HAZARD

EPA's Final Air Quality Criteria Document (AQCD) for Lead (US EPA, 2006) provides an extensive review of the most recent data available on lead. This document updates the 1986 AQCD for Lead (US EPA 1986a), associated Addendum (US EPA, 1986b) and the 1990 Supplement (US EPA, 1990). In an effort not to duplicate efforts, pertinent sections in this Hazard Assessment for the LRRP are taken directly from the Final 2006 AQCD for Lead, hereafter referred to as the AQCD.

Blood Lead as a Biomarker

Chapter 4 of the AQCD presents an extensive discussion of the use of blood lead as both a biomarker of lead body burden and a biomarker of exposure (Sections 4.3.1.4, 4.3.1.5, and 4.3.1.6). In addition, a summary of these sections is presented in Section 8.3.2. A summary of the pertinent points made in these sections follows.

Blood-lead concentration is extensively used in epidemiologic and toxicologic studies as an index of exposure and body burden. The prevalence of the use of blood lead as an exposure metric is mainly due to the feasibility of incorporating its measurement into human studies relative to other potential dose indicators (e.g., lead in kidney, plasma, urine, or bone) and due to the variety of health effects associated with lead exposure that have been reported in the literature. Lead is exchanged between blood and bone and blood and the soft tissues. The exchanges between the blood and bone vary with duration and intensity of exposure, age and other variables. Resorption of bone in pregnant or nursing women or in postmenopausal women (through osteoporosis) results in a mobilization of lead from bone to circulation. Therefore, the blood lead concentration measured in an individual will be determined by the recent exposure history of the individual as well as by the long-term exposure history that gives rise to accumulated bone lead stores.

In comparison to adults, bone mineral is rapidly turning over much more quickly in children as a result of growth. Therefore, changes in blood lead concentration in children are thought to more closely parallel changes in total body burden. Several recent studies have shown that blood lead levels reflect lead exposures. These studies have shown that dust lead, as well as lead in air and soil reflect blood lead levels.

Neurocognitive Effects of Lead in Children

Emphasis in this document is placed on discussion of the neurocognitive effects of lead exposure in children. As described in detail in Section 6.2 of the AQCD, neurocognitive effects in children are of particular concern due to the increasingly lower levels at which they have been reported and the potential for lifelong impact. The negative influence of lead on neurobehavior has been reported with remarkable consistency across numerous studies of various study designs, populations studied, and developmental assessment protocols, even following adjustment for numerous

confounding factors. Collectively, the prospective cohort and cross-sectional studies have reported that lead exposure affects intellectual attainment of preschool and school age children at blood lead levels <10 μg/dL (most clearly in the 5 to 10 μg/dL range, but possibly lower). Several studies have reported quantitative relationships between measures of IQ and current blood lead levels for children aged 2 to 11 years old. Children are particularly at risk due to sources of exposure, mode of entry, rate of absorption and retention, and partitioning of lead in soft and hard tissues. As described in Section 6.2.11 of the AQCD, the neurocognitive effects reported in children appear to persist into adolescence and young adulthood in the absence of marked reductions in environmental exposure to lead. Excessive accumulation of lead in childhood has latent and/or persistent adverse health effects on both the peripheral and central nervous systems of human adults assessed 19-29 years later (see AQCD Section 8.4.2.8). Also, chelation studies in humans and animals show that medical interventions involving chelation decreases total body lead burden, but does not necessarily fully reverse lead-induced cognitive deficits (see AQCD Sections 6.2.11, 8.5.2, and 5.3.5).

In view of the strength of evidence for association with blood lead levels below 10 ug/dL, and the strength of the dose-response information at these exposure levels, as well as the persistence of cognitive effects in the absence of reduced exposure levels, neurocognitive impact, specifically decrement in IQ in young children, is the focus of this quantitative risk assessment.

Epidemiologic Studies on Neurocognitive Effects of Lead in Children

As described in Section 6.2.3 of the AQCD, the most widely used measure of cognitive function in epidemiologic studies is the intelligence quotient or IQ score. An IQ score is a global measure reflecting the integration of numerous behavioral processes. Lead effects on human neurocognitive ability have been assessed in epidemiologic studies largely by use of age-appropriate, standardized IQ tests. A broad net approach using global assessments of cognition, such as IQ, has proven to be the most consistently sensitive across studies of various design and sample characteristics. Such measures combine subscales that are representative of a broad number of underlying cognitive functions; thus, they are likely to pick up exposure-related deficits across cohorts that differ in their functional expressions of toxicity. Global measures of IQ have also been used so widely because of their outstanding psychometric properties. Although the definition of "intelligence" is quite abstract, IQ remains a useful outcome measure as it is correlated with important measures of life success, such as academic achievement, earnings, and social status.

Epidemiologic studies linking lead exposure to health effects are presented in detail in Chapter 6 of the AQCD, and Chapter 5 presents the toxicologic data. Synthesis of the most salient health-related findings and conclusions are presented in Chapter 8. Based on the AQCD, it is evident that neurotoxic effects in children are of great public health concern. There are numerous epidemiologic studies, as well as extensive experimental animal evidence substantiating the plausibility of these epidemiologic

findings, that demonstrate inverse relationships between children's blood lead concentrations and IQ.

The studies most relevant to the OPPT LRRP risk assessment that are identified in the AQCD are Canfield, et al., 2003 and Lanphear et al., 2005. These large, well-conducted studies provide both qualitative and quantitative evidence of neurocognitive deficits in children at blood lead levels less than 10 µg/dL. Descriptions of these 2 studies, taken from Sections 6.2.3.1.9 and 6.2.3.1.11 of the AQCD, are presented below.

The Rochester prospective study, initiated in 1994, examined the relationship between blood lead levels and IQ at 3 and 5 years of age in 172, predominantly African-American, lower SES children (Canfield et al., 2003). Participants were enrolled when children were 5 to 7 months of age in what was originally a study of lead dust control methods (Lanphear et al., 1999). Blood lead concentrations were assessed at 6-month intervals until 2 years and annually thereafter. No data were available on prenatal exposure. The measure of IQ was the abbreviated Stanford-Binet Intelligence Scale-4th Edition (SBIS-4). Potential confounders assessed included gender, birth weight, iron status, HOME scores, maternal IQ, SES, and tobacco use during pregnancy.

Blood lead concentrations in the Rochester cohort were quite low for an urban population as this study was conducted after public health measures to reduce blood lead levels in children were already having a dramatic impact in the U.S. population. Blood lead levels peaked at 2 years of age (mean 9.7 µg/dL). The mean lifetime average blood lead concentration was 7.7 µg/dL at the age of 3 years and 7.4 µg/dL at the age of 5 years. At 5 years of age, 56% of the children had a peak blood lead concentration below 10 µg/dL. Following adjustment for covariates, there were significant inverse associations with full scale IQ at both 3 and 5 years of age for all blood lead variables, including lifetime average up to age of behavioral assessment.

The effect of lead on IQ was estimated in all children using lifetime average, peak, concurrent, and average in infancy (6-24 months) blood lead levels. Lead effects on IQ for the subgroup of children whose peak lead concentration never exceeded 10 µg/dL also was estimated. Covariate-adjusted changes in IQ for each 1 µg/dL increase in blood lead concentration for all children and children with peak blood lead concentrations below 10 µg/dL were estimated. In all cases, the effect estimates were larger in the subsample of children with peak blood lead concentrations below 10 µg/dL. For example, the overall estimate including all children indicated that an increase in the lifetime average blood lead concentration of 1 µg/dL was associated with a decrease of 0.46 points (95% CI: 0.15, 0.76) in IQ. In comparison, a 1 µg/dL increase in lifetime average lead concentration was associated with a decline of 1.37 points (95% CI: 0.17, 2.56) in children with peak blood lead concentrations below 10 µg/dL. In an accompanying editorial of the Canfield et al. (2003) study, Rogan and Ware (2003) noted that the steepness in the concentration-response relationship below 10 µg/dL might have been influenced by 10 children with blood lead concentrations at or below 5 µg/dL and IQs above 115. However, they added that it was unlikely that the associations reported by Canfield et al. were solely due to these values. Regression diagnostics performed by

Canfield et al. identified only one potential outlier (a child who had a low IQ and low lead concentration); however, this value was retained in all analyses as it did not pass the discordancy test. In the Rochester study, the relationship between children's IQ score and their blood lead level was found to be nonlinear. A semiparametric analysis indicated a decline of IQ of 7.4 points for a lifetime average blood lead concentration of up to 10 μg/dL, while for levels between 10 to 30 μg/dL a more gradual decrease of approximately 2.5 points IQ was estimated. The authors concluded that the most important aspect of their findings was that effects below 10 μg/dL that have been observed in previous cross-sectional studies (e.g., Chiodo et al., 2004; Fulton et al., 1987; Lanphear et al., 2000) have been confirmed in this rigorous prospective longitudinal investigation.

Lanphear et al. (2005) reported on a pooled analysis of seven prospective studies that were initiated prior to 1995. The analysis involved 1,333 children with complete data on confounding factors that were essential in the multivariable analyses. The participating sites included Boston, MA; Cincinnati, OH; Cleveland, OH; Rochester, NY; Mexico City; Port Pirie, Australia; and Kosovo, Yugoslavia. A prospective cohort study conducted in Sydney, Australia was not included because the authors were unable to contact the investigators (Cooney et al., 1989, 1991). The sample size of 175 for children at age 7 years in the Sydney cohort and the wide confidence intervals of the effect estimates, as implied by the lack of significant associations, indicate that the nonavailability of this study is unlikely to influence the results of the pooled analysis by Lanphear et al.

The primary outcome measure was full scale IQ measured at school age (mean age at IQ testing was 6.9 years). All children were assessed with an age-appropriate version of the Wechsler scales. Four measures of lead exposure were examined: concurrent blood lead (blood lead level closest in time to the IQ test), maximum blood lead level (peak blood lead measured at any time prior to the IQ test), average lifetime blood lead (mean blood lead from 6 months to the concurrent blood lead test), and early childhood blood lead (defined as the mean blood lead from 6 to 24 months). A pooled analysis of the relationship between cord blood lead levels and IQ also was conducted in the subsample for which cord blood lead tests were available.

Multivariate regression models were developed adjusting the effect of blood lead for site as well as assessing ten common covariates likely to be confounders of the relationship between lead and cognitive development, including HOME scores, birth weight, maternal education and IQ, and prenatal substance abuse. A thorough statistical analytic strategy was employed to determine the linearity or nonlinearity of the relationship between blood lead levels and full-scale IQ. Regression diagnostics also were performed to ascertain whether lead coefficients were affected by collinearity or influential observations. The fit of all four measures of postnatal blood lead levels was compared using the magnitude of the model R^2. The blood lead measure with the largest R^2 (adjusted for the same covariates) was nominated a priori as the preferred blood lead index relating lead exposure to IQ in subsequent inspections of the relationships. The

primary analysis was done using a fixed-effects model, although a mixed model treating sites as random effects was also examined.

The median lifetime average blood lead concentration was 12.4 μg/dL (5th-95th percentile 4.1-34.8) with about 18% of the children having peak blood lead levels below 10 μg/dL. The 5th to 95th percentile concurrent blood lead levels ranged from 2.4 to 30 μg/dL. The mean IQ of all children was 93.2 (SD 19.2) but this varied greatly between studies. All four measures of postnatal exposure were highly correlated. However, the concurrent blood lead level exhibited the strongest relationship with IQ, as assessed by R^2. Nevertheless, the results of the regression analyses for all blood lead measures were very similar. Multivariable analysis resulted in a six-term model including log of concurrent blood lead, study site, maternal IQ, HOME Inventory, birth weight, and maternal education.

Various models, including the linear model, cubic spline function, the log-linear model, and the piece-wise linear model, were investigated in this analysis. The shape of the dose-response relationship was determined to be non-linear; the log-linear model was found to be a better fit for the data. Using the log-linear models, the authors estimated a decrement of 1.9 points (95% CI: 1.2, 2.6) in full scale IQ for a doubling of concurrent blood lead. However, the IQ point decrements associated with an increase in blood lead from <1 to 10 μg/dL compared to 10 to 20 μg/dL were 6.2 points (95% CI: 3.8, 8.6) versus 1.9 points (95% CI: 1.2, 2.6). The individual effect estimates for the seven studies used in the pooled analysis also generally indicate steeper slopes in studies with lower blood lead levels compared to those with higher blood lead.

Ernhart (2006) expressed the concern that one study site was driving the results and that the HOME score was not always measured with the IQ test. Other limitations were also mentioned, such as the use of capillary finger stick for the early blood lead tests rather than venous blood lead samples. Lanphear et al. (2006) noted that though they agree that using an early measure of the HOME inventory in the Rochester cohort was a potential limitation, excluding this cohort, from the pooled analysis changed the coefficient by <3%. Sensitivity analyses reported in Lanphear et al. (2005) indicated that no single study was responsible for the estimated relationship of lead and deficits in IQ; thus, diminishing concerns about unique attributes or potential limitations for any specific sites.

In summary, the log-linear model in Lanphear et al. estimated a decline of 6.2 points in full scale IQ for an increase in concurrent blood lead levels from <1 to 10 μg/dL. This effect estimate was comparable to the 7.4 point decrement in IQ for an increase in lifetime mean blood lead levels up to 10 μg/dL observed in the Rochester study (Canfield et al., 2003), as well as other studies presented in the AQCD.

Influence of Timing of Exposure on Risk

Epidemiological studies investigating blood lead and IQ effects have considered various blood lead metrics, including but not limited to blood lead levels concurrent to

the time of the IQ measurement taken, average over the "lifetime" of the child at measurement, peak or maximum levels at a specific age range, and early childhood concentrations (usually the mean concentration for 6-24 months of age). All of these blood lead metrics have been correlated with IQ measurements.

Available studies do not provide a definitive answer to the question of whether lead associated neurodevelopmental deficits are the result of exposure during a circumscribed critical period or of cumulative exposure. Although support can be cited for the conclusion that it is exposure within the first few postnatal years that is most important in determining long-term outcomes (Bellinger et al., 1992), other studies suggest that concurrent blood-lead level is as predictive, or perhaps more predictive, of long-term outcomes than are early blood-lead levels (Canfield et al., 2003; Dietrich et al., 1993a,b; Tong et al., 1996; Wasserman et al., 2000). Because of the complex kinetics of lead, an accumulative toxicant, it is extremely difficult to draw strong conclusions from these observational studies about windows of heightened vulnerability in children. The high degree of intra-individual "tracking" of blood lead levels over time, especially among children in environments providing substantial, chronic exposure opportunities (e.g., residence near a smelter or in older urban dwellings in poor repair), poses formidable obstacles to identifying the time interval during which exposure to lead caused the health effects measured in a study. It could be that damage occurred during a circumscribed period when the critical substrate was undergoing rapid development, but that the high correlation between serial blood lead levels impeded identification of the special significance of exposure at that time.

Under such circumstances, an index of cumulative blood lead level or concurrent blood lead level, which might be a good marker of overall body burden under conditions of relatively steady-state exposure, might bear the strongest association with the effect. Under these circumstances, however, it might be incorrect to conclude that it was the later exposures, incurred around the time that the effect was detected, that was responsible for producing it. While some observations in children as old as adolescence indicate that exposure biomarkers measured concurrently are the strongest predictors of late outcomes, the interpretation of these observations with regard to critical windows of vulnerability remains uncertain. Additional research will be needed to distinguish effects that reflect the influence of later lead exposures from effects that reflect the persistent of effects resulting from exposure during some prior critical window. Resolving this issue solely on the basis of data from observational studies will be difficult due to the high intercorrelation among blood lead measures taken at different ages.

WEIGHT OF EVIDENCE: LEAD AND IQ IN CHILDREN

As stated in the AQCD, the effects of lead on neurobehavior have been reported with remarkable consistency across numerous studies of various designs, populations studied, and developmental assessment protocols. The negative impact of lead on IQ and other neurobehavioral outcomes persists in most recent studies following adjustment for numerous confounding factors including social class, quality of caregiving, and parental intelligence. Moreover, these effects appear to persist into adolescence and young

adulthood in the absence of marked reductions in environmental exposure to lead. In addition, although there are no direct animal tests parallel to human IQ tests, "in animals a wide variety of tests that assess attention, learning, and memory suggest that lead exposure results in a global deficit in functioning, just as it is indicated by decrements in IQ scores in children" (AQCD, 2006).

Neurotoxic effects in children are among those best substantiated as occurring at blood-lead concentrations as low as 5 to 10 μg/dL (or possibly lower). Consistently, several recent epidemiologic studies have observed significant lead-induced IQ decrements in children with peak blood lead levels < 10 μg/dL (e.g., Canfield, et al., 2003; Lanphear, et al.., 2005) and, in some cases possibly below 5 μg/dL (Bellinger and Needleman, 2003; Tellez-Rojo et al., 2006). An international pooled analysis of seven prospective studies with a total of 1,333 children estimated a decline of 6.2 IQ points for an increase in concurrent blood lead levels from <1 to10 μg/dL.

Due to the strength of evidence for association with blood lead levels below 10 ug/dL, and the strength of the dose-response information at these exposure levels, neurocognitive impact, specifically decrement in IQ in young children, is a focus of this assessment.

References

Bellinger, D. C.; Stiles, K. M.; Needleman, H. L. (1992) Low-level lead exposure, intelligence and academic achievement: a long-term follow-up study. Pediatrics 90: 855-861.

Bellinger, D. C.; Needleman, H. L. (2003) Intellectual impairment and blood lead levels [letter]. N. Engl. J. Med. 349: 500.

Canfield, R. L.; Henderson, C. R., Jr.; Cory-Slechta, D. A.; Cox, C.; Jusko, T. A.; Lanphear, B. P. (2003) Intellectual impairment in children with blood lead concentrations below 10 μg per deciliter. N. Engl. J. Med. 348: 1517-1526.

Chiodo, L. M.; Jacobson, S. W.; Jacobson, J. L. (2004) Neurodevelopmental effects of postnatal lead exposure at very low levels. Neurotoxicol. Teratol. 26: 359-371.

Cooney, G. H.; Bell, A.; McBride, W.; Carter, C. (1989) Low-level exposures to lead: the Sydney lead study. Dev. Med. Child Neurol. 31: 640-649.

Cooney, G.; Bell, A.; Stavrou, C. (1991) Low level exposures to lead and neurobehavioural development: the Sydney study at seven years. In: Farmer, J. G., ed. International conference: heavy metals in the environment, v. 1; September; Edinburgh, United Kingdom. Edinburgh, United Kingdom: CEP Consultants, Ltd.; pp. 16-19.

Dietrich, K. N.; Berger, O. G.; Succop, P. A.; Hammond, P. B.; Bornschein, R. L.
(1993a) The developmental consequences of low to moderate prenatal and postnatal lead
exposure: intellectual attainment in the Cincinnati Lead Study Cohort following school
entry. Neurotoxicol. Teratol. 15: 37-44.

Dietrich, K. N.; Berger, O. G.; Succop, P. A. (1993b) Lead exposure and the motor
developmental status of urban six-year-old children in the Cincinnati prospective study.
Pediatrics 91: 301-307.

Ernhart, C. B. (2006) Effects of lead on IQ in children [letter]. Environ. Health Perspect.
114: A85-A86.

Fulton, M.; Raab, G.; Thomson, G.; Laxen, D.; Hunter, R.; Hepburn, W. (1987) Influence
of blood lead on the ability and attainment of children in Edinburgh. Lancet (8544):
1221-1226.

Lanphear, B. P.; Howard, C.; Eberly, S.; Auinger, P.; Kolassa, J.; Weitzman, M.;
Schaffer, S. J.; Alexander, K. (1999) Primary prevention of childhood lead exposure: a
randomized trial of dust control. Pediatrics
103: 772-777.

Lanphear, B. P.; Dietrich, K.; Auinger, P.; Cox, C. (2000) Cognitive deficits associated
with blood lead concentrations < 10 μg/dL in U.S. children and adolescents. Public
Health Rep. 115: 521-529.

Lanphear, B. P.; Hornung, R.; Khoury, J.; Yolton, K.; Baghurst, P.; Bellinger, D. C.;
Canfield, R. L.; Dietrich, K. N.; Bornschein, R.; Greene, T.; Rothenberg, S. J.;
Needleman, H. L.; Schnaas, L.; Wasserman, G.; Graziano, J.; Roberts, R. (2005) Low-
level environmental lead exposure and children's intellectual function: an international
pooled analysis. Environ. Health Perspect. 113: 894-899.

Lanphear, B. P.; Hornung, R.; Khoury, J.; Yolton, K.; Dietrich, K. N. (2006) Lead and IQ
in children: Lanphear et al. respond [letter]. Environ. Health Perspect. 114: A86-A87.

Rogan, W. J.; Ware, J. H. (2003) Exposure to lead in children ― how low is low enough?
N. Engl. J. Med. 348: 1515-1516.

Téllez-Rojo, M. M.; Bellinger, D. C.; Arroyo-Quiroz, C.; Lamadrid-Figueroa, H.;
Mercado-García, A.; Schnaas-Arrieta, L.; Wright, R. O.; Hernández-Avila, M.; Hu, H.
(2006) Longitudinal associations between blood lead concentrations < 10 μg/dL and
neurobehavioral development in environmentally-exposed children in Mexico City.
Pediatrics 118: e323-e330.

Tong, S.; Baghurst, P.; McMichael, A.; Sawyer, M.; Mudge, J. (1996) Lifetime exposure
to environmental lead and children's intelligence at 11-13 years: the Port Pirie cohort
study. Br. Med. J. 312: 1569-1575.

U.S. Environmental Protection Agency. (1986) Air quality criteria for lead. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA-600/8-83/028aF-dF. 4v. Available from: NTIS, Springfield, VA; PB87-142378.

U.S. Environmental Protection Agency. (1986a) Air quality criteria for lead. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA/600/8-83/028aF-dF. 4v. Available from: NTIS, Springfield, VA; PB87-142378.

U.S. Environmental Protection Agency. (1986b) Lead effects on cardiovascular function, early development, and stature: an addendum to U.S. EPA Air Quality Criteria for Lead (1986). In: Air quality criteria for lead, v. 1. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; pp. A1-A67; EPA report no. EPA-600/8-83/028aF. Available from: NTIS, Springfield, VA; PB87-142378.

U.S. Environmental Protection Agency. (1990) Air quality criteria for lead: supplement to the 1986 addendum. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report no. EPA/600/8-89/049F. Available from: NTIS, Springfield, VA; PB91-138420.

U.S. EPA. (2006). Air Quality Criteria Document for Lead. National Center for Environmental Assessment, Research Triangle Park. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=158823

Wasserman, G. A.; Liu, X.; Popovac, D.; Factor-Litvak, P.; Kline, J.; Waternaux, C.; LoIacono, N.; Graziano, J. H. (2000) The Yugoslavia prospective lead industry study: contributions of prenatal and postnatal lead exposure to early intelligence. Neurotoxicol. Teratol. 22: 811-818.