHG will be soon updated to include the current paradigm.

OEHHA Response: A statement that the PHG is under review has been added.

In Table 6: Other Sources of Lead Exposures, the document estimates an upper limit of blood lead contribution of 2.9 µg/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.*

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

HERD REPLY TO RESPONSE: Please refer to our responses for Parts a – d of this section.

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.*

Response: This has been corrected; a new term has been proposed.

HERD REPLY TO RESPONSE: The March 2006 draft version of the document has been updated in this regard.

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 µg/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.*

Response: The relative source contribution has been eliminated.

HERD REPLY TO RESPONSE: The March 2006 draft version of the document has been updated in this regard.

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.*

Response: 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.

HERD REPLY TO RESPONSE: The text of the March 2006 draft version of the document has been updated to clarify that the 97.5 upper confidence limit was used.

d. 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.*

Response: The specific example has been deleted from the document.

HERD REPLY TO RESPONSE: The March 2006 draft version of the document has been updated to delete this specific example.

7. 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.*

Response: The newer information has been added.

HERD REPLY TO RESPONSE: HERD concurs with the updates included in the document.

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.*

Response: The newer information has been added.

HERD REPLY TO RESPONSE: HERD concurs with the updates included in the document.

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.*

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

HERD REPLY TO RESPONSE: We cannot identify any modifications to the paragraph.

OEHHA Response: The current version is further revised.

Lesley and coworkers (2000) reported an IC₅₀ of 0.55 uM for inhibition of ³H-MK-801 binding by lead, which is a value at least 50-fold greater than the free lead concentration present in brain interstitial fluid of animals exposed at environmentally relevant levels. They concluded that a direct inhibitory effect of lead on the NMDA receptor does not appear to occur at environmentally relevant exposure levels. Instead, exposure-induced changes in NMDA receptor function are likely mediated by other mechanisms. HERD recommends modifying the paragraph which specifically describes that lead blocks post-synaptic NMDA receptors at concentrations in the range that affect learning in children (1st paragraph of page 20).

OEHHA Response: The contradiction referred to has been eliminated.

d. 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.*

Response: The original OEHHA text is in agreement with the proposed text, albeit in a more general manner.

HERD REPLY TO RESPONSE: HERD concurs with the response.

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February 12, 2007

Mr. Leon Surgeon
Integrated Risk Assessment Branch
Office of Environmental Health Hazard Assessment
P.O. Box 4010
1001 I Street, MS-12B
Sacramento, California 95812-4010

Dear Mr. Surgeon,

We would like to thank you for the opportunity to provide comment on the final Draft Report "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" (here after referred to as "the assessment").

The assessment is noteworthy to us, as experts in the field of children's environmental health, because we are unaware of any other lead assessment that has used the most recent data to arrive at a health guidance value for lead as low as 1 ug/dL. We support the assessment's conclusions and the use of 1 ug/dL change in blood lead level as a health guidance value for infants and children, as well as school students and staff.

We agree with the assessment that there is likely no "safe" dose for lead exposure, and that the linear (non-threshold) model used in the assessment is appropriate. The Office of Environmental Health Hazard Assessment analysis is consistent U.S. EPA's Integrated Risk Information System (IRIS) file for lead (available on line at www.epa.gov/iris), which states that "It appears that some of these effects, particularly changes in the levels of certain blood enzymes and in aspects of children's neurobehavioral development, may occur at blood lead levels so low as to be essentially without a threshold."

We also note that the benchmark response analysis applied in the assessment seems to be consistent with U.S. EPA's benchmark dose methodology (Draft, 2000). This document recommends a point be calculated at 10% response for comparison purposes, but suggests that for continuous data the biologically significant change can be used as the benchmark response. The latter is what has been presented for IQ decrement in the assessment, as the small difference is "highly significant on the population basis."

Overall, we support the School Site Risk Assessment efforts in California and the derivation of child-specific reference values for the purpose of protecting children's health. Please note, we provide these comments based on our professional and scientific expertise in

the field of children's environmental health, and not in our role as staff of the U.S. EPA's Office of Children's Health Protection and Environmental Education.

Sincerely,

Brenda Foos, MEM



Elizabeth Blackburn, RN



Devon Payne-Sturges, DrPH