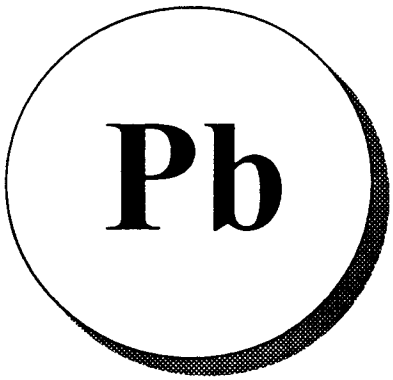
California Environmental Protection Agency

Air Resources Board

Technical Support Document

Proposed Identification of Inorganic Lead as a Toxic Air Contaminant



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Health Effects of Airborne Inorganic Lead

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Office of Environmental Health Hazard Assessment
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HEALTH EFFECTS OF AIRBORNE INORGANIC LEAD

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Section 1. Summary

The health effects of inorganic lead have been reviewed and evaluated to assist in the determination of whether inorganic lead should be classified as a toxic air contaminant as defined by California Health and Safety Code Section 39650 et seq. In this document, "lead" refers to inorganic lead, including elemental lead. People may be exposed to lead from air, water, soil, foods, consumer products, dust and lead-based paint chips. While this document is especially concerned with the impact of airborne inorganic lead, at current ambient concentrations, air lead, on average, is a minor contributor to a child's overall lead exposure. Lead particulate matter is the primary form of lead present in the air. Once absorbed, lead is distributed throughout the body.

Investigation of the distribution of blood lead levels in the U.S. population has been conducted by the Centers for Disease Control (CDC) in large cross-sectional national surveys. The results indicate a substantial decline in blood lead levels from National Health and Nutritional Examination Survey (NHANES) II (1976 to 1980) to NHANES III (1988 to 1991). There was an overall decrease in blood lead levels of 78% for persons aged one to 74 years of age over this time period. In NHANES II (1976 to 1980) an estimated 88.2% of one to five year old children in the U.S. exhibited blood lead levels greater than or equal to 10 μg/dL. In the NHANES III survey (1988 to 1991) only 8.9% of 1 to 5 year olds were determined to have blood lead levels equal to or greater than 10 μg/dL. A decrease in blood lead levels of a similar magnitude (greater than 70%) was observed not only for the total population, but also for subgroups stratified by race/ethnicity, gender, urban status and income levels. However, the number of children aged one to five with blood lead levels greater than or equal to 10 μg/dL is disproportionately higher for non-Hispanic African-American children.

The dramatic decline in blood lead levels is consistent with, and undoubtedly related to, continued reduction in exposure to lead from environmental sources which began in the late 1970's. From 1976 to 1990, the amount of lead used in gasoline decreased 99.8% nationally (from 205,810 tons to 520 tons). In California, there has been an approximate 30-fold decrease from 1976-1980 in average ambient air lead levels compared to current ambient air lead levels (see Figure IV-2, p. A-6, Part A of this document). From 1980 to 1990, the amount of lead used in soldered cans also decreased dramatically. In 1980, 47% of the food and soft drink cans were lead soldered, and by 1990 this figure had decreased to only 0.85%. As of November 1991, lead soldered food and soft drink cans were no longer manufactured in the U.S. The manufacture of lead-based paint was limited by the Consumer Product Safety Commission in 1978. Still, lead-based paint remains a potential source of exposure for residents of older housing with deteriorating paint. The authors of NHANES III have concluded that the reduction of lead in gasoline is most likely the greatest contributor to the observed decline in blood lead levels during the period of the national survey. The major remaining sources of environmental lead that pose a potential public health threat appear to be localized sources of lead, including but not limited to continued deterioration of lead-based painted surfaces in older buildings, lead that has already accumulated in dust and soil, and near source air emissions.

Lead has been reported to cause many different health effects, as discussed in Sections 2 and 3. Based on current knowledge, potential adverse health effects that are of concern occur at relatively low blood lead concentrations (at or near 10 μg/dL) are: (1) neurodevelopmental effects in children, and (2) increased blood pressure and related cardiovascular conditions in adults.

There is also evidence for carcinogenicity of lead at higher doses in animals which could extend to humans. Of these three outcomes, the neurodevelopmental effects are likely of greatest public health significance since, as suggested by several human epidemiologic studies, the effects may be irreversible. Section 3 reviews the studies relevant to these three adverse health outcomes.

Unlike most toxicological risk assessments and previous assessments of toxic air contaminants, most of our conclusions are based on human studies. The uncertainties in the risk assessments for adverse neurodevelopmental effects and increased blood pressure are considered to be much less than those for the cancer endpoint. Four major uncertainties, usually encountered in risk assessments, are those due to (1) animal-to-human extrapolation, (2) high-to-low dose extrapolation, (3) accounting for sensitive members in the human population, and (4) small numbers of subjects. Often, for risk assessments, results in animals are extrapolated to humans. For the noncancer endpoints from lead exposure, the data used were obtained in humans so that uncertainty due to interspecies extrapolation is not an issue. The second concern, the degree of uncertainty introduced by extrapolation from high to low doses, is small for the noncancer endpoints. Only limited extrapolation is necessary, since most results have been obtained at blood lead levels within a factor of two to five of the current estimated mean blood lead levels in California.

The third source of uncertainty, differential sensitivity in the population, is relatively small for adverse neurodevelopmental effects and increased blood pressure, since sensitive individuals were considered within the studies evaluated. However, for effects on neurodevelopment and blood pressure, a threshold level has not yet been clearly identified in humans. In addition, within these identified groups (children and adults), there may be particularly sensitive subgroups not considered. The fourth source of uncertainty, arising from the small numbers of subjects typically evaluated in animal or human studies, is relatively insignificant. For lead there are multiple studies, including a large number of people: nearly 2,000 children in the neurodevelopment studies and more than 10,000 adults in the blood pressure studies. Consequently, the uncertainty in the noncancer risk assessment for lead is small relative to that usually encountered in risk assessments for toxic chemicals.

The relationship of blood lead level to neurodevelopmental effects in children has been examined in 5 prospective studies conducted in Boston, Cleveland, and Cincinnati, and in Port Pirie and Sydney, Australia. Taken together, these studies indicate an association between general measures of intelligence and both pre- and postnatal blood lead concentrations. The blood lead levels at which these effects have been observed are 10 to 15 micrograms per deciliter (μg/dL) (National Research Council, 1993). In one cohort, effects on intelligence (using Bayley's Mental Development Index) were observed in infants from lower socioeconomic backgrounds with umbilical cord blood lead levels as low as 6 to 7 μg/dL (Bellinger et al., 1989b). More recent studies (see Section 3.1), indicate associations between postnatal exposure to lead and intelligence quotient (IQ) as measured by the WISC-R full scale IQ test. These effects appear to result from both pre- and postnatal exposure to lead. The cohort studies suggest that up to at least age seven, exposure to lead may be associated with subsequent neurodevelopmental effects. Based on these findings, the Office of Environmental Health Hazard Assessment (OEHHA) concurs with the U.S. EPA and the U.S. Centers for Disease Control that 10 μg/dL should be regarded as the level of concern for children. A no observed adverse effect level (NOAEL) has not yet been identified, and a recent analysis, specifically focusing on the determination of a

threshold, was unable to detect one (Schwartz, 1993). Therefore, a threshold for neurodevelopmental health effects, based on blood lead values, has not been identified.

While the level of concern is described as 10 μg/dL, CDC has also identified different levels above 10 μg/dL and associated responses. For example, when many children in a community are between 10 and 14 μg/dL (a "border zone" range), community-wide childhood lead poisoning prevention activities should be initiated. All children with blood lead levels at or above 15 μg/dL should receive nutritional and educational interventions and more frequent blood lead screening. Between 15 and 19 μg/dL, environmental investigation (including a home inspection) and remediation should be done if the blood lead levels persist. A child between 20 and 44 μg/dL should receive environmental evaluation and remediation and a medical evaluation. Such a child may need pharmacologic treatment for lead poisoning. Above 45 μg/dL, a child would receive both medical and environmental interventions, including chelation therapy. (CDC, 1991)

Lead in the environment, including the occupational setting, has also been correlated with increased blood pressure in adults. Several large population-based studies have examined the relationship between blood lead and either systolic or diastolic blood pressure. A relationship between diastolic blood pressure and blood lead appears to exist across a wide range of blood lead values, possibly extending down to as low as 7 μg/dL for middle-aged Caucasian men, with some evidence of effects in women and other age groups as well (See Section 3).

Lead can cause gene mutations and cell transformation in mammalian cells in culture. Lead also interferes with DNA synthesis in mammalian cells in culture. Many studies have shown that feeding lead compounds to rodents induces kidney tumors. Available epidemiologic studies of people occupationally exposed to lead give some indication that occupational exposure to lead may cause cancer. However, in these studies, lead was only one of several known or putative carcinogens present in the occupational environment.

The International Agency for Research on Cancer (IARC) has concluded that there is sufficient evidence for the carcinogenicity of lead and inorganic lead compounds in experimental animals; in humans, the evidence for carcinogenicity was found to be inadequate. Overall, based on both the animal and human data, IARC considers that lead is possibly carcinogenic in humans (Class 2B). The United States Environmental Protection Agency (U.S. EPA) designates lead as a probable human carcinogen (Group B2). The U.S. EPA defines Group B2 substances as those for which there is sufficient evidence of carcinogenicity from animal studies, but inadequate or no data from epidemiological studies. OEHHA concurs with these conclusions. In addition, no evidence for a threshold level for lead-induced cancer in laboratory animals has been found, although a threshold is theoretically possible. Finally, the State of California has identified several lead compounds as carcinogens and lead as a reproductive toxicant for purposes of the Safe Drinking Water and Toxic Enforcement Act of 1986 ("Proposition 65") (Health and Safety Code 2549.5 et seq.; California Code of Regulations, Title 22, Section 12000 et seq.).

Since epidemiologic studies use lead concentration in blood as an indicator of exposure, it is necessary to relate changes in air lead (expressed as micrograms of lead per cubic meter of air or $\mu g/m^3$) to changes in concentrations of blood lead (expressed as micrograms of lead per deciliter of blood or μg/dL). Section 4 provides a review of the studies that relate changes in air lead exposure to changes in blood lead concentrations. These studies indicate a strong and consistent association between ambient concentrations of lead in the air and subsequently measured blood lead levels in children and adults. OEHHA used these studies as the basis for an

"aggregate" model which quantitatively relates exposures from ambient air lead concentrations, both directly through inhalation and indirectly through other media impacted by airborne lead (for example soil and dust) to blood lead levels. The aggregate model was used to estimate the effects of changes in ambient air lead levels on the subsequent blood lead levels in adults and children. Current evidence suggests that the blood lead to air lead relationship for adults is approximately 1.8 μg/dL per μg/m^3, while the relationship for children is approximately 4.2 μg/dL per μg/m^3 with a range of geometric means from 3.3 to 5.2 μg/dL per μg/m^3. These slopes are assumed to be linear within the range of blood and air concentrations currently experienced in California. OEHHA also used the U.S. EPA's Integrated Exposure Uptake Biokinetic (IEUBK) model to estimate the impact of changes in ambient air lead concentrations on blood lead levels in children (see Sections 4.2, 5.5 and Appendix C). Recent studies of the model carried out by the U.S. EPA using the supplemental equations (Eqs. 4-4 and 4-6) for East Helena (EH) data and data from 40 communities (AGG) yielded slopes of 3.7 (EH) and 5.3 μg/dL per μg/m^3 (AGG) as air lead concentration changed from 1.5 to 2.5 μg/m^3 (Hogan, 1995). OEHHA also looked at the slopes generated by incremental increases between 0 and 1 μg/m^3. In this range of air lead concentrations, the IEUBK model predicts approximate slopes ranging from 4.8 to 6.7 μg/dL per μg/m^3 for the EH data and from 6.8 to 10 μg/dL per μg/m^3 for the AGG data with the higher slopes occurring at lower air lead concentrations. The air lead to blood lead slopes of the IEUBK model are dependent upon the magnitude of the input parameters for lead from other environmental media (water, food, etc.) Thus the use of the slope of 4.2 μg/dL per μg/m^3 from the aggregate model is based on the best available information and is consistent with the slopes derived from the IEUBK model.

Section 5 evaluates the potential health effects from a range of air lead exposure using the aggregate model and the IEUBK model. Estimates of the effects of alternative air lead concentrations on both the mean decrease in IQ and the population distribution of blood lead levels are provided. Data from the third National Health and Nutrition Examination Survey (NHANES III), representative of the U.S. population, were used to estimate the current blood lead distributions for residents of California. For neurodevelopmental effects of lead, the results of the prospective cohort studies indicate a potential mean decrease of 1.39 IQ points per μg/m^3 air lead. Applying this mean change to the cohort of 4.73 million children in California below age 7 suggests that the current ambient lead concentration of 0.06 μg/m^3 is associated with a potential mean loss of 0.08 IQ points per child. A small difference in a mean score between two groups can result in large differences in the proportion of the population at extreme values, since the entire distribution is shifting. At 0.06 μg/m^3, the proportion of children with IQ scores below 80 increases by 1% relative to zero air lead. At a hypothetical elevated concentration of 0.20 μg/m^3, OEHHA predicts an average loss of 0.28 IQ points. The proportion of scores below 80 increases by 3%. The effects of changes in air lead on the distribution of blood lead for the subgroup of children with the highest mean blood lead levels, one and two year old children, were also determined. To quantify the potential impact of the current average ambient air lead concentration of 0.06 μg/m^3 on children one and two years old, blood lead values based on the aggregate slope model were extrapolated to zero air lead. The estimated percentage of children above the 10 μg/dL level of concern decreases from 11.5 % to 10.9%. Thus, even after subtracting out the "background" average ambient air lead level, potentially 131,000 (10.9%) of one and two year old children in California could still have blood lead levels exceeding 10 μg/dL due to exposures form other environmental sources such as water, food, contaminated soil and

house dust, lead-based paint, and possibly near source air lead exposures above the background level. In addition to these children being further impacted by the background air lead level, there would be a smaller number of children (0.06%) who would otherwise be just below 10 μg/dL due to the average ambient air lead concentration of 0.06 $\mu g/m^3$. Similar calculations using US EPA's IEUBK model with input parameters based on two empirical data sets (East Helena [EH] and an aggregate of forty communities [AGG]) predicted approximately 2% of one and two year olds could have blood leads above 10 μg/dL due to the average ambient lead level. However, these estimates of 0.6% and 2% have considerable uncertainty because the major exposure pathways for lead are indirect, that is the exposures result from accumulation of lead in environmental sources such as soil and house dust. It is difficult to estimate the true contribution of the current low level of air lead in soil because of pre-existing lead levels that may have been deposited prior to the phase out of leaded gasoline or from deteriorating lead-based paint used in some older housing. For comparison, the effects of a hypothetical elevated air lead concentration of 0.20 $\mu g/m^3$ were also evaluated. The aggregate slope model predicted 3.6%, or an additional 3% (3.6% - 0.6% = 3%) of one and two year old children exposed at this air concentration could have blood lead levels above 10 μg/dL when compared to the average ambient air lead concentration. Again, there is uncertainty in both the amount of this predicted increase and when it might occur because of the time required to accumulate air lead into environmental sources that result in the greater exposures (for children, soil and house dust ingestion). For the NHANES III national survey, it is of interest that the children most at risk from elevated environmental sources of lead are African-Americans and Hispanics residing in large metropolitan areas. However, our analysis indicates that for California children as a whole, overall exposure to the average ambient air lead concentration contributes only a small fraction of their total daily lead exposure.

As indicated above, most of the lead exposure can be attributed to sources other than the average ambient airborne lead concentration of 0.06 $\mu g/m^3$. These sources include tap water, lead-based paint, contaminated food or soil, as well as possible near source airborne lead exposure exceeding the ambient average. The contribution of alternative sources, as well as the likelihood that a child's blood lead levels exceeds 10 μg/dL, will depend on characteristics of the home environment and community. For these reasons, Section 5 also illustrates how the information generated from the IEUBK model can be used to evaluate the relative impacts of alternative sources (air and non-air) of lead exposure. The model allows the user to hypothetically change the level of alternative sources and to estimate how blood lead levels in the community might change in response to varying each source separately.

The IEUBK model and the aggregate model are both useful tools for risk managers. The aggregate model can be used to determine the potential impact of an airborne lead concentration on the proportion of children exceeding the 10 μg/dL level of concern. Alternatively, the IEUBK model, which uses data from all of the major sources of lead exposure can be used to estimate the expected community blood lead distribution and may be useful in determining an appropriate mitigation strategy to reduce childhood blood lead levels for a given community. We recommend that further risk management guidance in this area be developed by the Air Resources Board staff with the participation of OEHHA.

Section 6 quantifies the risks for blood pressure changes in adults aged 40 to 59 associated with changes in ambient air lead concentrations. Our models estimate increases in the diastolic blood pressure and how the increases may result in hypertension (change in the diastolic blood pressure $\geq$ 90 mm Hg), non-fatal heart attacks or mortality. Specifically, the estimates

indicate that the current average ambient air lead concentration of 0.06 $\mu g/m^3$ may result in 26,000 cases of hypertension (change in the diastolic blood pressure $\geq$ 90 mm Hg) with a 95 percent confidence interval of 6,100 to 60,800. In addition, the current ambient lead levels may result in 72 additional cases of fatal and non-fatal heart attacks and sudden deaths from coronary heart disease per year (95 percent confidence interval of 12 to 164) and 74 additional deaths per year (95 percent confidence interval of 9 to 218). Although some of the health outcomes are derived from nonlinear models, linear approximations fit the data well and can be used to estimate the impacts of changes in air lead concentrations over ranges seen in California.

While such estimates are based upon the best available scientific data, they rely on models which contain many assumptions and uncertainties. Care should be taken to not ascribe a greater precision to these risk estimates than is warranted by the underlying assumptions and uncertainties in the risk models.

For cancer effects, as described in Section 7, OEHHA recommends the range of carcinogenic risks from ambient exposures to lead be based on the upper 95% confidence limits predicted from fitting a multistage model to the best available animal data set, kidney tumors induced in rats by oral exposure to lead compounds. The use of upper confidence limits are recommended because they are more statistically stable than mean values and because they are thought to better protect the more sensitive members of the human population. Use of the upper bound estimate means that the "true risk" will not exceed the risk estimate derived through the use of the model, and is likely to be less than that predicted and may be zero. The upper bound individual excess lifetime cancer risk for humans is the risk estimated from an average 24-hour-per-day exposure to ambient airborne concentrations of lead over an average 70-year lifetime. This upper bound range of risk is estimated to be 1.2×10^{-5} to 6.5×10^{-5} per $\mu g/m^3$. The best value of the unit cancer risk for air was selected as 1.2×10^{-5} per $\mu g/m^3$ since it is based on the best dose-response study available (See Section 7.5). This corresponds to an upper bound estimate of 24 excess cancer cases from the average ambient concentration of 0.06 $\mu g/m^3$ in an estimated total California population of approximately 34 million.

As with any cancer risk estimate, the sources of uncertainty should be considered. First, there is statistical uncertainty due to the number of animals in the experiment to which the model was applied. Other general sources of uncertainty include the extent of absorption of lead by various routes, variability of response to lead in different species, the choice of animal-to-human scaling factors, the choice of the high dose to low dose extrapolation model, and the large range of extrapolation (5 orders of magnitude) from the high lead concentrations used in the animal experiments to current low ambient levels.

Based on the findings of neurodevelopmental effects in children, elevations in blood pressure in adults, and potential carcinogenicity, OEHHA finds that ambient inorganic lead is an air pollutant that may cause or contribute to an increase in mortality or an increase in serious illness. Furthermore, a threshold has not been clearly identified for neurodevelopmental effects, effects on blood pressure, or carcinogenicity.

Section 2. Overview of Health Effects

A thorough review of health outcomes associated with lead exposure is provided by U.S. EPA (1986,1990a), ATSDR (1990) and the National Research Council (1993). Much of this overview relies on those documents. The information discussed below is provided as background for our examination of lead's primary health effects at lower exposure levels. Some effects represent biological markers of unknown pathophysiological significance.

Lead has no known physiologic or metabolic value. Current levels in human blood are a result of its usefulness in industry and commerce. Based on studies of bone samples, modern humans are estimated to have total body burdens of lead approximately 300-500 times those of our preindustrial ancestors, because lead has been extensively mobilized from the earth's crust by our activities (NRC, 1993). Flegal and Smith (1992) estimate that the natural concentration of blood lead is 0.016 μg/dL.

At very high blood lead concentrations (80 μg/dL and above in children), lead causes encephalopathy (brain damage) and an associated high risk of death. Many children with blood lead levels in this range, with or without evidence of encephalopathy, experience permanent neurological damage such as severe mental retardation and recurrent convulsions. Other acute symptoms, which result from blood lead levels of 60 μg/dL or greater, may include lethargy, vomiting, irritability, loss of appetite, and dizziness.

Since lead accumulates in the body and is only slowly removed, repeated exposures to small amounts over months to years will produce elevated blood lead levels. Chronic exposure to lead can cause blockage of the proximal tubule in the kidney and kidney failure. Lead-induced chronic nephropathy (kidney damage) has been seen in occupationally exposed workers at blood lead levels as low as 40 μg/dL and other renal effects, such as decreased vitamin D metabolite levels, have been observed at 30 μg/dL. The lowest blood lead level at which these effects might occur has not been determined.

Lead appears to inhibit production of vitamin D, as measured by the hormonal metabolite 1,25-dihydroxyvitamin D, at levels of 30 μg/dL in adults and as low or lower than 12 μg/dL in children. A threshold blood lead level for this effect has not been determined. In one study, Koo et al. (1991) measured vitamin D metabolites in 105 children aged 21 to 33 months who were enrolled in the Cincinnati prospective study. In this group no association was found between low to moderate lead exposure and alterations in Vitamin D metabolism. Since this hormone is involved in cell differentiation and immunoregulation, its deficit may affect the function of many types of cells and tissues throughout the body. Altered levels of vitamin D hormone may affect calcium homeostasis and thus calcium-dependent processes essential to several enzyme systems, the transport of and response to various hormonal and electrical stimuli, and cyclic nucleotide metabolism. Lead may also affect the role of vitamin D in cell differentiation/maturation, immunoregulation, pancreatic function, and mediation of tumorigenesis (reviewed in U.S. EPA, 1986).

Lead is also associated with several adverse reproductive and developmental outcomes. In male industrial workers, sperm abnormalities, reduced fertility, and altered testicular function have been observed at levels of 40-50 μg/dL. However, a study by Coste et al. (1991) found no relationship between lead exposure in men and fertility.

Lead has also been associated with adverse effects on the fetus. Since lead in blood does cross the placenta, the fetus may be affected by an elevated maternal blood lead level due to

current or past exposure. While there is no metabolic barrier to uptake of lead by the fetus, the timing and amount of lead transferred to the fetus is uncertain. Ernhart (1992a) reviewed evidence indicating that lead may cross the placenta at different rates during pregnancy. Lead in the blood of the mother can affect the developing fetus. Lead has been detected in the human fetal brain as early as 13 weeks. The fetus is probably exposed to equivalent levels throughout pregnancy but the younger fetus is presumably more sensitive (Goyer, 1990). Lead appears to be mobilized from bone during menopause and pregnancy. Silbergeld et al. (1988) found that blood lead levels in menopausal women were higher than in pre-menopausal women. Levels were highest in those menopausal women who had never been pregnant, suggesting that lead is leached from bone during pregnancy. On the other hand, a study by Ewers et al. (1990) of 3,098 German women aged 55-66 did not find an association between bone demineralization (osteoporosis) and lead mobilization among post-menopausal women with high blood lead levels. Zaric et al. (1987) found higher blood lead values in pregnant women living near a lead smelter. These studies indicate that blood lead levels of pregnant women may be higher than population averages. Still, at least one other study showed a statistically significant increase in blood lead level in women 6 months after giving birth, but no significant increase during the pregnancy (Ernhart and Greene, 1992). Mahaffey (1991) estimated that the umbilical cord blood lead concentration is 85-90% as high as the mother's blood lead concentration. (Reviewed also in ATSDR, 1990 and Ernhart, 1992a.)

Several prospective studies have examined the association of blood lead levels with pre-term delivery and birth weight. In females, blood lead levels of 12-14 μg/dL and above have been associated with pre-term delivery and low birth weight in some of these studies. Effects on pre-term delivery were seen in cohorts from Cincinnati (Bornschein et al., 1989) and Port Pirie, Australia (McMichael et al., 1986). Average maternal lead levels in both of these cohorts were between 5 and 10 μg/dL. Prospective studies in Glasgow (Moore et al., 1982), Cincinnati (Bornschein et al., 1989), and Boston (Bellinger et al., 1991) report an inverse association between maternal lead level and birth weight. In the Boston cohort, this association was demonstrated in women with blood lead levels down to 15 μg/dL. However, there was no relation between lead and birth weight or pre-term delivery in a prospective study of 907 women from Titova, Mitrovica with midpregnancy blood lead concentrations as high as 45 μg/dL (Litvak et al., 1991). No effects on birth weight were observed in the Cleveland cohort (Greene and Ernhart, 1991).

Studies of lead's effects on childhood growth have had varying results. In one study, using National Health and Nutrition Examination Survey (NHANES) data, small but significant reductions in early childhood growth were observed with no apparent threshold across a range of 5-35 μg/dL (Schwartz et al., 1986). This study did not adjust for parental stature, however. In a study by Shukla et al. (1987) of pregnancies in the Cincinnati cohort, the investigators found that those infants born to women with lead concentrations greater than 8 μg/dL during pregnancy had lower than expected growth rates if they continued to have increased lead exposure for 15 months after birth. This effect was not observed in any children whose mothers had blood lead concentrations lower than 8 μg/dL. In a later study of the same group Shukla et al. (1991) reported that sustained exposure to lead levels of 20 μg/dL or greater during the first 33 months of life was associated with reduced stature. Another study of children living near a smelter found a threshold for this effect at 40 μg/dL (Lauwers et al., 1986). Two other studies which did adjust for parental stature did not find a relationship between maternal lead level and growth (Greene

and Ernhart, 1991; Sachs and Moel, 1989). Lead at low levels has also been associated with postural sway (Bhattachaya et al., 1995). The U.S. EPA noted that differences in study composition and lead exposure levels could account for the different findings (U.S. EPA, 1989d). The authors of the NRC report stated that the weight of evidence points toward adverse effects on fetal development at lead concentrations as low as 10-15 μg/dL (NRC, 1993). These lead levels are found in a "substantial fraction" of women of childbearing age (ATSDR, 1988). Lead levels of 10 μg/dL and below have also been associated with decreased hearing acuity (Schwartz and Otto, 1987).

Levels of lead below 25 μg/dL cause both clinical and subclinical effects on many other organ systems. The nervous system is a critical target for low-level lead effects. Several long-term prospective studies have reported an association of pre- and postnatal lead exposures with intelligence in infants and young children. These findings will be discussed in more detail in section 3.1, a review of lead's effects on neurodevelopment. *In vitro* and *in vivo* studies reveal changes in neurotransmission and brain mitochondrial function within minutes of exposure to submicromolar concentrations of lead. The lowest levels at which these effects occur in humans have not been determined, but these neurochemical changes could plausibly form the basis for neurodevelopmental effects observed in children. Some evidence suggests that lead may impair peripheral nerve conduction in children at levels as low as 20-30 μg/dL (ATSDR, 1990; U.S. EPA, 1986). However, a review by Ehle et al. (1986) found almost no effects below 60 μg/dL leading the author to question the clinical significance of this effect. Changes in brain wave patterns have been observed at levels of 15 μg/dL with no evident threshold, although the biological and functional significance of changes observed at levels <30 μg/dL is not known. Some of these changes persisted for at least 2 years after exposure (ATSDR, 1990; U.S. EPA, 1986).

While the level of concern is described as 10 μg/dL, CDC has also identified different levels above 10 μg/dL and associated responses. For example, when many children in a community are between 10 and 14 μg/dL (a "border zone" range), community-wide childhood lead poisoning prevention activities should be initiated. All children with blood lead levels at or above 15 μg/dL should receive nutritional and educational interventions and more frequent blood lead screening. Between 15 and 19 μg/dL, environmental investigation (including a home inspection) and remediation should be done if the blood lead levels persist. A child between 20 and 44 μg/dL should receive environmental evaluation and remediation and a medical evaluation. Such a child may need pharmacologic treatment for lead poisoning. Above 45 μg/dL, a child would receive both medical and environmental interventions, including chelation therapy.

In addition to neurological effects, lead interferes with the synthesis of heme, which is essential for the functioning of cells in many organ systems, especially the brain, kidney, liver, and blood-forming tissues. Heme is a component of hemoglobin, the oxygen-carrying pigment of red blood cells. An elevated lead level can impede hemoglobin synthesis resulting in anemia. Heme is also a constituent of cytochrome P-450 and electron transfer cytochromes. Lead can impair the function of heme-dependent liver enzymes (cytochrome P-450), which can increase vulnerability to the harmful effects of other toxic chemicals. Lead's effects on vitamin D hormone synthesis are mediated through its effects on heme. Finally, interference with heme biosynthesis may play a role in lead's neurological effects. Decrements in an enzyme involved in heme synthesis (ALA-D) have been observed at blood lead levels as low as 10 μg/dL although the biological and medical

significance of effects at this level are not well understood. (Reviewed in ATSDR, 1990, U.S. EPA, 1986 and NRC, 1993).

Recent studies using large population-based data sets have indicated an association of lead in blood with blood pressure in adults, particularly men, at lead levels as low as 7 μg/dL of blood. These studies are reviewed in greater depth in Section 3.2.

Many of these health effects are consistent with those seen in animal and cellular studies at very low levels. Therefore, the lead levels at which these health effects are seen in humans should not be considered as threshold values, but rather as levels below which there is less certainty of the presence of adverse health effects.

Investigation of the distribution of blood lead levels in the U.S. population has been conducted by the CDC in large cross-sectional national surveys. The results indicate a substantial decline in blood lead levels from NHANES II(1976 to 1980) to NHAHES III (1988 to 1991). There was an overall decease in blood lead levels of 78% for persons aged one to 74 years of age over this time period. In NHANES II (1976 to 1980) an estimated 88.2% of one to five year old children in the U.S. exhibited blood lead levels greater than or equal to 10 μg/dL. In phase one of the NHANES III survey (1988 to 1991) only 8.9% of one to five year olds were determined to have blood lead levels equal to or greater than 10 μg/dL. A decrease in blood lead levels of a similar magnitude (greater than 70%) was observed not only for the total population, but also for subgroups stratified by race/ethnicity, gender, urban status and income levels. However, the number of children aged one to five with blood lead levels greater than or equal to 10 μg/dL is disproportionately higher for non-Hispanic African-American children.

The dramatic decline in blood lead levels is consistent with, and undoubtedly related to, continued reduction in exposure to lead from environmental sources which began in the late 1970s. From 1976 to 1990, the amount of lead used in gasoline decreased 99.8% nationally (from 205,810 tons to 520 tons). In California, there has been an approximate 30-fold decrease from 1976-1980 in average ambient air lead levels compared to current ambient air lead levels (see Figure IV-2, p. A-6, Part A of this document). From 1980 to 1990, the amount of lead used in soldered cans also decreased dramatically. In 1980, 47% of the food and soft drink cans were lead soldered, and by 1990 this figure had decreased to only 0.85%. As of November 1991, lead soldered food and soft drink cans were no longer manufactured in the U.S. The manufacture of lead-based paint was limited by the Consumer Product Safety Commission in 1978. Still, lead-based paint remains a potential source of exposure for residents of older housing with deteriorating paint. The authors of NHANES III have concluded that the reduction of lead in gasoline is most likely the greatest contributor to the observed decline in blood lead levels during the period of the national survey (Pirkle et al. 1994). The major remaining sources of environmental lead that pose a potential public health threat appear to be localized sources of lead, including but not limited to continued deterioration of lead-based painted surfaces in older buildings, lead that has already accumulated in dust and soil, and near source air emissions.

Section 3. Health Effects of Particular Concern

This section reviews the health effects of lead of greatest public health significance: (1) neurodevelopmental effects in children, (2) effects on blood pressure and related cardiovascular events in adults, and (3) cancer. The two noncarcinogenic outcomes have been observed in human populations at relatively low blood lead levels and they both constitute significant public health outcomes. This review does not attempt to be comprehensive but rather serves to summarize the major findings from the most well-designed studies.

3.1. Neurodevelopmental Effects in Children

Lead's neurodevelopmental effects at low and moderate exposure levels (40 μg/dL and below) include: decreased intelligence, short-term memory loss, reading and spelling underachievement, impairment of visual motor functioning, poor perception integration, disruptive classroom behavior, and impaired reaction time (U.S. EPA, 1989d; ATSDR, 1994; Fergusson et al., 1993; Fergusson and Horwood, 1993; Hansen et al., 1985; Winneke et al., 1994; Thompson et al., 1989; Rothenberg et al., 1994; Sciarillo et al., 1992; Yule et al., 1984; Leviton et al., 1993; Bellinger et al., 1994a; Bellinger et al., 1994b; Needleman et al., 1996).

Children are more vulnerable than adults when exposed to lead partly because they: (1) have hand-to-mouth behaviors that result in more ingestion of lead in soil and dust; (2) are more likely to exhibit pica (abnormal ingestion of non-food items); (3) absorb substantially more lead from the gut than adults, especially when they are below 2 years of age; (4) have a faster metabolic rate, resulting in a proportionately greater daily intake of lead through food; (5) have a less developed blood-brain barrier and therefore greater neurologic sensitivity (Smith, 1989); (6) have a faster resting inhalation rate; and (7) tend to breathe through their mouths when at play. (Less inorganic lead particulate is trapped in the nasal passages in mouth-breathers.) Furthermore, children from economically disadvantaged backgrounds are especially vulnerable because they are more likely to have diets that are deficient in elements that suppress lead absorption, such as iron and calcium.

Tissue lead levels can be measured by analyzing teeth, bone, or blood. Teeth and bone reflect the cumulative dose of lead. However, teeth are naturally shed only at certain ages, making it almost impossible to include children under 4 years of age. In addition, tooth lead concentration varies with the position of the tooth in the mouth and with parts of the tooth measured as well as which the age at with the tooth is sampled (Fergusson et al., 1989; Rabinowitz et al., 1993). Tooth lead is most strongly related to blood lead levels near the time the tooth is shed but does not reflect exposure well during the child's first 2-3 years (Rabinowitz et al., 1993). X-ray fluorometry, a technology for measuring bone lead has now been used in several studies (Hu et al., 1995; Hu et al., 1994; Kosnett et al., 1994) including two in which bone lead was related to neurodevelopment (Bellinger et al., 1994a; Needleman et al., 1996). In most current studies, blood lead is used as the indicator of exposure. Blood lead levels mostly reflect recent exposures (from the past 1 to 3 months) but are also influenced by past exposures, i.e., lead mobilized from bone and other storage sites. Like bone and tooth lead, blood lead is not a completely accurate measure of either the total body burden of lead or of current exposure. However, levels of lead in blood are indicative of the level of lead to which soft tissue is currently exposed. In addition, blood lead levels are reproducible (to within ± 1 μg/dL) and can be

compared across studies to indicate relative levels of exposure (Smith, 1989). All of the prospective neurodevelopmental studies reviewed below followed children since birth and reported prenatal as well as postnatal measures of blood lead concentrations. Some of these cohorts also examined the relationship of tooth lead and intelligence in order to evaluate the impact of cumulative lead exposure. It has long been assumed that tooth lead and blood lead levels were fairly well correlated, but a recent large cross-sectional study showed very poor correlation (Winneke et al., 1990). Therefore, our review of the prospective cohorts emphasizes the outcomes associated with blood lead levels but also includes relevant tooth lead studies. Effects relating to blood lead levels are more relevant for this risk assessment since changes in blood lead can be linked directly to changes in ambient air lead (see Section 4).

Early studies of neurotoxic effects of lead were conducted by Needleman et al. (1979) using lead levels in the teeth of first and second graders. Children were classified into 2 groups according to dentine lead levels. Groups representing the 90th (>20 ppm) and 10th (<6 ppm) percentiles of lead values were compared on a variety of neuropsychological parameters. The authors detected a significant association of increased dentine lead level and decrements in intelligence quotient (IQ). In further analyses in which dentine lead was treated as a continuous variable, the association of dentine lead and IQ remained significant (U.S. EPA, 1984; Needleman et al., 1985; Schwartz, 1993). The association was still evident when the children were tested 5 and 11 years later (Bellinger et al., 1984b; Needleman et al., 1990). This pioneering study had some problems which have since been resolved by longitudinal studies. For example, statistical power was lost when those children from the middle of the distribution of lead levels were excluded from the study. In a subsequent reanalysis of the data using the full sample, the reported effects were stronger than in the original analysis (Schwartz, 1993). Since children were observed in school, there was no way in which to assess their home environment (as assessed by Home Observation for Measurement of the Environment (HOME) score). HOME score has proved to be an important confounder for lead's effects on intelligence. Finally, tooth lead was used as a surrogate for blood lead exposure.

Since the Needleman et al. (1979) article appeared, many studies have been published with varying findings. Most of the early studies were cross-sectional in nature and, like many epidemiological studies of this type, were limited by concerns about exposure assessment and the ability to control for potential confounders. Despite their problems, the cross-sectional studies appear to indicate an association between blood lead and IQ.

In an attempt to characterize the overall findings of several cross-sectional studies, Needleman and Gatsonis (1990) undertook a meta-analysis of the existing IQ-blood lead studies. The meta-analysis helped to resolve statistical problems related to small sample size and low study power to detect a significant effect. All available studies published since 1972 were reviewed for inclusion. Studies were excluded for several reasons including: (1) inadequate control for socioeconomic factors; (2) overcontrol for factors that reflect lead exposure; (3) inclusion of subjects with clinical lead poisoning; and (4) inadequate quantitative information. Of the 24 studies initially identified for inclusion in the analysis, 12 remained after the exclusion criteria were applied. Of these, 7 used blood lead as the measure of exposure. Six of these studies reported regression coefficients relating increased blood lead to decrements in IQ scores (Yule et al., 1981; Schroeder et al., 1985; Hawk et al., 1986; Lansdown et al., 1986; Hatzakis et al., 1987; and Fulton et al., 1987).

Of these 6 studies, 3 used the WISC-R full scale IQ test: Lansdown et al. (1986) studied 194 urban children age 6 to 12 from London (mean blood lead = 12.9 μg/dL), Hatzakis et al. (1987) examined 509 children age 7 to 12 from a rural Greek town (mean blood =23.7 μg/dL), and Yule et al. (1981) examined 166 children age 6 to 12 from outer London (mean blood lead = 13.52 μg/dL). Two of the studies used the Stanford-Binet IQ scale: Schroeder et al. (1985) examined 104 children age 1 to 6.5 years from North Carolina (median blood lead = 30 μg/dL) and Hawk et al. (1986) studied 75 children age 3 to 7 form North Carolina (mean blood lead = 21 μg/dL). The sixth study, Fulton et al. (1987) used the British Ability Scales for 855 children age 6 to 9 from central Edinburgh (mean blood lead of 10.4 μg/dL). All of the studies controlled for age and socioeconomic status in the multiple regression analysis and several controlled for many other factors including maternal IQ, HOME score, sex, birth weight and parental education. Five of these studies reported a fairly consistent coefficient relating blood lead to full scale IQ. For comparative purposes, those models that used log blood lead as the independent variable were linearized using the mean blood lead. Four of the coefficients for blood lead level were between -0.20 and -0.37. Only the study by Lansdown et al. (1986) reported a non-significant association between lead and IQ. The estimates of these 6 studies can be combined by weighting each beta (effect size) by the inverse of its variance to estimate an overall effect of lead on IQ.

The authors of the meta-analysis concluded from their analysis that each 1 μg/dL increase of blood lead results in a 0.24 point decrease in IQ. Although these studies are not used for the risk assessment below, they support the conclusions of the more recent prospective studies. A later meta-analysis by Schwartz (1993) considered these 6 studies along with the prospective study of Bellinger et al. (1991). The mean effect, obtained by weighting each study coefficient by the inverse of its estimated variance, indicated that a 1 μg/dL increase in blood lead level was associated with a 0.25 (s.e. = 0.04) point decrease in the measure of intelligence ($p<0.00001$). In addition, separate meta-analyses were performed on cross-sectional and prospective studies (Schwartz, 1994). Schwartz calculated that the IQ decline associated with a 1 μg/dL increase in blood lead level was 0.27 IQ points in the cross-sectional studies and 0.23 IQ points in the prospective studies (discussed below).

Bone lead, measured by K x-ray fluorescence, has been recently investigated as a measure of body lead burden. In their study of a cohort of overtly asymptomatic boys, followed from ages 7 to 11, Needleman et al. (1996) reported that elevated bone lead levels were associated with increased risk for antisocial and delinquent behavior as measured by the Child Behavior Checklist and by teachers', parents' and self reports. At 11 years of age, there were significant associations between bone lead and teachers' and parents' reports of somatic complaints, anxious, aggressive and depressed behavior, and attention deficits. Over the 4 year observation period, the behavior and delinquency scores of high-lead subjects were more likely to worsen than were those of low-lead subjects. The study also reported a positive association between bone lead and IQ that was limited to African-American subjects. African-Americans with high bone lead levels and higher IQ scores (> 105), had mothers with higher IQs, more education, higher socioeconomic status, were more likely to come from two-parent families, and had fewer siblings than those with low bone lead. These findings led Needleman et al. to conclude that in this population, social factors, rather than bone lead, may have more strongly influenced IQ scores. Needleman and colleagues indicate that these were unexpected findings and suggest that measurement error or incomplete measurement of confounders may explain the positive association between bone lead and IQ in their study. However, stratified analysis revealed that, within each IQ stratum, subjects with high

bone lead scored higher on a measure of antisocial and delinquent behavior, a finding that is consistent with the overall results of their study. In another study using bone lead, Bellinger et al. (1994a) did not find a relationship with school performance but did find one between dentine lead levels (14 μg/g on average) and certain cognitive skills relating to executive and self-regulation functions.

Since cross-sectional studies use a single blood lead measurement as a surrogate for earlier, potentially etiologically relevant exposures, they are more likely to suffer from exposure classification errors than prospective studies (McMichael et al., 1994). As a result, large, prospective studies were conducted in Boston, Cincinnati, Cleveland, and Port Pirie and Sydney, Australia. In addition to minimizing recall bias, prospective studies allow investigators to measure temporal changes in outcome relative to prior levels of exposure. Because the child is followed over time, researchers can examine the effects of lead exposure at different times as well as estimate the effects of cumulative exposure. While differential loss to follow-up can lead to biases in cohort studies, the bias can be better characterized than in cross-sectional studies. Prospective studies face a different set of problems, however. They are very expensive to conduct, and as subjects drop out of the study at later ages, sample sizes can become small, reducing both the statistical power to detect small differences between test groups, and the generalizability of the results to other populations.

The 5 prospective studies reviewed in this section all used blood lead as their primary measure of exposure. Each began examining blood lead levels at or before the birth of the child (in utero). While many other health effects were examined, the data on intelligence were most complete. Bayley's Mental Development Index (MDI), a general measure of intelligence, was used in all 5 studies for children 3 years old or younger. The MDI has a mean of 100 and a variance of 16. Various IQ tests (Stanford-Binet, Wechsler Preschool and Primary Scale of Intelligence (WPPSI), the Kaufman Assessment Battery for Children (K-ABC), and the General Cognitive Index (GCI) of the McCarthy Scales) were used to measure intelligence in children 4 years or older. These tests all have normal distributions and standardized scores but cannot be compared directly to one another since they measure intelligence differently. They also measure different mental functions from one another and from Bayley's MDI (Smith, 1989). After age 5, the 3 prospective studies which continued to publish data all used the same intelligence test, the Wechsler Intelligence Scale for Children-Revised (WISC-R). Some of the cohorts were also examined for the relationship of lead concentration to classroom performance.

Since children seem to be most sensitive to the effects of lead at very young ages, each prospective study examined the association of blood lead level with postnatal measures of intelligence. Prenatal blood lead levels were measured indirectly using the mother's blood during pregnancy, just before the baby's birth, more directly from the umbilical cord at the time of delivery, or from the baby itself just after birth or 10 days later. Postnatal lead levels were usually taken at 6 month or yearly intervals. These studies are ongoing. The findings to date from the 5 major prospective studies are summarized below. Selected analyses using tooth lead have also been included. See Table 3-1 for a summary of the designs of each of the prospective studies. The means and ranges of the lead levels are given in Table 3-2.

Table 3-1. Characteristics of Prospective Studies of Lead and Intelligence

Study	Pre-Natal Measure	Blood Lead Tests	Developmental Tests	Eligibility/Characteristics
Boston (n=249)	Cord	6, 12, 18, 24, 57 months-- capillary 10 years -- venous	Bayley's MDI at 6, 12, 18 and 24 months; McCarthy's GCI at 57 months; WISC-R and KTEA at 10 years.	Single mothers included; alcoholic mothers not excluded; more advantaged; English speakers only; 85% white; excluded people from unsafe neighborhoods; high, low and medium groups only.
Cincinnati (n=305)	Maternal 10-day	Quarterly to 7 years Mostly venous	Bayley's MDI at 3, 6, 12, 24 months; K-ABC at 3, 4, 5 years; WISC-R at 6.5 months.	Single mothers included; alcoholic and addicted mothers excluded; very poor cohort; excluded low birth weight and gestational age.
Cleveland (n=359)	Cord Maternal	6, 12, 24, 36, 48, 58 months -- venous	Bayley's MDI at 6, 12, 24 months; KID at 6 months; Stanford-Binet at 36 months; WPPSI at 58 months.	50% of sample has history of alcoholism; excluded those with history of narcotic use; English speakers only. Non-alcoholic mothers had significantly greater loss to follow up.
Port Pirie (n=745)	Cord Maternal	6, 15, 24, 36, 48, 60, 72 months -- capillary	Bayley's MDI at 24, 36 months; McCarthy's GCI at 4 years; WISC-R at age 7.	No exclusions; 100% white
Sydney (n=298)	Cord Maternal	Every 6 months to 4 years -- capillary and venous	Bayley's MDI at 6, 12, 24 months; McCarthy's GCI at 3, 4, and 5 years.	Single mothers excluded; middle class cohort; 100% white; highest and lowest decile only.

Table 3-2. Mean and Range of Blood Lead Levels in Five Prospective Studies.

Age	Boston	Cincinnati	Cleveland	Port Pirie[a, b]	Sydney[b]
Maternal	--	**8.2** 1-27	**6.5** 2.7-11.8	**9.5**	**9.1**
Cord	**6.6** 0-24.9	**6.3** 3-35	**5.8** 2.6-14.7	**8.3**	**8.1**
6-month	**6.2** 0-48.6	**7.7** 1-34	**10.1** 5-24	**14.4**	**16.7**
1 year	**7.7** 0-30.6	**15.2** 5-46	--	**20.9**[c]	--
2 year	**6.8**	**17.5** 4-70	**16.7** 5.4-41.8	**21.2**	**16.5**
3 year	--	**16.2** 4-50	**16.7** 6.4-41.6	**19.5**	**13.8**
5 year	**6.4**[d] 0-23.3	**11.9** 3-38	--	**15.4**	--
10 year	**2.9** 0.5-16.0	--	--	--	--

a Geometric means
b Ranges not provided
c Lead levels taken at 15 months
d Lead levels taken at 57 months

3.1.1. Boston, Massachusetts

Bellinger et al. (1984a; 1985; 1986; 1987a,b; 1989a,b; 1990. 1991, 1992) and Stiles and Bellinger (1993) have studied a group of 249 middle and upper-middle class children in Boston from birth to 10 years to examine the relationship of umbilical cord and postnatal blood lead levels to neurobehavioral development. Subjects were grouped by umbilical cord lead levels into low (<3 μg/dL), middle (6-7 μg/dL), or high (10-25 μg/dL) categories. Adjusted MDI scores were lower in the high-lead group when the children were tested at 6, 12, 18, and 24 months of age. A 4- to 8- point deficit in MDI score was observed at each of these ages between the high and low cord lead groups. No effect of postnatal blood-lead level on MDI score was observed (Bellinger et al., 1985, 1986, 1987a) from 6 months to 2 years.

Bellinger et al. (1989a) determined that the observed IQ differences between the high- and low cord lead groups were not due solely to the very high levels within the high group since most concentrations were in the 10 to 15 range. The results of this analysis of the entire cohort indicate that effects on neurodevelopment can occur at cord blood lead levels as low as 10 μg/dL.

In a subsequent analysis, Bellinger et al. (1989b) compared those in the highest socioeconomic status (SES) group with the other groups to investigate the effect of SES on the observed results. In the lower SES group, infants with cord blood lead levels of 6 to 7 μg/dL (the middle category) had significantly lower MDI scores compared to infants with cord blood lead levels of less than 3 μg/dL. The lower SES group in this cohort would be among the higher classes of other study cohorts. Also, exposure to lead was higher in the higher SES groups.

At 57 months of age, the inverse association of cord blood lead and cognitive performance measured by the General Cognitive Index (GCI, mean = 100, standard deviation = 16) of the McCarthy Scales was no longer statistically significant. However, Bellinger et al. (1990) found that those with high cord blood lead levels (≥10 μg/dL) had increased risk of lower GCI scores at 57 months, if they had a high postnatal exposure (≥10 μg/dL) or less optimal socio-demographic characteristics. Males were shown to be more sensitive to these influences than females in the cohort. Furthermore, there was a significant relationship between the 24-month blood lead level and the GCI score with a deficit of 3 GCI points for a unit increase in the log of blood lead. Specifically, an increase from 3 to 20 μg/dL (i.e., 2 natural log units) at 24 months of age was associated with a decrease of 5.9 GCI points. The association of blood lead measures at 18 and 57 months and GCI score at 57 months did not achieve statistical significance when adjusted for several potential confounding variables but there was a significant effect at 18 months in an unadjusted analysis when blood lead and dentine lead alone were related to MDI score (Bellinger et al., 1987b, 1990, 1991). Schwartz (1993) examined the dose-response relationship between GCI score of the McCarthy scale and blood lead levels as reported by Bellinger et al. (1991) to determine whether there was evidence of a threshold. A non-parametric, locally weighted smoothing technique was used to allow the data to determine the shape of the dose-response function, rather than imposing a specific shape. The results indicated the lack of a threshold down to blood lead levels of 1 μg/dL.

At age 10 years, the children were examined again using the WISC-R, a measure of cognitive function, as well as the KTEA (Kaufman Test of Educational Achievement) (Bellinger et al., 1992; Stiles and Bellinger, 1993). Higher levels of blood lead at 24 months were associated with significantly lower scores on FSIQ (full score IQ) and verbal IQ. The authors observed a

decrease of almost 6 points on FSIQ and 9 points on KTEA Battery Composite score for each 10 μg/dL increase in lead level at 24 months. These estimates include adjustments for maternal age, race, marital status, number of residence changes and HOME score.

The authors redid the analysis using a child's maximum lead score up to the age of 10 and found a smaller coefficient at that age than that found using the child's blood lead level at 24 months. Therefore it may be the timing of exposure as well as the magnitude which affects cognitive function. They also noted that the data at 24 months were less impacted by adjustment for socio-demographic variables than blood lead data at other ages (Bellinger et al. 1992). Visual inspection of the results suggests a continuous response across the entire range of blood lead levels and the lack of any threshold.

In summary, in the Boston cohort, effects on intelligence were evident at prenatal levels as low as 6 μg/dL for children of lower SES. Effects on intelligence in those with cord blood lead levels of 10 μg/dL or greater persisted until 24 months for the cohort as a whole, and to 57 months for certain subgroups. For the entire cohort, postnatal blood lead levels at 24 months were significantly associated with FSIQ at age 10 and to some neurological function tests requiring attention for good performance. One study found that lead impacted classroom behavior, although this study did not investigate the impact of postnatal blood lead. Therefore, evidence from these studies suggests that both prenatal and postnatal exposure may be associated with adverse impacts on cognitive performance with effects from postnatal exposure persisting to at least 10 years of age. The effects of later postnatal exposure seem to be strongest.

3.1.2 Cincinnati, Ohio

In a longitudinal study of inner-city children conducted in Cincinnati, Ohio, there were both indirect and direct inverse associations of prenatal lead and MDI score (Dietrich et al., 1986, 1987a,b; Bornschein et al., 1989). Prenatal lead exposure was estimated by maternal blood lead levels at the end of the first trimester. Lead was taken from the infant at 10 days and then quarterly thereafter. Annual lead levels represent the average of the 4 measures taken each year. Prenatal lead levels, measured indirectly by maternal blood lead concentration (the mean time in pregnancy at which blood lead was measured was 16 weeks gestation), were associated with reduced birth weight, and reduced birth weight was associated with lower MDI scores, indicating an indirect relationship between the two (Dietrich et al., 1986, 1987a,b; U.S. EPA, 1990a). In a separate categorical analysis, Bornschien et al. (1989) found a drop in birth weight in the 13-18 μg/dL group compared with the 7-12 μg/dL group, suggesting a level of effect of 13-18 μg/dL and possibly lower.

After adjusting for covariates, 3- and 6- month MDI scores were significantly associated with maternal and cord blood lead levels. Neonatal blood lead levels (taken at 10 days) were significantly related in an inverse manner to 6- and 12-month MDI scores (Dietrich et al. 1989). However, there were no statistically significant inverse relationships between pre- or postnatal blood lead values and MDI scores at 24 months of age. As in the Boston cohort, Dietrich et al. (1987a,b, 1990) noted that male children from lower SES groups were more sensitive to lead's effects on MDI score. When these children were examined at 4 years of age, neonatal blood lead levels in those children from the poorest families were associated with poorer performance on all subscales of the K-ABC. Maternal blood lead levels were not related to K-ABC performance. The authors noted a weak relationship between postnatal blood lead values and performance on a

K-ABC subscale which assesses visual-spatial and visual-motor integration skills (Dietrich et al., 1991).

At age 5 years, the authors examined cognitive development as well as central auditory processing abilities in 259 children (Dietrich et al., 1992). Ten-day lead levels were no longer significantly related to K-ABC scores. But mean lead level at age 4 was associated with the simultaneous processing subscale (SIM) ($p=0.05$). Nearly significant associations were observed for blood lead levels at age 5 with SIM and blood lead at age 4 with the nonverbal subscale of the K-ABC.

Small but significant or nearly significant effects of lead at 10 days were observed in children at 5 years for the Filtered Word Subscale of SCAN (screening test for auditory processing disorders.). A consistent relationship was found with blood lead and this type of auditory processing in the right but not the left ear ($0.10<p<0.01$) with lead levels at 10 days, 2, 3, 4 and 5 years as well as mean blood lead level over the child's lifetime (MPbBLIFE), paralleling results of a large national cross-sectional study done by Schwartz et al. (1987).

The children were examined again at 6.5 years using WISC-R (Dietrich et al., 1993). In the crude (unadjusted) regression model, FSIQ was associated ($p<0.001$) with blood lead levels at ages 3, 4, 5 and 6 years as well as the mean blood lead level over the child's lifetime (MPbBLIFE). Blood lead levels at ages 1 through 6 and MPbBLIFE were all significantly associated ($p<0.05$) with performance IQ (PIQ) in the unadjusted analysis. A significant association was also observed between verbal IQ (VIQ) and blood lead level at age 6. The PIQ is equivalent to the subscales of the K-ABC affected by lead when children were studied at 4 and 5 years. After adjustment for HOME score, maternal IQ, birth weight, birth length, gender, and cigarette consumption during pregnancy, the investigators found a significant inverse association between lead levels at 5 and 6 years and FSIQ, as well as associations between lead levels at ages 3, 4, 5 and 6 and MPbBLIFE levels and PIQ. The authors report a decrement of FSIQ of 3.3 points per 10 μg/dL increase in blood lead. Lifetime average blood lead concentration accounted for 4.1% of the variance in PIQ following adjustment for these covariates. Next the authors converted MPbBLIFE into a categorical variable representing blood lead quartiles. Using these quartiles, the authors demonstrated a dose-response relationship through the entire range of responses, with no evidence of a threshold.

In summary, as in the Boston cohort discussed above, prenatal and neonatal (10-day) lead levels were associated with neurodevelopmental (MDI) scores up to 2 years of age. Postnatal exposures affected some developmental subscales at age 5 and were significantly related to FSIQ at age 6.5 years.

3.1.3 Cleveland, Ohio

In the Cleveland cohort, Bayley's MDI was administered at 6, 12, and 24 months, the Stanford-Binet IQ test at 36 months, and the WPPSI at 58 months. Postnatal blood lead levels were measured at 6, 24, 36 and 58 months. This study was designed so that over 50% of the mothers enrolled were alcoholic as measured by the Michigan Alcoholism Screening Test (MAST). After controlling for covariates, maternal blood lead levels, an indirect measure of fetal exposure, accounted for a significant amount of the variance in 6-month MDI scores. The average maternal blood lead level was 6.5 μg/dL, and the range of lead values (2.3 to 11.8 μg/dL) was narrower than in the other cohort studies (see Table 3-2) (Ernhart et al., 1987, 1988; Ernhart

and Morrow-Tlucak, 1989). Since alcohol use during pregnancy correlated with lead and intelligence, the effects of alcohol and lead cannot be distinguished in this study.

At 58 months, the children's intelligence was tested using the WPPSI (Ernhart and Morrow-Tlucak, 1987). Blood lead and WPPSI score were not significantly associated after adjusting for 13 covariates.

Significantly more MAST-negative subjects were lost to follow up inflating the proportion of current or former alcoholics in the study. Therefore, it is not known whether the observed neurodevelopmental deficits are related to an independent effect of lead, an interactive effect of alcohol and lead, or an independent effect of alcohol.

Unlike the Boston and Cincinnati cohorts, effects from prenatal lead exposure (as measured by maternal blood lead levels) in this cohort were only observed at 6 months. No effects of postnatal lead exposure were observed.

3.1.4 Port Pirie, Australia

In the Port Pirie, South Australian cohort (Vimpani et al., 1985), postnatal but not prenatal blood lead levels were associated inversely with MDI scores. Blood lead levels were taken at birth, at 6 and 15 months and annually to age 7, but unlike other cohort studies, intelligence tests were not administered until age 2. The 6-month blood lead level (geometric mean of 14.4 μg/dL) was most strongly related to MDI performance at 24 months, with a p-value of 0.07 (one-tailed) after adjustment for HOME score. A child's MDI at 24 months was calculated to be 1.6 points lower for every 10 μg/dL rise in blood lead at 6 months. The correlation of postnatal blood lead levels with MDI score was not found in the Boston, Cincinnati, Cleveland and Sydney cohorts. The different pattern of results observed may be due to the 2-year delay in administering the MDI (obscuring a potential effect at 6 and 15 months) and/or high blood lead levels observed postnatally in the cohort (Davis and Svendsgaard, 1987; U.S. EPA, 1990a). One-third of children in this study had levels above 25 μg/dL at some point during their first 4 years of life (McMichael et al., 1988).

The GCI and other McCarthy scales were administered to 537 children within 6 months of their fourth birthday (McMichael et al., 1988). Using multiple regression, GCI scores were significantly related to the log of blood lead at 6, 24, and 36 months as well as to an integrated average for the 4-year postnatal period. Using the integrated average, scores declined about 7.2 points as blood lead increased from 10 to 30 μg/dL, representing a 7% decrease in GCI score in a child with average values for the other covariates (McMichael et al., 1988).

Other analyses indicated that the effect of lead on GCI score appeared to be related to both cumulative exposure across the entire postnatal period and recent exposure (McMichael et al., 1988).

At age 7 years, 494 children were tested again using WISC-R. After adjustment for sex, parent's level of education, maternal age at delivery, parental smoking, SES, HOME score, birth weight, birth order, feeding method, duration of breast feeding and whether the child's parents were still living, the postnatal relationship between blood lead and intelligence persisted, especially with respect to blood lead at ages 15 months to 4 years. The regression showed that for an increase in blood lead from 10 to 30 μg/dL, IQ dropped between 4.4 to 5.3 points. Girls had a steeper decline in IQ as levels of lead increased (7.8 points versus 2.6 points for boys for a 20

μg/dL increase in lead level). The authors concluded that low-level exposure to lead remains inversely associated with neuropsychological development through the age of 7.

The authors interpreted a strong correlation ($r=0.65$, $p<0.001$) of FSIQ at age 7 and McCarthy's GCI at age 4 as showing that the same children had decrements in intelligence due to their lead exposure (Baghurst et al., 1992).

The children were also assessed at age 7 with the Beery Developmental Test of Visual Motor Integration (VMI), devised as a measure of the degree to which visual perception and motor behavior are integrated (Baghurst, 1995). After adjustment for the covariates described above, blood lead exhibited an inverse association with child's VMI score. For an increase in lifetime average blood lead concentration from 10 μg/dL to 30 μg/dL, the expected deficit was estimated to be 1.6 points. The Block Design subscore of the WISC-R was highly predictive of VMI score, leading the authors to conclude that, in this cohort, there is a consistent inverse association between lead exposure and abilities involving visual-motor processes.

The Port Pirie cohort had a somewhat different pattern of results from that seen in the Boston, Cleveland and Cincinnati cohorts. No effects of prenatal or cord blood lead levels were observed although, as noted above, children were not tested until the age of 2, when effects from prenatal exposure had begun to attenuate or had disappeared in other cohorts. Like the Boston and Cincinnati cohorts, this cohort shows clear effects of postnatal exposure to age 7.

3.1.5 Sydney, Australia

A group of 318 children from Sydney, Australia was recruited from 1982 to 1983. The investigators decided to supplement the initial sample with 123 more children in 1985 because of concern that some capillary samples may have been contaminated with environmental lead (Cooney et al., 1989b). When compared to census data for the entire population of Sydney (Cooney et al., 1989a), the cohort's parents were more likely to be professional and to have completed high school education than the Sydney population.

Maternal and cord blood lead levels were measured at the time of delivery. Blood was taken from the children every 6 months thereafter until the age of 4 years, and then again at the age of 5 years. Bayley's MDI was administered at 6, 12, and 24 months, and the McCarthy's GCI at 3, 4, and 5 years.

Results reported by Cooney et al. (1989a) of children up to the age of 3 years used only the first cohort and only the prenatal (maternal and cord) blood lead levels. The mean maternal and cord blood lead levels were 8.1 and 9.1 μg/dL, respectively. Unadjusted bivariate correlations between maternal or cord lead level and the intelligence subscales (MDI and GCI) were never both negative (the expected direction) and significant (Cooney et al., 1989a).

At 48 months, 207 children remained in the study. Using correlation analysis, no association was found between increased blood lead levels including yearly cumulative average exposures, and diminished 48-month GCI. In fact, an occasional positive association was found. HOME score was the covariate which most influenced GCI. Results from the second cohort were not included in either of these analyses.

The biggest problem in interpreting this study relates to the contamination of the capillary samples by environmental lead, leading to inflated estimates of blood lead levels in the first 2 years of the study. Early venous and capillary samples, taken as little as a week apart, differed by as much as 10 μg/dL, with the higher samples being capillary. At 6-months, blood lead was

measured exclusively from capillary samples. At 24-months, 50% of the samples were still capillary. At later ages, samples were mostly venous. It is important to note that two of the prospective studies which detected an effect found the association between lead level and intelligence within the first 24 months. To account for possible contamination of capillary samples, investigators analyzed separate distributions for capillary and venous samples. Averages from the venous samples were 1 to 2 μg/dL lower than capillary samples for each age group, a statistically significant difference. However, the standard deviations were similar. Each sample was then standardized against its respective distribution, and both capillary and venous samples were used in the same analysis (Cooney et al., 1989b). Since venous samples and capillary samples were analyzed together, sporadic contamination may have obscured a relationship between postnatal blood lead levels and measures of intelligence.

3.1.6. Interpretation of Prospective Studies of Neurodevelopmental Effects in Children

Clearly, taken together, the above studies indicate an association between blood lead and neurodevelopment. However, at least two major questions arise when one reviews the findings of the prospective studies. First, is there an explanation for the different study findings? Regarding prenatal and early postnatal lead and intelligence, all 5 of the prospective studies show some effect, but only 3 of the studies exhibit an association after adjustment for covariates. In addition, significance is not found for every age at which exposure or intelligence was measured. Second, do pre-natal and early postnatal effects persist? In those studies which do show an effect of prenatal blood lead level on intelligence after adjustment, the effect seems to decline by the time the child is 2 to 4 years old. However, after age 5, a postnatal effect of blood lead level was present in all 3 prospective studies which continued to analyze data when children reached this age. Thus, studies in three cohorts show a strong and consistent effect of postnatal exposures on intelligence at even older ages (up to age 10 years). In addition, there is evidence that effects continue beyond this age (Needleman et al., 1996). These questions are addressed and a basis for interpretation are provided below.

3.1.6.A. Different Study Findings

As noted in Thacker et al. (1992), which reviewed findings from the five longitudinal studies up to 1991, all 5 studies showed an inverse relationship between either pre- or postnatal exposure to lead and MDI in unadjusted analyses. The prospective studies conducted in Boston, Cincinnati and Port Pirie, Australia found a significant inverse association between lead and intelligence. In the Cleveland study, the association did not remain significant after adjustment for several covariates. In the Sydney cohort, no significant relationships in the expected direction were found. In the Boston and Cincinnati cohorts, investigators found a relationship between prenatal lead levels and postnatal intelligence after adjustment, while the Boston, Cincinnati and Port Pirie cohorts demonstrated an effect of postnatal lead level. Differences in study results may be due to the following:

(1) Collinear variables in the regression models: In an attempt to minimize confounding in the regression analysis, most researchers have included several explanatory variables that may covary with blood lead (e.g., birth weight, gestational age, HOME score, maternal age, and intelligence). The inclusion of factors correlated with blood lead and with measures of

intelligence will tend to increase the standard error associated with the estimated blood lead regression coefficient (and decrease the likelihood of rejecting the null hypothesis of "no effect"). The reduction in the standard error when a collinear variable is dropped must be balanced against the possible addition of bias due to the omission of relevant variables. Part of the decision of whether or not to include a particular variable is dependent on the degree of certainty of an effect that the researcher is implicitly incorporating into the risk analysis. Ideally, the influence of a given covarying factor could be reduced if the researcher was able to stratify by the factor in the analysis (e.g. analyze only low income children or nondrinking mothers). Since each of the prospective studies reviewed here used a different set of covariates along with blood lead in the regression models on intelligence, differences in results may arise. For example, Bellinger et al. (1992) suggest that the confounding between blood lead and other covariates is lowest for children tested at age 2. This is also the age at which the strongest association with subsequent IQ is demonstrated.

One method to minimize the impact of confounding is to follow each child over a given time period during which potential confounders are relatively constant. Usually, it is difficult to observe changes in blood lead over such a time period. However, one intervention study specifically lowered blood lead in children and observed changes in subsequent IQ. Ruff et al. (1993) studied 154 children aged 13 to 87 months with blood lead levels between 25 and 55 μg/dL. An edetate calcium disodium (EDTA) lead mobilization test was performed to determine eligibility for chelation therapy. Eligible children were treated with EDTA to chelate lead, and iron was administered to iron deficient children. Housing inspections and abatement was performed for all children. Cognitive function was measured by Bayley's MDI (for children aged 30 months or younger) or the Stanford-Binet Intelligence scale (for children older than 30 months) before the lead mobilization test, and then both 7 weeks and 6 months after the test. Blood lead was also measured at these three points in the study. Short-term (7-week) improvements in cognitive scores were not associated with the short-term reductions in blood lead. However, increases in cognitive scores taken 6 months later were significantly associated with the six-month reductions in blood lead ($p<0.05$). The analyses controlled for potentially confounding variables such as age, sex, birth order, household size, socioeconomic status, HOME score, prenatal and perinatal complications and language of test administration (Spanish/English). The standardized score increased 0.33 points for every 1 μg/dL decrease in blood lead.

(2) Omitted or varied explanatory factors: Differences in studies could occur because various factors related to intelligence were included or not included in the analysis or were measured with error. For example, a recent study (Vega et al., 1993) found a high prevalence of drug use, including alcohol and cigarettes, in pregnant women in California, with rates as high as 14.2% in certain subgroups. Although maternal use of illicit drugs might affect the intelligence levels of offspring, it is not always included as a covariate in the prospective neurodevelopmental studies. While most researchers controlled for alcohol and smoking in the prospective studies, not all controlled for use of other drugs. In another study, iron deficiency was shown to be related to a reduction in MDI scores (Lozoff et al., 1991), although blood lead level was not included in that analysis. None of the prospective lead studies measure iron level directly, although some do collect data on erythrocyte protoporphyrin level and serum ferritin, both indirect measures of iron deficiency anemia. These unmeasured variables present a problem only if they are correlated with blood lead levels. Erythrocyte protoporphyrin levels, a measure of anemia, correlate with lead at

levels of 30 μg/dL and above, but are a very poor predictor of lead levels at the concentrations being considered here.

(3) Differing study populations: Even if equivalent covariates were used in a regression, one might still observe different relationships between blood lead level and intelligence because of underlying differences in the study populations. For example, in the Cleveland cohort, half of the mothers, by design, had a history of alcoholism as determined by the MAST test, a rate that was presumably higher than that in the other cohorts. On the other hand, children of alcoholic mothers were excluded from the Cincinnati cohort. The Sydney cohort was the only study to exclude single mothers. The Port Pirie cohort lived near a lead smelter and was exposed to much higher levels of a different lead compound than the other four cohorts. In addition, according to Dietrich et al. (1993), HOME score in the Cincinnati cohort was more highly correlated with blood lead level than in the Boston or Port Pirie cohorts. They proposed that "a major source of the so-called inconsistencies among the various neurological epidemiology studies of lead is the level of confounding of the exposure and effect variables with other socioheredity and biomedical factors" (Baghurst et al., 1990). Finally, the Boston and Sydney cohorts were of a higher SES than cohorts of the 3 other studies. Therefore, each study sample has a different lead-cofactor distribution which could give rise to different blood lead - IQ relationships.

(4) Different study quality. Thacker et al. (1992) rated each of the cohorts reviewed in this section. After an error in the initial report was detected (Thacker et al. 1993) it was revealed that based on a blind assessment of overall quality by a CDC review panel "in all cases the Boston study scored the highest and the Cleveland study, the lowest." The authors also note that: "All five studies appeared to have been carefully designed and executed." Given that the Boston study found the strongest effects of lead and the Cleveland study produced negative findings, this assessment may have significant implications for the range of quantitative estimates of the effects of lead (measured as blood lead) on learning abilities.

3.1.6.B. Assessing the Persistence of Effect

In 2 of the 3 prospective studies that found a relationship between prenatal blood lead level and intelligence, as reviewed in this document, the association seems to have disappeared by the age of 57 months. Dietrich et al. (1986) found that the association between prenatal blood lead level and MDI score was not statistically significant at 24 months. Bellinger et al. (1987b) found an association of lead and MDI and GCI at 24 months, but none at 57 months for GCI for the cohort as a whole. However, in those children with cord blood lead levels of >10 μg/dL and with equivalent levels at 24 months, the decrement persisted implying that higher postnatal exposures affect persistence of prenatal exposures. The association become apparent again in the 3 cohorts (Boston, Cincinnati and Port Pirie) which continued to produce data at ages 5 to 10 years using the WISC-R (a measure of intelligence appropriate to these age groups and roughly equivalent to the MDI). Thus, the prospective studies indicate that effects may occur through childhood and may be related to both pre- and postnatal exposure. Differences in persistence from prenatal exposure might be explained by differences in the following:

(1) Measure of effect: Although all 5 prospective studies use Bayley's MDI until the age of 3, they measure intelligence after 3 years and up to age 5 using different IQ scales. When an similar intelligence scale is later used (WISC-R), the results become more consistent. Schwartz (1994) states that IQ in school age children is much more stable and more predictive of future outcomes than Bayley's MDI and other measures of pre-school intelligence. Furthermore, these measures of intelligence may not be sensitive enough to capture some of lead's effects on intelligence, or the measures may suit certain populations better than others. Even if the IQ scales used to measure outcome were measured without error, they are likely to be only surrogates of lead's full effects on intelligence. Grant and Davis (1989) noted that classroom performance measures other than IQ scales may be more sensitive indicators of lead's effects. Indeed, the study demonstrating the longest persistence of lead's effects used more general measures of classroom performance (such as probability of graduation) (Needleman et al., 1990). Unfortunately, cross-sectional classroom studies, such as those done by Needleman et al. (1979; 1990; 1996), did not adjust for the home environment, a potentially significant confounder when measuring lead's effects on intelligence. Bellinger et al. (1994a) hypothesize that attention, as expressed in deficiencies in IQ and classroom performance, may be the strongest candidate for the primary neuropsychological deficit produced by lead. Most of the studies examining the impact of lead on classroom behavior or attention have used dentine lead as the measure of exposure. However, on occasion, cord blood lead was used. In a study of Boston children by Leviton et al. (1993), girls with elevated umbilical cord blood lead levels were more likely than their peers to be dependent and not persistent in completing tasks. Boys with elevated cord lead concentrations were more likely than others to have difficulty with both simple directions and sequences of directions. In girls, elevated dentine lead levels were associated with reading and spelling difficulties. Bellinger et al. (1994b) also investigated the association of pre- and postnatal lead (measured as cord blood and dentine levels, respectively) on behavior problems, (as rated by teachers on the standardized Teacher Report Form of the Child Behavior Profile) in Boston children born in the same time-period as children in the Boston cohort. Only children in the upper and lower deciles of the distribution participated in the prospective studies discussed above. Cord blood lead was not associated with the prevalence or nature of behavior problems among 8-year olds followed prospectively for one year. However, tooth lead level was significantly associated with problem behavior scores. Postnatal blood lead levels were not examined in the analysis. These analyses were adjusted for several potential confounders including socioeconomic status and maternal IQ although, as stated above, they did not adjust for HOME score. In a study of lead's impacts on attention, Bellinger et al. (1994a) examined current blood lead, dentine and bone lead from a cohort of 19- and 20-year olds only observed effects between dentine lead and the ability to focus. Only 30% of the original cohort participated in this study but the investigators didn't believe the results were biased by the nonparticipation. Finally, in their study of boys ages 7 to 11, Needleman et al. (1996) reported that elevated bone lead levels were associated with factors that may relate to classroom performance such as attention problems, and increased risks of antisocial and delinquent behavior based on data reported by teachers, parents, and the subjects themselves. Overall, since none of the prospective studies use postnatal blood lead, its impact on classroom behavior and general indicators of attention is uncertain. However, the available evidence indicates that the effects of lead exposure are likely to persist.

(2) Imperfect measures of lead exposure:, The actual body burden from lead exposures may not be measured well by blood lead, if for example, long-term cumulative exposures rather than short-term acute exposures impact intelligence. Also, some studies used venipuncture and others used finger stick capillary sampling, which is known to be prone to surface skin contamination.) For example, according to Schwartz (1994), the Boston study used capillary sampling (finger sticks) until the children were aged 2 years. Perhaps, the increase in effect observed after 2 years may relate to the manner in which blood lead was measured.

(3) Lack of statistical power: Large sample sizes are necessary to detect small effects of lead on intelligence. A sample of 400 or more would be needed to detect an increased risk of 1% with power of 0.80 at an alpha of 0.05, one-tailed (Cohen, 1977). Power calculations for 4 of the 5 prospective studies were presented at a meeting sponsored by the Australian Government (Australian/International Meeting, 1992). The power to detect a small effect was <0.58 for the Boston cohort at age 24 months, 0.51 for the Sydney cohort at age 5 years, 0.58 in the Cincinnati cohort at age 4 years, and 0.87 in the Port Pirie cohort at age 4 years. In all of the prospective studies, sample sizes, and the resulting power to detect an effect, have declined significantly over time. For example, in the Boston cohort, 249 children participated initially. Only 148 children were still in the cohort at age 10. Prospective studies which have adequate sample sizes at later ages may help to clarify the duration of lead's neurobehavioral effects. The authors of the NRC report (1993), however, point out that effects on intelligence became clearer at later ages when sample sizes were even smaller.

(4) Family advantage/Catch-up effect: Certain subgroups, such as those with parents in higher SES groups, may differ in their ability to overcome the deficits in intelligence due to lead. In the Boston study, children from lower SES families (relative to that cohort) still showed effects at 57 months. Those children with high pre- and postnatal values also showed a relationship between lead and intelligence at 57 months. If "family advantage" were a factor however, one would expect that those cohorts with lower SES children and less educated parents would exhibit a more persistent effect, yet this was not observed. In fact the cross-sectional study of Needleman et al. (1990), which demonstrates persistence to age 18, presumably has a study population that is as advantaged as the Boston cohort.

(5) Age of population studied: While the effects of prenatal exposure seem to abate, the three cohorts that have reported results from children older than age 5 (Boston, Cincinnati and Port Pirie) show a consistent association between postnatal blood lead and the FSIQ score. The WISC-R FSIQ was used because it is a reliable and valid test of intelligence in children above the age of 5. One explanation for the difference in effect by age of exposure, is that intelligence tests are likely to be less reliable for children of younger ages to blood lead among very young (Schwartz, 1994).

When the findings of studies examining IQ for those above age 5, a more consistent pattern emerges. Table 3-3 summarizes the results of the findings associated with later postnatal exposure for the Boston, Cincinnati and Port Pirie cohorts. In each case, the findings at the oldest ages are used. Regression coefficients representing the effect of a 1 μg/dL change in blood lead on FSIQ are reported for the crude (univariate) models and the fully adjusted (multivariate) models. The adjusted models control for factors such as sex, birth order, gestational age,

maternal drug or alcohol use, smoking, race, parental education and IQ, SES, and HOME score. As displayed in Table 3-3, the results indicate a consistent effect of postnatal exposure on FSIQ.

For the Boston cohort, Stiles and Bellinger (1993) and Bellinger et al. (1992) indicated that FSIQ at age 10 is associated with blood lead at 2 years in both crude and adjusted regression models. However, the coefficient for the average blood lead between ages 2 and 10 years was greater than that associated with age 2 alone, indicating exposures after age 2 may also be relevant. For the crude model, the estimated beta coefficient (indicating the effect of a 1 μg/dL change in blood lead on FSIQ score) is -0.71 (s.e. = 0.25; $p = 0.005$), while for the adjusted model, beta is -0.58 (s.e. = 0.21; $p = 0.007$). For the Cincinnati cohort, Dietrich et al. (1993) report that in the crude model, FSIQ at age 6.5 is associated with blood lead levels at ages 3, 4, 5 and 6 and with lifetime average blood lead level, with the latter years being more statistically significant. For example, based on the average blood lead at age 6, a 1 μg/dL increase in blood lead is associated with a decrease of 0.58 IQ points (s.e. = 0.13; $p < 0.001$). In the adjusted model, FSIQ is associated with blood lead at age 5 and age 6. At age 6, a one unit increase in blood lead is associated with a decrease of 0.33 IQ points (s.e., = 0.14; $p < 0.01$). Finally, from the Port Pirie cohort (Baghurst et al. 1992), IQ at age 7 is associated with blood lead between ages 15 months and 4 years. Specifically, after fully adjusting for covariates (coefficients for the crude model were not presented), the estimated beta coefficient indicating the effect of a ln (blood lead) change on FSIQ is -4.6. Linearizing this, using the study mean blood lead of 19.6, indicates that a 1 μg/dL increase in blood lead results in a -0.24 decrease in FSIQ (s.e.= 0.123; $p<.05$). Therefore, these studies of effects at later ages appear stronger and more consistent than effects from pre-natal exposures.

3.1.7 Meta-Analyses of Neurodevelopmental Effects of Lead

In addition to reports by the NRC (1993), ATSDR (1994), U.S. EPA (1990a) and CDC (1990), several researchers have reviewed or conducted qualitative or quantitative meta-analyses of the prospective studies relating low-level blood lead exposures to neurodevelopmental effects in young children.

Researchers with the CDC (Thacker et al., 1992) reviewed 35 pre-natal and early postnatal studies conducted on the five prospective cohorts reviewed in this document. They limited their analyses to the five longitudinal studies in which pregnant women were identified and serial blood lead levels in infants were measured for 2-5 years after birth. They noted that all five studies showed an inverse relationship between prenatal and [early] postnatal exposure to lead and the MDI in unadjusted analyses. They did not complete a quantitative meta-analysis because of perceived inconsistencies in the methods used to analyze and report data. They concluded, however, that the weight of evidence suggested an adverse relationship between lead on the intelligence of children.

The American Council of Industrial Hygienists (ACGIH, 1995) reviewed six ongoing prospective studies as part of the justification for the revised Biological Exposure Index for lead. The ACGIH focus is on evaluating occupational and not environmental exposures. The studies reviewed include the five cohorts included in this section and a study of gestational age and birthweight (Factor-Litvak et al., 1991) which is reviewed in Section 2. ACGIH concluded that the relationship between maternal antenatal blood lead and neonatal blood lead and the current IQ of the child becomes non-significant beyond the child's second year but that "children who are born to mothers with high . . .

[blood lead levels] and whose own . . . [blood lead level] remains elevated throughout the preschool years, continue to score poorly on intelligence tests." The report suggests that prenatally acquired lead is displaced by environmentally acquired lead as the primary determinant of lead-related neurodevelopmental deficits. This conclusion is consistent with OEHHA's conclusion that children's cognitive development is related to environmental lead.

Pocock et al. (1994) reviewed several types of studies to quantitate the relationship between IQ measured by 3 different tests (WISC-R, WPPSI, and BAS) and body burden of lead. In prospective studies that controlled for covariates, no association of cord blood lead or maternal blood lead with IQ was found. However, there was strong evidence of an inverse association of blood lead at age 2 with IQ. Cross-sectional studies of blood lead also showed a significant inverse association with IQ. Finally, tooth lead (an outcome not reviewed in our report) showed a consistent inverse association with IQ. Overall, the results indicate that an increase in blood lead from 10 μg/dL to 20 μg/dL is associated with a 1-2 point IQ deficit.

Schwartz (1994) conducted meta-analyses of both longitudinal and cross-sectional neurodevelopmental studies. He used all studies published before 1993 which reported blood lead and measured full scale IQ. For the longitudinal cohorts, he selected those studies which measured exposure during the first 3 years of life when the neural network is most vulnerable to neurotoxicants. Schwartz calculated that the IQ decline associated with a 1 μg/dL increase in blood lead level was 0.27 IQ points in the cross-sectional studies and 0.30 IQ points in the prospective studies. He concluded that the two study designs were not capturing different effects and combined them in a meta-analysis which indicated a 0.26 point IQ decrease for every 1 μg/dL increase in blood lead. Examining results across studies, he noted that the roughly similar size of effects argues against the possibility that residual confounding explains the observed effects.

To provide an estimate and range for the risk assessment, OEHHA conducted a simplified meta-analysis (Hedges and Olkin, 1985) of cohort studies conducted in children older than 5 years (see Table 3-3). This age group was used because it is likely to provide the most accurate assessment of the impact of blood lead. Estimates of the mean effect were derived by weighting each of the regression coefficients by the inverse of its variance. This generated a mean decrease of 0.33 IQ points per μg/dL blood lead with a 95% confidence interval of 0.32 to 0.34. Thus, this central estimate suggests that a 1 μg/dL increase in postnatal blood lead is associated, on average, with a 0.33 point decrease in FSIQ. This level is close to the range of estimates derived from previous meta-analyses and equal to that reported by Ruff et al. (1993). OEHHA has used this value in the risk assessment of neurodevelopmental effects in Section 5.

3.1.8. Summary of Neurodevelopmental Effects

Table 3-1 provides a review of the studies conducted on each cohort. In summary, 3 of 5 prospective studies indicated deficits in Bayley's Mental Development Index (MDI) scores of 2- to 8- points with a 10 μg/dL increase in blood lead level. Among the sample of children above age 5, 3 of 3 prospective studies report deficits in Wechsler Intellegence Scale for Children-Revised (WISC-R) full-scale IQ (FSIQ) of 2 to 6 points per 10 μg/dL. Specifically the Boston study found a 4 to 8 point deficit in 6- to 24-month MDI scores per 10 μg/dL increase in cord blood lead. Also, the Boston study indicated a 6-point deficit in WISC-R at age 10 related to a 10 μg/dL increase in blood lead at age 2. The Cincinnati study found an 8.4-point decrease in boys' 6-month MDI scores with a 10 μg/dL increase in maternal blood lead level, and a 3 point

Table 3-3. Regression Coefficients Indicating Change in IQ per 1.0 µg/dL Increase in Blood Lead for Crude and Adjusted Models in Prospective Studies at Later Ages

Crude Model:		
Study	Intelligence Measure	Coefficient (s.e.)
Boston[a]	WISC-R (FSIQ)	-0.71 (0.25)
Cincinnati[b]	WISC-R (FSIQ)	-0.58 (0.13)
Adjusted Model:		
Study	Intelligence Measure	Coefficient (s.e.)
Boston[c]	WISC-R (FSIQ)	-0.58 (0.21)
Cincinnati[d]	WISC-R (FSIQ)	-0.33 (0.14)
Port Pirie[e, f]	WISC-R (FSIQ)	-0.24 (0.12)
Meta-Analyses:		
Study	Intelligence Measure	Coefficient (s.e.)
Needleman and Gatsonis[g]	Varied	-0.25 (0.04)
Schwartz[h]	Varied	-0.24 (0.04)

a PbB at age 2, WISC-R at age 10, unadjusted analysis
b Mean PbB at age 6 (PbB taken quarterly), WISC-R at age 6.5
c Adjusted for HOME score at 10 years, maternal age, race, marital status, and number of residence changes prior to 57 months
d Adjusted for HOME score, maternal IQ, birth weight, birth length, child sex, and cigarette consumption during pregnancy
e Averaged PbB at ages 0-4, linearized using PbB mean of 19.59, WISC-R at age 7
f Adjusted for sex, parent's level of education, maternal age at delivery, parental smoking status, SES, HOME score, birth weight, birth order, feeding method, duration of breast feeding and whether or not child's parents were still living together
g Meta-analysis of six cross-sectional studies of blood lead and intelligence
h Meta-analysis using same six cross-sectional studies and one additional prospective study by Bellinger et al. (1991).

Sources: Stiles and Bellinger (1993); Bellinger et al. (1992), Dietrich et al. (1993), Baghurst et al. (1992), Needleman and Gatsonis (1990), Schwartz (1993).

deficit in WISC-R at age 6.5 was associated with a 10 μg/dL increase in blood lead level at age 6. Finally, the Port Pirie study showed: (1) a 1.6 point decrease in 24-month MDI score per 10 μg/dL of blood lead at 6 months, (2) a 7-point decrease in General Cognitive Index of the McCarthy Scales (GCI) score at age 4 years using an integrated average of the child's lifetime exposure, and (3) a 2.4 point decrease in WISC-R score at age 7 associated with a 10 μg/dL increase in blood lead averaged over ages 0 to 4. Ruff et al. in their study of short-term effects in children with high lead exposures showed a 0.33 IQ point decrease for every 1 μg/dL increase in blood lead. Interestingly, these effects are within range of the slope of 2.4 IQ points loss per 10 μg/dL blood lead level increase inferred by the Needleman and Gatsonis (1990) meta-analysis of cross-sectional studies. The population-level impact of IQ is also important to consider. Grant and Davis (1989) have demonstrated that, if one shifts down a normal distribution of MDI scores (mean=100, standard deviation=16) by 4 points, the number of children scoring 80 or below increases by 50%. The impact of such a shift applies across the entire distribution of scores, reducing the number of children who score above the norm as well as increasing the number scoring below the norm. Thus, while a 4-point IQ loss might not have much impact on an individual child, this decrease could have a significant public health impact in a community. Similarly, a shift of 3.3 points would increase the percent of children scoring 80 or below from 10.56% to 14.74%, a 39.5% increase (see Appendix D for details on computing this calculation). This level of change could be observed, for example, in older homes with lead paint, but are unlikely to result from changes in current levels of ambient air lead.

Among the prospective studies, the Boston study was designed best to determine a level at which blood lead effects might be detected. To ensure a relatively uniform distribution of blood lead levels at birth, initially only those infants with blood lead levels that fell into their arbitrary low, medium and high ranges were enrolled in the study. In the Boston study, effects on MDI up to the age of 24 months were seen for those with umbilical cord blood lead levels of 10 μg/dL or greater. In a review of the early prospective studies, Davis (1990) noted that, since the investigators created the low, medium and high lead groups arbitrarily, effects on intelligence may actually occur at levels lower than 10 μg/dL for the cohort as a whole. In fact, subsequent analysis by Schwartz (1994) failed to detect a threshold in this population. Furthermore, the Boston study indicated that the MDI deficits can be detected at 6-7 μg/dL cord blood lead in children of "lower" SES within their cohort (Bellinger et al., 1989a,b). As noted in the U.S. EPA's revised literature review, since the children in this investigation came from relatively advantaged backgrounds, the lower SES group in this study probably represents the median of the US population (U.S. EPA, 1990a). An additional analysis, expressly aimed at identifying a threshold for lead's effects on intelligence, finds a continuum of effects down to 1 μg/dL (Schwartz, 1993).

Given the results of the studies discussed above, we will use 10 μg/dL as the level of concern for effects on intelligence, although effects may occur at lower levels. This "level of concern" is consistent with those identified by the U.S. EPA (1990a), the CDC (1991b), the National Research Council (1993) and the ATSDR (1990). Finally our meta-analysis of studies conducted at older ages (5 to 10) indicates that a 1 μg/dL increase in postnatal blood lead is associated, on average, with a 0.33 point decrease in FSIQ.

3.2. Effects on Blood Pressure in Adults

The association between lead and blood pressure was first observed in animals. This effect has been shown across a range of doses and in several species (Victery, 1988), and also has been examined in occupational and population-based epidemiological settings. This section provides a brief review of these studies. Because they are more relevant to potential exposures from ambient air lead and involve lower levels of exposure, the population-based, non-occupational studies will be used as the basis for the quantitative estimates of the risk assessment. Studies were selected for inclusion on the basis of meeting several criteria. These include (1) proper study design and methodology, (2) concern for minimization of confounding and omitted variables, (3) sufficient sample size to detect an effect, and (4) a reasonably complete analysis of the data including a careful exploration of the primary hypothesis as well as an examination of the robustness and sensitivity of the results to alternative functional forms, specifications, and influential data points.

Several studies in animals have examined the effects of lead on blood pressure (summarized by Victery et al., 1988; Sharp et al., 1987; Staessen et al., 1995) (Table 3-4). These include studies with chronic, high-level exposures and chronic, low-level exposures. Other studies have examined effects in spontaneously hypertensive animals. Most investigators have used rats; a few studies have been completed in dogs and pigeons. Since an animal's blood pressure will rise with handling, researchers had to ensure that the hypertensive effects were due to lead treatment itself. Some studies in which animals were exposed chronically to high levels of lead showed effects on blood pressure (see discussion in Victery, 1988). However, the most relevant studies to the present report were several studies with chronic, low-level lead exposure in rats (Perry and Erlanger, 1978; Iannaccone et al., 1981a,b; Victery et al., 1982a; Victery et al., 1982b; Carmignani et al., 1983; Boscolo et al., 1992). Exposure levels varied from 0.1 to 500 ppm lead, usually in drinking water. There were usually 6 to 20 rats at each exposure level. In two studies rats were exposed in utero (Victery et al., 1982a; Victery et al., 1982b). Exposure varied from 5 months (Victery et al., 1982b) to 18 months (Perry and Erlanger, 1978). In 5 of the 6 studies, systolic blood pressure rose on average between 12 and 54 mm Hg. There was some consistency among the studies. For example, both Iannaccone et al. (1981a,b) and Carmignani et al. (1983) had similar increases in blood pressure with 50 ppm lead (54 and 48 mm Hg, respectively), while Perry and Erlanger (1978) showed a much lower increase at 5 ppm lead (12-14 mm Hg). On the other hand, the first Victery et al. study (1982a) showed only a 17 mm Hg increase at 100 ppm lead and no increase at 500 ppm, while the second study (Victery et al., 1982b) showed no increase in blood pressure after 5 and 25 ppm lead exposure. (The lack of an effect at high levels of lead has been seen in some earlier studies using higher doses. A recent high dose study found an increase in blood pressure at 10,000 ppm after 15 months (Nowack et al., 1993) but a study by Khalil-Maneh et al. (1993) found no change at 5000 ppm after 12 months (Table 3-4).) Three studies determined blood lead levels which reflected the level of lead exposure (see Table 3-4). Other studies (e.g., Evis et al., 1987; Bogden et al., 1991; Boscolo and Carmignani, 1988; Lal et al., 1991) also showed increased systolic blood pressure and increased blood lead levels after lead ingestion. Overall, the studies indicate that chronic, low-level, ingestion of lead elevates systolic blood pressure in animals.

Victery (1988), as summarized by Moller and Kristensen (1992), mentions four possible pathophysiologic mechanisms that may explain the effects of blood lead on blood pressure and

Table 3-4. Summary of Animal Studies Relating Chronic Lead Exposure to Change in Systolic Blood Pressure

Reference	Sex/Species	n	Exposure (ppm)	Blood Lead (μg/dL)	Duration of Exposure	Age Exposure Began	Mean SBP Increase (mm Hg)
Perry and Erlanger (1978)	F Rat	45	0	--			
	F Rat	15	0.1		3 months	wean	5
	F Rat	15	1.0		3 months	wean	12[e]
	F Rat	15	5.0		3 months	wean	11[e]
Kopp et al. (1980)	F Rat	18	0	--			
	F Rat	10	5		3 months	wean	19[e]
Aviv et al. (1980)	M&F Rat	5	0	17.0			
	M&F Rat	5	10,000	23.5[a]	6 weeks[a]	wean	13[e]
Revis et al. (1981)	M Pigeon	[b]	0.8		6 months	3 months	13[e]
Iannaccone et al.(1981a, b)	M Rat	8	0	13.6			
	M Rat	8	50	38.4	160 days	adult	54[e]
Webb et al. (1981)	M Rat	28	0	2.2[c]			
	M Rat	31	100	40.4[c]	7 months	in utero	14[e]
Victery et al. (1982a)	M Rat	20	0	1.4			
	M Rat	20	5	5.6	5 months	in utero	0
	M Rat	13	25	18.2	5 months	in utero	-5
Victery et al. (1982b)	M Rat	19	0	2.2[c]			
	M Rat	19	100	40.4[c]	3.5 months	in utero	17[e]
	M Rat	13	500	70.8	3.5 months	in utero	-6
Carmignani et al. (1983)	M Rat	10	0				
	M Rat	10	50		180 days	wean	48[e]
Evis et al. (1987)	M Rat	11	0	3.6			
	M Rat	11	250	17.0	3.5 months	in utero	-10
	M Rat	11	1000	38.1	3.5 months	in utero	15[e]
Boscolo & Carmignani (1988)	M Rat	10	0	3.9			
	M Rat	10	15	7.4	18 months	wean	4
	M Rat	10	30	11.5	18 months	wean	12
	M Rat	10	60	16.7	18 months	wean	26[e]
Fine et al. (1988)	F Dog	6		9.2	-	-	
	F Dog	6	(1 mg/kg)	35.8	5 mo	3 mo	12[e]
Bogden et al. (1991)	M Rat	8	0	1.5			
	M Rat	8	1	3.5	31 weeks	wean	8
	M Rat	8	100	39.1	31 weeks	wean	14[e]
Lal et al. (1991)	M Rat	5	0	12.9			
	M Rat	5	2500	135.2	3 months	adult	30
	M Rat	5	5000	191.2	3 months	adult	37[e]
	M Rat	5	10000	311.0	3 months	adult	46[e]

Table 3-4 (continued)

Reference	Sex/ Species	n	Exposure (ppm)	Blood Lead (μg/dL)	Duration of Exposure	Age Exposure Began	Mean SBP Increase (mm Hg)
Boscolo et al. (1992)	M Rat	6	-	-	-	-	-
	M Rat	6	15	-	14 mo	wean	6
	M Rat	6	30	-	14 mo	wean	16[e]
	M Rat	6	60	-	14 mo	wean	24[e]
Khalil-Manesh et al. (1993)	M Rat	?	-	-	-	-	-
	M Rat	?	100	<30	12 mo	8 wk	18[e]
	M Rat	?	5000	>59	12 mo	8 wk	1
Nomiyama et al. (1993)	M Rat	8	-	-	-	-	-
	M Rat	8	3	-	16 wk	6 wk	"0"[d]
	M Rat	8	30	-	16 wk	6 wk	"0"[d]
	M Rat	8	300	-	16 wk	6 wk	"0"[d]
Nowack et al. (1993)	M Rat	24	-	-	-	-	-
	M Rat	19	10,000	-	15 mo	-	(14)[e,f]

a Exposure between 3 and 9 weeks, measurement of BP at 25 weeks of age.
b 64 pigeons in 4-way factorial design encompassing exposure to other metals.
c Exact blood lead concentrations and standard errors reported, but different protocols and subject numbers.
d Some values were interpolated from bar graphs in the original reports.
e $p<.05$ or better. In several instances, values of $p<.01$ and even $p<.001$ were obtained.
f Mean arterial pressure.

cardiovascular disease: "(1) Lead can increase blood pressure by an alteration in intracellular calcium, but the level of intracellular free calcium ion is also important. (2) Creatinine kinase, a calcium-dependent enzyme affected by lead, can promote smooth muscle contractions. (3) A prime target for lead is the endothelial cells of the blood vessel wall; these cells contribute to the conversion of angiotensin I into angiotensin II, and since the level of angiotensin II in some reports is observed to be low, this may be a result of the direct action of lead on the endothelial cells. (4) Lead could alter calcium entry or calcium cycling from the sarcoplasmic reticulum, which can affect contractile systems."

Among the epidemiologic evidence, several studies indicate a relatively consistent association between blood lead and both systolic and diastolic blood pressure. These studies typically have used multiple regression to explain the variation in blood pressure. Besides blood lead, several other covariates such as age and body mass index (BMI), are included in the regression. Additional covariates are used to control for the influence of other factors such as alcohol use, diet, and blood biochemisty. To the extent that these factors (e.g., alcohol) may be correlated with blood lead, their inclusion may reduce the effect size and statistical significance of blood lead. In general, the associations with systolic blood pressure appear to be larger and more significant but the results are dependent on the actual study, the sample size and the covariates used in the regression specifications.

Several investigators have used data from the National Health and Nutrition Examination Survey (NHANES II) to investigate the relationship between blood lead level and blood pressure (Schwartz et al., 1985; Harlan et al. 1985; Pirkle et al., 1985; Schwartz, 1985a,b, 1986a,b; Schwartz, 1988; Harlan, 1988; Landis and Flegel, 1988; Gartside 1988; Sorel et al., 1991). This survey was designed to measure and monitor the health and nutritional status of the U.S. population. NHANES II is a large, individual-level database that includes information on a variety of potentially confounding factors. Therefore, by using NHANES II data, these studies avoided common study design problems (e.g., healthy worker effect, workplace exposures to other toxic agents, selection bias, and problems of control group selection). The Survey uses a stratified multistage probability cluster sample of households and is considered to be representative of the U.S. population.

Using NHANES II data, Harlan et al. (1985) demonstrated statistically significant linear associations ($p<0.001$) between the log of blood lead concentrations and both systolic and diastolic blood pressure among males aged 12 to 74 years, after adjusting for several covariates. The analyses by Pirkle et al. (1985) focused on white males, aged 40 to 59 years. This age group was used to reduce any potential confounding effects of age since both blood lead and blood pressure change with age. Besides blood lead, other factors that may affect blood pressure were considered including age, BMI, cigarette and ethanol consumption, and nutritional and biochemical variables such as dietary sodium, potassium, calcium, and serum Vitamin C, hemoglobin, cholesterol, and zinc. In the subgroup studied, significant associations were found between the log of blood lead and blood pressure even after controlling for all risk factors known to be correlated with blood pressure. Furthermore, no threshold for the effect was observed across a blood lead range of 7 to 34 μg/dL.

During the 4 years in which NHANES II data were collected, there were declines nationally for both blood lead and blood pressure. In addition, sites were sampled at different times without revisitation. The variations observed in these sampling sites over time could be due to these national declines, resulting in the observed association. Schwartz (1985a,b, 1986a,b,

1988) reanalyzed the data of Pirkle et al. (1985) and showed that the association decreased but remained significant for both systolic and diastolic blood pressure when adjusted for site. In an additional analysis, Schwartz et al. (1985) used a logistic analysis to demonstrate a relationship between blood lead and the probability of hypertension, defined as diastolic blood pressure greater than or equal to 90 mm Hg.

Landis and Flegal (1988) examined the robustness of the association of lead and diastolic blood pressure in males aged 12-74, adjusting for age, BMI, and sampling site. The association remained statistically significant at the $p < 0.05$ level across 478 subgroups. They concluded that the NHANES II findings could not be dismissed as due to concurrent secular trends across the 4-year survey period. Furthermore, this analysis indicates that the blood lead - blood pressure relationship holds for all adult males, age 20 to 70.

Gartside (1988) analyzed the association across ages 21 to 65 by dividing the sample into 20-year age spans. For the 40 to 59 age group, a statistically significant association ($p = 0.005$) was reported between blood lead and systolic blood pressure, but not with diastolic blood pressure ($p = 0.19$). The difference in findings relative to the earlier analyses is likely due to the inclusion of a variable indicating the date of examination. The date of examination will not have an effect on blood pressure independent of blood lead (which does vary with time during the 4 year survey) but it would be correlated with blood lead. Therefore it would reduce both the magnitude of the effect and statistical significance of the estimated blood lead coefficient.

In another reanalysis of the NHANES II data, Coate and Fowles (1989) attempted to correct for apparently questionable blood pressure data from certain cities in the sample. Although the magnitude of the effects was found to be lower, their analysis confirmed an association between blood lead and blood pressure among the male cohort aged 40 to 59. For several other age groups, the association was not significant. However, blood lead was associated with both systolic and diastolic blood pressure among a cohort including blacks and whites of both sexes for subjects ages 12 to 39 and ages 60 to 74.

Sorel et al. (1991) also used data from NHANES II among a cohort of black and white subjects between the ages of 18 and 74. For this cohort, an association was detected between blood lead and diastolic blood pressure in men, but not in women. Blood lead was a less important predictor of systolic blood pressure.

Schwartz (1991) examined the influence of blood lead on males and females aged 20 to 74. Besides age and BMI, the regressions controlled for factors such as race, family history of hypertension, cholesterol, serum zinc, smoking, exercise, and dietary levels of potassium, sodium, and vitamin C. A statistically significant association was reported for both males and females.

Generally, across these studies using data from NHANES II, a doubling of blood lead corresponded to approximately a 2 mm Hg increase in systolic blood pressure and a 1 mm Hg increase in diastolic blood pressure.

The association between blood lead and blood pressure has also been examined for cohorts outside of the U.S. However, due to differences in diet, exercise, genetics and other factors that may alter blood pressure, generalizing these findings to the U.S. population is more tenuous.

Pocock et al. (1988) analyzed blood pressure data from the British Regional Heart Study (BRHS). For 7,371 men aged 40-49 there was a small but significant association of both systolic ($p=0.03$) and diastolic ($p = 0.001$) blood pressure with blood lead level when adjusted for site in multiple regression analyses. Analyses were also adjusted for BMI, age, alcohol intake, smoking,

social class, and location. The magnitude of the effect of blood lead on diastolic blood pressure was very similar to that found in the analysis of NHANES II. Specifically, an estimated mean increase of about 1.2 to 1.4 mm in both systolic and diastolic blood pressure occurs for every doubling of blood lead concentration in adult males. The relationship between diastolic blood pressure and blood lead level appears to hold across a wide range of blood-lead values extending possibly down to 5 μg/dL for middle-aged men.

Data from the Canada Health Survey, in which over 2,000 male and female subjects aged 25 years to 64 years were studied, support the above findings (Neri et al., 1988). The authors observed a statistically significant relationship ($p = 0.04$, one-tailed test) between diastolic blood pressure and blood lead level when controlling for age, sex and BMI. When hemoglobin and serum zinc were added to the regression model specification, the statistical significance was reduced ($p = 0.10$). The effects of lead were especially pronounced among those with high blood pressure who were not taking antihypertensive medication.

Moller and Kristensen (1992) studied 1052 males and females in Copenhagen, Denmark. This cohort was examined earlier by Grandjean (1989). Subjects were prospectively examined at ages 40, 45 and 51. In an unadjusted model, there was an association between blood lead and systolic but not diastolic blood pressure for males, while for females, blood lead was associated with both measures of blood pressure. The magnitude of the effects on systolic blood pressure reported for males aged 40, 45 and 51 and females aged 40 and 45 (those age 51 were not resampled) were 1.5 to 3.5 mm Hg for a change from 8 to 16 μg/dL blood lead; very similar ranges were reported in the NHANES II and British studies described above. The statistical significance of blood lead decreased as adjustments were made first for tobacco, BMI and physical activity, then for alcohol, and finally for hemoglobin. In the final models, only diastolic blood pressure in women was still statistically significant.

Hense et al. (1993) studied 1703 males and 1661 females age 28 to 67 in Augsburg, Germany. Mean blood leads were 8.3 μg/dL for the males and 6.0 μg/dL for the females. Controlling for age and BMI, an association was found between blood lead and systolic and diastolic blood pressure for both men and women. When alcohol and hematocrit were added to the regression specification, systolic blood pressure in men and diastolic blood pressure in women remained significant at the $p < 0.05$. Again, the estimated ranges are quite similar to those reported in the studies using NHANES II.

Among the smaller non-occupational studies, Orssaud et al. (1985) examined the systolic blood pressure of 431 Parisian men, age 24 to 55. The authors report an association between systolic blood pressure and blood lead for both an unadjusted and adjusted (i.e., for age, BMI, and alcohol consumption) analysis. The authors indicate that their findings are similar to those of Pocock (1985) in that the association between blood lead and blood pressure appears stronger at the lower concentrations. Blood lead and blood pressure are correlated until a certain level at which point other factors, they suggest, such as age (which is correlated with blood lead), increases blood pressure by a greater amount than does blood lead. This demonstrates that restricting the age range under study serves to reduce the confounding effects of age.

Moreau et al. (1988) examined the association between blood lead and blood pressure among a sample of 129 adult males, ages 23 to 57, who were not occupationally exposed to lead. After adjustment for age, BMI, and alcohol intake, blood lead was modestly associated with systolic blood pressure ($p = 0.09$), but not with diastolic blood pressure ($p = 0.15$).

Kromhout et al. (1985) and Kromhout (1988) examined the association between lead and other metals and blood pressure among a cohort of 152 men aged 57 to 76 in Zutphen, the Netherlands. Blood lead was found to be associated with both diastolic and systolic blood pressure in a regression model adjusting for age and BMI. However, after the individual with the highest blood lead was dropped, lead was significantly associated with systolic but not diastolic blood pressure.

Morris et al. (1990) examined 251 subjects participating in a clinical trial for non-pharmacologic management of blood pressure. In an unadjusted model for males, blood lead was associated ($p < 0.05$) with both systolic and diastolic blood pressure, while no such association was found among females in the sample. For males, a doubling of blood lead from 8 to 16 μg/dL related to changes of 3.67 mm Hg and 1.94 mm Hg in systolic and diastolic blood pressure, respectively. In a model incorporating covariates via stepwise regression, blood lead was selected along with age and ionized calcium to explain systolic blood pressure while lead, age, hemoglobin and smoking status were selected to explain diastolic blood pressure. In these models, the estimated effect of a doubling of blood lead decreased to 3.17 mm Hg and 1.32 mm Hg, for systolic and diastolic blood pressure, respectively.

In a study conducted in Italy, Apostoli et al. (1992) examined 254 males and 271 females with a mean age of 37. After controlling for several covariates, they reported an association between blood lead and both diastolic and systolic blood pressure for both males and females. However, a regression equation quantitatively relating blood lead to blood pressure was not presented. The researchers also found an association between blood lead and the increased likelihood of hypertension (defined as systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 90 mm Hg) using a logistic model.

Menditto et al. (1994) examined the impacts of blood lead among 1,800 men aged 55 to 75 living in the Rome area. The regression model tested for the inclusion of factors such as age, BMI, heart rate, cholesterol, triglycerides, glucose, daily cigarette smoking, alcohol consumption, and skinfold tightness. Blood lead was reported to be associated with both systolic and diastolic blood pressure.

Regarding the shape of the dose-response function indicated by these positive studies, several researchers have found that a semi-log model provides the best fit of the data (Schwartz, 1988, Pocock 1988), although visual inspection of the Pocock data indicates a linear fit may do equally well. Schwartz (1988) provided the most complete analysis of the shape of the dose-response function. There is no evidence for an exponential or power function fit. As indicated by Schwartz (1988), "the natural log of blood lead was more normally distributed, more significant, and gave a higher R^2 than untransformed blood lead, blood lead squared, blood lead + blood lead squared, the square root of blood lead, or blood lead to other fraction powers. All of the results reported here are for the natural log of blood lead, but regressions for untransformed lead gave very similar results."

Additional support for the magnitude of the effect of blood lead on diastolic blood pressure is provided by a study of 342 San Francisco bus drivers (Sharp et al., 1988). Multiple regression analysis was used to examine this association while controlling for age, BMI, sex, race and caffeine intake. The results indicate a change of 1.83 to 2.45 mm Hg in diastolic blood pressure associated with a 1 unit change in the natural log of blood lead. Further analysis of this data (Sharp et al., 1990) showed that the effect of blood lead on blood pressure was greater for blacks than non-blacks. Weiss et al. (1988) examined the effects of lead among 89 Boston policemen. This study is of particular interest since it is one of the few longitudinal studies

examining the relationship of blood lead to blood pressure. Since repeat measures are taken of the same population over time, this study is able to minimize the potential for confounding. A statistically significant association between blood lead and systolic blood pressure was reported. Other studies reporting a positive association between blood lead and blood pressure, typically in occupational settings, include de Kort et al. (1987), Weiss et al. (1988) and Egeland et al. (1992). Also, Rabinowitz et al. (1987) assessed the relation between pregnancy hypertension (as diagnosed by physicians providing care), blood pressure during labor, and blood lead among 3851 Boston women. A statistically significant association was found between lead and both the incidence of pregnancy hypertension (as diagnosed by physicians providing care) and systolic blood pressure after controlling for maternal age, parity, hematocrit, BMI, race diabetes, and tobacco use. However, blood pressure readings were made with clinical grade instruments and were not standardized. Alcohol use was not correlated with blood pressure.

Contradictory findings were reported in 2 studies conducted in Wales by Elwood et al. (1988). The Welsh Heart Programme (WHP) used a stratified random cluster sample of 21,000 households. Complete blood lead, blood pressure, and other key data were available for 865 men and 856 women (age 18 to 64) selected for the study. The relationship of lead and blood pressure was not statistically significant for either group. However, in these analyses, there was no apparent adjustment of covariates, and it is likely that blacks were not included in the sample. It is also possible that demographic and socioeconomic factors for this sample differed greatly from those described above. In the other study conducted in Wales, investigators for the Caerphilly Collaborative Heart Disease study used data from the first 1,137 men seen in the first follow-up of a cohort of 2,500, aged 49 to 65 years, living in a small Welsh town. No significant association was found between blood pressure and blood lead level. Visual inspection of the data for Wales suggests a dose-response function up to approximately 35 μg/dL, a finding similar to that observed by Orssaud et al. (1985) and Pocock (1985).

Although these Welsh studies both showed no association, Pocock et al. (1988) graphed the findings of the studies discussed above and concluded that the overlapping confidence limits indicated a possible weak but positive statistical association with relatively consistent findings. Specifically, systolic blood pressure in adult men increases by about 1 mm Hg when blood lead increases from 8 to 16 μg/dL (Pocock et al., 1988).

Finally, Staessen and colleagues . (1991, 1993, 1996) have produced several analyses of a cohort from a cross-sectional study examining cadmium in Belgium (Cadmibel study). Blood pressure readings were carefully standardized and each individual was characterized by the average of 10 blood pressure measurements. Staessen et al. (1996) involved a cohort of 359 males and 369 females ages 20 to 82. The cohort was recruited from 2 regions: one polluted by emissions from a nonferrous smelter and one relatively nonpolluted. However, 59% of the sample in the polluted region and 17% of the sample in the unpolluted region included workers employed at the smelter, who presumably were occupationally exposed. Subjects in the highest lead quartiles had higher blood pressures ($p < 0.001$) but were also older. After adjustment for age, the blood pressures were similar in the lowest and highest quartiles. The regression model considered the influence of such covariates as age and age^2, BMI, hemoglobin or hematocrit, indices of alcohol intake and physical activity, social class, smoking, and serum calcium. Results of the 1996 study indicated no association between blood lead and blood pressure for males, but an association with diastolic blood pressure in females. In fact, for males, an inverse (protective) effect from lead was often reported. Unfortunately, the impact of pooling occupationally exposed

workers with the general unexposed population was not examined. While the cohort from the polluted region had higher blood lead concentrations, their blood pressures were similar to those in the unpolluted region. This may indicate some confounding via the "healthy worker" effect. In an editorial accompanying this publication, the editors suggest several additional reasons for the failure to find a positive association including selection bias (complete data were available for only half of the sample) and the lack of the sensitivity of the study (likely due to sample size) (Lenfant, 1996). The editorial also states that the findings contradict a case-control study using better measures of lead burden (Hu et al. 1996).

Hu et al. (1996) used data from a long-term study of participants aged 48 to 92 in the Department of Veterans Affairs Normative Aging Study to investigate the association between lead in the body and the likelihood of hypertension. Long-term lead accumulation was measured by lead in bone using K x-ray fluorescence (KXRF). Blood lead levels ranged from less than 1 to 28 μg/dL, with a mean of 6.3 μg/dL. Using a logistic regression model, factors such as age, race, BMI, family history of hypertension, cumulative smoking and ethanol ingestion, and sodium and calcium intake were examined along with blood and bone lead for their ability to explain hypertension. A statistically significant association was reported between tibia bone lead and hypertension indicating that cumulative lead burden may be a significant risk factor for the development of hypertension.

Two meta-analyses (Schwartz, 1995; Staessen et al., 1995) and one literature review (Hertz-Picciotto and Croft, 1993) have been conducted to summarize the weight of evidence. Since the statistical significance of an individual study is dependent on sample size, model specification, and the degree of collinearity between blood lead and other factors, the evaluation of several studies is warranted. Schwartz (1995) assessed the association between blood lead and systolic blood pressure among adult males, aged 20 to 76. Results of the meta-analysis indicate a "highly significant and moderately consistent" association between blood lead and systolic blood pressure. A decrease in blood lead from 10 μg/dL to 5 μg/dL was associated with a 1.25 mm Hg decrease (95%CI = 0.87 - 1.63 mm) in systolic blood pressure. Sensitivity analysis indicated that the results were robust to deletion of the most significant study, and that the effect increased to 1.44 mm with the deletion of the most negative study. In addition, the results found that if eight new studies were published and reported a zero effect of blood lead on systolic blood pressure, the combined effect of blood lead on systolic blood pressure would remain statistically significant. A greater effect is found if the sample is restricted to older males.

Staessen et al. (1995) analyzed the results of studies including males and females aged 10 to 88, as well as several occupationally-exposed cohorts. For systolic blood pressure for males, their results were similar to that of Schwartz (1995). They reported that a doubling of blood lead was associated with a 1.2 mm Hg increase in systolic blood pressure (95%CI = 0.2 to 2.2). For diastolic blood pressure, the effect size due to a doubling of blood lead was 0.5 mm Hg (95%CI - -0.1 to 1.1). This effect is lower than that reported for most of the analyses of NHANES II. This is due to several factors. First, a wider age range -- 10 to 88 -- was included while our risk assessment (Chapter 6) focuses on males aged 40 to 59. Second, results for blacks and whites were pooled, although available results for these two groups appear quite different. Third, there were many occupational exposure studies included in the analysis. Their relevance to exposures of the general population is questionable. Finally, the rationale for selection of a particular study, when several were available using the same data set, was unclear. For example, as indicated above, there have been many studies using data from NHANES II that report a positive and

statistically significant association between blood lead and blood pressure. However, the Gartside study (1988) appears to be the one used in the meta-analysis. As another example, Pocock (1984) was used rather than an improved reanalysis (Pocock, 1988) which reported a positive and significant effect when controlling for location. In our own independent quantitative review of the available studies relating blood lead to diastolic blood pressure, we deleted occupational studies, used Schwartz (1991) instead of Gartside (1988) for the analysis of NHANES II, and included several newer studies. Our analysis generates an estimate that is more than twice that of Staessen et al. (1995) and that does not include zero within the 95% confidence interval. As in the meta-analysis by Schwartz (1995), we found that the results were relatively robust to deleting the highest or lowest study or to the inclusion of potentially new studies finding no effect.

In their review of the association between blood lead and blood pressure, Hertz-Picciotto and Croft (1993) examined 8 major population-based studies in addition to several occupational studies. They concluded that overall the evidence suggests a small but statistically significant association between blood lead and blood pressure with a dose-response through the range of blood lead of up to 30 or 40 μg/dl. After extensive consideration of potential methodological problems including measurement of blood pressure and blood lead, and several statistical issues including confounding, the authors state that the literature is strongly suggestive, but not definitive, of an association. However, no other explanation for the association, other than the causal one, was felt to exist. The authors add that, although the risks appear small, "a small influence of blood lead on blood pressure might have rather large consequences for debilitating and fatal cardiovascular disease," and that, based on the available evidence, "public health measures to reduce exposures may be deemed justified."

. Other reviews have been undertaken as well. In the 1986 Addendum to the Lead Criteria Document, the U.S. EPA concluded that, overall, the analyses of data from the NHANES II and British Regional Heart Study collectively provided convincing evidence demonstrating a small but statistically significant association between blood lead and blood pressure. The association appears to exist for both males and females and over a wide age range.

There is reasonable agreement about the size of the effect of blood lead on blood pressure. Several international review groups including those sponsored by U.S. EPA (Victery et al., 1988), the International Programme for Chemical Safety (IPCS) (1993), U.S. EPA's external Science Advisory Board, and the National Research Council (1993) have concluded that a doubling of blood lead is associated with a 1 to 2 mm Hg increase in systolic blood pressure. For example, in their most recent review of the effects of lead on blood pressure (U.S. EPA, 1990a), U.S. EPA concludes: "Sufficient evidence exists from both the four large-scale general population studies discussed above and numerous other smaller-scale studies to conclude that a small but positive association exists between blood lead levels and increases in blood pressure. Quantitatively, the relationship appears to hold across a wide range of blood-lead values, extending down to as low as 7 μg/dL for middle-aged men and, furthermore, an estimated mean increase of about 1.5-3.0 mm in systolic blood pressure appears to occur for every doubling of blood lead concentration in adult males and something less than 1.0-2.0 mm Hg for adult females." In addition, the IPCS states in their conclusion, "Lead exposure is associated with a small increase in blood pressure. The likely order of magnitude is that for any two-fold increase in blood lead (for example, from 0.8 to 1.6 μmol/liter, i.e., from 16.6 μg/dL to 33.3 μg/dL) there is a mean 1 mm Hg increase in systolic blood pressure." Also, the National Research Council (NRC, 1993), in their review of the blood lead - blood pressure studies, stated, "Overall, a considerable majority reported significant

associations". Their review of the epidemiologic studies suggest a similar magnitude of effect to that described above. Therefore, the OEHHA conclusions are similar to those from leading international scientific groups; i.e., there appears to be a small but consistent association between blood lead and blood pressure.

The U.S. EPA, WHO, and other scientific experts (Sharp et al., 1987) have indicated that the animal experiments, unconfounded by covariates and providing clear measures of exposure, provide a plausible mechanism for an effect of lead on blood pressure. In addition, several of the epidemiologic studies lend support to this hypothesis. Typically, it is very difficult for an epidemiologic study to prove causality, especially when the effect size is small. However, there is not universal agreement on causality. For example, after indicating that animal studies provided a biological mechanism for an effect of lead on blood pressure and that several epidemiologic studies suggest an association, the IPCS stated "However, from such a small magnitude of statistical associations in the presence of important confounders, one cannot infer that low level lead exposure is causally related to blood pressure," and added, that in their opinion "until issues of confounding are adequately resolved, the relationship cannot be classified as definitive (ICPS, 1993)." In contrast, Hertz-Piccioto and Croft (1993) state that "while not ruled out, the probability that confounding explains most of the findings appears to be low" and indicate that several covariates included in the regression analyses that relates blood pressure to blood lead may have reduced the apparent lead effect. In its review of the ambient lead standard, U.S. EPA (1990a) concluded: "The plausibility of these relationships observed in epidemiologic studies of human populations being of causal nature is supported by controlled animal studies demonstrating increased blood pressure effects clearly attributed to lead, with an apparent biphasic dose-response relationship being involved." In addition, the recent review of lead by the National Research Council (1993) stated: "Overall, a considerable majority reported significant associations. Combined with the strong animal model, mechanistic results, and the moderate concordance of effect size, this suggests overwhelming evidence for the causality of the association."

It is useful to review the frequently cited criteria for inference developed by Bradford Hill (1965), and examined by U.S. EPA in their review of the ambient standard for particulate matter standard (U.S. EPA, 1982). Causal inference in epidemiology is an informal process, involving consideration of several guidelines or criteria. Ultimately, the satisfaction of several criteria has been proposed including: (1) consistency of the association; (2) specificity of the association; (3) existence of a dose-response curve; (4) strength of the association; (4) coherence of the association with other known facts; and (5) biological plausibility of the association. It is also emphasized that no single element is definitive by itself nor is it necessary that all criteria be fulfilled in order for a determination of causality. The association between blood lead and blood pressure meets most, if not all, of the above criteria. For example, the effects, as reviewed in the OEHHA analysis, are generally consistent across several different populations, covariates, and lead levels. The endpoints, diastolic and systolic blood pressure, are very specific outcomes, and dose-response relationships have been clearly demonstrated in epidemiologic studies. The association is indeed a weak one, likely due to several factors such as difficulties in measuring both exposure and outcome, and difficulty in controlling for all potential confounders. However, these circumstances also reduce the power to detect an effect, making it particularly notable that such an effect is consistently reported. The association is coherent with other known facts about lead exposure such as associations found between lead and electrocardiogram changes and

between lead and abnormal electrocardiograms indicative of left ventricular hypertrophy (Schwartz, 1991). Finally, as discussed above, a biological mechanism is fairly well established in the animal experiments. Taken together, these studies provide compelling evidence of an effect.

In the context of the epidemiologic studies of blood lead and blood pressure, the consideration of potential confounders is important. All of the studies include basic covariates such as age, sex, and BMI. Many of the other studies also include covariates such as tobacco use, hemoglobin, alcohol use, hematocrit, fitness, dietary vitamin C, and potassium. In their analysis of the NHANES II data, Pirkle et al. (1985) also considered 87 nutritional and biochemical variables in a stepwise regression. The inclusion of additional covariates that are correlated with blood into the regression equation explaining blood pressure will likely increase the variance of the blood lead coefficient, thereby lowering its statistical significance. Therefore, caution must be exercised in both the determination of which and how many variables should be included and in the interpretation of p-values. Of particular interest is the role of alcohol consumption as a confounder in the association between blood lead and blood pressure. Several authors (Pirkle et al., 1985; Schwartz, 1991; Pocock, 1988) continue to find a statistically significant association between lead and blood pressure after alcohol is included in the model. Others (Moller and Kristensen, 1992; Hense et al., 1993) report that the inclusion of alcohol use decreases the significance of the blood lead variable. In both of these latter studies, the issue of whether alcohol should be included in the regression analysis is discussed. If lead has an independent effect on blood pressure and lead and alcohol are collinear, the inclusion of alcohol will reduce the impact of lead in the model. Hense et al. (1993) specifically test for the relationship between both lead and alcohol on serum lipids. If blood lead is only a marker for alcohol, then it should be related to serum lipids. However, in their data, it is found that alcohol, but not blood lead, was related to the ratio of high-density lipoprotein to total cholesterol. Therefore, Hense et al. argue that lead exerts an independent effect on blood pressure. In addition, since alcohol use increases the amount of lead in blood and lead plays an intermediate role in the causal pathway for alcohol, "a certain amount of underestimation of the true magnitude of the blood lead-blood pressure association can be anticipated in cross-sectional analyses controlling for alcohol consumption, owing to the potential for overadjustment described above." Moller and Kristensen (1992) agree that this is a difficult issue and that lead is not a simple confounder: "there is a risk of error regardless of whether or not adjustments are made for alcohol intake." For this reason, we have described, in our review, the results of both adjusted and unadjusted analysis.

Several investigators have attempted to predict the impact of the observed increase in blood pressure on other significant cardiovascular events. Large-scale epidemiological studies including the Pooling Project Research Group (1978) and the Framingham study (McGee and Gordon, 1976) have shown that elevated blood pressure increases the risk of stroke and coronary heart disease (MacMahon et al., 1990).

The Pooling Project combined the results of 5 longitudinal studies that examined the onset of coronary heart disease (CHD) in middle-aged white men. The first incidence of CHD, defined as fatal or nonfatal myocardial infarction and sudden CHD death, was measured over a 10-year period. Using logistic analysis, the research indicated that smoking, serum cholesterol, and diastolic blood pressure were major risk factors in the incidence of CHD (Pooling Project Research Group, 1978).

The Framingham study (McGee and Gordon, 1976) was one of the studies included in the Pooling Project. Besides estimating the incidence of CHD, this study of white middle-aged men

considered the incidence of deaths from all causes. Both systolic and diastolic blood pressure were identified as significant predictors of all-cause mortality. Analysis of the Framingham data by Kannel et al. (1987) indicated that both systolic and diastolic blood pressure were strong predictors ($p < 0.001$) of both electrocardiographic (ECG) left ventricular hypertrophy (LVH) and myocardial infarction in both men and women. The authors further show that among people who exhibit ECG LVH, the risks of coronary artery disease, myocardial infarction, stroke, congestive heart failure, and intermittent claudication are increased. D'Agostino et al. (1991) also analyzed the Framingham data set. Using a logistic model, they reported a statistically significant association between the likelihood of death from coronary heart disease and both diastolic and systolic blood pressure ($p < 0.0001$ for each). In a review of the relationship between diastolic blood pressure and myocardial infarction, Cruickshank (1988) describes six studies reported in 1987 and 1988 that find an association over much of the range between diastolic blood pressure and myocardial infarction. In addition, Alderman et al. (1989) reported an association between diastolic blood pressure and myocardial infarction using a sample of 1700 previously untreated mild to moderate hypertensives. In their review of the associations between blood pressure and heart disease, MacMahon et al. (1990) report: "The associations of diastolic blood pressure (DBP) with stroke and with coronary heart disease (CHD) were investigated in nine major prospective observational studies: total 420,000 individuals, 843 strokes, and 4856 CHD events, 6-25 (mean 10) years of follow-up. The combined results demonstrate positive, continuous, and apparently independent associations, with no significant heterogeneity of effect among different studies. Within the range of DBP studies (about 70 - 110 mm Hg), there was no evidence of any "threshold" below which levels of DBP were not associated with lower risks of stroke and CHD." The authors also report that the diluting effects of random fluctuations in measurement of DBP have lead to a substantial underestimate of the effect of DBP. Levy et al. (1996) reported that hypertension (measured as systolic blood pressure above 140 mm or diastolic above 90 mm) was the most common risk factor for congestive heart failure. Finally, in his recent review, Kannel (1996) states that both systolic and diastolic blood pressure are important predictors of cardiovascular disease.

Based on these findings of an association between either systolic or diastolic blood pressure and more serious cardiovascular outcomes, the additional consequences of blood lead-mediated changes on blood pressure are estimated. Earlier estimates of the effects of changes in blood lead on subsequent CHD and mortality are provided by Pirkle et al. (1985) and Schwartz et al. (1985) in the analysis of the effects of reducing lead in gasoline. Using coefficients relating hypertension (defined as diastolic blood pressure $\geq$ 90 mm Hg) to other cardiovascular events derived from the Pooling Project and the Framingham studies, Pirkle et al. (1985) estimated that the 37% drop in blood lead levels from 1976-1980 resulted in a 4.7% decrease in incidence of fatal and nonfatal myocardial infarction over 10 years, a 6.7% decrease in the incidence of fatal and nonfatal strokes over 10 years, and a 5.5% decrease in the incidence of death from all causes over 11.5 years. In addition, as a result of the blood lead decrease observed in NHANES II, they estimated that the number of white males 40-59 with hypertension (as measured by diastolic blood pressure greater than 90) decreased by 17.5%. There is considerable uncertainty, however, regarding the most appropriate model and blood lead/blood pressure coefficients to be used in projecting more serious cardiovascular outcomes (U.S. EPA, 1990a). In addition, with general improvements in diet, exercise, and medical treatment of heart disease over time, the impact of any change in risk factors on CHD may currently be lower than that predicted by the Pooling

Project. Moreover, because of the multifactorial etiology of atherosclerotic heart disease, the relative risk of cardiovascular outcomes from small changes in blood pressure alone may be low in individuals. Nonetheless, the National Research Council (NRC, 1993) report states: "Lead exposure is not the only risk factor for hypertension, but is more amenable to reduction or prevention than behavioral factors that are refractory to change. Furthermore, the relation of lead to blood pressure persists across a dose-effect continuum, so reducing lead exposure of all magnitudes has public-health and societal ramifications. Lead's impact is noteworthy also because of the importance of associated cardiovascular morbidity and mortality, even for an agent that contributes less than a major risk."

Any clear associations between lead exposure and more serious cardiovascular outcomes would be difficult to directly demonstrate in any prospective epidemiologic study (Pocock, 1988). Very large study cohorts would be necessary to have sufficient statistical power to detect the relatively small increased risk levels expected for these health outcomes. This is suggested by the NRC (1993) in their recent review of the effects of lead, where they state: "Given the estimated changes in blood pressure, a study would need extremely large sample sizes to test whether the expected consequences of increased blood pressure on myocardial infarction occur. No study done to date has had the power to detect relative risks of 1.05. Two studies have focused on intermediate, and more common, cardiovascular end points. Kirkby and Gyntelberg (1985) reported that lead exposure was associated with electrocardiogram changes associated with ischemic heart disease. This was confirmed in a general population study by Schwartz (1991). In this latter study, the relationship between abnormal electrocardiograms, indicative of left ventricular hypertrophy (LVH), and blood lead levels was examined. A statistically significant coefficient ($p<0.01$) for an association between blood lead levels and increased prevalence of LVH was found by logistic regression after adjusting for age, race, sex, and smoking. Since these abnormalities are an early indicator of cardiovascular disease that is more common than actual myocardial infarctions, the statistical power to detect an association is enhanced. This paper provides support for the possibility that blood lead levels may affect the incidence of serious cardiovascular outcomes.

The term "intermediate" is used in the NRC (1993) report to indicate that electrocardiographic changes indicative of ischemia and left ventricular hypertrophy are of "intermediate severity" in the continuum of outcomes from elevated blood pressure to heart failure or myocardial infarction. The relationship between elevated blood pressure and cardiovascular disease is very strong. According to a recent analysis of the Framingham Heart Study, a prospective, population-based investigation of cardiovascular disease, hypertension is the most common condition antedating heart failure (Levy et al., 1996). In this study, hypertension accounted for 39% of cases of congestive heart failure in men and 59% in women. Moreover, only 24% of men and 31% of women survived 5 years following the onset of hypertensive heart failure. The majority of deaths due to hypertension result from myocardial infarction or congestive heart failure. Myocardial infarction due to ischemia and heart failure may be late sequelae of ventricular hypertrophy due to hypertension.

3.3. Lead as a Carcinogen

The U.S. EPA, IARC, and the State of California have all determined that, based on animal studies, lead is a carcinogen. The relevant animal studies have been reviewed by U.S. EPA and IARC (IARC 1980, 1987a, U.S. EPA 1986, 1989a, 1989d). U.S. EPA has classified lead and lead compounds in class B2, probable human carcinogens. This conclusion is based on sufficient animal evidence and inadequate human evidence. IARC has concluded: "There is sufficient evidence that lead subacetate is carcinogenic to mice and rats and that lead acetate and lead phosphate are carcinogenic to rats." There are inadequate human data. IARC classifies lead in Group 2B, possibly carcinogenic to humans.

The strongest evidence for carcinogenicity comes from a large number of studies in rodents in which lead compounds were administered by the oral route, either in feed or in drinking water. Although other types of tumors are occasionally seen, the principal finding has been kidney tumors, both benign and malignant, in rats. Important studies are summarized in Table 3-5.

No long-term studies in animals to investigate carcinogenicity due to lead inhalation have been conducted. Intratracheal instillation of lead oxide was employed in one study of cancer (Kobayashi and Okamoto, 1974). No tumors were seen in 20 hamsters after 10 intratracheal instillations of 1 mg of lead oxide, which gave a comparatively low total dose of 10 mg. In that study, however, simultaneous administration of lead with benzo(a)pyrene (10 instillations of 1 mg), which by itself also did not cause tumors, did act to produce lung tumors. Lead might be acting as a promoter or cocarcinogen for benzo(a)pyrene-initiated carcinogenicity.

Epidemiological studies and case reports of people occupationally exposed to lead provide some evidence of carcinogenicity but are not convincing due to lack of controlling for confounders such as smoking and to the simultaneous exposure of some workers to known human carcinogens including arsenic and cadmium. These studies have been reviewed by several agencies (IARC, 1980; U.S. EPA, 1986, 1989a, 1989d; ATSDR, 1990).

The epidemiologic study by Selevan et al. (1985) suggested that human cancer may be induced in the same organ in which cancer is induced in animals. A cohort of 1,987 lead smelter workers was studied. The study confirmed previous reports of occupationally-induced, chronic, fatal renal disease after long term exposure to lead and yielded a Standardized Mortality Ratio (SMR) of 204 for kidney cancer, but the numbers were small (6 cases observed) and the SMR for kidney cancer was not statistically significant.

Recently the study has been updated to include 11 years of follow-up and 363 additional deaths (Steenland et al., 1992). No additional deaths from nonmalignant kidney disease had occurred but 3 additional deaths from kidney cancer had occurred. The updated SMR from kidney cancer was 193 (9 total kidney cancer deaths, 95% confidence interval (C.I.) = 0.88, 3.67, i.e., not statistically significant at the 5% level). The SMR for kidney cancer for those with the highest lead exposure was statistically significant (SMR = 239 based on 8 cancers, 95% C.I. = 1.03, 4.71). The study suffers from lack of detailed data on lead exposure levels and from potential confounding exposures to cadmium, arsenic, and tobacco smoke. However, the authors indicate that lead levels were high while arsenic and cadmium exposures were low. The authors provide a useful summary of prior epidemiologic studies of lead workers in Table 1 of their paper (Steenland et al., 1992).

In an epidemiologic study of 7,121 deceased California plumbers and pipefitters, Cantor et al. (1986) found increased cancer incidence for all neoplasms and for cancers of several sites including the respiratory system, kidney, and stomach. In addition to lead, these workers were exposed to carcinogens such as asbestos and chromium. Since excess mesotheliomas were observed (16 observed, 2 expected), asbestos exposure likely contributed to the observed increase in stomach and respiratory system cancer. Asbestos, chromium, and cigarette smoking are likely contributors to lung cancer but are not generally considered causes of kidney cancer. However, there was a statistically significant deficit in deaths due to chronic kidney disease, thus indicating an absence of kidney toxicity. Although interesting, this study is only suggestive of an association between kidney cancer and lead exposure.

There are 2 case reports of renal cancer in men occupationally exposed to toxic levels of lead (Baker et al., 1980; Lilis, 1981). Baker et al. (1980) thought that the histology in the renal tumor in their case report was similar to that of kidney tumors in lead-exposed animals. Despite the long history of human lead exposure and the chronic nephropathy induced by lead, the data on lead-induced, human renal cancer is meager, and lead is likely to be only a weak carcinogen for the kidney in man.

In regard to induction of cancer in organs other than the kidney, the largest occupational cohort studied for lead-induced cancer included approximately 6,800 employees of 6 lead smelters and recycling plants and 10 battery manufacturing plants in the United States (Cooper and Gaffey, 1975; Cooper, 1976; Kang et al., 1980; Cooper, 1981; Cooper et al., 1985; Cooper, 1988). At various times in the analysis and updating of the data, statistically significant increases in cancer have been reported for total malignant neoplasms in lead production workers (Cooper and Gaffey, 1975), total malignant neoplasms and cancers of both the digestive tract and the respiratory tract in lead production workers and in battery workers (Kang et al. 1980), no sites (Cooper, 1981, 1988), and total malignancies in the battery workers (Cooper at al., 1985) principally due to cancers of the respiratory and digestive tracts. The 1985 report stated that several factors including cigarette smoking could not be ruled out as confounders.

Ades and Kazantzis (1988) studied 4,293 men at a zinc-lead-cadmium smelter in Great Britain. An effect of lead exposure on lung cancer was noted but lead exposure was highly correlated with exposure to arsenic, a known respiratory carcinogen, and no data on cigarette smoking were reported.

Fu and Boffetta (1995) have conducted a meta-analysis of the published studies on cancer and workplace exposures to inorganic lead compounds. The studies include the 2 case reports, 16 papers dealing with cohort studies, and 7 papers dealing with case-control studies. The meta-analysis showed a statistically significant, excess relative risk of cancer overall (RR = 1.11, 95% CI = 1.05-1.17), of stomach cancer (RR = 1.33, CI = 1.18-1.49), of lung cancer (RR = 1.29, CI = 1.10-1.50), and of bladder cancer (RR = 1.41, CI = 1.16=1.71). The relative risk for kidney cancer did not reach statistical significance (RR = 1.19, CI = 0.96-1.48). A separate analysis of studies involving workers heavily exposed to lead found higher relative risks for stomach cancer (RR = 1.50, CI = 1.23-1.43, based on 4 studies) and lung cancer (RR = 1.42, CI = 1.29-1.62, based on 4 studies). The meta-analysis is further indication of a relationship between lead exposure and cancer, but it is limited by the paucity of information in the various studies on confounders such as cigarette smoking, dietary habits, and other occupational carcinogens at many of the workplaces studied (Fu and Boffetta, 1995).

There are corroborative findings relevant to the potential of lead to be both an initiator and a promoter of carcinogenicity from biochemistry and genetic toxicology (Goyer, 1992). First, lead acetate concentrations in vitro, possibly as low as 10^{-15} molar, stimulate the enzyme protein kinase C from rat brain (Markovac and Goldstein, 1988). The usual activator of the enzyme is calcium; activation by calcium begins at much higher concentrations. Lead chloride and lead citrate also activate the enzyme, while several other toxic metals are not stimulatory. Some known tumor promoters activate this kinase and, when activated, the enzyme can phosphorylate oncogenes and other receptors. Thus, lead may have similar tumor-promoting properties (Goyer, 1992). Unlike the high concentrations of lead required for many effects, this activation occurs at very low concentrations. Second, a single injection of lead acetate increases DNA synthesis and subsequent cell division in kidneys in vivo (Choie and Richter, 1974a,b), a mitogenic response consistent with activity as a promoter or cocarcinogen. Third, chromosome breakage can predispose a cell to cancer. Chromosomal aberrations have been correlated with lead exposure in some studies, but other studies have shown no effects (summarized by ATSDR, 1990; IARC, 1987b). Fourth, some lead compounds (e.g., lead acetate) can transform mammalian tissue cells in culture, a cellular response relevant to cancer (e.g., DiPaolo et al., 1978; other studies summarized by ATSDR, 1990). Fifth, lead can interfere with the fidelity of replication of DNA (Sirover and Loeb, 1976), a property of certain toxic metals which are indirect genotoxic carcinogens. Sixth, both insoluble lead sulfide and soluble lead nitrate have been shown to cause mutations at the hprt (hypoxanthine guanine phosphoribosyl transferase) locus, a sex-linked gene in mammalian (Chinese hamster) cells (Zelikoff et al., 1988). However, these mutations are not necessarily point mutations; they could be due to alterations in chromosome structure. Overall, some lead compounds demonstrate genotoxicity, but many studies have been negative (IARC, 1987b).

Table 3-5. Kidney Tumors Induced by Lead Compounds

Author (s)	Pb Compound	Species	Sex	Route	Time [a]	Concentration	Total Lead Dose (g)	Tumor Incidence
van Esch and Kroes (1969)	subacetate	hamster	M, F	diet	24 mo	0.1% 0.5%	7 35	M 0/22, F 0/24 M 0/22, F 0/24
van Esch and Kroes (1969)	subacetate	mouse	M F	diet	24 mo	0.1% 0.1%	2 2	6/26 2/25
Schroeder et al. (1970)	nitrate	rat	M	water	life	25 ppm	0.5	0/52
Zawirska and Medras (1968)	acetate	rat	M F	po / feed	18 mo	3mg/day then 4 mg/day	1 1	58/94 14/32
Nogueira (1987)	acetate	rat	M	feed	6 mo	0.5% 1.0%	9 17	0/12 9/10
Azar et al. (1973)	acetate	rat	F	diet	24 mo	0-2000 ppm	0-26	up to 13/20 see Table 7-1
Boyland et al. (1962)	acetate	rat	M	diet	12 mo	1.0%	34	15/16
Kasprzak et al. (1985)	subacetate	rat	M	feed	18 mo	1.0%	38	13/29
Koller et al. (1985)	acetate	rat	M	water	18 mo	2600 ppm	38	13/16
van Esch et al. (1962)	subacetate	rat	M, F M, F	diet	24 mo 24 mo	0.1% 1.0%	10 97	M 5/12, F 6/13 M 6/7, F 7/9
Mao and Molnar (1967)	subacetate	rat	M	diet	life	1.0%	97	31/40

a Time is in months unless otherwise noted.

Section 4. The Contribution of Airborne Lead to Blood Lead Level

For this risk assessment, it is necessary to determine the quantitative association between changes in lead present in the air and subsequent concentrations of lead in the blood of exposed populations. OEHHA is considering not only exposure to lead directly emitted into the air but also exposure to lead present in soil, dust, and food originally from air. The relationship between air lead and blood lead has been extensively studied in both field studies and experimental chamber studies. Studies in experimental chambers in which air exposures are well characterized have only been conducted using adults. Since young children have higher metabolism and inhalation rates, and since they ingest more dirt and dust (Smith, 1989; Chamberlain, 1983), one would expect air lead levels to have a greater impact on blood lead in children than in adults. Thus, when assessing risks from air lead, it is important to examine the relationship between air lead and blood lead (or the blood lead/air lead "slope") in adults and children separately. Most of these studies were conducted before 1985 when both air and blood lead levels were much higher than they are now. Slope estimates derived from these studies may not be relevant to current air lead levels if the slopes are not constant across a wide range of air and blood lead concentrations. In our review of the relevant studies, we examined both the magnitude of the slope estimate and the implications for linearity. We reviewed experimental chamber studies in adults, a population-based study of adults using personal monitors, and several population-based studies of children using outdoor fixed-site monitors.

Early inhalation studies assessed the effects of inhaled lead using human subjects in experimental chambers. These chamber studies allow direct calculation of the effects of inhalation on the blood lead/air lead slope. The study design also allows one to look at variations among individuals, and the relationship of blood lead to air lead concentration over time. The chamber studies are useful because exposures were well characterized; however, they uniformly used much higher levels of lead than are currently found in ambient air.

There are three methods available to determine the contribution of air lead concentrations to blood lead levels, and the subsequent health effects associated with different air lead concentrations. These methods include: disaggregate models, aggregate models and uptake biokinetic models. In the disaggregate model and in the biokinetic uptake model, the total effect of air lead is estimated by separately analyzing the associated changes between blood lead and inhaled air lead, as well as the association between changes in blood lead due to exposures to lead deposited onto soil, dust, food and water (U.S. EPA, 1989b). Once the impact of each separate pathway on blood lead is determined, as well as the impact of air lead on other pathways such as soil and household dust, the total effect of a change in air lead on blood lead can be determined. The focus on other pathways is important since there is a high correlation between lead in the air and lead from several other sources. For example, in a survey of 9 different studies covering 13 different populations of children, Brunekreef (1984) reported high correlations between air lead and dustfall ($r = 0.92$), soil ($r = 0.62$) and house dust ($r = 0.88$). This disaggregate approach has been used for many toxic air contaminants. While this approach may yield more precise estimates of the relationship of air lead and blood lead, the contribution of each pathway must be modeled and any errors or uncertainties in these variables will reduce the precision of the estimated total exposure.

One method for developing a disaggregate model is to use a multivariate regression approach to explain blood lead (PbB) with separate explanatory variables representing soil, dust

and air lead (PbA) in the model specification. This method yields a slope (the partial derivative with respect to the air lead term) that reflects only the direct but not the indirect (e.g. through soil and dust) contributions of air lead to blood lead. For example, including a variable in the model to represent the effect of dust lead levels on blood lead would remove some of the impact of the effect of air lead on blood lead through the dust pathway. Furthermore, since one would expect air, soil and dust lead (as well as lead on hands) to be correlated, the coefficient of air lead may be highly unstable. Using a disaggregate model for children, U.S. EPA (1986) estimated a slope of 2 when only accounting for the direct influence of air lead, and a slope of 5 when incorporating both direct and indirect influences of air lead (U.S. EPA, 1989b). The latter estimate is most relevant for our aggregate assessment since it incorporates all air-related pathways.

A second method to estimate the effects of change in air lead on changes in blood lead is an aggregate model. This model implicitly takes into account both the direct and indirect sources of air lead. One can derive an estimate of the slope using either of two approaches. First, a regression model attempting to explain the variation in blood lead with air lead as an explanatory variable, but unadjusted for soil or household dust, can be used. Ideally, such a model would adjust for age, smoking, ethnicity and other non-environmental confounders. Second, a slope can be calculated using blood lead levels and air lead levels from at least two points in time or between two populations. For example, blood lead levels in a highly exposed and a control community can be related to corresponding ambient air lead levels. Slopes are calculated by comparing groups using the following formula:

$$\beta_A = \frac{\text{difference in blood lead between group II and group I } (\mu g/dL)}{\text{difference in air lead between group II and group I } (\mu g/m^3)}$$

In these studies, other sources of lead such as exterior lead paint and lead in food are assumed to be similar for both communities. Factors that might predispose children to higher lead levels such as condition of housing, overall nutrition and proportion of children living in poverty are also assumed to be similar. If these conditions hold, these studies provide useful estimates of the aggregate effect of air lead on blood lead (i.e. both direct and indirect pathways). However, if levels of confounders are different in the two communities, the slope estimates will be inaccurate. By design, aggregate models do not distinguish between indirect effects of air lead mediated through other environmental pathways such as dust, and associations that are correlated but not causally related to air lead. For example, if living near an industrial source of lead correlates with lead in paint, then some of the increase in dust lead attributed to air in an aggregate model might actually be due to paint. However, the advantage of aggregate estimates is that they implicitly incorporate both direct and indirect pathways of air lead. Since this risk assessment attempts to determine the total impact of air lead emissions from stationary sources on children's blood lead, aggregate slopes are most relevant in that they incorporate all air-related pathways.

The third method for estimating blood lead levels in relationship to exposures from various media is the uptake biokinetic model. This model estimates specific intake, uptake and distribution of lead in the body, taking into account the route and rate of exposure, a child's age and baseline exposure. The processes of absorption, distribution, storage, mobilization and excretion are directly modeled (U.S. EPA, 1989b). One example of a uptake/biokinetic model is the Integrated Exposure Uptake Biokinetic (IEUBK) model developed by the U.S. EPA (1994). This personal computer-compatible model calculates probability distributions of blood lead levels

for children of different ages based on a multipathway exposure analysis. Categories of exposure input variables include concentrations of lead in air, drinking water, soil, house dust, paint, diet and maternal blood lead (to account for newborn blood lead), with each having default or user-defined values. Exposures are converted into an uptake component based on amounts of lead absorbed from the lungs and gastrointestinal tract. The absorbed doses of lead are then biokinetically modeled into six different body tissues or compartments over 84 monthly time points (age 0 to 7 years) to account for age-dependent physiological parameters (e.g., increases in inhalation rates and body weights) and soil ingestion rates. The results for blood lead levels are reported for each year of age up to seven years. Apparently, earlier versions of the IEUBK model may have overestimated blood lead levels. Several validation efforts (Hogan et al., 1995a; U.S. EPA, 1994a; U.S. EPA, 1994b) show that the model does very well in predicting blood lead distributions.

As currently configured, the IEUBK model is useful in describing the probability distribution of blood lead levels in children in 1 year increments up to 7 years of age. The model does not use a single blood lead/air lead slope to relate air lead concentration to blood lead concentration. To actually calculate a slope, U.S. EPA uses the aggregate and disaggregate methods described above (U.S. EPA, 1989b). Nevertheless, with some adjustment to the IEUBK model recommended by its authors (Hogan, 1995b), aggregate slopes can be determined and are presented below for comparison purposes. However, it is not necessary to calculate a slope for blood lead to air lead to use the IEUBK model.

It is important to note that the slope may be a nonlinear function of the actual air lead and blood lead levels being investigated. Many researchers report a relationship that is supralinear with steeper slopes at lower air and blood lead levels (Brunekreef, 1984; Chamberlain, 1983; Hammond, 1981; O'Flaherty, 1993). If this is true, then studies conducted at higher air and blood lead concentrations might underestimate the blood lead/air lead slope associated with relatively low air concentrations.

The studies discussed below are reviewed in detail in order to arrive at an estimate of the blood lead/air lead slope using the aggregate method. Some of these studies could be used to derive a disaggregate slope. The linearity of slopes across a range of air and blood lead concentrations is also examined. Since children aged 1-5 are more sensitive to toxic effects of lead, these studies will be reviewed with a particular interest on the relationship between air lead and blood lead in this age group. The blood lead/air lead slope predicted using the IEUBK model will be evaluated in Section 4.2.

4.1. Determining Slope using Aggregate and Disaggregate Methods

4.1.1. Chamber Studies

Experimental chamber studies measure the contribution of inhalation of lead independent of other exposure pathways. In this review, results of the chamber studies in adults will be contrasted with the contribution to blood lead of direct inhalation and indirect ingestion of airborne lead deposited onto soil, dust or food as empirically determined from epidemiological studies. The relationship between lead in air and lead in blood was first examined in experimental chamber studies. The chamber studies, which were all conducted before 1985, have been reviewed by U.S. EPA (1986), Hammond et al. (1981) and Chamberlain (1983). In these studies, a fixed concentration of airborne lead was pumped into a chamber and the subject's blood lead

level was periodically measured. Since these studies were longitudinal in design, slopes for both individuals and groups could be calculated. These slopes reflect the impact of inhaled lead alone.

Kehoe conducted the first and most extensive of the experimental chamber studies (Kehoe, 1961). Over a period of more than 20 years, he studied 11 men and 1 woman in a study designed to simulate occupational exposures. Subjects (his employees) worked in a chamber for 7.5 hours each day, 5 days a week for up to two years. They were then followed up for an additional 2 years. Their blood lead levels were taken daily. All subjects were given a range of exposures that tended to be quite high; only six of the twelve subjects had exposures lower than 10 $\mu g/m^3$. In this study, subjects were exposed to lead sesquoxide (similar to lead oxide emitted from automobiles using leaded gasoline) with particle diameters of 0.05 or 2 microns, therefore all of the lead was presumably in the inhalable fraction. Gross (1981) attempted to fit Kehoe's data using quadratic and linear models and found that both models were equally satisfactory. Using linear models, he calculated a range of slopes from 0 to 2.6 $\mu g/dL$ per $\mu g/m^3$. U.S. EPA (1986) estimated a weighted slope of 1.25 ± 0.35 $\mu g/dL$ per $\mu g/m^3$ using these data. Interestingly, the two individuals with the lowest range of exposures (0.6 to 4 $\mu g/m^3$ and 0.6 to 7.2 $\mu g/m^3$ respectively) had the largest slopes (2.60 and 1.31 $\mu g/dL$ per $\mu g/m^3$) while those individuals with the highest exposure (9 to 36 $\mu g/m^3$) had the smallest slopes (0.67 and 0.64 $\mu g/dL$ per $\mu g/m^3$). Gross (1981) also calculated slopes for each individual at each air lead dose. Hammond et al. (1981) noted that in the individuals exposed to a wide range of lead concentrations, there was a clear decrease in slope with increasing air lead.

Griffin et al. (1975) exposed adult male prisoner volunteers to levels of 3.2 or 10.9 $\mu g/m^3$ lead oxide. Control groups for each exposure level were put in the chamber and exposed to air without any lead. Eight of 24 men exposed to the higher concentration of lead remained in the study for at least 60 days. Over this time period, blood lead levels in the exposed group increased approximately 25% above baseline. U.S. EPA used these data to calculate slopes for each individual. U.S. EPA (1986) calculated slopes of 3.00 and 1.77 $\mu g/dL$ per $\mu g/m^3$ for the groups exposed to 3.2 $\mu g/m^3$ and 10.9 $\mu g/m^3$ respectively. Controls for the lower exposed group had a slope increase of 1.48 $\mu g/dL$ per $\mu g/m^3$. Therefore, U.S. EPA adjusted the slope estimate for the lower exposed group to 1.52 $\mu g/dL$ per $\mu g/m^3$ assuming that the observed increase in blood lead in controls was explained by lead in food and seasonal changes that all of the prisoners experienced simultaneously. U.S. EPA (1986) calculated a weighted slope of 1.75 ± 0.35 $\mu g/dL$ per $\mu g/m^3$ for the Griffin study.

The unit increase in blood lead for a unit increase in air lead changes with particle size. In order to measure the effect of lead in automobile exhaust on blood lead levels, Chamberlain et al. (1985) labeled tetraethyl lead with radioactive isotope ^{203}Pb, mixed it with gasoline and had volunteers inhale the mixture after it was burned in a 4-cylinder engine. Particle size varied from 0.02 to 0.7 microns. Absorption increased as particle size decreased.

Rabinowitz et al. (1974, 1976, 1977 as reviewed in U.S. EPA, 1986) used stable lead isotopes to track kinetics of lead in the bodies of 5 adult male volunteers. Subjects were placed in a chamber with a low concentration of lead in air for 22 to 24 hours per day for 25, 40, and 50 days. They then were exposed to Los Angeles air which had much higher air lead concentrations than either the chamber or the hospital ward in which they lived. The investigators then tracked the amount of lead in different body compartments over time. In this study, although dietary lead was very well characterized, air lead levels were not. Using the data, U.S. EPA (1986) estimated a blood lead air lead slope of 2.14 $\mu g/dL$ per $\mu g/m^3$ with a standard deviation of 0.47.

Based on these studies and the study by Azar et al. (1975) discussed below, Hammond (1981) theorized that the slope is a function of both the air lead concentration and the baseline blood lead level. U.S. EPA (1986) combined weighted slope and standard error estimates from the Griffin et al., Kehoe, and Rabinowitz et al. studies to yield a pooled weighted slope estimate of 1.64 ± 0.22 μg/dL per μg/m^3. When the subjects exposed to very high air lead levels (up to 36 μg/m^3) were excluded, they estimated an average slope of 1.9 μg/dL per μg/m^3. OEHHA concurs with U.S. EPA's (1986) assessment of the slope from the chamber studies noting that the exposure levels were relatively high in these studies and that the aggregate slope may be nonlinear, with steeper slopes at lower air and blood lead levels.

4.1.2. Personal Exposure Monitors in Adults (Environmental)

There have been many occupational studies of adults using both personal and stationary monitors. These studies have not been reviewed in this document since they involve very different types of exposures than would be experienced by children as part of their daily activities. One observational study of adults conducted by Azar et al. (1975) is relevant, however, because air exposures were measured for 24 hour periods. In this study, Azar et al. (1975) used personal monitors to study the impact of air lead on blood lead in adult males. He measured blood lead levels in cab drivers in Los Angeles and Philadelphia, office workers in Los Angeles, and DuPont employees in Florida and Wisconsin. Air lead exposure was monitored for 24 hours a day for 2-4 weeks. Because air lead exposure was monitored for 24 hours a day, this study provides information on "real world" exposures using exposure data not available in other studies. There were 30 subjects in each of the 5 groups. Blood lead levels were taken once or twice a week. Dietary sources of lead were not monitored.

Air lead levels ranged from 0.8 μg/m^3 for the Florida DuPont workers to 6.1 μg/m^3 for the Los Angeles cab drivers. Mean blood lead levels ranged from 12.2 to 24.2 μg/dL in the five groups of workers. Azar et al. (1975) observed no significant relationships when the five groups were analyzed separately using multivariate regression. They then tested for differences in slopes and intercepts in each of the five groups, and determined that there were no group level interactions but observed significantly different intercepts which were attributed to different background lead levels in each group. Data from the 149 subjects were pooled using "dummy" variables to model the different intercepts in order to arrive at an average slope (Azar et al., 1975). Using the data of Azar et al. (1975), U.S. EPA used an average intercept value of 1.23 to give a slope of 10.1 μg/dL per μg/m^3 at an air lead level of 0.2 μg/m^3 and a slope of 0.40 μg/dL per μg/m^3 at an air lead level of 9 μg/m^3. The model, log(blood lead concentration) = 1.23 + .153 log(air lead concentration) accounted for 44% of the variance in blood lead. Snee (1982) reanalyzed this data using a power function model:

$$\log (PbB) = \log [12.1(PbA + \text{background lead})^{0.2669}] \qquad \text{(Eq. 4-1)}$$

where PbB = blood lead level (μg/dL)
PbA = air lead level (μg/m^3) and
background lead = assumed concentration of lead in food and water

and calculated a slope of 1.29 μg/dL per μg/m^3 at an air lead of 0.2 μg/m^3 and a slope of 0.51 μg/dL per μg/m^3 at an air lead of 9 μg/m^3, using an average background level of 3.28 μg/dL. U.S. EPA (1986) took advantage of the high quality of air exposure data and developed five different models for the data in part to evaluate linearity of the blood lead/air lead slope (discussed in more detail below). Their slope estimates ranged from 1.26 to 1.34 μg/dL per μg/m^3 assuming a 1.0 μg/m^3 air lead level. Using a linear model, the one ultimately selected by U.S. EPA, the slope was 1.32 μg/dL per μg/m^3. Although the authors had good data on exposure to air, no data on dietary or other lead sources were collected. Data collection was during different times of the year for each group without adjustment for seasonality, a known confounder of air and blood lead. Overall, however, this is the best data on the relationship of "real-world" air exposures to blood lead levels for adults.

Other population studies of adults reviewed by Snee (1981) and reviewed in U.S. EPA (1986) have less well characterized air exposures but indicate a slope of between 1 and 2 μg/dL per μg/m^3 for adults. U.S. EPA (1986) combined the results of population studies in adults and experimental chamber studies to get a weighted average slope of 1.4 in adults. They then adjusted the estimate to account for mobilization of lead from bone. Chamberlain et al. (1978) estimated this factor to be 1.3. Using this factor yields an adult slope of 1.8 μg/dL per μg/m^3 (1.4 x 1.3 = 1.8). This slope estimate will be used in Section 5 to quantify the effects of changes in air lead concentrations on blood pressure effects in adults.

4.1.3. Population-Based Studies in Children

As reviewed in Section 3.1., young children are more sensitive to the toxic effects of lead. Since young children have higher metabolism resulting in greater inhalation rates, and since they ingest more dirt and dust, and have a higher dose of lead than adults exposed to the same level because of their lower body weight, one would expect air lead levels to have a greater impact on blood lead in children than in adults. Thus, when assessing risks from air lead, it is important to examine the relationship between air lead and blood lead in adults and children separately.

All of the studies in children measured exposures using stationary monitors and related average blood lead levels to average air lead levels to estimate slopes. Because these studies used stationary monitors, they were subject to a variety of exposure assessment problems (reviewed in U.S. EPA, 1986). For example, stationary monitors miss some exposures such as those one would get riding in a car that burns leaded gasoline. Conversely, monitors may under or overestimate exposure by not accounting for lead levels in indoor environments. Finally, since children live, learn and play different distances from the monitor, there is differing ability to measure their exposures. However, the general direction of bias in the slope estimate is uncertain and depends on the specific sample. While these studies are obviously less precise than the chamber studies and the personal exposure study by Azar et al. (1975), they are the only available studies to explore the relationship between air lead and blood lead in children. Many of these studies were conducted before 1985 when both air and blood lead levels were much higher than they are now due to the use of lead in gasoline as well as higher concentrations of lead in food. Furthermore, those populations with very high air lead levels were more likely to be studied. In many cases, U.S. EPA (1986) recalculated slopes, or used recalculated values of Brunekreef (1984) from his comprehensive review, to develop aggregate slope values. The findings of the

studies reviewed below are summarized in Table 4-1. Unless indicated in the review, these studies were used in estimation of the blood lead/air lead slope for children.

Brunekreef et al., 1983

Venous blood samples were taken from a representative sample of 195 school children aged 4 to 6 years from two cities in the Netherlands. Geometric mean lead levels ranged from 7.9 μg/dL in the suburbs to 13.1 μg/dL in an urban community. Information was collected on a variety of potential confounders that did not covary with air lead including age of home, drinking water, food and calcium intake. Unadjusted estimates yielded slopes as high as 24.5 μg/dL per $\mu g/m^3$. Multiple regression analyses comparing the most highly exposed community to the one that was least exposed resulted in a slope of 8.5 μg/dL per $\mu g/m^3$. Brunekreef (1984) speculated that the slopes in this study might have been especially high because (1) there were very small differences in air lead and blood lead in the two communities; such that small errors in measurement of blood lead levels could have resulted in large differences in slope and (2) the blood lead/air lead relationship might be curvilinear, resulting in a steeper slope at air lead levels below 0.25 $\mu g/m^3$. It is possible that lead derived from paint covaried with atmospheric lead if, for example, inner city older housing was associated with mobile or industrial sources of lead. If this were the case, lead from paint would be included in the estimates of the aggregate slope, but it would be unlikely that changes in atmospheric lead would affect exposure from lead derived from paint. The slope may also be greater than in other studies because children in both areas were exposed primarily to lead from mobile sources which has smaller particles and may be absorbed more readily (Chamberlain et al., 1985). Finally, this study was hampered by a very low participation rate (24%) which may affect the representativeness of the blood lead levels and the slope.

Zielhuis et al., 1979; Brunekreef et al., 1981

Venous blood lead levels of very young children living different distances from a smelter in the Netherlands were related to air lead levels. Data were collected over a three year period. Children were divided into groups according to the distance of their residence from the smelter, 400-1000 meters, 1000-2000 meters and more than 2000 meters. According to Zielhuis et al. (1979), air lead levels varied from 0.8 to 21.6 $\mu g/m^3$ in one area and 0.5 to 2.5 $\mu g/m^3$ in another area. Brunekreef (1984) assumed an air lead difference of 2 $\mu g/m^3$ between the most and least exposed regions but didn't specify the rationale for this assumption. Using this air lead difference, a slope of 3.6 μg/dL per $\mu g/m^3$ (adjusted) was found for the first two years studied. There was no relationship between air lead and blood lead in the third year of the study when only those children living closest to the smelter were studied.

It is hard to interpret this study given that the difference in air lead levels between the two groups of interest is not known with any degree of certainty. Therefore, these studies were not included in our estimation of the blood lead/air lead slope.

Angle et al. (1979); Angle et al. (1984)

Effects from exposure to a primary and secondary smelter in Omaha were studied from 1970-77 in 831 children aged 1 to 18. Children were chosen from suburban, urban-commercial and urban residential areas. Only 6-12 year olds were sampled from the urban-commercial area, the area with the highest air lead levels.

In Angle et al. (1979), the authors pooled all samples and calculated both bivariate (unadjusted) and multivariate (adjusted) regressions of air lead levels on blood lead levels. The unadjusted slopes were -2.63 μg/dL per μg/m^3 for children 1 to 5 (urban residential v. suburban), 2.10 μg/dL per μg/m^3 for 6 to 18 year olds (urban, commercial and suburban) and 0.66 μg/dL per μg/m^3 for children overall. Because the 1-5 year olds did not include children living in commercial areas, it is misleading to pool the slopes from the two age groups. Even though the focus of the risk estimate in subsequent sections is primarily on younger children, the data for the 6-18 year old subgroup was included in our analysis. In an independent reanalysis of the data, Brunekreef (1984) calculated a slope of 15.8 μg/dL per μg/m^3 based on group means in the urban-commercial and suburban groups. This slope is probably inaccurate because there was a profoundly different racial makeup between the suburban and urban communities. Differences in ethnicity could introduce confounding bias due to cultural and socioeconomic factors and were not adjusted for in subsequent analyses of the data.

In a reanalysis completed by Angle et al. (1984), the relationship between air lead and blood lead was examined in a multiple regression model that included soil and hand lead (lead from dust and soil on hands). The regression predicted that blood lead increased 1.92 μg/dL for every 1.0 μg/m^3 increase in air lead for 1-18 year olds. In the subgroup of 6-18 year olds which included 6-12 year olds from the commercial area, the slope was 4.4 μg/dL per μg/m^3. However using a multipathway model to estimate the impact of air lead on blood lead via soil and hand lead, they calculated a slope of 5.02 μg/dL blood for every 1 μg/m^3 increase in air lead for 6-18 year olds. To use the multipathway model, the authors first determined the additional lead in soil and dust due to air, then used these values along with the direct relationship of air to lead to get a blood lead/air lead slope that reflected the total impact of air on blood. Thus, they used a disaggregate approach to estimate the total contribution of air lead. Geometric mean air lead levels for the latter years of this study (0.04 to 0.46 μg/m^3) were within the range of what is experienced today, relative to those of some other early studies from which slopes were generated.

As noted above, this study unfortunately did not account for some important confounders. For example, although the suburban children were mostly white, and the children from the urban groups were mostly African-American, race (as a proxy for sociocultural factors) and certain socioeconomic status (SES) variables were not included in the regression model. There was also no adjustment for other potential confounders such as condition of housing and exterior lead paint (i.e. levels were assumed to be the same in control and exposed communities). Finally, the recruitment method was not specified but the participants were described as "volunteers" so the average blood lead levels calculated may not have been representative.

Roels et al., 1976; Roels et al., 1980

Blood lead levels of 148 Belgian children aged 10-15 years living less than 1 or 2.5 kilometers from a lead smelter were compared to separate control groups of rural and urban children. Air lead levels ranged from 0.3 to 3.67 μg/m^3. Roels et al. (1980) regressed several environmental variables on blood lead and found that hand lead and not air lead was the most significant contributor to children's blood lead levels. The regression indicated a slope of 5.3 μg/dL per μg/m^3 when all years were pooled. However, in the adjusted analysis, air lead and hand lead were used in the same model even though they were highly correlated ($r>0.99$) making

it impossible to separate the impacts of ingestion and inhalation. The high air and hand lead correlation was likely due to air lead being the major source for lead on hands.

Brunekreef (1984) used the data to evaluate the impact of exposure level on slope by calculating slopes for different exposure scenarios. He compared: (1) groups with large differences in exposure (those living closest to the smelter versus the rural population), (2) those with small differences in air lead concentrations at high exposure levels (the populations living <1 versus 2.5 km from the smelter) and finally (3) groups with small differences in air lead concentrations at low levels (those living 2.5 km from the smelter versus rural children). Computing slopes for each of the five years, then averaging, gave slopes of 5.9, 4.6, and 13.7 μg/dL per μg/m^3 respectively. The slopes were reasonably consistent over the five years. The higher slopes at lower exposure levels are consistent with a supralinear relationship of air lead and blood lead.

Children in this study were older than those most sensitive to the toxic effects of lead on neurodevelopment. Given mouthing and play behaviors of very young children, one would expect the slopes in this study to be lower than those of younger children. It is of interest that even in a study based on 10-15 year olds, the slope is relatively high.

Cavalleri et al., 1981

Cavalleri et al. studied children attending school and/or living near a lead smelter and compared them to children attending school 4 kilometers away. Children were divided into two age groups, 3-6 year olds and 8-11 year olds, because the older exposed children had much higher historical exposures to air lead from the smelter. During the study, the average air lead level for the unexposed group was 0.6 μg/m^3. Readings from two monitors 150 and 300 meters from the smelter were averaged to determine an air lead concentration of 2.88 μg/m^3 for those living close to the smelter. Brunekreef (1984) used these air lead readings and the arithmetic means reported by the authors to construct a crude estimate of the slope. Mean blood lead differences were 8.6 μg/dL for the younger group, and 9.3 μg/dL for the older, more highly exposed group. Using group comparisons, Brunekreef derived a slope of 3.7 μg/dL per μg/m^3 for the younger group and 4.0 μg/dL per μg/m^3 for the older group. Since no confounders were considered, the calculated slope could easily be biased. The monitors for the exposed population were situated very close to the smelters and may have overestimated the actual air lead concentration to which children were exposed. If so, the actual air lead difference would be smaller and the corresponding slope would be larger.

Yankel et al., 1977; Walter et al., 1980; Snee, 1982b

Several analyses of children living near a smelter in Indiana, usually referred to as the "Silver Valley" studies, examined the effect of very high air lead levels (up to a monthly average of 30 μg/m^3) on blood lead levels in children aged 1-10. Two separate studies were conducted, one in 1974 when air lead levels were quite high (averaging 16.7 μg/m^3) and one in 1975 when many of the children with high lead levels had moved out of the area. Because of the selective out-migration, the 1975 data are problematic. Regressions used data from the earlier study only. Analyses were adjusted for soil and dust lead levels even though soil and air lead levels were correlated (r=0.52). The authors also used a single-log model which predicts higher slopes at high air lead levels. Walter et al. (1980) predicted a change in blood of 1.00 μg/dL per unit increase in air lead at 1.0 μg/m^3, and a 2.4 μg/dL increase in blood lead for every 1 μg/m^3 increase

in air lead at an air exposure of 22 $\mu g/m^3$. Although a single-log model fits the data, this pattern is contrary to that observed in chamber studies and to the other field studies. Because of the aberrant relationship between air and blood lead, Brunekreef (1984) and U.S. EPA (1986) expressed concern with the quality of the blood lead analyses. Furthermore, one of the comparison communities had high mean blood lead levels of 29-38 $\mu g/dL$ probably due to a history of lead mining in the area. Use of this control group in group comparisons would bias the slope estimate downwards. Snee (1982b) reanalyzed the data using a log-linear model and calculated essentially the same slope as that of Walter et al. (1980).

Billick et al (1979; 1980)

Billick et al. (1979; 1980) analyzed air and blood lead levels in more than 175,000 samples drawn from New York City children from 1970-1976. Air lead levels ranged from 2.2 $\mu g/m^3$ in 1971 to 0.8 $\mu g/m^3$ in 1976 (Billick et al., 1980). A model adjusting for age and race indicated a blood lead-air lead slope of 5.16 $\mu g/dL$ per $\mu g/m^3$. The model accounted for 60% of the variation in blood lead. Air lead levels measured at one site in Manhattan were used to estimate exposures for all New York City children. Not only might this incorrectly assess air lead levels for most children, the air lead monitor was elevated and later it was shown that air lead concentrations were 45% higher at street level than at the height of the monitor (Lioy et al., 1980). Therefore the slope of 5.16 $\mu g/dL$ per $\mu g/m^3$ probably is an overestimate. Using the differential air concentrations at building height and street levels, Brunekreef (1984) reestimated the slope to be 2.9 $\mu g/dL$ per $\mu g/m^3$. Slopes relating air lead to blood lead were higher for blacks (3.48) and Hispanics (2.84) than whites (2.66). In addition, the authors did not account for other changes that could have taken place over the time period. For example, in the New York City lead screening program at that time, screening was not mandatory. The basis for selection could have changed over time.

Hayes et al. (1994)

In this study, a sample of blood lead screening records for high-risk children aged 6 months to 5 years was examined (Hayes et al., 1994). Median blood levels for each quarter from 1974 to 1978 were regressed against mean air lead levels from the same period recorded at air-monitoring stations in Chicago. The authors noted a change in the blood lead/air lead slope in conjunction with changes in air and blood lead concentrations. A regression model using log-transformed median blood and air lead levels fit the observed data better than a linear model. Using the log-transformed regression model, the results suggest a decline of 5.6 $\mu g/dL$ for each 1.0 $\mu g/m^3$ decline in mean air lead level with air lead levels near 1.0 $\mu g/m^3$. The predicted slope was 16.2 $\mu g/dL$ per $\mu g/m^3$ for air lead levels below 0.25 $\mu g/m^3$. The finding of a higher slope at lower exposure levels is consistent with that found by Brunekreef (1984) in his reanalysis of the Roels et al. studies (1976, 1980). The later years of this analysis are the ones in which lower air leads were more likely to be found due to the phase out of leaded gasoline. The air lead levels at which the higher slope is predicted are well within the range of current California air lead levels (the current ambient average air lead concentration is 0.06 $\mu g/m^3$), although the slope is higher than those predicted by most other studies reviewed in this document. This estimate does not account for changes that might have taken place over time in lead in food, water and in those children participating in the screening program.

East Helena Study (unpublished)

We have been provided data for East Helena, Montana, a community in which relatively high levels of lead in air have been observed in emissions from a local smelter (Lewis & Clark City - County Health Department, 1991). We have no data on the contribution of other environmental exposures such as lead from paint so, as with other studies of this type, we would assume that any difference between environmental lead levels are due to air. Unfortunately, air lead data is only provided for the most highly exposed community and not for the control community of Townsend, Montana. As with the Arnhem lead studies (Zielhuis et al., 1979; Brunekreef et al., 1981), since the difference in air lead between the two communities is unknown, it is impossible to calculate a slope estimate. Since air lead levels averaged more than 2 $\mu g/m^3$, we might expect a lower slope than in studies conducted in communities with lower air lead levels.

Hacienda Heights Study (unpublished)

This study was not designed to assess the relationship of air lead and blood lead, but rather attempted to see if blood lead levels in a community near a smelter (Hacienda Heights), were elevated relative to a control community (West Covina). Although the study has not yet been published, data were provided to OEHHA (Wohl, 1994). Unfortunately, no slope can be calculated from the data because over 70% of the blood leads were below the study's detection limit of 5 $\mu g/dL$. Therefore it is not possible to directly calculate a geometric mean or to assess whether or not the geometric mean lead level between the two communities is different.

Summary of Studies in Children

The studies examining the relationship of blood lead and air lead in children are listed in Table 4-1. OEHHA has estimated the slope by taking the best estimate from each of the studies and calculating a geometric mean. Brunekreef et al. (1983) found a slope of 8.5 $\mu g/dL$ per $\mu g/m^3$ in a population exposed to much lower air lead concentrations than in most of the other studies. The studies by Angle et al. (1979; 1984) and Angle and McIntire (1979) showed a slope of 1.92 $\mu g/dL$ per $\mu g/m^3$ when data were pooled and used in a multiple regression with soil and hand lead. The studies by Roels et al. (1976, 1978, 1980), as reanalyzed by Brunekreef, gave slopes of 4.6, 5.9 and 13.7 $\mu g/dL$ per $\mu g/m^3$ depending on the groups being compared. Roels et al. (1980) calculated a slope of 5.3 $\mu g/dL$ per $\mu g/m^3$ when the data were pooled. The study by Cavalleri et al. (1981) gives a slope of from 3.3 to 4.0 $\mu g/dL$ per $\mu g/m^3$ depending on age group; a best estimate is 3.65. The Silver Valley studies (Yankel et al., 1977; Walter et al., 1980; Snee, 1982b) showed a range of slopes from 1.0 to 2.4 $\mu g/dL$ per $\mu g/m^3$ giving a mean slope of 1.70. Data provided by Billick et al. (1979;1980) indicate a slope of 2.9 $\mu g/dL$ per $\mu g/m^3$. Hayes et al. (1994) noted higher slopes than other studies; the authors observed a slope of 5.6 $\mu g/dL$ per $\mu g/m^3$ at air lead concentrations of 1 $\mu g/m^3$ or greater and a slope of 16.2 $\mu g/dL$ per $\mu g/m^3$ when air lead concentrations were 0.25 $\mu g/m^3$ or lower. Since current concentrations are closer to 0.25 $\mu g/m^3$, the slope of 16.2 $\mu g/dL$ per $\mu g/m^3$ is used from this study. Table 4-1 lists the best estimates from each of the studies along with a range of values when available. The geometric mean of the best estimates is 4.2 $\mu g/dL$ per $\mu g/m^3$. Incorporating the lower end of the range of slopes where a range of values was given (see Table 4-1) results in a slope of 3.27 $\mu g/dL$ per $\mu g/m^3$. Using the highest slope in a range gives a slope of 5.18 $\mu g/dL$ per $\mu g/m^3$. Therefore the best estimate of the slope for the aggregate model is within a range of 3.3 $\mu g/dL$ per $\mu g/m^3$ to 5.2 $\mu g/dL$ per $\mu g/m^3$.

Table 4-1. Best Estimates and Range of Slopes in Population-Based Studies in Children.

Study	Best Estimate[a]	Range[a]	Ages
Brunekreef et al., 1983	8.50	NR[b]	4 to 6
Angle et al., 1974; Angle and McIntire, 1979; Angle et al., 1984	1.92	NR	6-18 6-12 1-18
Roels et al., 1976; 1978; 1980 Brunekreef, 1984	5.30	4.6 to 13.7	10-15
Cavalleri et al., 1981	3.65	3.3 to 4.0	3-6 6-11
Yankel et al., 1977; Walter et al., 1980; Snee, 1982b.	1.70	1.0 to 2.4	1-10
Billick et al., 1979, 1980; Billick, 1983.	2.90	NR	NR
Hayes et al., 1994	16.2	5.6 to 16.2	6 months to 5 years
Combined	4.2	3.3 to 5.2	

a $\mu g/dL$ per $\mu g/m^3$
b NR= not reported.

This estimate (4.2 μg/dL per μg/m^3) assumes linearity across the range of air and blood lead concentration found in these studies, although the actual response may not be strictly linear.

In addition, blood lead/air lead slopes in children might decline after age 2. Since one and two year old children have higher metabolism and inhalation rates and ingest more dirt and dust than other children, one would expect the blood lead/air lead slope for one and two year olds to be higher than that of older children and teenagers. Since studies of children across a range of ages (1-18) were used to obtain a best value of the slope, the slope of 4.2 μg/dL per μg/m^3 may be an underestimate.

U.S. EPA uses a subset of the above studies to estimate the direct inhalation slope (i.e., the disaggregate method). For children, they report a slope of 1.97 μg/dL per μg/m^3 (U.S. EPA 1986, 1989b); this slope does not account for deposition of airborne lead on soil and resulting exposure to soil and re-suspended dust. Based on the aggregate model, U.S. EPA (1986) concludes that a slope of 4.2 is appropriate for children.

4.1.4. Linearity of Blood Lead/Air Lead Slope

The chamber studies and the study by Azar et al. (1975) have been used to study the linearity of the relationship between air and blood lead. Many researchers have indicated that the relationship is supralinear (Barry, 1973; Brunekreef, 1984; Chamberlain, 1983; Hammond et al., 1981; O'Flaherty, 1993) with steeper slopes at lower blood and air lead levels. This is not surprising given that a curvilinear relationship has also been described for lead in drinking water and lead in diet (Hammond et al., 1981; Chamberlain, 1983; U.S. EPA, 1986). There is disagreement, however, on the degree of curvilinearity, as well as the air lead-blood lead range over which the relationship could be estimated by a linear function.

Several biological explanations for the nonlinearity have been proposed. The lower responses at higher doses might be due to decreased uptake from the lung or gut, decreased transfer of lead to red blood cells, a faster rate of excretion, a dynamic equilibrium in which the body tries to maintain a certain concentration of lead independently of uptake (Chamberlain, 1983) or aggregation of particles at higher doses, leading to lower inhalation and higher ingestion rates (Hammond et al., 1981). Rate of excretion with increasing dose has been examined in some of the chamber studies by using labeled lead and collecting urine. Chamberlain (1983) saw no evidence of increased excretion using his own data but Kehoe (1961) showed increased urinary output with increasing exposure. If aggregation of particles were the cause of the nonlinearity, then the blood lead/air lead relationship might be linear to a certain level and nonlinear thereafter.

If the relationship is curvilinear throughout the range of air and blood lead concentrations, then slopes calculated from data at higher air exposures will likely be underestimates of the true slope at lower air concentrations. Chamber studies tended to use very high concentrations of lead relative to current ambient concentrations. Chamberlain (1983) and Snee (1982a) concluded that the slope began to level off above 10 μg/m^3. If the slope is linear until that point, then nonlinearity is not of concern since the current lead standard is 1.5 μg/m^3 and the methods used to extrapolate slope are reasonable. However, other researchers believe that nonlinearity is found at levels far below 10 μg/m^3. U.S. EPA (1986) concluded that linearity was a good approximation of the relationship at concentrations less than 3.2 μg/m^3 and blood lead levels under 30 μg/dL. However, Hayes et al. (1994) noted differences in slope at air concentrations of 0.25 μg/m^3 and 1.0 μg/m^3.

Snee (1982) noted that the log-log model originally used was misleading in that it predicted blood lead levels of minus infinity at zero air lead, and air lead levels of zero at zero blood lead. He also believed that it overestimated slopes at lower levels. To replicate the association without using a log-log model, he developed a power function model that incorporated the contributions of all environmental lead sources to model the different background levels observed in the original analysis. Using the data of Azar et al. (1975), the fitted model was:

$$\text{Blood lead} = 12.1(\text{Air lead} + B_i)^K \qquad \text{(Eq. 4-2)}$$

where $K=0.267$ and $B_i = [b_1(\text{lead in food}) + b_2(\text{lead in water}) + ...]$
and b_1 and b_2 are regression coefficients associated with lead in food, lead in water and lead in any other media.

In this model, B_i is intended to characterize the background lead levels for each group. This model was able to nearly reproduce the predictions of the fitted log-log model used originally. U.S. EPA (1986) noted that blood lead levels are highly skewed even in populations with relatively homogeneous exposure and that the variability in blood lead level is roughly proportional to the geometric mean blood lead. In linear regression, the residual error is assumed to be normally distributed. In the case of lead, U.S. EPA noted that deviations are multiplicative and lognormally distributed. They modified Snee's model (1982a) to include an error term with a geometric mean of 1 and a geometric standard deviation of e^{σ}:

$$PbB = (PbA + PbEnv)e^{\sigma z} \qquad \text{(Eq. 4-3)}$$

where (as before) PbB = blood lead, PbA = air lead and PbEnv = non-air sources of environmental lead such as food and water and Z is a random variable with mean 0 and standard deviation 1. U.S. EPA used this and several other models, both linear and nonlinear, to reanalyze the Azar data. They found no significant differences in the residual sum of squares for any of the models and decided to use a linear model (power function = 1) for ease of interpretability.

ARB (1984) analyzed the U.S. EPA's power function model, which they judged to be essentially the same as Snee's, and found that it was quite robust to the power function used, producing very similar residual sums of squares over power estimates of 0.15 to 1.00, but very different slopes. They questioned U.S. EPA's assertion that the linear model, which assumes a power function of 1.00, was the best choice. They state:

> "The possibility of relationships having significantly different properties of potentially great interest for standard-setting must be taken into account. In particular, the assertion that a constant blood lead-air lead slope exists for air lead in the range 0.1 to 3.0 $\mu g/m^3$ is questionable."

Using a power function of 0.245, the function with the smallest error sum of squares, at 10 µg/dL blood lead, they found a slope of 6.71. Using a linear relationship (power function of 1.0) they found a slope of 1.32 at the same blood lead level. While they also detected no significant differences between likelihood ratios for linear and nonlinear models, they concluded that the

results could be interpreted to mean that the relationship is nonlinear. They expressed concern that using a linear model might result in an underestimate of slope.

The population-based data, while problematic in terms of exposure estimates, also show evidence of nonlinearity. To assess nonlinearity, Brunekreef (1984) compared slopes calculated using group comparisons of data collected by Roels et al. (1980). As reviewed above, the highest slopes were found when moderately exposed children (who lived more than 2 km away from the smelter with average exposures ranging from 0.49 to 1.00 $\mu g/m^3$) were compared to rural controls (with average exposures ranging from 0.29 to 0.37 $\mu g/m^3$). In addition, the data of Hayes et al. (1994) predicted dramatic increases in slope when air lead levels were less than or equal to 0.25 $\mu g/m^3$. Also, Brunekreef (1983) reported high slopes, and observed relatively low geometric mean blood leads (7.9 to 13.1) and air lead concentrations (0.25 $\mu g/m^3$ in the more highly exposed community, 0.13 $\mu g/m^3$ in the less exposed community). While the slopes calculated from these studies must be interpreted with caution because of limitations in study design and measurement of exposure, they indicate the potential for nonlinearity in the slope of air lead to blood lead which may be particularly relevant at the current, relatively low, ambient lead concentrations in California (the average ambient air lead concentration is 0.06 $\mu g/m^3$).

4.2. Integrated Exposure Uptake Biokinetic Model (IEUBK)

A third method for estimating the blood lead/air lead slope in children takes advantage of exposure, uptake and biokinetic models developed by U.S. EPA. The Integrated Exposure Uptake Biokinetic Model (IEUBK) for Lead in Children is a stand-alone PC-compatible software package consisting of several related computer programs. Initial versions of the computer simulation model appeared in 1985, with the most recent version (0.99d) and technical support manual released February, 1994 (US EPA, 1994a). This model accounts for specific intake, uptake and distribution of lead in the body, including the route and rate of exposure, and a child's age and baseline exposure. The model also takes into account the amount of lead in the body that results from the biological interactions of absorption, distribution, storage, mobilization and excretion and directly models these processes (U.S. EPA, 1989b). The IEUBK model calculates mean blood lead levels and probability distributions of blood lead levels for children of different ages based on a multipathway exposure analysis. Categories of exposure input variables include concentrations of lead in air, drinking water, soil, house dust, paint, diet and maternal blood lead (to account for newborn blood lead), with each having alternative selectable subcategories or user-defined values. Exposures are converted into an uptake component based on amounts of lead actively and passively absorbed from the lungs and gastrointestinal tract. The absorbed doses of lead are then biokinetically modeled into six different body tissues or compartments over 84 monthly time points (age 0 to 7 years) to account for age-dependent physiological parameters (e.g., increases in inhalation rates and body weights) and soil ingestion rates. The results for blood lead levels are reported for each year of age up to seven years. The model has 45 selectable parameters and 102 that have been set by U.S. EPA (1989b). While the software is based on sophisticated algorithms, it is user-friendly and generates clear and concise reports.

Unlike aggregate and disaggregate models described earlier, the IEUBK model does not use a single blood lead/air lead slope to relate air lead concentrations to blood lead concentrations. The model recognizes that the uptake of lead is not strictly linear with dose because at high exposure concentrations and body burdens of lead the active transport mechanism

is saturable and simply cannot absorb lead any faster. The computer algorithms account for both the non-linear active transport and linear passive transport of all lead entering the body by using simultaneous equations so that children's blood lead levels can be estimated over a wide range of exposures. In effect, the IEUBK model has a curvilinear absorption dose curve for lead that more nearly approximates the human condition than the linear absorption curve that is assumed in an aggregate model.

Evaluation of exposures to air lead occurs at four points in the IEUBK model. First, inhalation exposure to outdoor air lead is determined from the ambient air lead level input by the user. Second, inhalation exposure to indoor air lead can be defined by the user as a percentage of outdoor air lead (default is 30% outdoor-to-indoor "penetration" value). Third, the deposition of indoor air lead contributes to lead in household dust which can be ingested by children. Fourth, the model assumes that some fraction (default of 70%) of outdoor soil will contribute to lead in house dust. However, the contribution of air lead to outdoor soil lead levels is not determined by the model because this is a time dependent variable. It does not differentiate between lead deposited from the air and other sources contributing to soil lead (e.g., eroded house paint, natural soil lead levels). For house dust, the model will partition indoor air lead (30% of outdoor air lead value) into household dust based on a user-specified conversion factor. The default setting converts 1 $\mu g/m^3$ of indoor air lead to 100 $\mu g/g$ of lead (100 ppm) in house dust. This conversion factor may be appropriate when the community is impacted by a normal urban mix of air exposures but the conversion factor may not be appropriate when the area is impacted by a strong point source of lead emissions (e.g., a lead smelter). In the vicinity of such a point source, there will be significantly greater impacts from ambient air onto outdoor soil and consequently on indoor soil and house dust. In these cases, site-specific measurements of outdoor soil and indoor house dust lead levels will greatly improve the predictive capability of the IEUBK model since it is sensitive to house dust lead levels (U.S. EPA, 1994a).

As currently configured, the IEUBK model utilizes field measurements of current conditions. In contrast, it can be used as a predictive model to estimate the long term effect of changes in air concentrations. To effectively use the IEUBK model as a predictive tool for a point source impact, we recommend calculating the future concentration of dust and soil lead that will result from a change in ambient lead from a point source, rather than using the default values of the model. This ensures that the model will yield results that are reflective of the future site-specific conditions including both the direct (inhaled) and indirect (soil and dust ingestion) contribution of air lead to blood lead in children. As indicated in Appendix B of the EPA Staff Report on lead (U.S. EPA, 1989b), there are several linear equations available that relate soil lead and dust lead to air lead. They depend on the available information and are as follows:

Predicting soil lead (S) when air lead (A) is available:

$$S = a_0 + a_1 \times A \qquad \text{(Eq. 4-4)}$$

Predicting dust lead (D) when both air lead (A) and soil lead (S) are available:

$$D = b_0 + b_1 \times A + b_2 \times S \qquad \text{(Eq. 4-5)}$$

Predicting dust lead (D) when only air lead (A) is available:

$$D = c_0 + c_1 \times A \qquad \text{(Eq. 4-6)}$$

The values for the parameters that relate air lead concentrations to soil and dust lead concentrations (a_0, a_1, b_0, b_1, b_2, c_0 and c_1) are shown in Table 4-2 and are obtained from two data sets.

The term "AGG" in Table 4-2 refers to data developed from an average of 40 communities, while "EH" refers to a sample of households with young children obtained in 1983 in East Helena, Montana, by the Centers for Disease Control for the Montana Department of Health and Environmental Science (U.S. EPA, 1989b). As the document (U.S. EPA, 1989b) points out, these equations are not to be used recursively. If only A is known, then Eq. 4-4 may be used to estimate S and Eq. 4-6 may be used to estimate D. If data on S is available, then Eq. 4-5 can be used with information on both A and S to estimate D without an intermediate estimate of S from Eq. 4-1.

The model will also account for alternate sources of lead in house dust, such as from work, school or pre-school daycare, a second home, or from deteriorating interior paint when user-defined values are specified. It should be appreciated that while the concentration of lead in house dust can be estimated using various assumptions, the actual amount of house dust is a function of cleaning habits within the home. The actual inhalation of lead-contaminated air particulates assumes 32% of particulates reach the deep lung where 100% of the lead can be absorbed. For ingested house dust and soil, the model assumes 30% can be absorbed by children. The amounts of lead absorbed (in μg) are then pooled with other absorbed amounts (e.g., from the diet and tap water) and biokinetically modeled into different body compartments to estimate mean blood lead levels and probability distributions of lead in blood for each year of a child's age up to 7 years.

Useful outputs of the IEUBK model include the predicted average blood lead levels (μg/dL) by age in one year intervals up to 7 years old and a probability distribution of blood lead levels that would be expected for a child under the conditions of exposure defined by the user. The probability distributions can be compared to a user-defined blood lead level of concern (10 μg/dL) and the percent of blood lead levels above and below this level are automatically calculated. The probability distributions can be further tailored to the population of concern by selecting a specific age (e.g., 1 and 2 year olds) and a geometric standard deviation (GSD) characteristic of the variability of blood lead levels in a specific exposed population. The default GSD in the IEUBK model is 1.6 which is based on 3 site studies and "reflects child behavior and biokinetic variability, not variability in blood lead concentrations where different individuals are exposed to substantially different media concentrations of lead (U.S. EPA, 1994a)." Additional variability would have to be accounted for when evaluating large populations with different exposures to lead. Introducing a larger user-defined GSD than the default value of 1.6 results in increasing the percent of blood leads above the level of concern. An example of the typical output of the IEUBK model is presented in Appendix C (See Tables C-1 and C-2 and Figure C-1).

The U.S. EPA has developed a strategy for validating the IEUBK model for lead in children (US EPA, 1994b). Of particular interest will be confirmation of the model under conditions defined by empirical data. U.S. EPA has identified 11 data sets that include a range of environmental conditions, including lead from urban, industrial, mining and smelting sources. Recently, U.S. EPA reported the results of an assessment of the IEUBK model's prediction of blood lead levels in children based on environmental studies conducted by ATSDR and U.S. EPA in 1991 (Hogan et al., 1995a). Environmental measurements included lead in residential soil, house dust, drinking water, and lead-based paint. Predicted mean blood lead levels in three studies ranged from 99 to 108% of the observed blood lead levels, where sample sizes ranged from 110 to 507. (Of interest, house dust lead levels were similar to soil lead levels except where

Table 4-2. Linear Model Parameter Estimates for Association of Air with Soil and Dust Lead for the Integrated Exposure Uptake Biokinetic Model

Parameter	AGG	EH
a_0	53.0	88.1
a_1	510.0	206.0
b_0	31.3	184.0
b_1	638.0	267.0
b_2	0.364	0.894
c_0	60.0	220.0
c_1	844.0	551.0

Parameters relate air lead to soil lead and dust lead as follows:

Predicting soil lead (S) when air lead (A) is available:

$$S = a_0 + a_1 \times A \qquad \text{(Equation 4-4)}$$

Predicting dust lead (D) when both air lead (A) and soil lead (S) are available:

$$D = b_0 + b_1 \times A + b_2 \times S \qquad \text{(Equation 4-5)}$$

Predicting dust lead (D) when only air lead (A) is available:

$$D = c_0 + c_1 \times A \qquad \text{(Equation 4-6)}$$

AGG refers to data developed from an average of 40 communities, while EH refers to a sample of households with young children obtained in 1983 in East Helena, Montana, by the Centers for Disease Control for the Montana Department of Health and Environmental Science (U.S. EPA, 1989b).

lead-based paint was a factor in elevating dust lead levels.) The authors concluded that "Predicted blood lead levels agree well with observed blood lead levels on a group mean basis. However, when applied in a community setting with single measurements characterizing each environmental medium, the fraction with elevated blood lead is likely to be overestimated by the Model, while the central part of the distribution may still be accurately represented." Fortunately, the dispersion was only slightly overestimated (e.g., predictions of GSDs of 1.97, 2.11 and 1.72 versus observed GSDs of 1.96, 2.05 and 1.69, respectively). The baseline percent of the population above 10 μg/dL will be dependent on the GSD. However, sensitivity analysis indicates that the impact on the increase in the population with blood lead greater than 10 μg/dL, due to changes in airborne lead, is robust to assumptions about the GSD. Thus, alternative GSDs tend to be relatively insensitive in determining the incremental proportion that will move above 10 μg/dL as air lead changes. The IEUBK model appears to be a reasonable approach to estimating children's mean blood lead levels and conservatively predicts the probability of exceeding the 10 μg/dL level of concern.

The IEUBK model can be used to determine the aggregate slope related to changes in air lead. Since the model assumes a nonlinear relationship between environmental and blood lead concentrations, the slope will vary with air lead concentration. Recent studies of the model carried out by the U.S. EPA using the supplemental equations (Eqs. 4-4 and 4-6) for East Helena (EH) data and data from 40 communities (AGG) indicate aggregate slopes of 3.7 and 5.3 μg/dL per $\mu g/m^3$, respectively, for a change in air lead level from 1.5 to 2.5 $\mu g/m^3$ (Hogan, 1995b). OEHHA also looked at the slopes generated by incremental increases between 0 and 1 $\mu g/m^3$. In this range of air lead concentrations, the IEUBK model predicts approximate slopes ranging from 4.8 to 6.7 μg/dL per $\mu g/m^3$ for the EH data, and from 6.8 to 10 μg/dL per $\mu g/m^3$ for the AGG data with higher slopes at lower air lead concentrations. Conducting an IEUBK model run without use of the supplemental equations results in a slope of less than 1, because the impact of the changes in air lead concentrations on future house dust and soil lead concentration are not automatically taken into account. The reason for obtaining an implicit slope for inhalation only that is less than that calculated in the chamber studies is unclear, but is likely related to some of the default assumptions in the biokinetic model.

4.3. Consistency of Blood Lead to Air Lead Slope Estimates

As stated above, the population-based studies provide evidence of the relationship of air lead to blood lead using an aggregate model. They provide important information not available through chamber studies; i.e., "real world" exposure scenarios encompassing a wide range of behaviors, ages, microenvironments and climates. They indicate that "real world exposures" result in higher blood lead levels than would be directly predicted from chamber studies. This is reasonable because chamber studies only measure exposure from the inhalation route. The population-based studies include deposition, accumulation and exposure from other environmental pathways as well. Relative to studies in which pure concentrations of a pollutant are pumped into a chamber while the subject exhibits a proscribed set of behaviors, they are more representative. At the same time, the field studies may include unexplained covariates which

confound or modify the influence of air lead on blood lead. U.S. EPA (1989a) analyzed many of the same studies as discussed here and concluded that for children the aggregate model suggests a slope of 4 with a range of 3 to 5 μg/dL per μg/m^3.

Since an aggregate slope takes into account both inhalation and indirect ingestion pathways following deposition of airborne lead, one would expect it to be greater than slopes of 1.8 μg/dL per μg/m^3 found in chamber studies of adults which measure the impact of inhalation only. Furthermore, since ingestion of soil and dust would be expected to have some measurable and additional impact on blood lead levels, a slope of 4.2 μg/dL per μg/m^3 is still consistent with results of the chamber studies.

The slopes produced using the IEUBK model vary with air lead concentration, since the model assumes a nonlinear relationship between environmental and blood lead concentrations. The two data sources used to validate the IEUBK model produce different slope estimates because the data produce different coefficients for the supplemental equations (Eqs. 4-4 and 4-6). With incremental increases in air concentration between 0 and 1 μg/m^3, slopes range from 4.8 to 6.7 μg/dL per μg/m^3 for the EH data and from 6.8 to 10 μg/dL per μg/m^3 for the AGG data with higher slopes at lower air lead concentrations.

The aggregate slope estimated from the population-based studies is lower than those estimated using the IEUBK model for two reasons. First, as stated in Section 4.1.4, the relationship between air lead concentration and blood lead is not perfectly linear. Higher slopes are generally observed at lower air lead concentrations. Second, the aggregate slope was derived by averaging slope estimates from study populations with a wider and overall higher range of air lead concentrations. Because of the flexibility of the IEUBK model, OEHHA was able to model changes in slope over a narrow range of low air lead concentrations closer to concentrations currently experienced in California. Thus, the use of the slope of 4.2 μg/dL per μg/m^3 from the aggregate model is best available information and is consistent with the slopes derived from the IEUBK model. OEHHA concludes that the best aggregate slope to use to describe the blood lead/air lead relationship for children is the geometric mean of the available estimates from the population-based studies which results in a value of 4.2 μg/dL per μg/m^3.

Section 5. Estimation of Neurodevelopmental Risks

The next three sections provide estimates of the change in three health effects -- neurodevelopment, blood pressure, and cancer -- associated with changes in ambient air lead concentrations. For lead in the ambient environment, impaired neurodevelopment in young children has been determined to be a health effect of particular concern. For this reason, Section 5 provides estimates of the effects of alternative air lead concentrations on both neurodevelopmental outcomes and the population distribution of blood lead levels. Because changes in air lead may also result in changes in IQ points and the percent of children who may be exceed 10 μg/dL, we provide estimates of these changes at alternative ambient lead concentrations are provided.

Lead may affect blood pressure in adults at very low levels of exposure and result in additional cases of hypertension, myocardial infarction and death. Therefore, Section 6 quantifies the risks for blood pressure changes associated with changes in ambient lead. Finally, a quantitative cancer risk assessment is presented in Section 7. For the noncancer endpoints, the methodology used in Sections 5 and 6 is similar to that used previously by the U.S. EPA in its analyses of the effects of reducing lead in gasoline (Schwartz et al., 1985), of the effects of reducing lead in drinking water (Levin, 1986), and of the implications of its enforcement actions (Strock, 1990), and by the CDC in its assessment of lead intervention strategies (CDC, 1991).

The uncertainties in the risk assessments for the noncancer endpoints for lead impaired neurodevelopment and increased blood pressure are considered to be much less than for the cancer endpoint. Four major uncertainties, usually encountered in risk assessment, are those due to (1) animal-to-human extrapolation, (2) extrapolation from high to low doses, (3) accounting for sensitive members in the human population, and (4) small numbers of subjects. Often, for risk assessments, results in animals are extrapolated to humans. For the noncancer endpoints for lead, the data used were obtained in humans so that uncertainty due to interspecies extrapolation is not an issue. A second uncertainty concerns extrapolation from high-to-low doses, often over three to five orders of magnitude. In the case of the noncancer endpoints for lead, most results have been observed in blood lead levels that include or are within a factor of two of the likely current mean blood lead level in California.

The third source of uncertainty, the varying sensitivity of the population, is relatively small since two groups of sensitive individuals have been identified; children during their neurodevelopment and adults susceptible to hypertension and cardiovascular disease. A threshold level for the effects of lead on neurodevelopment and increases in diastolic blood pressure above 90 mm Hg has not been identified. Consequently, there is uncertainty about the level of protection afforded by reductions in lead exposure. In addition, within these identified groups, there may be particularly sensitive subgroups. The fourth source of uncertainty, which arises from the small numbers of subjects typically evaluated in animal and human studies, is small because there were nearly 2000 children in the neurodevelopment studies and more than 10,000 adults in the studies of lead and blood pressure. Consequently, the uncertainty in the noncancer risk assessment for lead is small relative to that usually found in other chemical-specific risk assessments.

In this Section, we describe and use a methodology to calculate the potential change in IQ and the potential increase in number of children that could experience blood levels of 10 μg/dL or above, as a result of increases in air lead concentrations. We conduct a statistical analysis of the

blood lead data and estimate the likely contributions of alternative air concentrations on blood lead levels in these children. To provide additional information to the risk manager, we calculate the contribution of air lead to the percent of children above the level of concern relative to other media; these calculations are made as airborne lead concentrations increase, using the aggregate approach and the IEUBK model. These predicted changes in blood lead levels can be combined with ambient air concentrations (measured or modeled) for receptors near a point source in order to better characterize the potential health impacts from airborne lead. Also, the IEUBK model can be used to evaluate the impact on blood lead levels in children by reducing lead concentrations in air, reducing lead concentrations in tap water, removing lead from residential soil, or removing lead-based paint. Thus, the analysis of changes in blood lead levels may be useful when considering various mitigation strategies. While the information is subject to some limitations, and still requires some key assumptions, the magnitude of the uncertainty in the calculated results is far less than that of other compounds evaluated in the Toxic Air Contaminant Program for noncancer effects, primarily because the data have been obtained almost entirely from studies in humans.

A 30-day average concentration is used for the current state ambient air quality standard for lead. This is in part based on the biokinetics of lead in the blood. The half-life of lead in blood is 28 to 36 days (reviewed in ATSDR, 1993; U.S. EPA, 1989b); however, the half-life of lead in blood associated with long-term exposure may be as long as several months (NRC, 1993). In addition, analysis of air lead and blood lead associations suggests that a 30 day average provides a reasonable fit of the data (Schwartz et al., 1986). That is, average air lead concentrations in a given month appear to correlate well with blood lead in the following month. Therefore, the current 30-day averaging time for lead concentrations appears to be reasonable for the calculation of subsequent health outcomes.

5.1. Key Assumptions Used in Developing Quantitative Estimates

To calculate a quantitative estimate of impacts to children in general, and subgroups of children at greater risk (e.g., because of age-related behavioral or socio-economic factors) from exposure to air concentrations of inorganic lead, there are several key underlying issues and factors to be considered. They are:

A) identification of the blood lead concentration that should not be exceeded in order to protect the health of children as 10 μg/dL, the "level of concern";

B) the lack of a clearly identified threshold in humans for the adverse effects of lead;

C) the aggregate blood lead/air lead slope factor for children is estimated to be 4.2 μg/dL per $\mu g/m^3$ and assumed to be linear over the ambient air lead concentrations of interest in California; and

D) description of California blood lead levels in one and two year old children, exposed to a mean 0.06 $\mu g/m^3$ of airborne lead, are considered to be comparable to one and two year old children in the NHANESIII national survey, i.e. lognormally distributed, and with a geometric mean of 4.1 μg/dL, and a geometric standard deviation (GSD) of 2.14, rounded

to 2.1, and for the subgroup of children at increased risk, a mean of 6.3 μg/dL and a GSD of 2.11, rounded to 2.1..

Each of the these issues will be discussed in turn below.

5.1.A. Identification of the Blood Lead Level of Concern

Based on current information it is currently not possible to identify a clear threshold blood lead level associated with adverse health effects in humans. As discussed in Section 3.1.7, a level of concern where human neurodevelopmental effects are seen in children exposed either prenatally or postnatally has been identified at 10 μg/dL. The Centers for Disease Control (CDC) has concluded that blood lead concentrations at or near 10 μg/dL present a public-health risk to infants, children and pregnant women (CDC, 1991). This blood lead level is the CDC level of concern for communities as a whole, as well as for individuals, (CDC, 1991). The level of 10 μg/dL has been designated by the U.S. Public Health Service as the maximum permissible concentration from the standpoint of protecting the health of children and other sensitive populations (NRC, 1993). In 1990, the Science Advisory Board of the U.S. EPA identified a blood lead concentration of 10 μg/dL as the maximum to be considered safe for individual young children (NRC, 1993). The National Research Council and U.S. EPA concur that neurodevelopmental effects in children are likely to occur at 10 μg/dL and possibly lower (NRC, 1993; U.S. EPA, 1990a). However, as the evidence continues to grow, it is possible that future levels of concern may drop below 10 μg/dL (NRC, 1993).

5.1.B. Threshold Identification

A key step in a risk assessment is to describe the quantitative relationship between the amount of exposure (the "dose") to a chemical and the likelihood or extent of toxic injury (the "response"). If a threshold for toxicity is identified, this association is then used to determine a level at or below which the public (including sensitive subgroups) can be exposed without any toxic effects. For noncancer health effects from airborne chemicals such toxicity criteria are often called reference concentrations (U.S. EPA) or reference exposure levels (Cal/EPA). If a threshold cannot be determined for an endpoint, a expression of the dose-response relationship is often used to indicate the potential for a toxic response at a given exposure condition. A non-threshold approach is commonly associated with carcinogenic endpoints, while the threshold approach has generally been associated with noncancer endpoints.

A threshold for the health effects of lead in humans has not been identified. For example, Dietrich et al. (1993) found a dose-response relationship of lifetime mean blood lead level in 6.5 year-old children to FSIQ in all four quartiles of exposure. The lowest quartile in this study included blood lead concentrations of 10 μg/dL and below. An analysis by Schwartz (1993) expressly aimed at identifying a threshold for lead's effects on intelligence, found a continuum of effects down to the lowest observed levels of blood lead. This study examined the data from Bellinger et al. (1991) linking blood lead at age 2 with the McCarthy GCI score and data from Needleman et al. (1979) linking tooth lead and IQ. A non-parametric, locally weighted smoothing technique was used to allow the data to determine the shape of the dose-response function, rather than imposing a specific shape. The results indicated the lack of a threshold down to blood lead levels of 1 μg/dL. A subsequent analysis by

Schwartz (1994) examined the similar question using data on FSIQ and blood lead from the Boston cohort (Bellinger et al. (1992). This cohort was used because it had the lowest mean concentration (6.5 μg/dL) and should be most informative about thresholds. Again, using a smoothing approach, no evidence of a threshold was found.

Several major evaluations, including those by the Centers for Disease Control, National Academy of Sciences, and Science Advisory Board of the U.S. EPA, conclude that blood lead levels of 10 μg/dL or above are of concern. While the "level of concern" is described as 10 μg/dL, CDC has also identified different levels above 10 μg/dL and associated responses. For example, when many children in a community are between 10 and 14 μg/dL (a "border zone" range), community-wide childhood lead poisoning prevention activities should be initiated. All children with blood lead levels at or above 15 μg/dL should receive nutritional and educational interventions and more frequent blood lead screening. Between 15 and 19 μg/dL, environmental investigation (including a home inspection) and remediation should be done if the blood lead levels persist. A child between 20 and 44 μg/dL should receive environmental evaluation and remediation and a medical evaluation. Such a child may need pharmacologic treatment for lead poisoning. Above 45 μg/dL, a child would receive both medical and environmental interventions, including chelation therapy. While adverse health effects have been associated with blood lead concentrations of approximately 10 μg/dL, some studies suggest that the adverse health effects could be occurring at lower levels.

Under the standard default procedure for a non-cancer endpoint for which a threshold has not been identified, one would identify a lowest observed adverse effect level (LOAEL) and apply uncertainty factors to develop a reference exposure level (REL). However, for the neurodevelopmental effects of lead, there is a considerable amount of additional information on adverse health effects that have been identified in the sensitive population of children whose blood lead levels can be carefully estimated. Therefore, methods that more precisely define the relationship between lead exposure and adverse effects are utilized, rather than the standard default procedures for reference concentrations and RELs.

In developing quantitative estimates of various reference doses or exposure levels, a primary issue is protection of sensitive subgroups within the population and protection of sensitive members within each subgroup. This can be done by identifying a threshold exposure level, below which no significant adverse health effects are anticipated (Health and Safety Code Section 39662(c)), and adding an ample margin of safety which accounts for the variable effects experienced in a heterogeneous human population (Health and Safety Code Section 39660 (c) (2)). The threshold exposure level is usually identified as the no observed adverse effect level (NOAEL).

Based on the available scientific evidence, it is currently not possible to identify a clear threshold exposure level for lead in humans. Furthermore, since a substantial portion of the young children already exceed the blood lead level of concern of 10 μg/dL, one cannot define an airborne lead exposure with an ample margin of safety for them. It is important to note that when a threshold (NOAEL) cannot be derived directly from scientific studies, the level is often estimated by dividing a LOAEL by a factor of 10 (Jarabek et al., 1990). While this is a accepted scientific practice in cases where data gaps exist, there is a substantial amount of data in children to characterize the risk of airborne lead exposure for adverse neurodevelopmental effects. Consequently, instead of estimating the threshold, a range of risks to humans resulting from

current or anticipated exposure to airborne lead will be determined as specified in the Health and Safety Code (Section 39660 (c) (2)).

5.1.C. Blood Lead/Air Lead Slope

Based on the studies described in Section 4, OEHHA estimates that increases in airborne lead concentrations can result in an increase in blood lead levels in children at an estimated rate of 4.2 μg/dL per $\mu g/m^3$, after all air-related exposure pathways are included and have been fully impacted by the change in air lead. Reasonable lower and upper bounds for the slope are 3.3 and 5.2, based on the range of geometric means. Although the studies reviewed in Section 4 include many different age groups, applying the results to the younger children appears reasonable. We have assumed that the slope is relatively linear near current ambient air lead concentrations and blood lead levels so that calculations for varied exposures near these levels can be made using the aggregate slope factor. As suggested in Section 4.1, however, this assumption of linearity may underestimate the true slope at lower air lead concentrations.

5.1.D. Geometric Mean Blood Lead Level for California

There currently are no population-based blood lead data that are both specific and representative for California as a whole. For this reason estimates of the geometric mean blood lead level for California children needs to be derived from other sources. These are described below.

Recent data from the third National Health and Nutritional Examination Survey (NHANESIII, 1994) conducted by the National Center for Health Statistics/Centers for Disease Control and Prevention provide nationally representative estimates of blood lead levels for several population subgroups, by age, sex and race/ethnicity. Specifically, data for the years 1988 through 1991 were provided for one and two year old children and disaggregated for non-Hispanic whites, African-Americans (defined as "non-Hispanic blacks" in NHANESIII), and Mexican-Americans. Survey sample weights were applied to the data in order to generate estimates that were representative of the U.S. population. Blood lead concentrations were measured by graphite furnace atomic absorption spectrophotometry, with a detection limit of 1 μg/dL. Analysis of each specimen was performed in duplicate, and the mean of the duplicate measurements was reported. "Blind" sample analyses and laboratory analytical quality control procedures were used to assure quality in the blood lead data analysis.

This data set of 13,201 people provides the best blood lead concentration information available for the United States. It contains standardized estimates with a high degree of both analytical standardization and laboratory quality control and quality assurance. For these reasons, it is reasonable to extrapolate the blood lead distribution characterized by NHANESIII to California. However, we are uncertain about how the levels in California compare to the national averages. Consequently, we report on sensitivity analyses conducted to determine the impact of assuming a lower mean for California than the national average. (The sampling design used in the NHANESIII survey does not provide representative state-level data, but regional summary data are available from the authors.) The mean blood lead level for one to five year olds for the Western region is 2.9 μg/dL. This value is in contrast to the 3.6 μg/dL value for children in the nation as a whole. The GSD for the Western region is 2.3 which is greater than the value for the

nation as a whole of approximately 2 (actual value not reported by Brody et al., 1994). The percent of children above 10 μg/dL is 3.5 for the Western region in contrast to 8.9 for the nation as a whole. States like Alaska, Montana, Idaho, Nevada, Utah, Wyoming and Colorado are included in the Western region data with California. California blood lead statistics may be closer to the national averages than to some of the western states because of demographics. For example, these other western states have fewer large cities, lower overall population densities, and greater population homogeneity than California. Also, the relevance of these differences by region is uncertain because of the sampling design used in the NHANESIII. As stated by Brody et al. (1994) in their presentation of the results of the survey: "For logistical reasons, the mobile examination centers were located in the Northeast and Midwest in the summer months and in the South and West in the winter months. A seasonal variation in blood lead levels has been demonstrated and may account for the apparent regional variability (higher blood lead levels in the Northeast) in this study (page 281)" Thus, it is likely that some of the regional difference can be explained by the seasonal nature of the sampling. Furthermore, nearly half of California's housing was built before 1950 when levels of lead in paint were much higher. Unlike the other states in the Western region, California has many communities in the Los Angeles and San Francisco areas with dense housing and deteriorating lead paint (Sutton, 1995). For these reasons, the national NHANESIII data (Brody et al., 1994,) were assumed to be more representative for California as a whole than the Western region data. However, our subsequent sensitivity analysis indicates that the general results of our risk analysis (i.e., estimating the increase in the percent of children above 10 μg/dL) is relatively insensitive to the choice of the geometric mean.

Although several recent studies have investigated the distribution of blood lead in certain populations of California children, they are not necessarily representative of the state's population. We discuss these studies below.

Between 1987 and 1989 the California Department of Health Services conducted studies of children perceived to be at higher risk for lead poisoning within the California communities of Los Angeles, Oakland and Sacramento (CDC, 1992). Communities chosen for these prevalence studies had a high proportion of older housing (built before 1940), a high proportion of children under age 6, and lead-emitting businesses (such as auto repair shops) interspersed with housing. The distributions described by these studies (see Table 5-1) are not useful for estimating geometric mean blood lead of children in California since the areas studied are not representative of the average California child's exposure. However, the studies indicate that during that time period, there existed communities in California with children having elevated blood lead levels. For example, the data from the Los Angeles area (Wilmington and Compton) indicate that 32% of those sampled were above the level of concern of 10 μg/dL, while between 47 and 67% (depending on the method of detection used) of the children sampled in Oakland and 14% of the children sampled in Sacramento had blood lead levels of 10 μg/dL or greater.

In a 1992-1993 study (CDC 1995, Molina et al., 1995), routine blood lead level testing was conducted for 2864 consecutive children ages 1 through 6. These children received care from a managed care organization that provides primary-care services to MediCaid beneficiaries in several locations in California (Los Angeles County, Orange County, San Bernardino County, Riverside County, Sacramento and Placerville). Data were not available about the number of children whose families did not consent to testing nor about those from whom blood could not be collected. Geometric means and standard deviations were not presented. Overall, 98% of the

Table 5-1. Blood Lead Levels in One to Six Year Old Children in Three High Risk Communities in California (1987-1989): Preliminary Results.

Blood Lead	Oakland[b] (n=544)	Los Angeles (n=199)	Sacramento (n=382)
< 10 μg/dL	33%	68%	86%
10-14 μg/dL	34%	23%	9%
15-19 μg/dL	10%	6%	5%
≥ 20 μg/dL	3%	3%	0%
≥ 10 μg/dL	67%	32%	14%

Source: CDC (1992)

b Initial blood lead samples were capillary. From those with capillary samples of ≥ 15 μg/dL venous follow-up samples were taken. Those that only had capillary samples taken are assumed to have the same distribution as those followed up with venous samples. It is also assumed that 50% of capillary blood lead levels of 10-14 μg/dL would have been < 10 μg/dL on follow-up. In Los Angeles and Sacramento, few capillary blood lead samples were taken.

children had blood leads less than 10 μg/dL; 1.7% had blood leads between 10-14 μg/dL, and 0.3% had levels greater than 15 μg/dL. The percentage of children with blood lead levels greater than 10 μg/dL did not vary significantly across age groups. Lead levels for black children were 25% higher than those of white children. In their commentary, the CDC editors discussed several possible reasons for the low prevalence of elevated blood lead levels among MediCaid recipients. Since the study was conducted in the winter months and the likelihood of lead exposure is greater in the summer, seasonal variations may have accounted for the differences between the findings of this and previous surveys. Some of the differences may be due to variations in the study design between this clinic-based study and previous population-based surveys conducted in California during 1987-1990 in Compton and Sacramento (CDC, 1992). The editors suggested that "because characteristics of children receiving care at [this] managed-care organization probably differ from those of other groups of children in California, the findings in this report cannot be generalized." Nonetheless, the results of this study may be indicative of a continuing downward trend in children's blood lead levels observed between NHANESII and NHANESIII and in the Los Angeles air basin from 1991 through 1994 (Williams et al., 1996). The complete phase-out of lead from automotive gasoline and other measures taken by California to remove lead from the environment, drinking water, tableware, and food containers are all likely to result in lowering blood lead levels in the near future.

Another recently published study (Haan et al., 1996) of HMO patients examined blood lead levels in 305 healthy children from employed, insured, middle-class families over a 5-month period in 1991-1992. In this study, the overall median and mean blood lead levels was 4 μg/dL and 4.65 μg/dL, respectively, for children ages 1 through 5. However, when age-specific rates are reported, the median for children below age 2 in the Vallejo area was 4.0 μg/dL, and the median for children below age 2 in the Oakland sample was 5.0 μg/dL. GSDs were not provided. Given the distribution, the means would be higher than the medians. Therefore, the means for the Vallejo and Oakland children are above 4 and 5 μg/dL, respectively. Also, Haan et al. state, "mean blood lead in black children was 25% higher than in non-Hispanic white children after adjustment for age, gender, study site, housing age, and mother's education ($p=0.0001$)." In this study both the range of the means and the differences between white and blacks are comparable to the NHANESIII data. Nevertheless, we conclude that this sample may not be representative of the state as a whole. Although this clinic-based sample was representative of the HMO studied, its characteristics differs from the population-based samples reflected in NHANESIII (Brody et al., 1994) used by OEHHA to estimate children's blood lead levels. Specifically, the sample used in the Haan et al. (1996) study consists of regular visitors to the well baby clinic. In addition, the population consists of employed families, most with two parents, with pre-paid health insurance.

As part of a cost analysis of the lead-testing program in Orange County, California, Gellert et al. (1993) analyzed a nonrandom sample of venous blood lead tests in 5115 children aged 1-5 years in the Child Health and Disability Prevention Program. The ethnicity of the sample was not representative of the state of California: 73.5% Hispanic; 12.2% Asian; 9.8% white; 1.2% African-American; 3.3% other. Blood lead levels were found to be greater than 10 μg/dL in 7.25% of children. The geometric mean and standard deviation were not provided. The major sources of blood lead levels $\geq$ 20 μg/dL in children in this study were shown to be related to pica, folk remedies, use of unglazed earthenware or peeling paint. While only 7.54% of houses in the county were constructed prior to 1950, no information on the location of residence were provided for the study population. The results of this study should not be generalized to the California

population because the sample was not randomly chosen, the ethnic makeup of this community differed from the state and because the age distribution of housing may not be representative of those in other urban areas.

Another survey to determine blood lead was conducted in Los Angeles County using two laboratories and a population of convenience from the CHDP program in 1993 (Jacobs and Papanek, 1995). There were apparent quality control differences between the two laboratories, but the blood lead distributions for the 1 to 2 year old group appeared to be fairly consistent. The authors report that for their subgroup of children age 1 and 2, the proportion of children above 10 μg/dL (10.1%) are indistinguishable for the estimates from NHANESIII (11.5%). As in some of the other studies reviewed above, OEHHA does not view these estimates as representative of levels in California. The estimates were based on a sample that happened to be collected at several laboratories, the sample consisted only of families in the CHDP program, there were differences in estimates by laboratories, and the sample was dominated by Hispanics (over 90%).

In conclusion, the studies conducted in certain areas within California are not generalizable to the entire state. They indicate, however, the wide range of blood lead distributions that exist in the state and suggest that site-specific analysis may be beneficial when examining effects of local sources.

An additional question concerns the shape of the blood lead distribution. To determine if the blood lead concentrations were lognormally distributed, as has been consistently reported in the literature, we used PROC RANK in SAS as our analytical tool. This procedure compares the raw data with the cumulative distribution that would result from a normal distribution. We took the log of the NHANESIII data to compare the values resulting from this distribution with a theoretical normal distribution. The results generated a correlation of 0.998 between the log of the original NHANESIII data and the normal distribution, indicating that the data are best described as being lognormally distributed. Therefore, we assume that the blood lead levels for California as a whole are also lognormally distributed.

Since the information in the NHANESIII is provided by age, one can focus on the age group at greater risk for lead poisoning, one and two year olds. For the subgroup of one and two year old children, the geometric mean blood lead was 4.1 μg/dL with a 95% confidence interval (CI) of 3.7 to 4.5 (Brody et al., 1994). Among this subgroup, 11.5 percent had blood lead levels over 10 μg/dL, with 1.8 percent above 20 μg/dL. The NHANESIII data also reveal that the geometric mean blood lead values vary by ethnicity within the group of one and two year old children. Blood lead levels for non-Hispanic white male children are the lowest, where the geometric mean blood lead was 3.5 μg/dL (95% CI = 3.1- 4.1). The geometric mean blood lead for African-American male children ages one to two years old was 6.3 (95% CI = 5.6 - 7.2) and the geometric mean blood lead for Mexican-American male children was 4.2 (95% CI = 3.5 - 5.3). Female, non-Hispanic white and Mexican-American children ages one and two years old had higher blood lead levels than their male counterparts. Regression analysis for all age groups together, as presented in the NHANESIII report, indicated that sex (male), urban status (residing in a central city above 1 million), race/ethnicity (African-American and Mexican-American), education of parents (below high school) and poverty were associated with higher blood lead levels (Brody et al., 1994).

Children between ages one and two tended to have higher blood lead levels with 8.5 % of non-Hispanic whites, 21.6 % of African-Americans, and 10.2% of Mexican-Americans having

levels of 10 μg/dL or greater. Thus, the percent of children that exceed the level of concern also differs by race/ethnicity. The GSD for these groups was 2.29 (non-Hispanic whites), 2.11 (African-Americans), and 2.06 (Mexican-Americans) (personal communication and Brody et al., 1994). African-American male children between ages 1 and 2 appear to be the subgroup most at risk based on the geometric mean blood lead concentration of 6.3 μg/dL and a GSD of 2.11 (Brody et al., 1994). For this reason African-American male children were considered to be the group at greatest risk for our analysis.

The value of the GSD used to describe the population distribution of blood lead levels in children impacts the estimates of the percent of the population exceeding 10 μg/dL level of concern. Use of the GSD of 2.14 is based upon the NHANESIII data, the best available population-based study. For consistency and ease of comparison, the GSD of 2.14 was used throughout this document as reflective of the greater population of California 1 and 2 year olds. However, it is acknowledged that a smaller population of children exposed primarily to a local point source may have more homogeneous characteristics and exposures in comparison to the California population as a whole, and therefore likely to have a GSD lower than 2.14. For example, Marcus et al. (1992) cite GSD values for several mining and smelter communities that ranged from 1.30 to 1.79. Considerations related to selection of the most appropriate GSD value for use in evaluating point sources should be a component of subsequent risk management guidance. When other than a published or default GSD is used in the models discussed in this document, it is highly recommended that the guidance on selection and interpretation of GSDs in Sections 4.2.2 through 4.2.7.5 of the US EPA Guidance Manual (1994) be reviewed.

5.2. The Impact of Airborne Lead on Mean Intelligence Levels

This subsection assesses the impact of a change in air lead on IQ points in young children. For lead in the ambient environment, impaired neurodevelopment in young children has been determined to be the principle health effect of concern. As summarized by the National Academy of Sciences, the adverse effects that have been noted at approximately 10 μg/dL include:

- Impairments of the central nervous system and other organ development in fetuses,
- Impairments in cognitive function and initiation of various behaviors in young children (NRC, 1993).

Thus, in children, blood lead concentrations in excess of 10 μg/dL may be associated with disturbances in early physical and mental growth and in later intellectual functioning and academic achievement (see Section 3). While a specific age-range definition of children at risk from lead poisoning is not available, zero to two years old, zero to six years old and zero to thirteen years old have been used by others (NRC, 1993). In the analysis presented in this section, the focus is on one to seven years old, the group apparently most sensitive to the health effects of lead. However, to obtain a complete picture of the implications of exposure to lead, the analysis of any specific scenario could include children from zero to thirteen and pregnant women, to account for potential impacts on the fetus.

As discussed in Section 3, several prospective cohort studies of neurodevelopment suggest a 0.33 (± 0.01) decrease in IQ points, based on the WISC-R full scale IQ test (FSIQ), per

μg/dL increase in blood lead. To convert the change in air lead to the effect on intelligence, we use the air-lead to blood-lead ratios as developed in Section 4. To fully characterize the uncertainty in this estimate, we use the lower and upper estimates for the slope (3.3 and 5.2) and the best estimate of 4.2 and multiply by the respective low, high and best estimate for the IQ effect. This implies that a mean decrease of 1.39 (0.33 x 4.2) IQ points may occur per $\mu g/m^3$ increase in air lead, with a range of 1.06 (0.32 x 3.3) to 1.77 (0.34 x 5.2). Applying the mean changes to the cohort of 4.73 million children in California below age 7 (California Department of Finance 1996 projections), the current ambient concentration of 0.06 $\mu g/m^3$ lead relates to an average loss of 0.08 IQ points. Obviously, this is a small change on a per person basis, though some individuals will experience greater changes and some will have less (or no change). In addition, the impact of such a change applies across the entire distribution of IQ scores reducing the number of children who score above the norm and increasing those who score below the norm. As noted by NRC (1993), "...a property of statistical distributions is that a small difference in mean score between two groups results in substantial differences in frequency of the extreme values between the two distributions. The distributional implications of small changes in population mean score have been confirmed by analysis of several lead-study data sets." Thus, while the average IQ score change may be small, certain individuals may experience large IQ score changes. Furthermore, small changes in a population's average IQ score may substantially impact the relative proportion of children at either very high or very low IQ levels. Needleman et al. (1982) and Davis (1990) are among those who have published analyses of the impacts on extreme IQ values due to small changes in mean IQ levels.

At the ambient average air lead concentration of 0.06 $\mu g/m^3$ which results in a decrease of 0.08 IQ points (relative to zero air lead), the number of children with IQ scores below 80 would increase from 10.56 to 10.66 percent. This represents a relative increase in the number of such children of approximately one percent (i.e. (10.66-10.56)/10.56 x 100 = 1%). Based on a cohort of 4.73 million children in California below age 7, the 0.06 $\mu g/m^3$ average air lead concentration relates to approximately 4,700 additional children that would be predicted to have IQ levels below 80, relative to a zero air lead level. To avoid any double counting, we estimate future impacts of the 0.06 $\mu g/m^3$ air lead on only a one-year age cohort that will be added to the full cohort of children below age 7. Thus, in each subsequent year, the models suggests that an additional 4,700 ÷ 6 or 780 children would be predicted to have IQ levels below 80.

The effects for an elevated exposure can also be estimated. For example, assume an ambient air concentration of 0.20 $\mu g/m^3$ above the current ambient concentration uniformly impacts a community of 2,000. In this example, the 279 children below age 7 in this community (based on California Department of Finance 1996 projections) would experience an average loss of 0.28 IQ points (i.e., 0.20 $\mu g/m^3$ x slope of 4.2 x 0.33 IQ points per μg/dL) or a total of 78 points. A 0.28 point shift in mean IQ would correspond to an increase of approximately three percent in the number of children with scores of 80 and below (i.e., (10.97-10.66)/10.66 x 100= 3%) (see Appendix D for details on calculation of IQ distribution changes). Using the range of blood lead/air lead slopes of 3.3 to 5.2, the range in potential lost IQ points is 61 to 96.). The actual changes in IQ that may occur and the number of children moving below an IQ of 80 are a function of many other variables and may be very difficult to detect for these small changes in ambient concentrations. OEHHA's estimates are intended to show the potential for IQ changes that would be expected to occur with changes in air lead over time if all other variables remained constant.

The potential magnitude of this change can also be reflected in the size of the total population loss. In this example, there would be an estimated total decrease of 392,000 IQ points among the population, with a range (varying both the slope and IQ loss per unit) of 301,000 to 502,000 IQ points. Recent research (Schwartz, 1994; Salkever, 1995) provides some insight into the implications of IQ loss in terms of lost wages and labor force participation.

5.3. The Range of Neurodevelopmental Risks for Children Using the Aggregate Model Approach

When a threshold, or exposure level below which no adverse health effects are anticipated, cannot be calculated for a substance, OEHHA is required to determine the range of risks resulting from current or anticipated exposure to the substance (Health and Safety Code Section 39660 (c) (2)). As stated in Section 5.1, the key factors involved in developing the range of risk include the existing blood lead distribution in children, the percent of children adversely affected by exposure to airborne lead, the concentration to which the children are exposed, and the population of children exposed. In this Section, OEHHA will utilize these factors in the calculation and will build on methodologies developed by U.S. EPA to develop a range of neurodevelopmental risks for California children. The focus is on the effects of changes in air lead on the distribution of blood lead for the subgroup of children with the highest mean blood lead and at the greatest risk: children ages one and two. However, to obtain a complete picture of the health impact of exposure to lead, the analysis of a specific scenario could include other subgroups such as children up to thirteen years old and the developing fetus exposed transplacentally. To do so requires including additional age-specific information in the analysis including the blood lead distribution (mean and GSD) and the blood lead/air lead slope for the relevant subgroup.

When the U.S. EPA developed its lead standard in 1978, the aim was to protect those children most exposed to lead. U.S. EPA considered the range of blood lead concentrations, the geometric mean and the GSD reported at that time. Then, they identified 30 μg/dL, the level of concern at the time, as a level not to be exceeded by 99.5% of children (U.S. EPA, 1978). From these assumptions the U.S. EPA developed the current ambient air quality standard of 1.5 $\mu g/m^3$. In a more recent analysis, U.S. EPA chose a ninety-five percent level of protection for site-specific preliminary soil remediation goals for lead at CERCLA sites and soil cleanup standards for lead at RCRA sites (Laws, 1994). The U.S. EPA calculation is designed to limit exposure such that children would have an estimated risk of no more than 5% of exceeding the 10 μg/dL level.

Our analysis is similar to the U.S. EPA (1978) methodology while incorporating more current information. The current level of concern is 10 μg/dL, not 30 μg/dL used by U.S. EPA in 1978. Second, at the current time approximately 11.5 percent of all one and two year old children are already above 10 μg/dL blood lead (Brody et al., 1994) due to exposure to lead from various media, such as water, food, consumer products, soil, and paint. Also, decreasing the current statewide average air lead concentration of 0.06 $\mu g/m^3$, even to zero air lead, would still not protect 99.5%, or even 95% of children from exceeding 10 μg/dL, based on NHANESIII data. For these reasons we focus on quantifying the incremental change in the proportion of children with blood lead levels exceeding 10 μg/dL that would result from exposures to various concentrations of air lead.

The first step in this analysis requires calculating the geometric mean blood lead levels associated with changes in air lead concentrations. We choose an appropriate mean and GSD, then calculate the percentage of children who would have blood lead levels of 10 μg/dL or above, after subtracting out the contribution of the average ambient air lead concentration. Then, we determine the shift in the geometric mean that will occur with various increases in air lead, using a blood lead/air lead slope of 4.2. (Note that since we are adding absolute changes, that is, the airborne lead concentration multiplied by the blood lead/air lead slope of 4.2, to the geometric mean of blood lead levels, we first convert the geometric mean to an arithmetic mean. After adding the absolute change, we convert the new arithmetic mean back into a geometric mean). Next, the proportion of the population having a blood lead level of 10 μg/dL or greater after each given increase in air lead is calculated. The details of calculating the geometric mean, standard deviation and blood lead changes from air lead exposures are provided in Appendix B. Using this method, the potential impact on the population of concern can be estimated over a range of air lead exposures.

Calculations were made based on NHANESIII data, where the geometric mean and standard deviation for all children between ages one and two are 4.1 μg/dL and 2.14, respectively, resulting in 11.5 % of this age group exceeding 10 μg/dL of blood lead. These calculations are summarized in Table 5-2 and are depicted in Figure 5-1 which displays the proportion of the population above 10 μg/dL for a range of air lead levels. To quantify the impact of possible ambient air lead levels, we first subtracted the estimated contribution of 0.06 $\mu g/m^3$ to determine the percentage of children who could have blood lead levels above 10 μg/dL even without this background level. When we adjust the population by subtracting out the average ambient lead concentration of 0.06 $\mu g/m^3$, the resulting geometric mean equals 3.91, with 10.9 percent of one and two year old children above 10 μg/dL. Thus, even after subtracting out average ambient lead levels, 10.9 percent of one and two year old children would be predicted to exceed the 10 μg/dL level of concern, presumably as a result of lead exposure from water, soil, dust and foods and other environmental sources of lead. Note that in certain cases, particularly near a source, the contribution of air lead might be greater than the background level of 0.06 $\mu g/m^3$. Thus, when local monitoring data are available, they could be used to determine the air-related source contribution to blood lead levels for the local area and the baseline calculation could be adjusted. Exposure to the current average ambient level of 0.06 $\mu g/m^3$ (i.e., a change in air lead from 0 to 0.06 $\mu g/m^3$) elevates 0.6 percent of the population of one and two year old children above 10 μg/dL. Using information in Table 5-2 and Figure 5-1, one can determine the theoretical proportion of one and two year old children that would be predicted to exceed the 10 μg/dL level of concern at various airborne lead concentrations. At an air lead concentration of 0.10 $\mu g/m^3$, an additional 1.4 percent of the population of one and two year old children in California would be predicted to exceed 10 μg/dL. At an air lead concentration of 0.5 $\mu g/m^3$, an additional 10 percent of the exposed population of one and two year old children would be predicted to exceed the CDC guideline of 10 μg/dL. At an air lead concentration equivalent to the current ambient standard of 1.5 $\mu g/m^3$, more than 32% of children aged 1 and 2 would have blood lead levels above the CDC guideline of 10 μg/dL according to the aggregate model (Table 5-2). The other models predict even higher numbers.

In a similar manner, one can evaluate the adverse impact of air lead changes on the subpopulation of children at greatest risk (who are described in the data from NHANESIII). This

subgroup, consisting of African-American male one and two year old children has a geometric mean blood lead level of 6.31 μg/dL with a GSD of 2.11 (Brody et al., 1994 and Brody, personal communication). The adverse impacts are summarized in Table 5-3 and are also depicted in Figure 5-1. When the population is adjusted by subtracting out the current average ambient lead concentration, the resulting geometric mean equals 6.13 μg/dL, with 25.6 percent of the subgroup above 10 μg/dL. We next calculated how increases in air lead would alter the geometric mean and the proportion of the subgroup above 10 μg/dL. Exposure to the average ambient level of 0.06 $\mu g/m^3$ elevates 1.1 percent of the population above 10 μg/dL. A 0.15 $\mu g/m^3$ air lead exposure would increase the geometric mean blood lead level from 6.13 to 6.61 μg/dL, elevating an additional 3.4 percent of the subgroup above 10 μg/dL. An increase of 0.5 $\mu g/m^3$ could elevate an additional 10.8 percent of the subgroup to those above 10 μg/dL. Sample calculations are provided in Appendix B.

We compared the impact of changes in air lead on the two subpopulations of one and two year olds (i.e., "all" children and male African-American). Figure 5-1 shows that for air lead concentrations up to 1 $\mu g/m^3$, there is no substantial difference between these two groups of children in the percent increase that would exceed the 10 μg/dL level of concern. Additional comparisons were made and we concluded that the choice of subpopulation (and different mean and standard deviation in the blood leads) did not substantially affect the percent of children that would be elevated above the level of concern as air concentrations are increased. That is, with the predictive aggregate slope model, the impact on the percent of children that would be elevated above the level of concern is fairly robust and is relatively insensitive to the mean value or the standard deviation when the full distribution is considered. For example, differences of up to 2 μg/dL in the initial mean blood lead will not significantly alter the subsequent affect of a given change in air lead. This is a result of statistical properties of the lognormal distribution which typically characterize blood lead concentrations. In addition, over time, reductions in the geometric mean appear to be associated with increases in the standard deviation. The blood lead distributions for the group of one and two year old children and for the subgroup of African-American male one and two year old children are displayed in Figure 5-2. As indicated in this figure, while the geometric mean blood lead concentration is higher for the subgroup of African-American male children, empirically the GSD is smaller. While the choice of geometric mean blood lead concentration and corresponding GSD does not appear to affect the calculation substantially, it is important to keep in mind that in order to protect children from high blood lead levels and lead poisoning one has to consider the distribution (i.e., variability) of blood lead levels and not simply the geometric mean blood lead level.

Based on the above information and discussions and the blood lead distributions from NHANESII, the blood lead/air lead slope factors can now be applied to specific scenarios of exposure. These scenarios include the average ambient background (0.06 $\mu g/m^3$), and exposure to a hypothetical elevated ambient concentration of 0.20 $\mu g/m^3$ above the ambient average. Using the relationship displayed in Figure 5-1, the percent of children potentially affected by a given airborne lead exposure can be quantified. Specifically, for any increase in airborne lead exposure, we can calculate the number of children who are already above 10 μg/dL who may be further impacted, and the number of children expected to have blood lead levels increase above 10 μg/dL.

Table 5-2. Impact of Increases in Air Lead on the Percent of the General Child Population, One and Two Years of Age Equal to and Above 10 μg/dL Blood Lead Using Aggregate and IEUBK Models: Baseline Mean of 4.1 and GSD of 2.14.[a]

Average Air Lead Concentration ($\mu g/m^3$)	Aggregate Model		IEUBK(EH) Model[b]		IEUBK(AGG) Model[c]	
	Percent ≥ 10 μg/dL	Increase in Percent ≥ 10 μg/dL Relative to 0 $\mu g/m^3$	Percent ≥ 10 μg/dL	Increase in Percent ≥ 10 μg/dL Relative to 0 $\mu g/m^3$	Percent ≥ 10 μg/dL	Increase in Percent ≥ 10 μg/dL Relative to 0 $\mu g/m^3$
0.00	10.9	0 (0)[d]	9.2	0 (0)	2.5	0 (0)
0.06	11.5	0.6 (5)	11.2	2.0 (18)	4.8	2.3 (48)
0.10	12.3	1.4 (11)	12.7	3.5 (28)	6.8	4.3 (63)
0.20	14.5	3.6 (25)	16.7	7.5 (45)	12.7	10.2 (80)
0.25	15.5	4.6 (30)	17.9	8.7 (49)	15.6	13.1 (84)
0.50	21.1	10.2 (48)	27.4	18.2 (66)	29.5	27.0 (91)
0.75	26.7	15.8 (59)	34.1	24.9 (73)	42.7	40.2 (94)
1.00	32.2	21.3 (66)	39.7	30.5 (77)	49.6	47.1 (95)

a Baseline mean and geometric standard deviation are based on data for one and two year old children from NHANESIII, phase I (Brody et al., 1994). Calculation assumes that baseline non-air sources of lead exposure including paint, household dust, soil, pottery, and tap water are constant. Use of the GSD of 2.14 assumes that a localized exposed population has the same characteristics as the larger California population; when quality site specific data are available, they may be used. The estimated increase in percent of children above 10 μg/dL is a future value that could be expected after long-term deposition of air lead to soil or when soil lead approaches a steady-state condition with air lead. The current mean ambient air lead level in California is 0.06 $\mu g/m^3$.

b IEUBK model with supplemental equations based on data from East Helena.

c IEUBK model with supplemental equations based on data from 40 communities

d Numbers in parentheses indicate, at each ambient air lead level, the percent of the children with blood lead levels of 10 μg/dL or greater that can be attributed to air lead.

Figure 5-1

Changes in lead and the associated population at risk

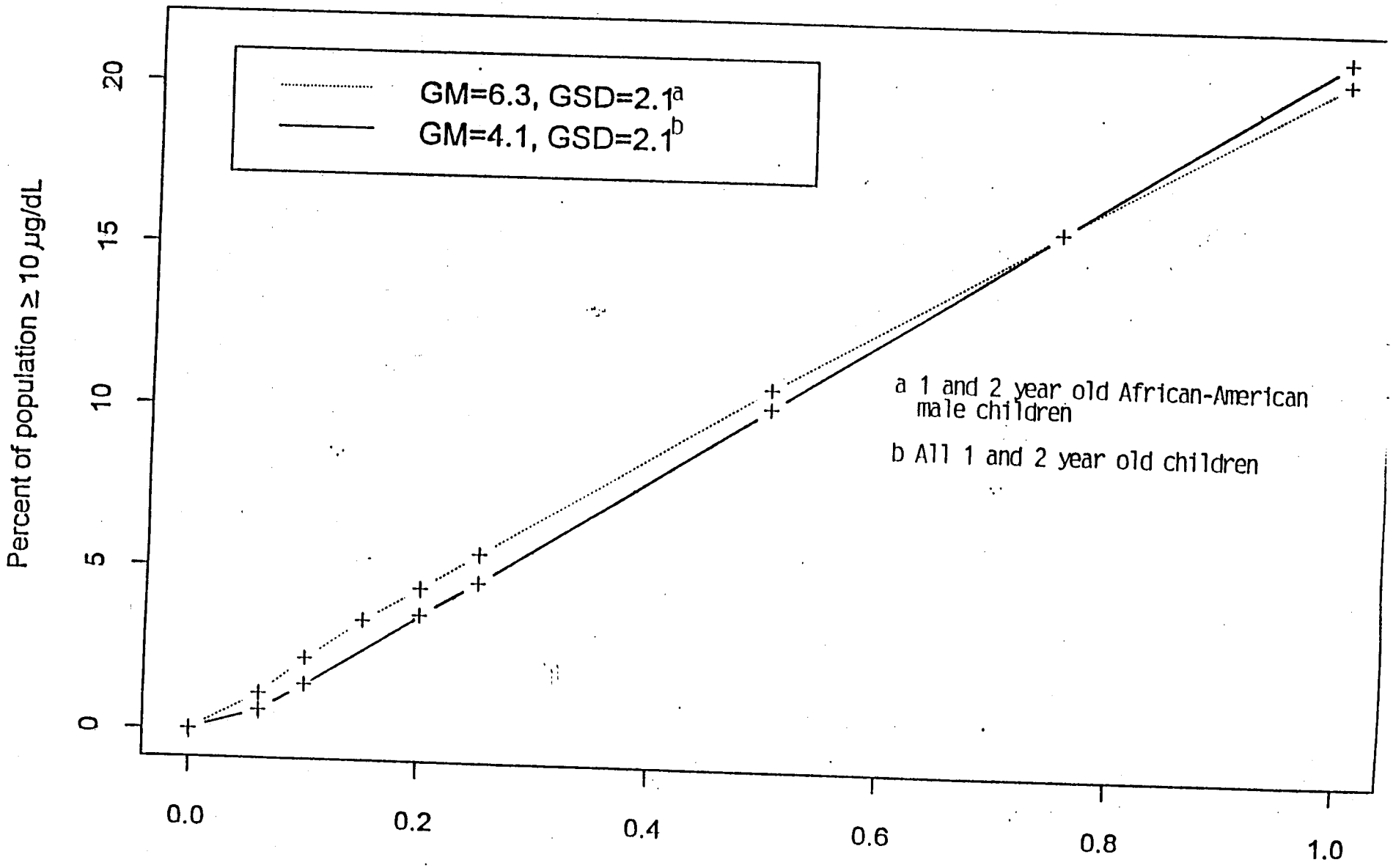


Table 5-3. Impact of Changes in Air Lead on the Percent of a Sensitive Population - One and Two Year Old African-American Male Children Equal to and Above 10 μg/dL Blood Lead. Baseline Mean of 6.3 and GSD of 2.11.[a]

Air Lead Concentration ($\mu g/m^3$)	Percent ≥ 10 μg/dL	Increase in Percent ≥ 10 μg/dL Relative to 0 $\mu g/m^3$
0.00	25.6	0
0.06[b]	26.7	1.1
0.10	27.8	2.2
0.15	29.0	3.4
0.20	30.0	4.4
0.25	31.1	5.5
0.50	36.4	10.8
0.75	41.4	15.8
1.00	46.2	20.6

a Baseline mean and geometric standard deviation are based on data for one and two year old African-American male children from the NHANES III, phase I survey (Brody et al., 1994). This subgroup has the highest mean blood lead levels among the children. Calculation assumes that baseline non-air sources of lead exposure including paint, household dust, soil, pottery, and tap water are constant.

b Current mean ambient air lead level in California

Note that the calculations below are made for children from one to two years of age, the age group of children at greatest risk because their blood lead levels are, on average, the highest in the age group of children one to seven years old.

5.3.1. Current Ambient Average Air Exposure Scenario

Application of the NHANESIII data to California suggests that 10.9 percent of the children are estimated to have blood lead levels above the 10 μg/dL level of concern, even after subtracting out the average ambient air lead concentration. These children are affected by other sources of lead exposure including lead from paint, tap water, and contaminated soil and household dust. (Note that even if a child is exposed to elevated environmental levels, only the average ambient level of 0.06 $\mu g/m^3$ has been subtracted out to establish the baseline). Two groups may be impacted from increases in air lead: those below 10 μg/dL of blood lead and those who are already above 10 μg/dL. For the group already above 10 μg/dL, the addition of airborne lead exposure increases these children's blood lead levels further above this level of concern, and further increases the likelihood of a neurodevelopmental impact. As indicated in Section 3, increases in blood lead levels in children may increase the severity of adverse impact. With an estimated total California population of 33.9 million the estimated number of one and two year old children is 1.2 million (California Department of Finance 1996 projections). Using this information and the percent of children estimated to have blood lead levels above 10 μg/dL due to exposures from sources other than air lead, the hypothetical number of children who may be additionally impacted by increases in airborne lead exposure can be calculated as follows:

10.9% x 1,200,000 = 131,000 one and two year old children above 10 μg/dL blood lead in California at zero air lead.

Based on the data of Brody et al. (1994) children with the highest blood lead levels are most likely to be those of color, in particular African-Americans and Hispanics. Furthermore, they are likely to reside in large metropolitan areas.

Considering those one and two year old children with blood lead levels below 10 μg/dL, exposure to an average ambient air concentration of 0.06 $\mu g/m^3$ could result in an additional 0.6 percent of children with blood lead levels of 10 μg/dL or greater. Using the above population figures for children between ages one and two, one can estimate the number of additional children who may have blood lead levels elevated above 10 μg/dL by the current average airborne lead exposure as follows:

0.6% x 1,200,000 = 7,200 additional one and two year old children in California that will move above 10 μg/dL due to current ambient air lead.

While such estimates are based upon the best available scientific data, they rely on models which contain many assumptions and uncertainties. Care should be taken to not ascribe a greater precision to these risk estimates than is warranted by the underlying assumptions and uncertainties in the risk models.

5.3.2. Near Source Air Lead Exposure Scenario

As indicated in Section 5.3.4, localized exposures may have higher airborne lead levels. To estimate the impact of an estimated near source exposure, one could make calculations like those above. Consider a hypothetical community of 2,000 exposed on average to an ambient air lead concentration of 0.20 $\mu g/m^3$ above the ambient average of 0.06 $\mu g/m^3$. This community scenario is based on the information in Part A, Tables IV-3 through IV-6, which reflects concentrations above background. Using Table 5-2, the additional neurodevelopmental risk for such an exposure can be approximated by subtracting the percent of the children predicted to above 10 $\mu g/dL$ at 0.06 $\mu g/m^3$ from the percent predicted at 0.25 $\mu g/m^3$ (assuming that the impact of a 0.19 $\mu g/m^3$ change is roughly similar to that of a 0.20 $\mu g/m^3$ change). Thus, the affect of a 0.20 $\mu g/m^3$ change above the baseline would be between 4 and 11% depending on the model used (Table 5-2). The aggregate model predicts the 4% increase. Using a total population exposure in this localized area of 2,000, the estimated number of one and two year old children (using the ratio for California as a whole) would be 72. The number of young children calculated to exceed the CDC blood lead guideline of 10 $\mu g/dL$ as a result of exposure to an average airborne lead concentration would be:

(4 to 11%) x 72 = 3 to 8 one and two year old children.

The number of children in the localized area that already exceed the 10 $\mu g/dL$ CDC guideline, and whose exposure to airborne lead would be further increased, can also be calculated. The total percent of 1 to 2 year old children calculated to have blood lead levels at 10 $\mu g/dL$ or above by sources other than lead is 10.9%. An additional exposure from an ambient air lead concentration of 0.20 $\mu g/m^3$ above the ambient average would be expected to increase these children's blood lead levels further above the 10 $\mu g/dL$ level and to increase the likelihood of a neurodevelopmental impact. As indicated in Section 3, increases in blood lead levels in children increase the severity of adverse impact. Using the localized population calculations described above, one can calculate the number of young children whose blood lead levels already may be at 10 $\mu g/dL$ and may be further above this level due to increases in airborne lead as follows:

10.9% x 72 = 8 one and two year old children.

The above calculations are made for children between one and two years of age, the age group at greatest risk. Although there is uncertainty about both the geometric mean and geometric standard deviation of blood lead in the children of California, the above risk calculations yield reasonable estimates for any given California subpopulation. Based on the sensitivity analysis we conducted, we found that increases in the percent of the population above 10 $\mu g/dL$ resulting from increases in air lead were insensitive to the geometric mean and geometric standard deviation used for blood leads at baseline levels of ambient air lead. For example, consider the NHANESIII data for the Western region, reported above. For the subgroup of children age 5 and below, these data suggest a geometric mean of 2.9 and a GSD of 2.3. To compare with the above calculations, we need to convert these statistics to describe the subgroup of 1 and 2 year olds. For this exercise, we assume that the ratio of the geometric mean and GSD of 1 and 2 year olds to that of those age 5 and below in the Western region is similar to

the ratio reported in the national data (Brody et al., 1994). For the national data, the geometric mean and GSD is 1.139 and 1.07 higher, respectively, for 1 and 2 year olds relative to those age 5 and below. Therefore, this predicts that for 1 and 2 year olds in the Western region, the geometric mean and the GSD will be 3.30 (2.9 x 1.139) and 2.46 (2.3 x 1.07), respectively. Using the methods detailed in Appendix B and the aggregate model, we can calculate the proportion of children that will be expected to have blood lead levels 10 μg/dL or higher at air lead concentrations of 0, 0.06 and 0.25 $\mu g/m^3$ using the Western data. At these three levels, the proportion of 1 and 2 year olds than are predicted to be at or above 10 μg/dL are 9.8%,, 10.9%, and 14.4%, respectively. Therefore, based on the NHANESIII data and our assumptions, moving air lead by approximately 0.20 $\mu g/m^3$ above background increases the proportion of children at or above 10 μg/dL in the Western region by approximately 4%. This is the same proportion that was estimated for the subgroup of 1 and 2 year olds using the national data from NHANESIII.

Since these predictive risk calculations incorporate statistical information from specific blood lead distribution, they are more precise than the standard methodology used to estimate reference concentrations (RfC), which incorporates order-of-magnitude uncertainty factors. These predictive risk calculations are also more explicit about the level of protection at a given air concentration.

The above calculations might be made more applicable to a specific localized situation if the exposure concentration of the population is carefully determined. The proportion of the population above a blood lead of 10 μg/dL for a range of air lead levels, e.g., as shown in Table 5-2, can be combined with specific ambient air concentrations measured or modeled at identified receptors to better characterize the expected impact on blood lead from the point source under study. In addition, estimates could be developed using modeled air concentrations at discrete receptors, the range of blood lead levels in that community, and the recommended aggregate blood lead/air lead slope factor of 4.2 μg/dL per $\mu g/m^3$. When one incorporates this information, the number of children with elevated blood lead levels above 10 μg/dL can be more precisely calculated for the localized scenario.

In summary, our estimates indicate that exposure to an airborne lead concentration of 0.06 $\mu g/m^3$ is associated with an increase of between 0.6 and 2.3 percent in the population of one and two year old children above the 10 μg/dL blood lead level of concern. This amounts to between 7,200 and 27,600 children in California. In addition, the approximately 131,000 one and two year old children that are predicted to be above 10 μg/dL even at zero air lead will be additionally impacted. Existing evidence indicates that the ambient air lead concentration of 0.06 $\mu g/m^3$ may be associated with a decrease of 392,000 IQ points or 0.08 IQ points per child below the age of 7. The 0.06 $\mu g/m^3$ air lead concentration is also associated with, relative to zero air lead, an additional 4,700 children that would be predicted to have IQ levels below 80. based on a elevated near source exposure of 0.20 $\mu g/m^3$ above the ambient average of 0.06 $\mu g/m^3$ for a small community of 2,000, our estimates indicate an additional 4 to 10% of the one and two year old children will move above the 10 μg/dL blood lead level. This amounts to between 3 to 8 children (of a total of 72 children in this age group), in addition to the 8 children predicted to be above the 10 μg/dL level even at zero air lead, that will be additionally impacted.

While such estimates are based upon the best available scientific data, they rely on models which contain many assumptions and uncertainties. Care should be taken to not ascribe a greater

precision to these risk estimates than is warranted by the underlying assumptions and uncertainties in the risk models.

5.4. Calculating the Relative Contribution of Air Lead to Blood Lead Compared to Other Media.

Since there are multiple sources of lead exposure (e.g., air, soil, household dust, paint chips, water, tableware), the relative impact of airborne lead is of interest. Air sources include the average background ambient air lead levels, localized airborne sources, and resuspension of contaminated dust and soil.

For one to two year old children, with blood lead levels above 10 μg/dL, we calculated the proportion associated with airborne lead relative to other lead sources. These calculations are based on the NHANESIII geometric mean blood lead level of 4.1 μg/dL, a GSD of 2.14, and the blood lead/air lead slope of 4.2 of the aggregate slope model. Specifically, we estimated what air lead concentrations would result in air lead contributing to 5, 10, 20, or 50% of children whose blood lead levels exceed the level of concern, 10 μg/dL, assuming that contributions from other sources remain the same. With the same set of formulas used in Section 5.3 (and detailed in Appendix B), we calculate a baseline blood lead level after subtracting out the average ambient air lead concentration; this is designated in the Tables as zero $\mu g/m^3$. While 10.9% of the children are still predicted to exceed the CDC guideline, 100% of these blood lead levels are assumed to be from background environmental sources of lead that are not likely to result from the current average ambient air lead concentration. Table 5-4 displays the potential relative impact of increased air lead levels that could be associated with incremental increases in air lead concentrations. The current ambient air lead concentration of 0.06 $\mu g/m^3$ is estimated to have a relative contribution of about 5% (0.6% out of 11.5%) of the children exceeding the CDC guideline of 10 μg/dL, based on the aggregate slope model. Using the estimated near source example in Section 5.3 and the aggregate model (which includes both direct and indirect exposures from air lead), and assuming an average exposure across this localized population, one can estimate that an airborne exposure of 0.20 $\mu g/m^3$ above the ambient average of 0.06 $\mu g/m^3$ is estimated to contribute to about 30% (4.6% out of 15.5%) of the increase in the number of children exceeding the 10 μg/dL CDC guideline in the localized area. The IEUBK model, used in conjunction with US EPA's supplemental equations applied to two empirical data sets (EH and AGG) to estimate possible air lead contributions to soil and housedust lead levels, predicts an even greater relative contribution from direct and indirect exposures to air lead. At a hypothetical ambient air concentration of 0.5 $\mu g/m^3$, and assuming an average exposure across this localized population, the aggregate slope model would predict ambient air lead levels to contribute to 48% of the increase (10.2% out of 21.1%) in the number of the children exceeding 10 μg/dL. Given that risks from lead exposure may never be zero, such information allows the risk manager to consider the potential relative increased risks from increasing airborne lead concentrations in the decision-making process.

The above comparisons show that while the current average ambient airborne lead concentration may be associated with exposure to many children, it may only contribute to a small percentage (approximately 5%) of one and two year old children exceeding 10 μg/dL blood lead.

Table 5-4. Percent of One and Two Year Old Children with Blood Lead Concentrations of 10 μg/dL or Greater Due to Airborne Lead Versus Other Media.[a]

Air Lead Concentration ($\mu g/m^3$)	Percent Attributed to Air: Aggregate Model	Percent Attributed to Air: IEUBK(EH) Model[c]	Percent Attributed to Air: IEUBK(AGG) Model[d]
0.00	0	0	0
0.06[b]	5	18	48
0.10	11	28	63
0.20	25	45	80
0.25	30	49	84
0.50	48	66	91
0.75	59	73	94
1.00	66	77	95

a Baseline mean of 4.1 and geometric standard deviation of 2.14 are based on data for one and two year old children from NHANES III, phase I (Brody et al., 1994). Calculation assumes that baseline non-air sources of lead exposure including paint, household dust, soil, pottery, and tap water are constant.

b Current mean ambient air lead level in California.

c IEUBK model with supplemental equations based on data from East Helena.

d IEUBK model with supplemental equations based on data from 40 communities. Note that the relatively high percent is due to the lower initial estimate of 2.5 percent of children at or above 10 μg/dL as described in Table 5-2.

Figure 5-2

The Distribution of Blood Lead Concentrations

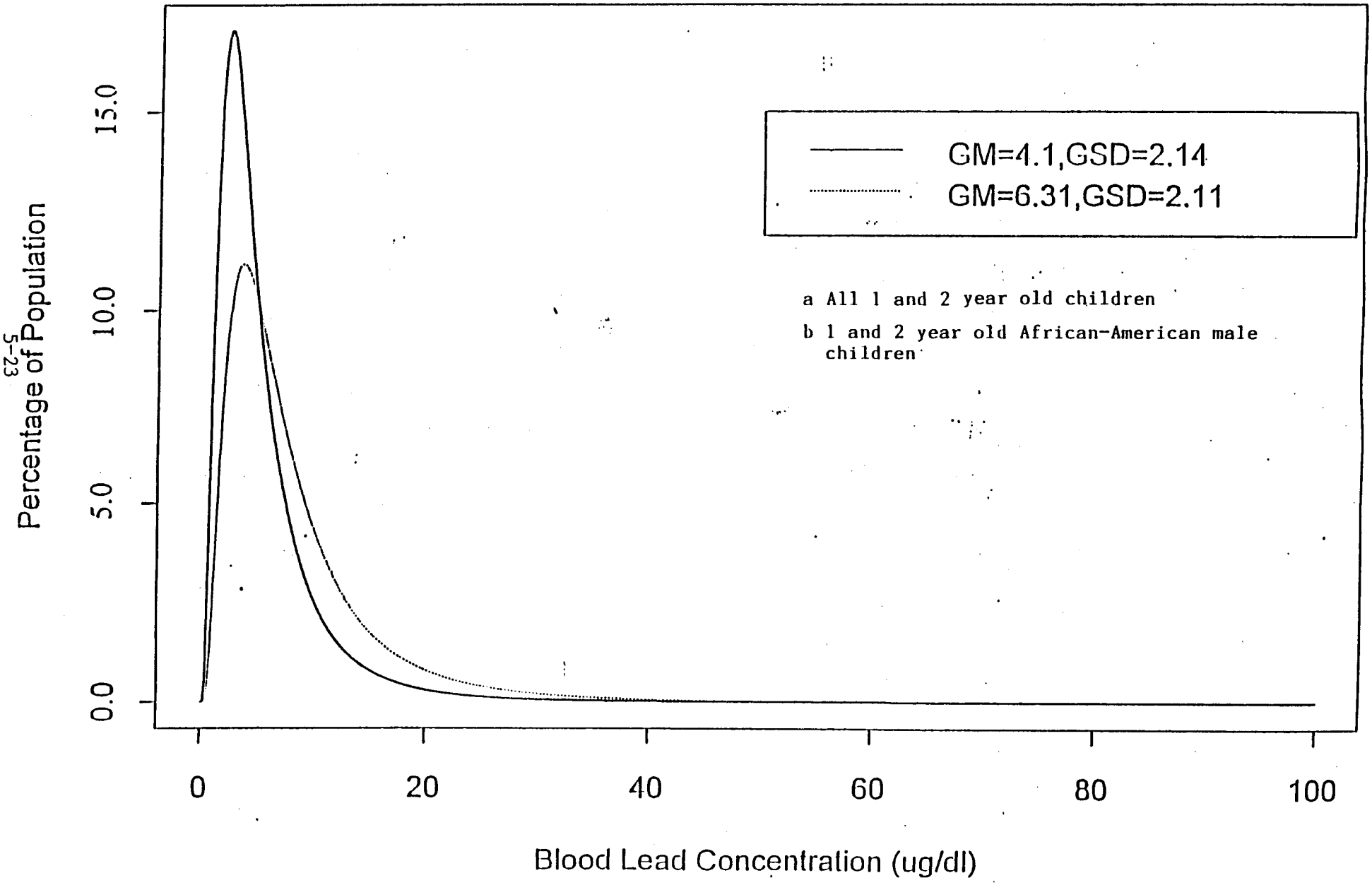
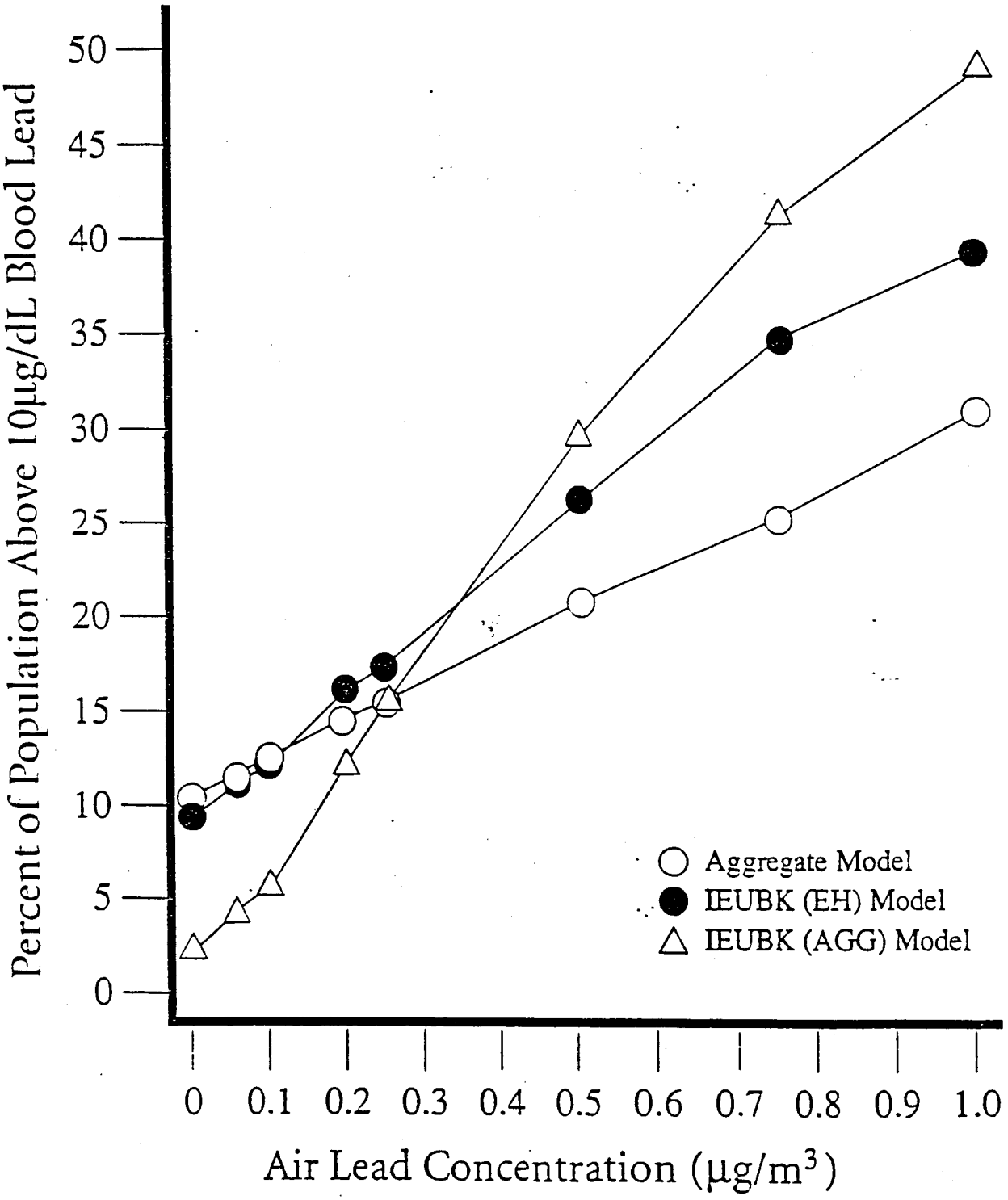


Figure 5-3.
Impact of Changes in Air Lead on the Percent of One and Two year Old Children Above 10µg/dL for Baseline Mean of 4.1 and GSD of 2.1



With regard to an estimated near source exposure situations, the relative contribution of airborne lead to the blood lead levels of young children may increase significantly over time with increases in airborne lead concentrations. However, uncertainties in these impacted population estimates will occur because actual soil lead concentrations from airborne lead are a function of particle deposition rates, time for deposition (past and/or future) and lead migration due to percolation or runoff. Lead in soil and indoor air contribute to house dust lead levels. Where soil lead levels are uncertain, house dust lead levels will also be uncertain. At relatively low air lead concentrations, children are more likely to be impacted by indirect exposures to air lead (e.g., ingestion of soil and house dust) than by direct inhalation exposures, therefore estimates of their blood lead levels reflect the uncertainties in the modeled or measured environmental sources of lead.

5.5. The Range of Neurodevelopmental Risks for Children Using the IEUBK Model

The U.S. EPA's Integrated Exposure Uptake Biokinetic (IEUBK) computer model was introduced in Section 4 as a tool for estimating probability distributions of blood lead levels in children in 1 year increments up to 7 years of age. An example of IEUBK computer model output is provided in Appendix C. As specified in Section 4.2, when the supplemental changes are incorporated that account for the full impact of air lead on the environment, the model can be used as an alternative to the aggregate model approach described in Sections 5.2 and 5.3 and summarized in Tables 5-2 through 5-4 and Figure 5-1. Specific instructions for use of this model have been developed by U.S. EPA (U.S. EPA, 1994).

There is close agreement between the predictions of the IEUBK model and the results reported in the NHANESIII study for children exposed to the average ambient air lead concentration of 0.06 $\mu g/m^3$. Using default parameters, the IEUBK model predicts mean blood lead levels for one and two year old children which are quite similar to those reported in NHANESIII (4.2 $\mu g/dL$ in the IEUBK (default) model versus 4.1 $\mu g/dL$ in NHANESIII). The IEUBK model also predicts that the percent of one and two year old children in California with blood lead levels in excess of 10 $\mu g/dL$ is essentially the same as that reported in NHANESIII (11.8% in the IEUBK (default) model versus 11.5% in NHANESIII). Using input parameters for soil lead and house dust lead calculated from EH and AGG empirical data and the US EPA supplementary equations (4-4 and 4-6), the IEUBK model predicts 11.2% and 4.8% of the population of one and two year old children would have blood lead levels greater than 10 $\mu g/dL$. Thus, the key factors identified and utilized in Sections 4 and 6 of this document are essentially the same as those predicted using the IEUBK model.

Output from the IEUBK model can be used to examine the impact of changes in air lead on the proportion of children who move above 10 $\mu g/dL$ (Table 5-2). These estimates can then be compared with those generated from the aggregate model. Also, to test the sensitivity of the IEUBK model, the supplemental equations relating air lead to soil and dust lead (Eqs. 4-4 to 4-6) were derived from the two data sets described in Section 4 (Table 4-2). The first data set, IEUBK(EH), is based on recent data obtained from East Helena, while the other, IEUBK(AGG), is based on the average generated from measurements from 40 communities. In our simulations using the IEUBK(EH) data set, default assumptions about the dietary intake and water concentrations were adjusted downward (4.78μg/day and 45 $\mu g/L$, respectively) for one to two year olds so that at an air lead concentration of 0.06 $\mu g/m^3$, approximately 11.5% of the population of one and two year old children (the percent indicated by the NHANESIII data)

would have blood lead levels greater than 10 μg/dL. This enhances the comparability of these results to those generated from the aggregate model. Next, the IEUBK(AGG) data were run using similar assumptions for water and dietary lead. Note that this data set generates a lower percent of the population with blood lead greater than 10 μg/dL at low levels of air lead because the AGG data set yields significantly less house dust lead levels at 0.06 $\mu g/m^3$ than does the EH data set (see Table 4-2). Using these data sets and equation 4-6, house dust lead levels of 113 ppm and 253 ppm are calculated for AGG and EH, respectively. However, the IEUBK (AGG) model output for blood lead levels increases at a greater rate in response to changes in air lead concentrations because the AGG data set is more sensitive to air lead concentrations, yielding higher soil and house dust lead levels than the EH data set (see Table 4-2), particularly at air lead concentrations above 0.35 $\mu g/m^3$ (see Figure 5-3). The differences in these two data sets and the consequences on calculating soil and housedust lead levels indicates the importance of collecting and measuring site- or facility- specific data when possible.

The impacts predicted from the two IEUBK data sets were generally similar to those predicted from the aggregate model for air lead concentrations up to about 0.50 $\mu g/m^3$. For example, as indicated in Table 5-2, the aggregate model predicts that at an ambient air lead concentration of 020 $\mu g/m^3$, 14.5 percent of the subpopulation of one and two year old children would be above 10 μg/dL versus 16.7 percent predicted from the IEUBK (EH) results and 12.7 percent from the IEUBK (AGG) results. At higher air lead concentrations, both IEUBK model runs (EH and AGG) predict higher percentages of the population above 10 μg/dL blood lead. At lower air lead concentrations, one of the IEUBK models (EH) generates a prediction of the percent of the subpopulation of one and two year old years above 10 μg/dL that is similar to that predicted by the aggregate model, while the other IEUBK model (AGG) predicts a lower percent relative to the aggregate model. Figure 5-3 displays the relationship between air lead concentrations and the percent of the population above 10 μg/dL using both data sets in the IEUBK model, and for comparison, the aggregate model.

The predictions by alternative models of the relative increase in the percent of one and two year old children with blood lead concentrations above 10 μg/dL, associated with airborne lead relative to other lead sources, are indicated in Table 5-2. Output from the IEUBK(EH) model runs suggest that the current average ambient airborne lead concentration may account for 18 percent of those one and two year old children with blood lead levels exceeding 10 μg/dL, versus the aggregate model prediction of 5 percent. The IEUBK(AGG) model runs suggest that average ambient air lead may account for 48% of those one and two year old children with blood lead levels exceeding 10 υg/dL, but this high number may be an artifact resulting from the low estimates of children affected by non-air lead sources predicted at baseline levels using these data. Table 5-2 indicates that at an air lead concentration of 0.50 $\mu g/m^3$, the IEUBK(EH) data predict that air lead could account for 64% of those children predicted to have blood lead levels greater than 10 μg/dL while the aggregate model estimates that air lead could account for 48% of those children predicted to have blood lead levels above 10 μg/dL.

The IEUBK model may be most useful in evaluating the relative impact on blood lead levels from changes in a single exposure medium. The evaluation could be conducted in the following manner. The appropriate parameters for each medium (e.g., air, water, soil, household dust, and paint) and the appropriate geometric standard deviation are first selected; site-specific data can be used to increase the accuracy of this model. Next, the input parameters to the model described in Section 4, or other algorithms or models should be incorporated to account for the

full future impact of air emissions through the indirect pathways (e.g., soil and housedust). Using the model, one then calculates the percent of children expected to have blood lead levels at or exceeding 10 μg/dL. The user can then estimate the potential reduction of the percent of children expected to have blood lead levels at or exceeding 10 μg/dL when the lead concentration in a particular medium is reduced. That is, the model allows the user to change the concentration of lead in a particular medium and to estimate how blood lead levels might change. For example, one could evaluate the impact on blood lead levels in children by separately or collectively reducing lead concentrations in air, reducing lead concentrations in tap water, removing lead from residential soil, or removing lead-based paint. Thus, the risk manager could consider the potential effectiveness of various mitigation strategies, either singly or collectively, by using the IEUBK model.

Appendix C provides more detail on the inputs and results that can be obtained using the IEUBK model. In the examples provided, the long term impact of ambient air lead concentrations of 0.06 $\mu g/m^3$ and 0.25 $\mu g/m^3$ are detailed. Also included are sample results comparing the relative efficacy of reductions in different sources of lead exposure. The impact on the distribution of children's blood lead concentrations (e.g., the geometric mean and the percent greater than 10 μg/dL) resulting from reductions in air lead from 0.25 $\mu g/m^3$ to 0.06 $\mu g/m^3$ is calculated. The reductions in blood lead due to changes in lead, soil and water are also determined using the model and presented for comparison. In addition, lead in paint, a large source of blood lead, can be varied in the IEUBK model, if the appropriate data are available.

Section 6. Estimation of Risks Related to an Increase in Blood Pressure

As indicated in Section 3, studies in both humans and experimental animals indicate that lead exposure is associated with a variety of effects on the cardiovascular system, including increases in blood pressure. Quantitative relationships between blood lead levels and blood pressure are available from several studies described in Section 3 including those of Harlan et al. (1985), Pirkle et al. (1985), and Schwartz et al. (1985). These analyses were based on evaluation of the NHANES II data, which provide information on blood pressure as well as on a variety of potentially confounding factors for a representative sample of the U.S. population. The results using NHANES II are supported by similar findings in other cohorts. Several reviews of these studies (U.S. EPA, 1990a; NRC, 1993; Schwartz, 1995; Hertz-Picciotto and Croft, 1993) have indicated that: (1) there is reasonable agreement about the size of the effect of blood lead on blood pressure; (2) the association exists across the range of blood leads with no evidence of a threshold; and (3) a causal association appears likely. As stated by the National Research Council (1993): "Overall, a considerable majority [of the studies] reported significant associations. Combined with the strong animal model, mechanistic results, and the moderate concordance of effect size, this suggests overwhelming evidence for the causality of the association." Based on these reviews and our own assessment of the evidence, it is reasonable to quantitatively estimate the effects of lead on blood pressure.

Our risk assessment relies on data and results drawn from NHANES II, which are considered to be representative of the U.S. population. Results of analysis of the NHANES II data are used to estimate the effect of a change in air lead on the change in the diastolic blood pressure $\geq$ 90 mm Hg, a level often defined as "hypertension" in adults. In addition, we also provide estimates of the potential effects of changes in air lead concentrations on more serious health outcomes in adult males, including myocardial infarctions (heart attacks) and death.

To estimate the change in blood pressure related to air lead we used dose-response information provided by Schwartz et al. (1985) and Schwartz (1986a, 1986b) with additional documentation from Pirkle et al. (1985). Part of the methodology is detailed in Brennan et al. (1986) in a report for the U.S. EPA (reviewed by a subcommittee of the Clean Air Science Advisory Committee). First, we estimate the effects of a change in blood lead on the probability of hypertension. Next, we estimate the effects of changes in blood lead on diastolic blood pressure and then its effects on more severe cardiovascular outcomes. The original estimates (Schwartz et al., 1995) were for the subset of the population of adult males age 40 to 59. There is also evidence in the above studies indicating that it would be reasonable to apply similar estimates to both males and females, age 20 to 70. However, for this risk assessment, we apply the risks (i.e., the probability) of inducing hypertension to the subgroup of males and females between age 40 and 59 since the evidence for the association is strongest for this subgroup. The effects of changes in air lead that are mediated by changes in blood lead, on hypertension (i.e., diastolic blood pressure $\geq$ 90 mm Hg) are based on logistic regression results from NHANES II.

Our risk assessment quantifies the potential increase in blood pressure that may be associated with an ambient average airborne lead concentration change of 0.06 $\mu g/m^3$ (evaluated as a change from 0 to 0.06 $\mu g/m^3$). Using our estimate of the blood lead/air lead slope for adults of 1.8 (see Section 4), an increase in air lead of 0.06 $\mu g/m^3$ would correspond to a 0.108 $\mu g/dL$ change (0.06 x 1.8) in mean blood lead. Using the regression results of Schwartz et al. (1985), the probability of diastolic blood pressure increasing to or exceeding 90 mm Hg and inducing

hypertension, can be predicted as a function of the natural log of blood lead and several covariates including body mass, albumin, hemoglobin, vitamin C, dietary potassium, total carbohydrates, and recreational exercise. Following Brennan et al. (1986), the adjusted effect of blood lead on hypertension, holding the other covariates constant, can be estimated by substituting the mean values of these covariates from the NHANES II sample into the estimated regression equation. These covariates then become part of the constant term (2.74) indicated in equation (6-1). This equation indicates the association between blood lead and the probability of inducing hypertension:

$$\text{change in } H = (1 + \exp -(-2.74 + b\ (\ln PbB_1)))^{-1} - (1 + \exp -(-2.74 + b\ (\ln PbB_2)))^{-1} \quad \text{(Eq. 6-1)}$$

where:

H = the probability of hypertension (change in the diastolic blood pressure ≥ 90 mm Hg)
PbB_1 = blood lead level (μg/dL) associated with 0.06 $\mu g/m^3$
PbB_2 = blood lead level (μg/dL) associated with 0 $\mu g/m^3$
b = regression estimate relating blood lead to hypertension (change in the diastolic blood pressure ≥ 90 mm Hg)

In this model, b = 0.79, with standard error of 0.25. Therefore, the 95% confidence level is 0.31 to 1.28.

Since estimates of current blood lead levels in adults in California are not available, we used data from NHANES III for adults (age 20 to 74) which identified a mean of 3.0 μg/dL (Pirkle et al., 1994). Using Equation (6-1), a 0.06 $\mu g/m^3$ increase in air lead exposure (which corresponds to a 0.108 μg/dL change in mean blood lead) would be associated with a predicted increase in the probability of hypertension of 3.26×10^{-3}, with a 95 percent confidence interval of 7.72×10^{-4} to 7.68×10^{-3}. Thus, for an estimated population of 7.92 million adults between the ages of 40 and 59 (California Department of Finance 1996 projections), current ambient air lead levels may be associated with an incremental 26,000 cases of hypertension (change in the diastolic blood pressure ≥ 90 mm Hg), with a confidence interval of 6,100 to 60,800 cases. Our estimates are not suggesting 26,000 new incident cases occur every year but that at any point in time, an airborne lead concentration of 0.06 $\mu g/m^3$ would be associated with 26,000 cases of hypertension within our defined cohort. Although the models are non-linear, sensitivity analysis indicated that results are robust to assumptions about either the initial blood lead level or the absolute change in air lead. Therefore, linear extrapolations of these results should still yield reasonable estimates of risk.

Next, we determined the impact of current ambient air lead on the more serious cardiovascular outcomes. The risks were calculated for adult males age 40 to 59, since currently available research is most extensive for this subgroup. Since the risks of several serious cardiovascular outcomes were presented as functions of diastolic blood pressure (Pooling Project, 1978; Shurtleff, 1974; McGee and Gordon, 1976), the empirical association between blood lead and diastolic blood pressure is a critical link between blood lead and cardiovascular outcomes. Available research also indicates that systolic blood pressure is a good predictor of subsequent changes in serious cardiovascular outcomes and could be used as well. As discussed in Section 3, there appears to be a fairly consistent effect of blood lead on diastolic blood pressure. Based on

Pirkle et al. (1985), a reanalysis of the NHANES II data by Schwartz (1986a,b) and a review provided by U.S. EPA (1989b), we used an estimate within the reported range of quantitative associations between blood lead and diastolic blood pressure. Results from the NHANES II data were used since it provides estimates for a representative sample of adult males in the U.S. Results from populations in other countries are less generalizable to the U.S. due to differences in diet, exercise, and other lifestyle factors. Likewise, results from occupationally exposed workers are less applicable to the general population. The original regression coefficient for log blood lead in relation to diastolic blood pressure from Pirkle et al. (1985) was 3.95. After adjustment for the geographic sites sampled in NHANES II, the coefficient decreased to 2.74, which is the value used in our analysis. Since this coefficient was statistically significant at $p < 0.05$, a standard error of 1.30 was assumed. The following relationship is generated:

$$\text{change in DBP} = 2.74 (\ln PbB_1 - \ln PbB_2) \qquad \text{(Eq. 6-2)}$$

where:

DBP = diastolic blood pressure (mm Hg)

PbB_1 = blood lead level (μg/dL) associated with 0.06 $\mu g/m^3$

PbB_2 = blood lead level (μg/dL) associated with 0 $\mu g/m^3$

This equation suggests that a doubling of blood lead from 5 to 10 μg/dL would result in a 1.9 mm Hg increase in diastolic blood pressure. To calculate the expected change in blood lead, we assumed a 0.06 $\mu g/m^3$ change (from 0 to 0.06 $\mu g/m^3$) in ambient air lead, a blood lead to air lead slope of 1.8, and a mean blood lead for adult males of 4.4 μg/dL based on NHANES III (Brody et al., 1994). The latter was derived by weighting the means of the three race/ethnicity categories for adult males (age 20 to 69). Means for the sample of male adults age 40 to 59 were not reported. For the assumed change in blood lead of 0.06 x 1.8 =0.108 μg/dL, Equation (6-2) predicts that the population average change in diastolic blood pressure would be 0.07 mm Hg since:

$$0.068 = 2.74 \{\ln 4.4 - \ln (4.4 - 0.108)\}.$$

Since this is the mean change, some individuals in the cohort will have greater increases in diastolic blood pressure in response to increases in blood lead.

With the expected change in diastolic blood pressure determined, the potential changes in several more serious cardiovascular outcomes can be calculated. Specifically, several large prospective cohort studies have been conducted to examine the association between several risk factors, including systolic and diastolic blood pressure, on subsequent heart disease (Pooling Project, 1978; Shurtleff, 1974; McGee and Gordon, 1976). The Pooling Project (1978) related the incidence of various cardiovascular disease outcomes to risk factors such as smoking and blood pressure. One of several endpoints considered, coronary heart disease events (CHD) are defined in the Pooling Project as fatal and non-fatal myocardial infarctions (heart attacks) and sudden death from coronary heart disease (defined as death within 3 hours of symptoms). Besides blood pressure, logistic regression was used to assess the influence of several factors such as age, serum cholesterol, smoking, and weight on CHD. The authors of the Pooling Project found consistent associations between blood pressure and several adverse cardiovascular outcomes. They concluded that a causal relationship was apparent and that the results of the Project could be

generalized to white, middle-age, American men. We use diastolic blood pressure as the predictor in our risk assessment since the Pooling Project includes more covariates in their predictive model for CHD when using diastolic versus systolic blood pressure. However, the quantitative results appear to be quite similar using either measure of blood pressure. Using the sample means and the estimated logistic regression coefficients of the covariates, which become part of the constant term in Eq. (6-3), the adjusted relationship between the change in blood pressure and the change in the probability of CHD during the succeeding 10 years can be expressed as:

$$\text{change in Pr(CHD)} = (1+ \exp -(-5.0 + b\ (DBP_1)))^{-1} - (1 + \exp -(-5.0 + b\ (DBP_2)))^{-1} \quad \text{(Eq. 6-3)}$$

where:

Pr(CHD) = the 10-year probability of fatal and non-fatal myocardial infarctions and sudden death from coronary heart disease

b = estimated regression coefficient relating diastolic blood pressure to CHD

DBP_1 = diastolic blood pressure level associated with current air lead

DBP_2 = diastolic blood pressure level associated with zero air lead

The regression coefficient relating diastolic blood pressure to CHD is 0.03 with an estimated standard error of 0.004. Therefore, the 95% confidence interval for the coefficient ranges from 0.022 to 0.038.

The mean diastolic blood pressure for white males in California in 1979 was 76 mm Hg (California Department of Health Services, 1982). Assuming a lead-induced change in diastolic blood pressure of 0.068 mm Hg as calculated above, the change in the probability of a myocardial infarction in 10 years is 1.22×10^{-4} or an annual change in risk of 1.22×10^{-5}. The confidence interval for the annual change in risk is 5.14×10^{-6} to 2.56×10^{-5}. Since there are distributions reflecting uncertainties in both the blood lead - blood pressure association and the blood pressure - CHD association, we used commercially available software to propagate the uncertainties in our risk calculations. The Excel macro "@risk" (Palisade Corporation, Newfield, NY) is used to generate a new distribution based on these two specified distributions. This macro uses Monte Carlo-like simulations to generate a new distribution. We specified that 5,000 runs be made, although convergence was reached after 2,000. Based on this model, the overall 95% confidence interval for the effects on CHD relating to the change in air lead of 0.06 $\mu g/m^3$ was 2.094×10^{-6} to 2.755×10^{-5}. Therefore, for the subgroup of 3.96 million adult males age 40 to 59 (California Department of Finance 1996 projections), the model indicates that a 0.06 $\mu g/m^3$ change in ambient lead (from 0 to 0.06 $\mu g/m^3$) is associated with an estimated 48 (95% confidence interval = 8 to 109) additional nonfatal heart attacks per year for the next 10 years. As in the estimates for risks for hypertension (change in the diastolic blood pressure $\geq$ 90 mm Hg), these results were robust to assumptions about either the population mean blood lead or the change in air lead. A linear extrapolation of our results for other changes in air or blood lead appears to be reasonable.

Finally, the impact of changes in ambient air lead concentrations on mortality was determined. The Framingham study (Shurtleff, 1974; McGee and Gordon, 1976) can be used to estimate the risks to mortality over a 12-year period due to the change in diastolic blood pressure. Controlling for serum cholesterol levels and smoking, the association can be estimated by:

$$\text{change in Pr(MORT)} = (1 + \exp -(-5.32 + b(DBP_1)))^{-1} - (1 + \exp -(-5.32 + b(DBP_2)))^{-1} \quad \text{(Eq. 6-4)}$$

where:

PR(MORT) = the 12 years probability of death.

The estimated regression coefficient relating diastolic blood pressure to mortality is 0.035 with a standard error of 0.007. Therefore, the 95 percent confidence interval for the coefficient is 0.021 to 0.049.

The change in diastolic blood pressure associated with a 0.06 $\mu g/m^3$ change in ambient lead (0.068 mmHg) results in a change in the 12 years probability of all-cause mortality of 1.50×10^{-4}. This is equivalent to a 1.25×10^{-5} risk per year, with a confidence interval of 2.82×10^{-6} to 4.72×10^{-5}. To incorporate the uncertainties in both the blood lead to blood pressure association and the blood pressure to mortality association, the Excel macro "@risk" was used. Based on this model, the overall 95% confidence interval for the effects on mortality relating to the change in air lead of 0.06 $\mu g/m^3$ was 1.575×10^{-6} to 3.741×10^{-5}. For the subgroup of 3.96 million males in California age 40 to 59, this results in an estimated additional 49 deaths per year for the next 12 years, with a confidence interval of 6 to 145. These estimates were relatively insensitive to the initial population mean blood lead level, and a linear extrapolation of the results for other changes in blood lead appears to be reasonable.

Similar estimates of the effect of blood lead on blood pressure may be made for women, although fewer studies have investigated this relationship in women. Overall, the studies that have examined this association have reported a statistically significant, but smaller magnitude of effect, in women. For example, Schwartz (1991) used NHANES II data to examine the relationship between blood lead and blood pressure in men and women aged 20 and older. Blood lead was a statistically significant predictor of diastolic blood pressure and of left ventricular hypertrophy in both males and females across the entire age range examined. The magnitude of the association for diastolic blood pressure was about half that reported for men. In contrast, in their meta-analysis of 23 studies, including previously published analyses of NHANES II data, Staessen et al. (1994), found that the blood lead-blood pressure association was generally similar in magnitude for both men and women.

In addition, for women, as in men, diastolic blood pressure has been associated with more serious cardiovascular outcomes. MacMahon et al. (1990) analyzed the combined results of nine prospective observational studies (8 Caucasian populations and 1 largely Asian population) to assess the effects of diastolic blood pressure on the incidence of stroke and coronary heart disease. Within the range of diastolic blood pressure examined (approximately 70-110 mm Hg), there was no evidence of any threshold below which lower levels of blood pressure were not associated with lower relative risks of stroke or coronary heart disease. The combined results showed no significant differences between the sizes of effects in men and women. Significant associations have been reported between systolic and diastolic hypertension and congestive heart failure (Levy et al., 1996), coronary artery disease (including myocardial infarction, and sudden death), stroke and peripheral artery disease (Kannel, 1996) in both women and men.

Based on the limited data available for women, we therefore have assumed that the effects of blood lead on diastolic blood pressure for women are approximately half of that for men. This may underestimate the risk, because there is some evidence that the risks for men and women are comparable. Therefore, for the subgroup of 3.96 million adult females age 40 to 59, the models predicts that a 0.06 $\mu g/m^3$ change in ambient lead (from 0 to 0.06 $\mu g/m^3$) is associated with an estimated 48 x 0.5 or 24 (95% confidence interval = 4 to 55) additional nonfatal heart attacks per year and an estimated additional 49 x 0.5 or 25 deaths per year, with a confidence interval of 3 to 73.

The results of NHANES II also indicate that African Americans have higher mean blood pressures than Caucasians and that this difference is pronounced for females (Sorel et al., 1991). Thus, African Americans, who are more likely to have higher baseline blood pressures, may represent a subgroup that is particularly susceptible to the cardiovascular effects of blood lead.

Thus, in summary, at the current ambient average lead concentration of 0.06 $\mu g/m^3$, airborne lead may be associated with an estimated 26,000 additional cases of hypertension (change in the diastolic blood pressure $\geq$ 90 mm Hg), and an estimated 72 non-fatal heart attacks and 74 deaths per year for the subgroup of adults aged 40 to 59. The summary of our estimates are provided in Table 6.1.

Such calculations should not be interpreted as precise measurements of mortality or morbidity associated with exposure to lead. For any individual, a change in blood pressure of 0.068 mm Hg will likely not be clinically measurable. Although based upon the best available scientific data, the calculations are derived from models which contain many assumptions and uncertainties.For the purposes of characterization of the risks associated with exposure to lead, such calculations should be viewed only as theoretical estimates. These estimates are useful in providing a perspective and appreciation for the potential magnitude and severity of individual health threats and population impacts. Since such estimates are not exact predictions of risk, care should be taken to not ascribe a greater precision to these risk estimates than is warranted by the underlying assumptions and uncertainties in the risk models. These predictions are based on the assumption of a "no threshold" model that fit the observable range of data used in our analyses for the effects of lead on blood pressure. While thresholds for non-carcinogenic responses are biologically plausible, one has not been identified for lead because it is likely to be below the lowest observed blood lead levels.

Table 6.1 Estimates of Cardiovascular Events Associated with 0.06 μg/m^3 Ambient Air Lead.

Effect	Low	Central	High
Hypertension	6,100	26,000	60,800
Fatal and Non-fatal Heart Attack	12	72	164
Mortality	9	74	218

Note: Estimates are associated with the 7.92 million males and females between ages 40 and 59.

Section 7. Quantitative Cancer Risk Analysis

7.1. Carcinogenic Risks

This section provides a quantitative cancer risk assessment based on the best available animal data set for risk assessment, male rat kidney tumors. The U.S. EPA Air Quality Criteria for Lead document (U.S. EPA, 1986) includes data on lead carcinogenicity but no quantitative risk assessment for cancer. A more recent document (U.S. EPA, 1989a) further examined lead's carcinogenicity but it also did not contain a formal quantitative risk assessment, although a multistage model was fit to animal data using ppm lead in the feed as the dose. OEHHA relied extensively on these U.S. EPA documents in the preparation of this report. However, a quantitative estimate of carcinogenic risk from inhalation exposure is not available from U.S. EPA. For this reason OEHHA developed one following similar methodology. It is also important to note that U.S. EPA has not developed a quantitative estimate of carcinogenic risk from oral exposure either; the reasons cited for this are the uncertainties primarily involving absorption and pharmacokinetics.

A large number of animal studies have shown kidney tumors following oral exposure to lead compounds (Tables 3-5 and 7-1), but there are no studies of carcinogenicity due to lead inhalation. The best tumor dose-response data for use in quantitative cancer risk assessment are those of Azar et al. (1973). Most studies of lead carcinogenicity have used one dose of lead; a few have used 2 doses (Table 3-5). However, in the Azar et al. study, lead as lead acetate was given to groups of male and female rats in the feed at concentrations of 0, 10, 50, 100, 500, 1000, and 2000 ppm (nominal concentrations) for 2 years. Kidney tumors, mainly adenomas, were seen in a dose-dependent relationship in the 3 highest dose groups in males (Table 7-1). Tumors were also seen in the 2000 ppm dose group in females (7/20 or 35%). Cancer risk at ambient levels was estimated by extrapolating at least 5 orders of magnitude from these data by means of the best fitting linearized multistage model. This model provides a health-protective risk estimate due to its property of being linear at low doses (California Department of Health Services, 1985).

7.2. Thresholds

A threshold dose of a toxicant is one below which a specified outcome does not occur in the exposed individual. Threshold models for carcinogenesis have been suggested for some chemicals based on their mechanism of action (for example, saturation of detoxification enzymes, the existence of DNA repair mechanisms, lack of genotoxicity, or recurrent toxicity). In the absence of evidence for such a mechanism for lead, a health-protective approach is to assume that no threshold exists.

An "epigenetic" mechanism that could in theory embody threshold doses has been invoked to explain the carcinogenic action of substances that do not directly produce genetic damage in short-term tests. Lead may induce cell death, cell proliferation, and repair, which may subsequently result in tumor formation. In addition, the interference by lead with the fidelity of DNA replication (Sirover and Loeb, 1976) occurs at lead concentrations (4 millimolar or 828

mg/liter) which are 4 orders of magnitude higher than blood lead levels that result in neurological impairment.

The experimental results of Azar et al. (1973), as summarized in Table 7-1, could be interpreted as suggesting a threshold for carcinogenic effects. An increase in kidney tumors was not observed at doses at and below 100 ppm (10.88 mg/kg-day). Whether or not this is indeed a threshold effect level for cancer cannot be answered by the experimental data alone. We cannot be certain if there is a true threshold level or whether the tumorigenic response rate was below the detection limit of the statistical power of the study. The ability to detect a small increase in the incidence of tumors in such a laboratory study is limited by its statistical power.

If lead were to be a threshold carcinogen, then theoretically there would be a dose below which the adverse effect of cancer would not be expected to occur. In such a case, the experimental No Observed Adverse Effect Level (NOAEL) could be divided by appropriate uncertainty and modifying factors (for example 10 to extrapolate from animals to humans and 10 to account for differing sensitivity in the human population) to obtain a threshold level for lead-induced carcinogenesis in humans. Doses below this level would not be expected to cause cancer in humans but could cause noncancer effects as discussed in the previous sections. Although it is plausible that cytotoxicity or other non-genotoxic ("threshold") mechanisms may play a role in the carcinogenic response in laboratory animals, the relationship between cytotoxicity, possible genotoxic action, and the observation of a carcinogenic effect is complex, and a scientific consensus which explains the observations has yet to be achieved.

For lead there is some evidence of genotoxicity because of electrostatic binding to DNA and mutagenicity in mammalian cells in culture (Section 3). The experimental observations that lead may cause mutation and can interfere with nucleic acid synthesis provide limited evidence that lead may act as an initiator of tumorigenesis (Section 3). Therefore, under current science policy, lead-induced carcinogenesis is presumed to be a nonthreshold phenomenon.

7.3. Rat Kidney Tumors and the Multistage Model

The data used to calculate cancer risk from the rat kidney tumors (Azar et al., 1973) are given in Table 7-1. Doses were first converted to human equivalent doses (HED) (Anderson et al., 1983). Using the computer software GLOBAL86 (Howe et al., 1986), a linearized multistage model was fit to the male kidney tumor dose-response data. The multistage model may be expressed as:

$$P(d) = 1 - \exp(-(q_0 + q_1 d + q_2 d^2 + \ldots + q_k d^k)) \qquad \text{(Eq. 7- 1)}$$

where P(d) is the lifetime probability of cancer from a given dose d of carcinogen, q_0 is a constant that accounts for the background incidence of cancer occurring in the absence of carcinogen, and q_1, q_2, ... q_k are coefficients that allow the data to be expressed to various powers of the dose of carcinogen to obtain the best fit of the model to the data. The male rat kidney tumor data yielded a maximum likelihood estimate (MLE) for q_1 (the linear or slope term, which relates the probability of cancer to the dose of carcinogen administered in the equation for the multistage model) of 0 $(mg/kg/day)^{-1}$ and an MLE for q_2 of 2.5×10^{-3} $(mg/kg/day)^{-2}$. Thus, the

MLE for the dose-response data is curvilinear. In the present case, higher order terms, up to 3, i.e., coefficients multiplied by dose raised to integral powers up to 3, were obtained. For the rat kidney tumor data, the equation therefore reduces to:

$$P(d) = 1 - \exp(-(q_0 + q_1 d + q_2 d^2 + q_3 d^3)) \qquad \text{(Eq. 7-2)}$$

An Upper 95% Confidence Limit (UCL) on q_1 (also known as q_1^* and as the cancer potency) of 8.5×10^{-3} $(mg/kg/day)^{-1}$ was obtained from the data. Such UCLs are calculated because they are health protective, i.e., there is only a 5% chance that the true value of q_1 is greater than the UCL, and because they are more stable statistically. Use of the upper bound estimate means that the "true risk" is not expected to exceed the risk estimate derived through use of this model, and is likely to be less than that predicted.

Available data in people indicate that approximately 50% of inhaled lead is absorbed compared to approximately 10% of ingested lead (summarized by Owen, 1990). For ingested lead, a wide range of values has been reported for absorption (ICRP, 1975). The value for absorption depends on the nutritional status of the individual and decreases with age, from approximately 40% in children to near 10% in adults. The ATSDR (1988) estimated 50% absorption in children and 15% in adults. The absorption in adults can increase during pregnancy and in fasting states. If the percentage of lead absorbed by inhalation is similar for rats and humans and if we use the standard assumption that an average adult human has a body weight of 70 kg and an average air intake of 20 m^3 per day, an oral intake of 1 mg/kg/day lead is equivalent to an inhalation exposure of 3,500 $\mu g/m^3$ for 24 hr. Using the latter units, the 95% UCL for q_1 equals 2.4×10^{-6} $(\mu g/m^3)^{-1}$, which assumes equivalent absorption by the 2 routes. If we assume that there is approximately 5 times higher absorption by the respiratory tract compared to the gastrointestinal tract (Owen, 1990), the inhalation risk can be multiplied by 5 and the corrected inhalation unit risk, still based on applied dose, is 1.2×10^{-5} $(\mu g/m^3)^{-1}$. For an ambient air concentration of 0.06 $\mu g/m^3$ the individual cancer risk is:

$$0.06\ \mu g/m^3 \times 1.2 \times 10^{-5}\ (\mu g/m^3)^{-1} = 7.2 \times 10^{-7} \qquad \text{(Eq. 7-3)}$$

Health and Safety Code Section 39650 *et seq.* requires that a range of risks be estimated. Therefore the study in Table 3-5 which showed the greatest sensitivity to lead's carcinogenicity, that of Koller et al. (1985), was selected to derive an inhalation unit risk. In that study, 13 out of 16 male rats drinking water containing 2600 ppm lead acetate developed renal tumors, compared to 0 of 10 in controls. Adult male Sprague-Dawley rats weigh 0.5 kg (U.S. EPA, 1988). Their daily intake of drinking water (U.S. EPA, 1988) is:

$C = 0.1\ (\text{body wt}^{0.7377}) = 0.1\ (0.5^{0.7377}) = 0.06$ liters = 0.06 kg
0.06 liters = 0.06 kg water x 2600 ppm = 156 mg lead as lead acetate
156 mg/day / 0.5 kg = 312 mg/kg-day

To scale the dose from rat to man:

$$312 \text{ mg/kg-day} / (70 \text{ kg}/ 0.5 \text{ kg})^{1/3} = 60.1 \text{ mg/kg-day (HED)}$$

Using the resulting human equivalent dose (HED) and the above tumor incidences in the GLOBAL86 program, an MLE for q_1 of 0.0279 $(\text{mg/kg-day})^{-1}$ and a 95% UCL, q_1^*, of 0.0455 $(\text{mg/kg-day})^{-1}$ are obtained. The latter potency is divided by 3500 to obtain a preliminary inhalation unit risk of 1.3×10^{-5} $(\mu g/m^3)^{-1}$, which, as was done above, must be corrected for the 5-fold greater absorption by inhalation compared to ingestion in humans (Owen 1990) to yield a final inhalation unit risk of 6.5×10^{-5} $(\mu g/m^3)^{-1}$.

Since cancer risk increases with age, this risk factor might be further adjusted by applying a correction factor (Anderson et al., 1983) for the less than lifetime length of the study, i.e. 76 weeks, versus the normal rat lifetime of at least 104 weeks. Since cancer incidence is thought to increase by at least the third power of age, the resulting factor is $(104/76)^3 = 2.53$. However, because the tumor incidence was already very high (over 81%) and would result in an incidence greater than 1, the use of this factor was not considered appropriate.

Thus the 95% Upper Confidence Limit obtained for the range of inhalation unit risks is:

$$1.2 \times 10^{-5} (\mu g/m^3)^{-1} \text{ to } 6.5 \times 10^{-5} (\mu g/m^3)^{-1}$$

Analysis of studies of lead subacetate in rats by Kasprzak et al. (1985) and by van Esch et al. (1962) yielded inhalation unit risks within this range. The data of Azar et al. (1973) are considered to provide the best data set for quantitative cancer risk assessment because of their extensive dose-response data (Table 7-1) which gives an indication of the shape of the dose-response curve. If only the control group and the highest dose group from the Azar et al. study are used with the GLOBAL86 model, a final inhalation unit risk of 1.3×10^{-4} $(\mu g/m^3)^{-1}$ is obtained, a value higher than any obtained above and 10 times that obtained using the entire dose-response curve. This indicates how the unit risk can be influenced by data other than the highest dose and the problem with using studies with a single dose (and small numbers of animals).

7.4. Estimate of Cancer Incidence in California due to Lead

Air monitoring of lead has yielded an estimated statewide mean population-weighted concentration of 0.06 $\mu g/m^3$ (range = 0.04-0.07). With an estimated population in California of 34×10^6 and an upper 95% confidence limit on individual risk of 7.2×10^{-7} (from a lead concentration of 0.06 $\mu g/m^3$) derived using the multistage model, the upper 95% confidence limit estimate of excess cancers over a lifetime due to exposure to ambient airborne lead would be:

$$34 \times 10^6 \times 7.2 \times 10^{-7} = \text{an upper bound of 24 excess cancers} \qquad \text{(Eq. 7-4)}$$

or an upper bound of 0.7 cases per million people exposed to this level of lead for a lifetime. This predicted number would occur in a background of approximately 6.9 to 8.1 million total cancer cases in a California population of approximately 34 million people, based on cancer incidence for Los Angeles County in 1972-1977 and on estimated current cancer incidence in California, respectively (World Health Organization 1982, Silverberg and Lubera 1987, Boring et al. 1991). The cancer risk estimate is based on extrapolating downward at least 5 orders of magnitude from the doses used in the animal bioassay to expected human doses. While a portion of the population around industrial sources could be exposed to concentrations of lead greater than 0.06 $\mu g/m^3$, others will be exposed to lower concentrations. However, near source exposures have not been considered in these estimates.

The U.S. EPA has classified lead and lead compounds as probable carcinogens, but it has declined to conduct a formal quantitative risk assessment for lead and has cited differences in absorption of different lead compounds, differences in absorption with age, and other uncertainties in pharmacokinetics (U.S. EPA, 1989a). All risk assessments involve uncertainty and the uncertainty in assessing the carcinogenic effects of lead is greater than for some other chemicals. One shortcoming is that many details of the animal cancer study used (Azar et al., 1973) are not available in the paper which appeared in the proceedings of a meeting. The paper mentions that the tumors were mainly adenomas, which are benign. Fortunately the tumor incidence data are consistent with other papers on lead carcinogenicity (Table 3-5) where renal tumors labeled by various authors as adenomas, adenocarcinomas, carcinomas, epithelial tumors, and renal neoplasms have been reported. In addition, the National Toxicology Program is independently reevaluating the pathology slides from the experiment to see if its assessment of tumors concurs with the observations of the original authors. A second uncertainty is introduced because lead acetate, lead subacetate, and lead phosphate were used to induce cancer in animals, but humans are exposed mainly to lead oxide and metallic lead. The cancer risk assessment only considers the risk due to direct inhalation of airborne lead and does not attempt to estimate the exposure from sources on which airborne lead has been deposited including soil, water, and produce. Such a multipathway cancer risk assessment is considered practical for individual sources, but not for statewide exposure. The Health and Safety Code Section 39650 states "(t)hat, while absolute and undisputed scientific evidence may not be available to determine the exact nature and extent of risk from toxic air contaminants, it is necessary to take action to protect public health." Thus OEHHA staff made the above calculations. The inhalation unit cancer risk for lead (1.2×10^{-5} - 6.5×10^{-5} $(\mu g/m^3)^{-1}$) is lower than that estimated by OEHHA for any other toxic metal (range: 2.6×10^{-4} $(\mu g/m^3)^{-1}$ for nickel to 1.4×10^{-1} $(\mu g/m^3)^{-1}$ for chromium VI). The cancer risk from the average concentration of environmental airborne lead is relatively small. There may still be a need for an inhalation study of lead in animals, in order to (1) complete the toxicological database, (2) make route-to-route extrapolation unnecessary, and (3) determine if lead may be like at least 2 other toxic metals, cadmium and chromium VI, which exhibit greater carcinogenic potency by the inhalation route compared to the oral route. Since a short-term inhalation study in rats using lead at concentrations of 1, 3, and 10 mg/m^3 for 3 weeks (Prigge and Greve, 1977) and a year-long inhalation study in rats and rhesus monkeys using lead at 21.5 $\mu g/m^3$ (Griffin et al., 1975b) have already investigated endpoints other than cancer, an inhalation study to investigate lead's carcinogenicity appears feasible.

Other sources of uncertainty in the cancer risk assessment include statistical uncertainty due to the relatively small number of animals used in the bioassay, the choice of the animal-to-human scaling factors, the choice of the extrapolation model, and the large range of extrapolation (at least 5 orders of magnitude) from the lead levels used in the animal experiments to current ambient levels. In addition, there is the possibility, in light of the absence of an epidemiological connection between exposure to lead and cancer, that the risks in rats and hamsters may not be applicable to humans, i.e., lead is only a potential human carcinogen. Since the risk estimate is made after route-to-route extrapolation, over at least 5 orders of magnitude, and in the absence of correlating human data, the uncertainty involved in the estimation of a unit risk for lead puts it in the bottom third of the chemicals evaluated to date in the toxic air contaminant program.

7.5. Best Value for Cancer Risk Assessment

In the absence of data for tumor induction due to the inhalation of lead, the oral lead acetate study in which kidney tumors were induced in rats is the most complete and largest data set for quantitative cancer risk assessment. Assuming that there is no threshold for lead-induced kidney tumors, the application of the linearized multistage model yields a 95% upper confidence limit unit risk of 1.2×10^{-5} $(\mu g/m^3)^{-1}$ (Table 7-1). This unit risk can be used to quantify the cancer risk associated with exposure to inhalation of bioavailable particulate lead. Estimates of individual excess lifetime cancer risk based upon this unit risk value provide a plausible upper limit to the risk consistent with a no-threshold mechanism of action. Such an estimate, however does not necessarily provide a realistic prediction of the "true risk" at low, environmentally relevant exposures. The actual individual excess lifetime cancer risk at environmental exposure levels of lead is likely to be less than that estimated with this unit risk value, and may be zero if a threshold mechanism is causally related to lead-induced tumorigenicity.

In the absence of data for tumor induction due to the inhalation of lead, the best value for quantitative cancer risk assessment is 1.2×10^{-5} $(\mu g/m^3)^{-1}$, the 95% upper confidence limit derived using the linearized multistage model from kidney tumor data in rats after feeding lead acetate (Table 7-1). This data set is the largest available for quantitative risk assessment of lead. The "true risk" is not expected to exceed this value and is likely to be less, and may even be zero.

Table 7-1 Kidney Tumors in Animals Fed Lead[a]

ppm lead in food		animal dose	HED[b]	Number of rats[c]			
added	measured	mg/kg/day	mg/kg/day	exp[d]	tumors	%	% died
0	3	0.225	0.038	20[f]	0	0	50
0	5	0.39	0.067	100	0	0	37
10	18	1.40	0.238	50	0	0	36
50	62	4.78	0.818	50	0	0	36
100	141	10.88	1.86	50	0	0	36
500	548	42.27	7.22	20	5	10	52
1000[e]	1130	79.65	13.6	20[f]	10	50	50
2000[e]	2102	162	27.2	20[f]	16	80	80

[a] Data from Azar et al., 1973.
[b] Human Equivalent Dose = daily dose x $(70/0.35)^{1/3}$.
[c] Among similar size groups of female rats, kidney tumors were seen only in 7 of 20 animals in the 2000 ppm group.
[d] Number of animals exposed to indicated level of lead in food.
[e] The rate of body weight gain was depressed in both groups. Since mortality was not increased in the 1000 ppm group, it can be considered a Maximally Tolerated Dose (MTD).
[f] The groups with only 20 rats per dose level were also studied for 2 years but were begun several months after the other dose groups.

Section 8. Conclusion

The health effects of inorganic lead have been reviewed and evaluated to determine whether inorganic lead may cause or contribute to an increase in mortality or in serious illness. Based on current knowledge, adverse health effects that may occur at relatively low blood lead concentrations include: (1) neurodevelopmental effects in children, (2) increased blood pressure and related cardiovascular conditions in adults, and (3) possibly cancer. Of these three outcomes, the neurodevelopmental effects may be of greatest public health significance since (1) a large number of children could be affected, (2) no clear threshold has been identified, and (3) the effects may be irreversible. Based on results from several carefully conducted prospective human epidemiological studies, there is an association between general measures of intelligence and both pre- and postnatal blood lead concentrations. Based on these studies, a blood lead level of 10 μg/dL has been identified by U.S. EPA and CDC as the level of concern for children.

Investigation of the distribution of blood lead levels in the U.S. population has been conducted by the CDC in large cross-sectional national surveys. The results indicate a substantial decline in blood lead levels from NHANES II (1976 to 1980) to NHANES III (1988 to 1991). There was an overall decrease in blood lead levels of 78% for persons aged one to 74 years of age over this time period. In NHANES II (1976 to 1980) an estimated 88.2% of one to five year old children in the U.S. exhibited blood lead levels greater than or equal to 10 μg/dL. In the NHANES III survey (1988 to 1991) only 8.9% of one to five year olds were determined to have blood lead levels equal to or greater than 10 μg/dL. A decrease in blood lead levels of a similar magnitude (greater than 70%) was observed not only for the total population, but also for subgroups stratified by race/ethnicity, gender, urban status and income levels. However, the number of children aged one to five with blood lead levels greater than or equal to 10 μg/dL is disproportionately higher for non-Hispanic African-American children.

The dramatic decline in blood lead levels is consistent with, and undoubtedly related to, continued reduction in exposure to lead from environmental sources which began in the late 1970s. From 1976 to 1990, the amount of lead used in gasoline decreased 99.8% nationally (from 205,810 tons to 520 tons). In California, there has been an approximate 30-fold decrease in average ambient air lead levels from 1976-1980 to the present (see Figure IV-2, p. A-6, Part A of this document). From 1980 to 1990, the amount of lead used in soldered cans also decreased dramatically. In 1980, 47% of the food and soft drink cans were lead soldered, and by 1990 this figure had decreased to only 0.85%. As of November 1991, lead soldered food and soft drink cans were no longer manufactured in the U.S. The manufacture of lead-based paint was limited by the Consumer Product Safety Commission in 1978. Still, lead-based paint remains a potential source of exposure for residents of older housing with deteriorating paint. The authors of NHANES III have concluded that the reduction of lead in gasoline is most likely the greatest contributor to the observed decline in blood lead levels during the period of the national survey (Pirkle et al. 1994). The major remaining sources of environmental lead that pose a potential public health threat appear to be localized sources of lead, including but not limited to continued deterioration of lead-based painted surfaces in older buildings, lead that has already accumulated in dust and soil, and near source air emissions.

Existing studies indicate a consistent association between ambient concentrations of lead in the air and subsequently measured blood lead levels in children and adults. OEHHA used

these studies as the basis for an "aggregate" model which quantitatively relates exposures from ambient air lead concentrations to blood lead levels, both directly through inhalation and indirectly through other media impacted by airborne lead, such as soil and dust. OEHHA also used the U.S. EPA's Integrated Exposure Uptake Biokinetic (IEUBK) model to estimate the effects of ambient air lead concentrations on blood lead levels in children. The estimated association between blood lead level and air lead level are generally similar in the aggregate and IEUBK models. With this association determined, quantitative risks could be estimated that relate levels of ambient air lead to adverse neurodevelopmental outcomes.

Threats to human health posed by lead exposure require consideration of exposure from multiple media including air, water, food, soil, house dust, and lead paint. The models and data sets used in our analyses of the impacts of environmental lead on blood lead indicate that from 4.8% to 11.5% of children aged one to two years may have blood lead levels in excess of 10 μg/dL. The contribution due to the average ambient air lead (0.06 $\mu g/m^3$) to blood lead ranged from 0.6% to 2.3%. The uncertainty indicated by these ranges of values may be attributable to the greater impact of indirect exposures to air lead than to direct inhalation exposures. Our analysis indicates that, for California children as a whole, overall exposure to the average ambient air lead concentration contributes only a small fraction of their total daily lead exposure. The aggregate model presented in the document is a useful tool to determine the potential impact of an airborne lead concentration on the number of children that may exceed the level of concern. However, due to the multiple sources of lead exposure and the inter-relationship of the various media, risks managers need to examine all sources of lead to determine the most effective manner to reduce childhood blood lead levels for a given community. The IEUBK model, which uses inputs from field measurements, may provide useful information when considering various mitigation strategies. Further risk management guidance in this area is recommended to be developed by the Air Resources Board staff, with the assistance of the OEHHA staff.

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

April 25, 1995

MEMORANDUM

SUBJECT: Use of the IEUBK Model to Estimate Blood Lead Attributable to Air Lead Exposure

FROM: Karen Hogan
Chair, IEUBK Model Validation Subcommittee of the Technical Review Workgroup for Lead

TO: Bart Ostro
California EPA

In response to your inquiry regarding the IEUBK Model's estimation of children's blood lead levels attributable to air lead exposure, the Model yields an approximate slope of 4-5 $\mu g/dl$ per $\mu g/m^3$ of air lead for the combined (aggregate) impact of direct (inhaled) and indirect (primarily soil and dust ingestion) contributions of air lead to blood lead in children.

Estimation of this combined impact requires an evaluation of the expected contribution of air lead to soil and dust lead levels. When there are no site-specific environmental data, the 1989 EPA/OAQPS Staff Report "Review of the National Ambient Air Quality Standards for Lead: Exposure Analysis Methodology and Validation" (EPA-450/2-89-011, pp. B-7,8, equations 3.1 and 3.3) recommends two similar models for estimating geometric mean soil and dust lead levels associated with point sources of air lead. A slope for the blood lead increment associated with the combined effect of direct and indirect exposure to air lead can be back-calculated from separate runs of the Model for each air- and associated soil- and dust-lead combination. My calculations at 1.5 and 2.5 $\mu g/m^3$ air lead yielded slopes of 3.7 (East Helena model) and 5.3 (40-community model) $\mu g/dl$ per $\mu g/m^3$ air lead, for 2-year-olds. These are consistent with the range of 3-5 provided in the literature summary in the EPA Air Quality Criteria for Lead document (1986, p. 11-189).

If you have any other questions, feel free to call me at 202-260-3895.

cc: E. Margosches
S. Griffin - Chair, Technical Review Workgroup for Lead

Appendix B. Calculations for Changes in the Geometric Mean.

We start with a geometric mean of 4 μg/dL, a geometric standard deviation of 2 and an ambient air lead level of 0.06 $\mu g/m^3$. We wish to determine the geometric mean associated with an air lead level of zero. We assume that the geometric standard deviation remains constant.

1. First, we convert the geometric mean of 6.31 μg/dL and GSD of 2.11 at ambient air lead (0.06 $\mu g/m^3$) to an arithmetic mean. The following equation (Eq. 1) is used:

$$\mu_C = \exp [\ln(\mu_G) + 1/2((\ln(\sigma_G))^2)]$$

where $\ln(\mu_G) = \ln(6.31) = 1.842$, and $\ln(\sigma_G) = \ln(2.11) = 0.747$

then, $\mu_C = \exp [1.842 + 1/2(0.747)^2] = 8.34$.

2. To calculate the arithmetic mean at zero air lead, subtract the expected reduction in air lead (0.06 $\mu g/m^3$) times the air lead/blood lead slope of 4.2 , from the current arithmetic mean of 8.34 (derived in Eq. B-3):

$$= 8.34 - (0.06 \times 4.2)$$
$$= 8.10.$$

3. To get the geometric mean at zero air lead, put the new arithmetic mean into Eq. 1 and solve for μ_G.

$$\mu_C = \exp [\ln(\mu_G) + 1/2((\ln(\sigma_G))^2)]$$
$$8.10 = \exp [\ln(\mu_G) + 1/2(.747^2)]$$
$$8.10 = \exp [\ln(\mu_G) + 0.279]$$
$$\ln(8.10) = \ln(\mu_G) + 0.279$$
$$2.09 = \ln(\mu_G) + 0.279$$
$$\ln(\mu_G) = 1.813$$
$$\mu_G = 6.13$$

4. Next, we can calculate a standardized normal deviate or Z-score, which will determine the percent of the distribution above a given level. .

$$Z = (\ln(10) - \ln(\mu_{Gi}))/\ln(\sigma_G)$$
$$Z = (\ln(10) - \ln(6.13))/\ln(2.11)$$
$$= 0.6562$$

Using a normal table, a Z-score of 0.6562 is associated with 25.6%. That is, based on the normal distribution, we standardize, and determine that 25.6% of the population will be above 10 given a geometric mean of 6.13 μg/dL and a geometric standard deviation of 2.11.

5. Calculate arithmetic means for increases in air lead of 0.05, 0.10, 0.15, 0.20, 0.25, 0.5, and 1.0 $\mu g/m^3$ respectively, starting at an initial level of zero air lead. The associated arithmetic means, for example, for an air lead of 0.15 $\mu g/m^3$ is:

$$8.10 + (0.15)(4.2) = 8.73$$

6. Calculate geometric means by substituting arithmetic means into Eq. 1 and solving for μ_G.

7. Calculate percent above 10 µg/dL using equation 2D to calculate a Z-score and looking up the result in a table of normal distribution values.

Summary of Calculations

The arithmetic mean associated with a geometric mean of 6.31 µg/dL and a geometric standard deviation of 2.11 is 8.34 µg/dL. Assuming a blood lead to air lead slope of 4.2 µg/dL per $\mu g/m^3$, the current contribution of the mean ambient air lead concentration of 0.06 $\mu g/m^3$ can be subtracted from the arithmetic mean of 8.34 to give a baseline arithmetic mean of 8.10 (8.34 - 0.06 x 4.2). The geometric mean corresponding to this arithmetic mean is 6.13 µg/dL. A z-score was calculated to determine that 25.6% of the population would be above 10 µg/dL at zero air lead. An increase to an air lead concentration of 0.15 is calculated to result in an additional 3.4% of the children above the 10 µg/dL blood lead level of concern.

Appendix C. Samples from IEUBK Model

In this Appendix, two sample exercises using the IEUBK model are provided. First, the impact of moving from an ambient concentration generated from a hypothetical near source exposure of 0.25 $\mu g/m^3$ back down to the current baseline concentration of 0.06 $\mu g/m^3$ is detailed. Second, the amount of reduction in air, water, or soil lead required to achieve a 0.5 $\mu g/dL$ reduction in blood lead is estimated using three alternative sets of assumptions.

The IEUBK model was used to estimate blood lead levels in children using available data for several input parameters. The statewide average ambient air concentration of lead is assumed to be 0.06 $\mu g /m^3$ with a hypothetical exposure level of 0.25 $\mu g /m^3$. To utilize the most recent NHANES III data, a geometric standard deviation of 2.1 was used in place of the default value of 1.6. Estimates of the dust (D) and household soil lead (S) concentrations were assumed to be a function of air concentrations (A) in terms of $\mu g/m^3$ and are based on the equations provided in Section 4 of this document. Using the parameters determined from the data from East Helena, the equations for these two sources of exposure are:

$$S = 88.1 + 206 \times A \qquad \text{(Eq. C-1)}$$

$$D = 220 + 551 \times A \qquad \text{(Eq. C-2)}$$

Thus, with an air concentration of 0.06 $\mu g/m^3$, soil was 100.5 μg of lead/gram and house dust was 253 μg of lead/gram. At 0.25 $\mu g/m^3$, soil was 140 μg of lead/gram and house dust was 358 μg of lead/gram. A level of 3.00 $\mu g/dL$ in tap water was used in place of the default value of 4 $\mu g/dL$. Also, for children 12 - 24 months of age, a daily diet including 4.78 μg of lead per day was used in place of the default of 5.78 μg/day. These water and diet values were used to ensure that the model generated a mean blood lead of 4.1 $\mu g/dL$, the national mean based on NHANES III, for 1 and 2 year old children. (The mean lead value would also be obtained if all default values were used, including defaults for household dust and soil lead. Soil and dust were allowed to vary with the air lead concentrations to more precisely assess both direct and indirect future air lead impacts. Thus, lower values for water and diet were necessary).

Typical computer outputs of the IEUBK model are shown in Tables C-1 and C-2, corresponding to 0.25 $\mu g /m^3$ and 0.06 $\mu g /m^3$ of lead in air, respectively. Figure C-1 is an example of the typical output, using an air lead of 0.06 $\mu g/m^3$, regarding the blood lead distribution and the percent of the population above a certain blood lead cutpoint such as 10 $\mu g/dL$. Using our input data and an air lead of 0.06 $\mu g/m^3$, the IEUBK model predicts a mean blood lead for 1 and 2 year old children of 4.1 $\mu g/dL$ with 10.48 percent of the subgroup above 10 $\mu g/dL$. At 0.25 $\mu g/m^3$, the mean blood lead is predicted to be 5.1 $\mu g/dL$ with 16.68 percent of the subgroup above 10 $\mu g/dL$. Note that the IEUBK model can also consider other age group levels and can calculate the proportion of the population above other blood lead cut points.

The guidance manual for the IEUBK model (U.S. EPA, 1994a) provides examples of how to incorporate site-specific information into the model when local data are different from the default values. The IEUBK model for predicting blood lead levels in children has both advantages and disadvantages over empirical treatments of environmental data to predict blood lead levels. Because IEUBK is a physiologically based pharmacokinetic model that accounts for both active

and passive transport of lead, it responds to increasing concentrations of environmental exposures in a curvilinear fashion. The model allows for a large number of user-selected inputs to reflect site-specific and/or population-specific data to better predict blood lead levels for children up to 7 years of age. Varying any one environmental concentration allows a sensitivity analysis of an exposure to that medium. The data printouts show the variability in children's activity patterns and exposures by age group. Therefore, in the second exercise, we use the model to determine changes in other environmental sources of lead exposure necessary to achieve a 0.5 μg/dL decrease in blood lead.

The model results are summarized in Table C-3. Three sets of data were generated based on two alternative methods for estimating house dust lead levels. The first method uses equation C-3 and the AGG and EH data sets with parameters defined earlier in Table 4-2. The second method uses IEUBK default parameters to calculate house dust. Specifically a default option in the model converts indoor air lead (30% of outdoor concentration) to dust lead in the proportion of 100 μg/g per each μg/m^3 in air and assumes that 70% of house dust originates from outdoor soil. In the first row of each data set are the results of a hypothetical exposure having an air lead concentration of 0.25 μg/m^3, water concentration of 10 μg/dL (ppb), and a yard soil lead level of 300 μg/g (ppm). In the second row, air lead is reduced to achieve the desired 0.5 μg/dL decrease in blood lead. House dust was allowed to vary as a function of air lead and soil lead using the following equation:

$$D = b_0 + (b_1 \times A) + (b_2 \times S) \qquad \text{(Eq. C-3)}$$

where A = air concentration (μg/m^3)

S = soil concentration(μg/g)

b_0, b_1, b_2 are defined in Table 4-2

Note, that this example assumes that the soil lead level is constant and does not vary with air lead. Decreases in soil lead would primarily result from remediation due to its persistence. Thus, this calculation may not reflect the actual air lead to blood lead slope. Instead, it demonstrates how various factors affect the models and the sensitivity of the model. In the third row of the table, water is reduced from 10 μg/L to a level that would give a corresponding 0.5 μg/dL reduction in mean blood lead concentration. In the fourth row, soil is decreased. House dust was allowed to vary as a function of yard soil lead concentrations, using Eq. C-3 (for AGG and EH model runs) or the IEUBK default option (for the Default model runs), to recalculate house dust lead levels corresponding to decreases in soil lead levels. The results of this exercise show the relative effects of changing environmental exposures on blood lead levels. The results demonstrate the sensitivity of the IEUBK model to assumptions about soil lead and house dust lead and the importance of using site-specific data rather than data from other locations.

In the first model run in Table C-3, the AGG input parameters were used. In the second example, the EH input parameters were used. In the third example, the default IEUBK input parameters are used to estimate house dust lead levels. As indicated above, the soil level is assumed to be the current concentration and is not allowed to vary as a function of air lead that would predict future concentrations in any of the examples. Thus the examples may not reflect

would predict future concentrations in any of the examples. Thus the examples may not reflect the complete potential impact of air lead and the slope for air lead should not be computed from the model runs. As discussed in Section 4, the IEUBK model is a powerful tool primarily designed to predict blood lead levels in children when environmental levels of lead are known. When the IEUBK model is run to predict potential future impacts or changes in environmental levels, the user must be more cognizant of the input and default parameters used. In particular, if the user is attempting to understand the potential full impact of increases in air lead levels, one must consider the appropriate supplemental equations. In comparing the AGG and EH model run results, one sees a substantial difference in blood lead results even when only house dust lead is allowed to vary with air lead levels while soil lead levels are held constant. This underscores the underlying uncertainties in using empirical equations to estimate soil and house dust lead rather than site-specific measurements.

The user of this model should be aware that components of the model are non-linear and that results may be sensitive to the input parameters. Therefore, users are encouraged to examine the sensitivity of the model to different assumptions. One could also experiment with using different household dust, water lead and lead paint assumptions, and altering assumptions about the amount of time spent outdoors. Over time, model assumptions should be updated as new empirical information becomes available. When characteristics (e.g., ages, soil lead, dust lead, and other lead exposures) of the population of children are known, GSDs for the geometric mean blood lead levels can be derived (see Appendix A of U.S. EPA, 1994). Specific instructions for use of this model are provided by U.S. EPA (U.S. EPA, 1994a).

Table C-1. Output of the IEUBK Model Corresponding to 0.25 µg/m³ in Air with User-Defined Inputs as Described on Pages C-1 and C-2.

LEAD MODEL Version 0.99d

AIR CONCENTRATION: 0.0250 µg Pb/m³
Indoor AIR Pb Conc: 30.0 percent of outdoor.
Other AIR Parameters:

Age	Time Outdoors (hr)	Vent. Rate (m³ day)	Lung Abs. (%)
0-1	1.0	2.0	32.0
1-2	2.0	3.0	32.0
2-3	3.0	5.0	32.0
3-4	4.0	5.0	32.0
4-5	4.0	5.0	32.0
5-6	4.0	7.0	32.0
6-7	4.0	7.0	32.0

DIET: daily Pb consumption by year as follows
0-1: 5.53 µg Pb/m³
1-2: 4.78 µg Pb/m³
2-3: 6.49 µg Pb/m³
3-4: 6.24µg Pb/m³
4-5: 6.01 µg Pb/m³
5-6: 6.34 µg Pb/m³
6-7: 7.00 µg Pb/m³

DRINKING WATER Conc: 3.00 5.53 µg Pb/L
WATER Concumption: DEFAULT

SOIL & DUST:
Soil: constant conc.
Dust: constant conc.

Age	Soil (µg Pb/g)	House Dust (µg Pb/g)
0-1	140.5	358.0
1-2	140.5	358.0
2-3	140.5	358.0
3-4	140.5	358.0
4-5	140.5	358.0
5-6	140.5	358.0
6-7	140.5	358.0

Additional Dust Sources: None DEFAULT

PAINT Intake: 0.00 µg Pb/day DEFAULT

MATERNAL CONTRIBUTION: Infant Model
Maternal Blood Conc: 2.50 µg Pb/dL

CALULATED BLOOD Pb and Pb UPTAKES:

YEAR	Blood Level (µg/dL)	Total Uptake (µg/day)	Soil+Dust Uptake (µg/day)
0.5-1	4.8	8.82	6.00
1-2	5.1	12.35	9.45
2-3	4.9	13.34	9.54
3-4	4.7	13.44	9.68
4-5	3.9	11.12	7.35

Table C-1. Output of the IEUBK Model Corresponding to 0.25 µg/m³ in Air with User-Defined Inputs as Described on Pages C-1 and C-2.

5-6	3.4	10.74	6.67
6-7	3.1	8.80	6.33

YEAR	Diet Uptake (µg/day)	Water Uptake (µg/day)	Paint Uptake (µg/day)	Air Uptake (µg/day)
0.5-1	2.50	0.27	0.00	0.05
1-2	2.14	0.67	0.00	0.09
2-3	2.94	0.71	0.00	0.16
3-4	2.87	0.73	0.00	0.17
4-5	2.83	0.78	0.00	0.17
5-6	3.01	0.83	0.00	0.23
6-7	3.34	0.84	0.00	0.23

Table C-2. Output of the IEUBK Model Corresponding to 0.06 µg/m³ in Air with User-Defined Inputs as Described on Pages C-1 and C-2.

LEAD MODEL Version 0.99d

AIR CONCENTRATION: 0.060 µg Pb/m³
Indoor AIR Pb Conc: 30.0 percent of outdoor.
Other AIR Parameters:

Age	Time Outdoors (hr)	Vent. Rate (m³ day)	Lung Abs. (%)
0-1	1.0	2.0	32.0
1-2	2.0	3.0	32.0
2-3	3.0	5.0	32.0
3-4	4.0	5.0	32.0
4-5	4.0	5.0	32.0
5-6	4.0	7.0	32.0
6-7	4.0	7.0	32.0

DIET: daily Pb consumption by year as follows
0-1: 5.53 µg Pb/m³
1-2: 4.78 µg Pb/m³
2-3: 6.49 µg Pb/m³
3-4: 6.24 µg Pb/m³
4-5: 6.01 µg Pb/m³
5-6: 6.34 µg Pb/m³
6-7: 7.00 µg Pb/m³

DRINKING WATER Conc: 3.00 5.53 µg Pb/L
WATER Concumption: DEFAULT

SOIL & DUST:
Soil: constant conc.
Dust: constant conc.

Age	Soil (µg Pb/g)	House Dust (µg Pb/g)
0-1	100.5	253.0
1-2	100.5	253.0
2-3	100.5	253.0
3-4	100.5	253.0
4-5	100.5	253.0
5-6	100.5	253.0
6-7	100.5	253.0

Additional Dust Sources: None DEFAULT

PAINT Intake: 0.00 µg Pb/day DEFAULT

MATERNAL CONTRIBUTION: Infant Model
Maternal Blood Conc: 2.50 µg Pb/dL

CALULATED BLOOD Pb and Pb UPTAKES:

YEAR	Blood Level (µg/dL)	Total Uptake (µg/day)	Soil+Dust Uptake (µg/day)
0.5-1	3.9	7.17	4.33
1-2	4.1	9.76	6.85
2-3	3.9	10.65	6.90
3-4	3.7	10.68	6.98
4-5	3.2	8.95	5.27

Table C-2. Output of the IEUBK Model Corresponding to 0.06 µg/m³ in Air with User-Defined Inputs as Described on Pages C-1 and C-2.

5-6	2.7	8.70	4.77
6-7	2.5	8.80	4.52

YEAR	Diet Uptake (µg/day)	Water Uptake (µg/day)	Paint Uptake (µg/day)	Air Uptake (µg/day)
0.5-1	2.55	0.28	0.00	0.01
1-2	2.19	0.69	0.00	0.02
2-3	3.00	0.72	0.00	0.04
3-4	2.92	0.74	0.00	0.04
4-5	2.86	0.79	0.00	0.04
5-6	3.04	0.83	0.00	0.06
6-7	3.37	0.85	0.00	0.06

Table C-3. Changes in air, tap water and soil lead levels needed to decrease blood lead levels 0.5 µg/dL in of children aged 1-2 years (IEUBK Model v.99d, GSD = 2.1)

Exposure Parameter Variable	House Dust Estimate	Air ($\mu g/m^3$)	Tap Water (µg/L)	Soil (µg/g)	House Dust (µg/g)	Mean PbB (µg/dL)	% Above 10 µg/dL
	AGG	0.25	10	300	300	6.3	25.4
Air	AGG	0.20	10	300	229	5.8	22.0
Water	AGG	0.25	3	300	300	5.8	22.0
Soil	AGG	0.25	10	230	274	5.8	22.0
	EH	0.25	10	300	519	7.8	34.3
Air	EH	0.00	10	300	452	7.3	31.8
Water	EH	0.25	3	300	519	7.3	31.8
Soil	EH	0.25	10	255	479	7.3	31.8
	Default	0.25	10	300	235	5.9	22.0
Air	Default	0.00	10	300	210	5.7	20.5
Water	Default	0.25	6	300	235	5.4	19.1
Soil	Default	0.25	10	275	193	5.4	19.1

Note: This table shows the relative effects of changing one environmental source of lead (either air, water, or soil/dust) in order to achieve a 0.5 µg/dL decrease in mean blood lead levels in a population of 1 or 2 year olds (12-24 months) as predicted by the IEUBK Model. A hypothetical ~~near-source~~ exposure is assumed to have an air concentration of 0.25 $\mu g/m^3$, a tap water level of 10 µg/dL (ppb), and a yard soil level of 300 µg/g (ppm). House dust lead levels are a function of both outdoor soil lead levels and indoor air lead levels. Consequently, when air lead or soil lead decrease (e.g., following remediation), house dust can be recalculated using equation 4-5 and parameters for AGG (40 communities) and EH (East Helena) defined in Table 4-2. The IEUBK Model will also calculate house dust lead levels by converting indoor air lead to house dust lead using a factor of 100 µg/g per 1 $\mu g/m^3$ and assuming 70% of house dust originates from outdoor soil. In the above examples, soil lead levels are assumed not to decrease when air lead levels decrease because of infinite half-life of lead in soil.

Appendix D Calculations for Changes in IQ

This appendix describes the method for calculating the number of children with IQ scores below 80 (see Part B, p.5-7). The first step is to find the percent of children with IQs below 80 given a normal distribution of IQ scores with a mean of 100 and a standard deviation of 16. One can use a z-distribution to look at this where z=(value - mean)/SD. The z-table used in these examples was one-tailed.

$$(80-100)/16=-1.25.$$
$$Z_{1.25}=0.3944$$
$$\text{and } 0.5-0.3944=0.1056.$$

Therefore, 10.56 percent of the population will have IQ scores below 80 given the above distribution. Next, find the percent of children with IQs below 80 assuming a 0.08 decrease in mean IQ. This is the increase associated with a shift in air lead from 0 to 0.06 $\mu g/m^3$.

$$(80-99.92)/16=-1.245$$
$$Z_{1.245}=0.3935$$
$$0.5-.3935=0.1066$$
$$(0.1056-0.1066)/.1056= 0.01 \text{ or } 1\%$$

Therefore, 10.66% of the population would have IQs below 80 given a mean of 99.92. Thus, holding other factors constant, the shift in the mean of 0.08 IQ points would result in a 1% increase from baseline of the proportion of children with IQs of 80 and below. The same method was used to evaluate the impacts of an ambient air concentration of 0.20 $\mu g/m^3$ above the current ambient average concentration (0.26 $\mu g/m^3$) on the proportion of IQs below 80.

An exposure 0.20 $\mu g/m^3$ above the ambient average would result in an IQ loss of .36 points on average. (0.26 $\mu g/m^3$ X 4.2 $\mu g/dL/\mu g/m^3$ X 0.33 IQ points / $\mu g/dL$ air lead = 0.36 IQ points)

$$(80-99.64)/16=-1.228$$
$$Z_{1.228}=0.3903$$
$$0.5-0.3903=0.1097.$$
$$(0.1056-0.1097)/.1056= -0.039$$
$$(0.1066-0.1097)/.1066= -0.029$$

Thus, holding other factors constant, the shift in mean of IQ associated with an exposure to 0.20 $\mu g/m^3$ above ambient average air lead would result in a 4% increase above baseline (zero air lead) in the proportion of children with IQs of 80 and below,b and a 3% increase above the current average ambient exposure of 0.06 $\mu g/m^3$.