2.0 HAZARD IDENTIFICATION

CHAPTER 2 SUMMARY

This chapter presents information on the toxicity of lead, through a discussion of how body-lead burden is measured, how lead works in the body, the resulting adverse health effects, and populations at risk. Elevated blood-lead concentration and selected Intelligence Quotient (IQ) measures are identified to represent the adverse health effects resulting from lead exposure. The elevated blood-lead concentration thresholds selected for this risk analysis are among those established by CDC as levels of concern. In addition, a large body of evidence suggests that IQ measures are impacted adversely in children exposed to lead. These endpoints are used in this risk analysis to estimate the benefits of the proposed §403 rule.

Blood-lead concentration is a commonly used measure of body lead burden. An extensive body of research relates health effects of lead exposure to blood-lead concentration. For example, lead-related reductions in intelligence, impaired hearing acuity, and interference with vitamin D metabolism have been documented in children at blood-lead concentrations as low as 10 to 15 µg/dL, with no apparent threshold. At higher exposure levels, these effects become more pronounced and other adverse health effects are observed in a broader range of body systems. Increased blood pressure, delayed reaction times, anemia, and kidney disease may become apparent at blood-lead concentrations between 20 and 40 µg/dL. Symptoms of very severe lead poisoning, such as kidney failure, abdominal pain, nausea and vomiting, and pronounced mental retardation, can occur at blood-lead levels as low as 60 µg/dL. At even higher levels, convulsions, coma, and death may result.

Figure 2-1 outlines the approach for the hazard assessment. The conclusions from the hazard assessment are presented in Section 2.6.

The goal of the hazard identification is to answer the following questions:

1. How is lead exposure measured in the human body?

2. What measure of body lead burden should be used in this risk analysis?

3. How does lead work in the body?

4. What adverse health effects are linked to lead exposure?

5. What is the best population for measuring the adverse health effects of lead exposure in this risk analysis?

6. What health endpoints should be quantified in the risk analysis?

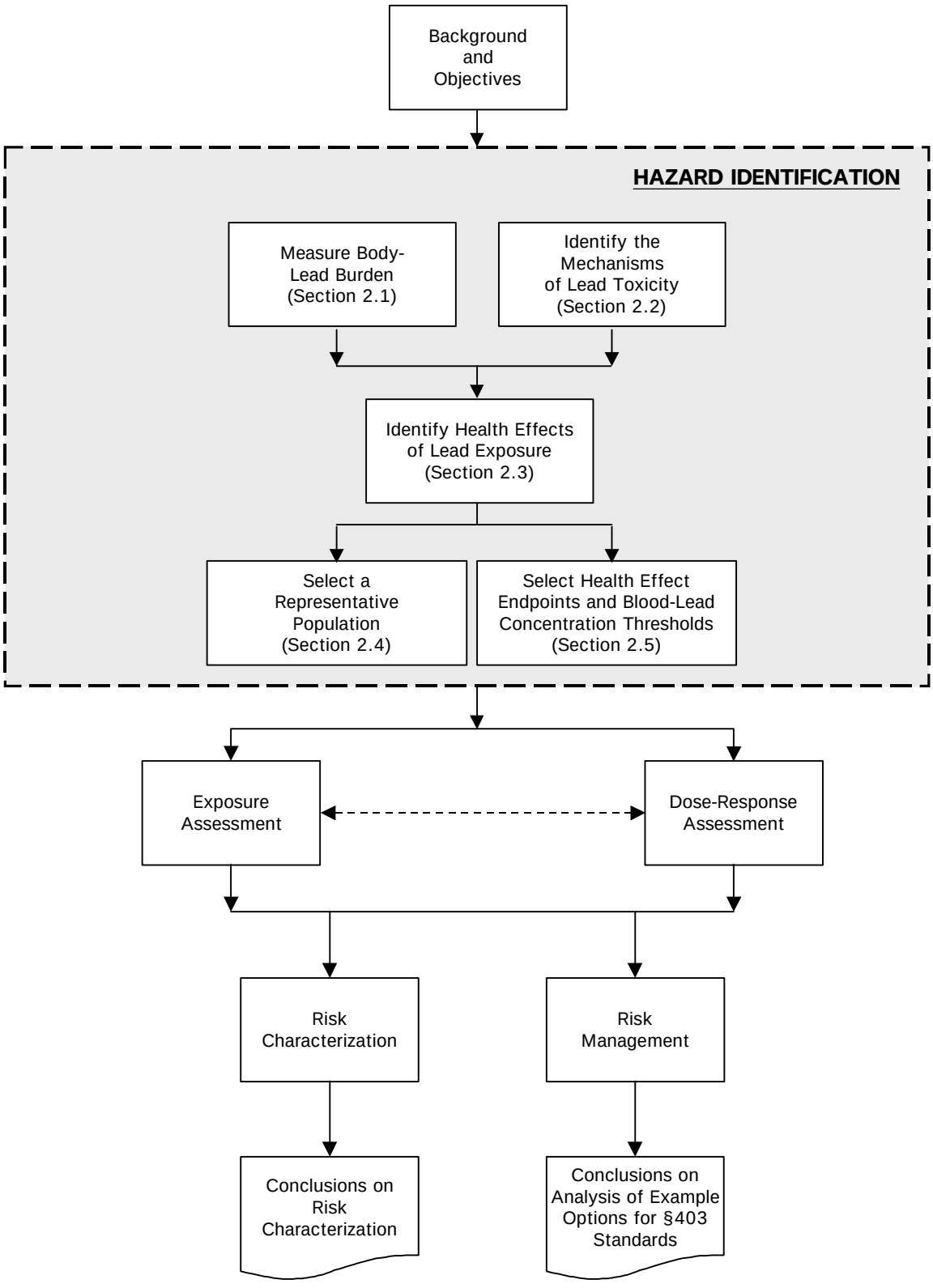

Figure 2-1. Detailed Flowchart of the Approach to Hazard Identification.

Questions 1, 3, and 4 identify the hazardous effects of lead exposure. Questions 2, 5, and 6 address how the risk due to lead exposure is assessed herein. Methods for quantifying the health endpoints identified in this chapter are described in the dose response assessment (Chapter 4). These methods are used in the risk characterization (Chapter 5) and risk management analysis (Chapter 6) to estimate the current and future risks of childhood lead exposure.

Figure 2-1 illustrates the relationship between the approach presented in this chapter and the risk analysis approach. The information presented in this chapter follows the flow of Figure 2-1 and the questions stated above. Namely, this chapter presents information on lead toxicity, through a discussion of how body-lead burden is measured (Section 2.1), how lead works in the body (Section 2.2), and the resulting adverse health effects (Section 2.3). This chapter documents several decisions that are relevant to the assessment of health risks due to lead exposure. These include the selection of blood-lead concentration as the measure of body lead burden (Section 2.1), selection of children aged 1-2 years as the representative population (Section 2.4), and selection of specific elevated blood-lead concentration and health effect endpoints (Section 2.5) that are used for the quantification of risk. The hazard characterization (Section 2.6) summarizes the materials presented in this chapter and addresses the strengths and weaknesses of the scientific evidence and decisions made, as they are relevant to this risk assessment.

There is an extensive body of literature relating health effects of lead exposure to measures of body-lead burden. This literature is summarized in several government reports, including

- Air Quality Criteria for Lead (USEPA, 1986)
- The Nature and Extent of Lead Poisoning in Children in the United States: A Report to Congress (ATSDR, 1988a)
- Air Quality Criteria for Lead: Supplement to the 1986 Addendum (USEPA, 1990a)
- Comprehensive and Workable Plan for the Abatement of Lead-Based Paint in Privately Owned Housing (HUD, 1990)
- Preventing Lead Poisoning in Young Children (CDC, 1991)
- Toxicological Profile for Lead (ATSDR, 1993)

These sources were used extensively in the next sections, although the original sources are cited for specific results whenever possible.

2.1 MEASURES OF BODY-LEAD BURDEN

For purposes of risk assessment, it would be ideal to precisely relate particular health outcomes, such as learning deficits or decreased motor coordination, to environmental lead levels. Unfortunately, most studies of lead in the environment use measures of body-lead burden, such as blood-lead concentration, as biomarkers of lead exposure. Similarly, studies that assess lead

hazard interventions tend to use blood-lead concentration to measure intervention effectiveness (USEPA, 1995b). There is extensive evidence that body-lead burden is associated with lead levels in environmental media (USEPA, 1986; CDC, 1991). In addition, there is an extensive body of literature relating health effects of lead exposure to measures of body-lead burden (ATSDR, 1993; CDC, 1991).

The most common screening and diagnostic measure of body-lead burden is blood-lead concentration. Blood-lead concentration has the advantage of being easily and inexpensively measured. A disadvantage, however, is that it reflects a mixture of both recent and past exposure. Because lead cycles between the blood and bone, a single blood lead measurement cannot distinguish between low-level chronic exposure and high-level acute exposure (ATSDR, 1993). Both types of exposure could result in the same blood-lead concentration. Despite this limitation, blood-lead concentration remains the one readily accessible measure that can demonstrate in a relative way the relationship of various effects to changes in lead exposure (ATSDR, 1993).

Other measures of body-lead burden include lead in bones, teeth, and hair. Of the other measures, bone and tooth lead may be used to measure cumulative exposure to lead, while hair lead is an indicator of more recent exposure. Bone-lead content may be measured by x-ray fluorescence (XRF), although the reliability of this method has been questioned in the past (Wedeen, 1988). While the reliability of the XRF method to measure bone-lead has improved in recent years, it is still used primarily for research. Since teeth can store lead up to the time of shedding or extraction, levels of lead in shed teeth have been used as an indicator of lead exposure in some studies (Smith et al., 1983; Bergomi, et al., 1989; Pocock et al., 1989; Needleman et al., 1990). Hair lead has been used as an indicator for intermediate exposure (2 months) in children (Wilhelm et al., 1989). However, artificial hair treatments such as dyeing, bleaching, or permanents, can invalidate metal analysis of hair in adults (Wilhelm et al., 1989). In addition, external surface contamination problems make it difficult to differentiate between externally and internally deposited lead (USEPA, 1986). Due to the disadvantages associated with using bone, tooth, and hair lead as biomarkers of exposure, most researchers in the area of lead exposure conclude that blood lead is the most efficient and useful way to assess body lead burden.

Physiological changes that are known to implicate lead exposure may also be used as biomarkers of exposure. For example, interference with heme synthesis following lead exposure can lead to a reduction of hemoglobin concentration in blood (Bernard and Becker, 1988) and an increase in urinary coproporphyrin (USEPA, 1986). In addition, the concentration of erythrocyte protoporphyrin (EP) rises above background at blood-lead levels of 25 to 30 µg/dL and there is an association between blood-lead levels and EP (Hernberg et al., 1970; CDC, 1985). The level of EP in blood is used as an indicator of past chronic exposure, since elevated EP reflects average blood-lead levels for about 4 months following the exposure (Janin et al., 1985). In the case of each of these physiological measures, other conditions may produce similar effects, leading to false positive outcomes when these measures are used alone as biomarkers for body lead burden. Thus, generally, blood-lead levels are determined concurrently with these physiological biomarkers.

2.2 MECHANISMS OF LEAD TOXICITY

Lead is a very dynamic element with a wide spectrum of effects in humans. Its effects are seen at the subcellular level as well as at the level of general function that encompasses all systems in the body. The subcellular mechanisms of action are included in this section, followed by a discussion of the neurotoxic effects and the heme effects of lead poisoning. Wherever possible, mechanisms included in the subcellular mechanisms section are related to the specific effects of lead on the nervous system and the blood. There remain many gaps, however, in the information needed to explain the varied mechanisms of lead in different organs.

Lead primarily enters the body through ingestion (eating and drinking) and inhalation (breathing in air). It can also pass through the skin. Lead is absorbed, distributed throughout the body, and removed from the body (excreted). The rate of lead absorption into the body depends on the chemical and physical properties of the form of lead and the physiological characteristics of the exposed person. For example, when inhaled, factors such as the lead particle size and shape and the individual's ventilation rate influence how lead will be deposited in and absorbed by the respiratory tract. Large particles, which may be encountered in an occupational setting, tend to be deposited in the upper airways and may be indirectly absorbed by swallowing and absorption in the stomach. Smaller particles tend to be deposited in the bronchial region of the lung, and particles less than one micron, which is typical for urban air, reach the lower respiratory tract where they can be directly absorbed across the thin walls of the alveolar sacs and enter the blood. Ventilation rate is important because altering the inhalation rate may increase or decrease the amount of the lead ultimately absorbed by the lung (Klaassen, 1993). The respiratory deposition of airborne lead encountered in the general population ranges from 30-50 percent (Kehoe, 1961 a,b,c; Nozaki, 1966; Chamberlain, 1978; Morrow, 1980; Gross, 1981). Several studies conducted in humans (Rabinowitz, 1977; Chamberlain, 1978; Morrow, 1980) and animals (Pott and Brockhaus, 1971; Boudene, 1977; Rendall, 1975; Morgan and Holmes, 1978; Greenhalgh, 1979) have indicated that lead deposited in the lower respiratory tract is completely absorbed. Thus, the absorption rate is governed by the deposition rate and 30-50% of inhaled lead is absorbed (USEPA, 1986). A respiratory deposition/absorption rate of 25-45% has been estimated for children (USEPA, 1989a).

The amount of lead absorbed from the gastrointestinal tract of adults is 10-15% of the amount ingested (Kehoe, 1961a,b,c; Hursh and Suomela, 1968; Harrison, 1969). In pregnant women and children, the amount of lead absorbed via ingestion can increase to 50% (Alexander, 1973; Heard and Chamberlain, 1982; Rabinowitz and Needleman, 1982; USEPA, 1979). The amount of lead absorbed by ingestion greatly increases during periods of iron or calcium deficiency. Once absorbed, lead is distributed by the blood to the mineralizing tissues (bone and teeth) and soft tissues (kidney, bone marrow, liver and brain). For adults, following exposure to a single dose of lead, one-half of the lead from the original exposure remains in the blood for about 25 days after exposure, in soft tissues it remains for about 40 days, and in bone for more than 25 years (Rabinowitz et al., 1976). Consequently, after a single exposure, a person's blood-lead concentration may begin to return to normal, but the total body burden (amount of lead in the body) may still be elevated.

2.2.1 Physiological Mechanisms

The biological basis for many aspects of lead toxicity appears to relate to lead's ability to bind (attach) to substances crucial to various physiological functions. For example, lead may interfere with cell function by competing with essential minerals such as calcium and zinc for binding sites on membranes and proteins. Lead binding to enzymatic proteins can inhibit the activity of the enzyme and alter the processing of other chemicals (metabolism). Lead binding to membranes or transport proteins can inhibit or alter ion transport across the membrane or within a cell. The effects of lead are modulated by its distribution in the body, its affinity for various binding sites, and differences in cellular composition and structure within tissues and organs. As a result, there is no single well-defined mechanism that explains the toxicological activity of lead in all tissues (USEPA, 1986).

Studies of the mechanism of lead toxicity at the cellular level implicate cell and subcellular (organelle) membranes as a primary target for lead (USEPA, 1986). Lead-induced alterations of ion transport, particularly calcium ions, are related to a number of the health effects associated with lead exposure. Effects on ion-transport lead to inhibition of enzymes and or signaling proteins and interferes with normal cellular processes. The overall impact of these effects is to disturb the development and functioning of many organ systems, particularly the central nervous system (USEPA, 1986).

The mitochondria appear to be particularly sensitive to lead (USEPA 1986). Lead causes both structural changes and disturbances in mitochondrial function. Mitochondria exposed to lead expand or swell and there is distortion and loss of the small folds of the inner membrane called the cristae. The mitochondrial enzymes responsible for cellular respiration are largely located within the cristae. Thus, lead uncouples energy metabolism and inhibits cellular respiration (USEPA, 1986). Lead also alters the mitochondrial distribution of calcium (USEPA, 1986).

2.2.2 Neurotoxic Effects of Lead

The mechanisms for lead neurotoxicity are not well understood. Several mechanisms have been proposed to explain why children are more sensitive than adults to the neurotoxic effects of lead and how lead affects the nervous system on the molecular level.

For over a decade, the hippocampus has been considered to be the principal target of lead in the brain because: 1) the hippocampus contains relatively high concentrations of zinc, and zinc-dependent functions may be sensitive to lead, 2) the hippocampus contains a dense plexus of cholinergic fibers that are affected by lead exposure, and 3) the hippocampus functions in memory and learning (Petit, 1983). More recent investigations have shown that other areas of the brain, particularly the mesolimbic system (Lasley and Lane, 1988; Moresco et al., 1988), where low levels of lead have been found, cannot be excluded as a target site. Continuing research may help to determine which areas of the brain have an affinity for lead and are affected by it.

A number of scientists working on the neurotoxicity of lead have proposed mechanisms of how lead affects the nervous system. Among these scientists, Silbergeld (1992) and Bellinger

(1995) both discuss possible mechanisms for lead neurotoxicity in the context of neurodevelopmental and neuropharmacological effects.

Neurodevelopmental Effects: During development, the central nervous system (the brain and spinal cord) goes through a number of changes involving an overall growth in cell numbers, with a resultant increase in the size of the organ. In addition, cells develop specialized functions and there is a proliferation and outgrowth of the nerve cell projections that establish connections between cells (Silbergeld, 1992). Many substances regulate these processes, including growth factors, neurotransmitters functioning as trophic agents, and glycoprotein cell adhesion molecules (Jacobson, 1990).

One of the potential mechanisms for lead's effect on the developing brain has been investigated by Goldstein (1990), who suggests that the immature endothelial cells forming the capillaries of the developing brain are more permeable to lead than are capillaries from mature brains. As a result, lead in the blood may easily pass into the newly forming compartments of the brain and affect many parts of this developing organ. In comparison, the capillaries of adults are developed and help to prevent the passage of lead (in its ionic form) across the blood-brain barrier. It has been suggested that lead may affect the differentiation of capillary endothelial cells in the fetal brain, similar to the way it affects developing neurons (Bressler and Goldstein, 1991). This hypothesis provides a basis for the increased risk of pregnant women, infants, and young children to the neurotoxic effects of lead.

Silbergeld (1991) found that exposure of fetal animals to lead affects both regional growth and neuron-specific differentiation/synaptogenesis (development of synapses) in the central nervous system. Of these, synaptogenesis appears to be the more sensitive (Regan, 1989; Silbergeld, 1991). A synapse is a junction where the axon of one neuronal cell (or neuron) terminates with the dendrite of another neuron. Nerve impulses move from one nerve cell to another by traveling through the synapse. The normally functioning brain seems to exhibit a deletion of synapses that are unused. Synapses which are frequently used are kept and strengthened. Goldstein (1990, 1992) suggests that lead may disrupt, or delay, this normal synaptic developmental process, and that perhaps the resulting connections in the brain are "poorly chosen," leading to functional impairment. Although this hypothesis is speculative, lead's ability to facilitate the unstimulated release or prevent the stimulated release of neurotransmitters, which are important for the morphological organization of neurons, may be related to how neurons are chosen to survive (Audesirk, 1985). This may result in a nervous system that appears normal but in which cell to cell connections are not normal. These abnormalities may be translated into neurobehavioral deficits which result in cognitive and behavioral deficits.

Neuropharmacological Effects of Lead: Lead may also act as a neuropharmacological toxicant in the brain (Silbergeld, 1992; Bellinger, 1995). Silbergeld (1992) proposes that lead interferes with the synaptic release of neurotransmitters from neurons and signal transduction. Theoretically, these effects are reversible if lead is removed from the synapse. However, exposure to lead for a long time may result in permanent alteration in cellular responsiveness at pre- and post-synaptic levels. The pharmacologic effects of lead may include facilitated transmitter release,

modulation of ion conductance and, as a result, altered the electrophysiological output of the neuron.

Disruption of ion transport at membranes may be the mechanism by which lead produces its pharmacologic effects in the nervous system. Lead can substitute for calcium and zinc in ion transport events at the synapse. While the exact biochemical mechanisms of lead toxicity are unknown, at least some of its deleterious effects are attributed to interference with the functions of sodium channels, calcium channels, calcium-binding modulators like calmodulin, messengers like adenyl cyclase and protein kinase C (Bessler and Goldstein, 1991). Lead may affect ion channels by occupying zinc-binding sites and preventing ion movements (Alkondon, 1990).

At the neuron, mitochondrial release of calcium is quite sensitive to lead (Silbergeld and Adler, 1978). Protein kinase C, which is very sensitive to lead, modulates receptor currents affecting long-term potentiation and other forms of synaptic response that may underlie learning and memory (Markovac and Goldstein, 1988). Dopamine-sensitive adenyl cyclate and (Na+,K+)-ATPase, are also relatively sensitive to lead (Ewers and Erbe, 1980, Fox, 1991). Neurotransmitter release or transmitter-gated ion channels are sensitive to higher concentrations of lead (Kostial and Vouk, 1957; Silbergeld et al., 1974; Audesirk, 1985; Minnema et al., 1986; Alkondon et al., 1990).

The differential ability to prevent lead entry into the neuron may be an important protective mechanism to prevent the neurotoxic effects of lead. There has been speculation of a lead-binding protein in humans (DuVal and Fowler, 1989) which may serve to concentrate and transport lead to certain parts of the brain.

Peripheral Neuropathy: Lead induces degeneration of the protective Schwann cells in the motor neurons of the peripheral nervous system. This causes segmental loss of the myelin covering of the neuron and possible neuron degeneration (Fullerton, 1966). Dyck et al., (1980) and Windebank et al. (1980) suggest that lead induces a breakdown in the blood-nerve barrier, allowing lead and fluid to enter the endoneurium and disrupt the myelin membranes. The degeneration of sciatic and tibial nerve roots is also possible. Sensory nerves are less sensitive to lead than motor nerves. Peripheral neuropathy is usually present only after prolonged high exposure to lead. Studies of occupationally exposed workers indicate that motor nerve dysfunction can occur at blood-lead levels below 70 µg/dL, possibly as low as 30 µg/dL (Araki et al., 1980 and 1992; Rosen et al., 1983; Seppalainen, et al., 1983; Hirata and Kosaka, 1993; Chia et al., 1996), when assessed clinically by the electrophysiologic measurement of nerve conduction velocities. There is some evidence that these effects may be reversible (Araki et al., 1980; Muijser et al., 1987).

2.2.3 Hematologic Effects of Lead

Lead has adverse effects on heme synthesis and red blood cell formation. These effects can result in anemia and decreased life span of red blood cells. Hemoglobin is a major constituent of red blood cells. Hemoglobin consists of the protein globin and heme, which is a metal complex consisting of an iron atom in the center of a porphyrin structure. The oxygenated form of

hemoglobin provides the red color to red blood cells. The effects of lead on heme synthesis and hemoglobin production are described in detail in two reports, the Air Quality Criteria for Lead (USEPA, 1986) and The Nature and Extent of Lead Poisoning in Children in the United States: A Report to Congress (ATSDR, 1988a). A short summary follows.

Effect of Lead on Heme Synthesis: When an individual is exposed, lead quickly reaches the blood, circulates in the body, and enters different tissues including the bone marrow, where it can have an impact on various reactions involved in the formation of heme. The process of heme biosynthesis starts with glycine and succinyl-coenzyme A, proceeds through the formation of a molecule called protoporphyrin IX, and culminates with the insertion of iron into the porphyrin ring to form heme. In addition to being a constituent of hemoglobin, heme is found in many hemoproteins, such as myoglobin, the P-450 component of the mixed-function oxidase system, and the cytochromes of cellular energetics. Therefore, disturbing heme biosynthesis by exposure to lead poses the potential for multiple-organ toxicity.

Lead's mechanism of action seems to be due to its effect on cellular mitochondria. Lead enters the mitochondria of the cell where it impairs mitochondrial function and thus adversely impacts the production of heme. In the mitochondria, lead increases the activity of the enzyme, δ-aminolevulenic acid synthetase (ALA-S), which increases the amount of δ-aminolevulinic acid (ALA) formed. Lead, in the cytosol of the cell, decreases the activity of δ-aminolevulenic acid dehydrase (ALA-D), an enzyme that catalyzes reaction of ALA in heme biosynthesis. The result is an increase in the level of ALA (a potential neurotoxin) and a decrease in the production of the porphyrin needed for heme synthesis.

Ferrochelatase, an enzyme also found in the mitochondria, catalyzes the incorporation of iron into protoporphyrin IX to form heme. Lead tends to inhibit ferrochelatase from incorporating the iron into the protoporphyrin ring, thereby preventing the formation of heme. Instead, there is an increase in erythrocyte protoporphyrin in the red blood cells. Erythrocyte protoporphyrin (EP) can be measured in blood as zinc protoporphyrin (ZPP) or free erythrocyte protoporphyrin (FEP).

Effect of Lead on Hemoglobin Production and Red Cell Formation: As described above, heme production is decreased by lead. Heme production mediates globin production through a synchrony between the rates of globin and heme syntheses. In the absence of heme, the polyribosomes disaggregate and globin synthesis ceases. Accordingly, globin production is decreased, resulting in decreased production of hemoglobin. These effects can lead to anemia (reduction in circulating red blood cell mass.) Lead exposure can lead to anemia in two ways. It causes increased destruction of the red blood cells (hemolysis) and impairs red cell formation resulting in hypochromatic (light colored) normocytic (normal size) cells.

The molecular mechanism for the diminished red cell life span is thought to be due to lead's inhibition of the active transport (Na+, K+)-ATPase enzyme system. If the active transport is paralyzed, the cells accumulate sodium and water until a critical volume is reached and then hemolysis (destruction of cells through rupture of the cell membrane) ensues. Also, enzymes such as glucose-6-phosphate dehydrogenase (G6PD) may be affected by lead. G6PD catalyzes the initial step in the pentose phosphate pathway of carbohydrate metabolism, through which the

reduced gluthathione reductase (GSH) is generated for maintaining the sulfhydryl groups within the red blood cell and perhaps the red blood cell membrane.

2.3 HEALTH EFFECTS OF LEAD EXPOSURE

Lead is a powerful toxicant with no known beneficial purpose in the human body (ATSDR, 1988a). The toxic effects of lead are seen primarily in the central nervous system, but virtually all parts of the body can be damaged at high exposure levels. Specific health effects from lead exposure, the blood-lead levels at which these effects have been observed, and the scientific literature in which the effects were reported are summarized in Table B-1 in Appendix B. This table is reproduced from the *Toxicological Profile for Lead* (ATSDR, 1993).

2.3.1 Neurological Effects of Lead

The most severe neurological effect of lead is encephalopathy. Early symptoms of encephalopathy include irritability, poor attention span, headache, muscular tremor, loss of memory, and hallucinations. As encephalopathy increases more severe symptoms appear, including delirium, convulsions, paralysis, coma, and death (Kumar et al., 1987). High-level exposure to lead produces encephalopathy in children, starting with blood-lead levels of approximately 80 to 100 µg/dL (Bradley and Baumgartner, 1958; Gant, 1938; Bradley et al., 1956; NAS, 1972; Rummo et al., 1979; Smith et al., 1983; EPA, 1986).

The effect of lead on intelligence quotient (IQ) and other developmental indicators is well-established for children with markedly elevated blood-lead concentrations. For example, five point IQ decrements, fine motor dysfunction, and altered behavioral profiles were reported among preschool children who ingested paint and plaster (pica) and whose blood-lead levels were greater than 40 µg/dL (mean of 58 µg/dL), when compared with matched controls who did not eat paint and plaster (de la Burde and Choate, 1972). At age 7 to 8, a three point IQ decrement and impairment in learning and behavior were reported for these children, even though blood-lead levels had declined (de la Burde and Choate, 1975). Blood-lead concentrations for control children were not reported, but, given the date of the study, children in the control population may have had what would now be considered elevated blood-lead levels. A study that included children who had previously had encephalopathy indicated that these children had increased incidence of hyperactivity and IQ decrements of approximately 16 points resulting from lead exposure (Rummo et al., 1979). In the same study, asymptomatic children with long-term exposure (mean blood-lead levels of 51-56 µg/dL) had IQ decrements of 5 points on average, compared to control children (mean blood-lead levels of 21 µg/dL).

Long-lasting impacts on intelligence, motor control, hearing, and neurobehavioral development of children also have been documented at blood-lead levels that are not associated with obvious symptoms and were once thought to be safe.

Results are available from four large-scale, longitudinal studies of lead exposed children conducted in Boston, Cincinnati, Cleveland, and Port Pirie, Australia. These studies indicate that disturbances in early neurobehavioral development occur at exposure levels that until recently were considered safe, or even normal. In the Boston study, 4-8 point differences in performance

on the Bayley Mental Development Index (MDI) were reported at 6, 12, 18, and 24 months, after adjusting for other covariates, when children with low blood-lead levels (prenatal mean of 1.8 µg/dL) were compared to children with high blood-lead levels (prenatal mean of 14.6 µg/dL) (Bellinger et al., 1985a, 1985b, 1986a, 1986b, 1987a). These findings were confirmed in more recent studies (Bellinger et al., 1989a, 1989b). Additional follow-up showed that deficits in McCarthy General Cognitive Index scores at age 5 were significantly correlated with blood-lead levels at age 24 months, although not with prenatal blood lead measures (Bellinger et al., 1991). Similar results were reported in the Cincinnati study (Dietrich et al., 1986, 1987a, 1987b). These study results suggest that the effect of prenatal lead exposure on the MDI was mediated in part through its effects on birth weight and gestational age, which were each significantly associated with MDI scores (Dietrich et al., 1987a). Results reported for the Cleveland study were mixed, but while the authors tended to conclude that there was not strong evidence of developmental effects of lead (Ernhart et al., 1985, 1986, 1987; Wolf et al., 1985; Ernhart and Green, 1990), other reviewers suggest that such effects may be inferred from the reported results (EPA, 1986; Davis and Svendsgaard, 1987; ATSDR, 1993). In the Port Pirie study, reduced MDI scores at 24 months were associated with postnatal blood-lead levels measured at age 6 months, but not with prenatal exposure measured through cord and maternal blood-lead levels (Vimpani et al., 1985, 1989; Baghurst et al., 1987; Wigg et al., 1988). Results of a follow-up neurobehavioral assessment conducted at age 3 to 4 years, using the McCarthy Scales of Children's Abilities, indicated significant inverse correlations between postnatal blood-lead levels (geometric means of 14 µg/dL at 6 months and approximately 21 µg/dL at 15 and 24 months) and ability test scores (McMichael et al., 1988).

In addition to the effects on early neurobehavioral development, all four studies report lower IQ scores at school-age for children who had earlier exhibited elevated blood-lead levels. In Boston, slightly elevated blood-lead levels at age 24 months (mean of 6.5 µg/dL) were associated with intellectual and academic performance deficits at age 10 years (Bellinger, 1992). In Cincinnati, postnatal blood-lead levels measured through age 3 years were inversely associated with IQ scores measured at age 5, although the effect was not statistically significant when adjusted for covariates (Dietrich et al., 1993). In Cleveland, a significant association was reported between blood-lead concentration at age 2 (mean of 16.7 µg/dL) and IQ measured at 5 years (Ernhart et al., 1989). In Port Pirie, statistically significant associations were reported between IQ measured at age 7 and blood-lead levels from birth through age 7, with the strongest associations for blood-lead levels measured at 15 months to 4 years (Baghurst et al., 1992).

Taken together, these studies provide strong evidence that low-level prenatal or early postnatal exposure to lead results in neurobehavioral developmental delays that persist through age 5. Strong relationships between blood-lead concentration in early childhood, age 15 months to 4 years, and IQ scores were also reported, even when only slight elevations in blood-lead levels were present.

Additional evidence of IQ point loss associated with lead exposure in school-age children is reported in cross-sectional studies throughout the world. For example, a study of Danish children related tooth-lead concentration to performance on several psychometric tests (Hansen et al., 1989). Children with elevated tooth-lead levels (above 18.7 µg/g) were matched by sex and

socioeconomic status with children with lower levels (below 5 µg/g). High lead children scored lower on the Wechsler Intelligence Scales for Children (WISC) IQ test than children with lower lead levels, although no difference in scores was observed for the Performance IQ and several experimental tests. Impaired neuropsychological functioning due to lead exposure was observed through differences in performance on the Bender Visual Motor Gestalt Test and on a behavioral rating scale. In addition, a study of school children in Edinburgh, Scotland (Fulton et al., 1987) found that elevated blood-lead levels (mean of 11.5 µg/dL) were associated with lower scores on IQ tests and on mathematical and reading attainment tests, after adjusting for covariates. No threshold in the relationship, below which lead does not have an effect on intelligence and attainment, was observed even for blood-lead concentrations below 10 µg/dL. A study of Chinese children (Wang et al., 1989) also reported a significant dose-response relationship between blood-lead concentration (above 10 µg/dL) and IQ scores, after adjusting for covariates.

A significant effect of lead on IQ is not uniformly reported, however. Children randomly selected from birth records in Birmingham, United Kingdom, were assessed using a variety of cognitive, performance, neuropsychological, and behavioral endpoints (Harvey et al., 1988). The effect of lead (mean of 13.5 µg/dL) was not significant for most endpoints, and for none of the three IQ measures. In a study of 6 year old children in London, both tooth lead and blood lead were examined as predictors of intelligence (Smith et al., 1983; Pocock et al., 1989). Neither measure of lead exposure was a significant predictor, once social factors were controlled. No evidence of an association between blood-lead levels (mean of 12.75 µg/dL) and intelligence was reported in another study of London children that included more middle class families (Lansdown et al., 1986).

A possible explanation for these seemingly contradictory results is that the effect of lead on IQ may be overshadowed by the effects of home and societal factors, such as birth order, parental IQ and level of education, and socioeconomic status. For example, a study of 104 children under age 7 and of lower socioeconomic status indicated that MDI and IQ scores were significantly associated with blood-lead levels ranging from 6 to 59 µg/dL, after controlling for socioeconomic and other factors (Schroeder et al., 1985). In a five-year follow-up of 50 of these children, IQ was inversely correlated with initial and concurrent blood-lead levels, but the effect of lead was not significant when socioeconomic status and other covariates were included in the analysis (Schroeder and Hawk, 1987). However, in a replication of the study among children of uniformly low socioeconomic status, the effect of lead was evident at both the initial and five-year follow-up (Hawk et al., 1986; Schroeder and Hawk, 1987). These results suggest that the effects of lead may be more easily detected in groups with similar home and societal backgrounds.

Both current and long-term indicators of lead exposure have been studied to establish which indicator was most strongly correlated with psychometric test scores (Bergomi et al., 1989). Total and verbal IQ scores were negatively correlated with tooth-lead levels and δ-aminolevulenic acid dehydrase activity. Tooth-lead levels were also negatively correlated with Toulouse Pieron test results, which evaluate figure identification ability, discrimination, and attention. The most predictive measure of lead exposure was tooth lead, which is indicative of cumulative lead exposure. Blood lead, which is indicative of a mix of current and past exposure, and hair lead, which is indicative of short-term exposure, had little predictive value in this study.

A study of the long-term effects of low-level lead exposure found that children with higher dentin lead levels were more likely to drop out of high school and have a reading disability (Needleman et al., 1990). Higher lead levels were also associated with lower ranking in high school class and increased absenteeism. Lower scores on vocabulary and grammatical-reasoning tests were reported, along with poor hand-eye coordination, delayed reaction times, and slowed finger tapping, compared to children with lower lead exposure. Earlier results indicated that children with high dentin lead levels had deficits in IQ scores, speech and language processing, attention, and classroom performance in first and second grades (Needleman et al., 1979). IQ deficits continued through the fifth grade. In addition, children with higher lead levels needed more special academic services and had a higher failure rate in school (Bellinger et al., 1986c).

A lead-related decrease in hearing acuity has been reported in young children, with hearing thresholds at 2000 Hz increasing with blood-lead levels in the range of 6 to 59 µg/dL (ATSDR, 1993). Analysis of NHANES II data indicated that the probability of increased hearing thresholds at 500, 1000, 2000, and 4000 Hz was associated with increased blood-lead levels from below 4 µg/dL to over 50 µg/dL. In addition, this study reported increased probability that a child was hyperactive and delayed developmental milestones (age at which child first sat up, walked, and talked) associated with elevated blood lead (Schwartz and Otto, 1987).

2.3.2 Other Effects of Lead

Hematological Effects: The effects of lead on the blood's biochemical functions are interrelated and have variable biological impact. Heme (the component of hemoglobin that binds iron) is critical to the basic function of all cells due to its presence in the cytochromes involved in energy production. As noted earlier, lead can disturb the formation of hemoglobin leading to anemia at high exposure levels. The heme-mediated generation of an important hormonal metabolite of vitamin D (1,25-dihydroxyvitamin D) may be disturbed by lead. This hormone serves a number of functions in humans, including the regulation of calcium metabolism. In addition to the direct effects of lead on heme biosynthesis, there are potentially significant indirect impacts on the central nervous system, caused by the accumulation of the potential neurotoxicant, δ-aminolevulenic acid. Lead also inhibits coproporphyrin utilization and the conversion of zinc erythrocyte protoporphyrin (ZPP) into heme. The effects of lead on heme biosynthesis are described in the *Air Quality Criteria for Lead* (USEPA, 1986).

Death: It is well known that severe lead poisoning can lead to encephalopathy and death. There is some evidence, too, of higher death rates due to cerebrovascular disease among lead workers (Malcolm and Barnett, 1982; Fanning, 1988; Michaels et al., 1991). In infants, high lead levels have been suggested to cause Sudden Infant Death Syndrome (SIDS) (Drasch et al., 1988).

Hypertension: There may be a relationship between lead exposure and hypertension. Increased heart rate and hypertension were observed in occupationally exposed workers after only four weeks of exposure to high levels of lead (Marino, et al., 1989). Hypertension has also been associated with lead exposure in the general population (Khera et al., 1980; Pirkle et al., 1985; Harlan, 1988; Harlan et al., 1988), although the evidence is mixed (Pocock, et al., 1984, 1985, 1988; Gartside, 1988; Coate and Fowles, 1989).

Gastrointestinal Effects: Colic is a consistent early symptom of lead poisoning. Colic is characterized by the following symptoms: abdominal pain, constipation, cramps, nausea, vomiting, anorexia, and weight loss. Although these symptoms typically occur at blood-lead levels of 100 to 200 µg/dL, they have sometimes been noted in workers whose blood-lead levels were as low as 40 to 60 µg/dL (Table B-1).

Renal Effects: Both acute and chronic nephropathy (kidney disease) are known to be caused by elevated lead exposure. The symptoms of acute nephropathy appear to be reversible. The symptoms of chronic nephropathy, on the other hand, are irreversible. Acute nephropathy has been reported in children and lead workers, while chronic nephropathy is usually reported only in lead workers. A summary of studies reporting acute or chronic nephropathy may be found in ATSDR, 1993. Additional detail is reported in USEPA, 1986.

Vitamin D Metabolism: Lead may interfere with the conversion of vitamin D to its hormonal form, 1,25-dihydroxyvitamin D. This effect is most apparent in studies of children with high lead exposure (Rosen et al., 1980; Mahaffey et al., 1982). No effect of lead on vitamin D metabolism was observed in a study of children who received adequate amounts of calcium, phosphorus, and vitamin D in their diet and had low to moderate lead exposure. The average lifetime blood-lead levels for these children ranged from 4.9 µg/dL to 23.6 µg/dL (Koo et al., 1991).

Thyroid: There is some evidence that lead may adversely affect thyroid function in occupationally exposed workers (Tuppurainen et al., 1988). However, no effects of lead on thyroid function have been reported in children (Siegel et al., 1989).

Growth: A number of epidemiological studies have reported an association between blood-lead levels and growth in children (Nye, 1929; Johnson and Tenuta, 1979; Lauwers et al., 1986; Schwartz et al., 1986; Lyngbye et al., 1987; Angle and Kuntzelman, 1989). However, a study of lead-poisoned subjects and nonexposed sibling controls failed to establish an association between blood-lead levels and growth or the genetic predisposition for adult height (Sachs and Moel, 1989). Moreover, a recent longitudinal study in Cleveland found no statistically significant relationship between blood-lead levels and growth (height, weight, and head circumference) from birth through age 4 years and 10 months (Greene and Ernhart, 1991). However, a separate analysis of 260 infants from this study found that growth rates, measured as covariate-adjusted increases in stature from 3 and 15 months of age, were inversely correlated with corresponding increases in blood-lead levels, although the observed relationship was statistically significant only for infants exposed to higher prenatal blood-lead levels (maternal blood-lead concentration >7.7 µg/dL) (Shukla et al., 1987, 1989).

Development: Lead-related effects on children's development, such as reduced birth weight, reduced gestational age, and neurobehavioral developmental deficits, have been reported. The evidence for effects on birth weight and gestational age is mixed, with some studies reporting reductions associated with lead exposure (Moore et al., 1982; McMichael et al., 1986), while others report no differences (Needleman et al., 1984; Factor-Litvak et al., 1991; Green and Ernhart, 1991). The evidence on neurobehavioral development is more consistent, with most

studies reporting an association between lead exposure and developmental deficits (Bellinger et al., 1985a, 1985b, 1986a, 1986b, 1987a, 1989a, 1989b; Vimpani, et al., 1985, 1989; Dietrich et al., 1986, 1987a, 1987b; Baghurst, et al., 1987; Wigg et al., 1988). A short summary of these results is included in Section 2.3.1. There is some evidence that early developmental deficits related to prenatal lead exposure may not persist until age 4-5 years (Bellinger et al., 1991).

Immune System: The data on immunological effects of lead in occupationally exposed adults are inconsistent, but indicate that, while lead may have an effect on the cellular component of the immune system, the humoral component is relatively unaffected (ATSDR, 1993). The data on immunological effects of lead on children are very limited, but no effects have been detected (Reigart and Graber, 1976; ATSDR, 1993).

Reproduction: High levels of lead have been shown to cause adverse effects on reproduction in both men and women. Women who are exposed to high levels of lead during pregnancy have experienced an increased rate of miscarriages and stillbirths (Nordstrom, et al., 1979; McMichael et al., 1986; Baghurst et al., 1987). In addition, women who were significantly exposed during childhood may be at increased risk of spontaneous abortion and stillbirth and their children more likely to experience learning disabilities (Hu et al., 1991). Effects of lead on male reproductive functions, including reduced sperm production, have been reported in studies of occupationally exposed males (Lancrajan et al., 1975; Wildt et al., 1983; Chowdhury, et al., 1986; Assennato et al., 1987). Reproductive effects of chronic low-level exposure are less known. A recent prospective study found no effect on the rate of spontaneous abortions among women who resided near a lead smelter compared to a control population of women who lived 25 miles away (Murphey et al., 1990).

Genotoxic Effects: While the available evidence is contradictory, there is some evidence to suggest that lead may have an effect on chromosomes. While increased frequencies of chromosomal aberrations have been observed in occupationally-exposed workers, (Nordenson et al., 1978; Huang et al., 1988), most studies report no such increase in workers (Schmid et al., 1972; O'Riordan and Evans, 1974; Bauchinger et al., 1977; Maki-Paakkanen et al., 1981), or in children (Bauchinger et al., 1977). Sister chromatid exchanges may (Grandjean et al., 1983; Leal-Garza et al., 1986; Huang et al., 1988), or may not (Maki-Paakkanen et al., 1981; Dalpra et al., 1983) be increased as a result of lead exposure. Concurrent exposure to other toxic substances is a common problem in occupational exposure studies. Selection criteria employed by Huang et al. were designed to minimize the effects of potential genotoxic factors other than lead.

Cancer: Occupational exposure to lead has been associated with increased cancer risk. Lead has been classified as a probable human carcinogen (Class B2) by EPA and a possible human carcinogen (Group 2B) by the International Agency for Research on Cancer, based on sufficient evidence of carcinogenicity in animals but inadequate evidence in humans (IARC, 1987; IRIS, 1993; EPA, 1989b). Increased risks of kidney cancer (Selevan et al., 1985; Steenland et al., 1992; Cocco et al., 1997), lung cancer (Cooper et al., 1985; Gerhardsson et al., 1986; Anttila et al., 1995; Lundstrom et al., 1997), glioma (Anttila et al., 1996), rectal cancer (Fayerweather et al., 1997), and total malignant neoplasms (Cooper and Gaffey, 1975; Cooper, 1976, 1981; Kang et al., 1980; Cooper et al., 1985; Anttila et al., 1995; Gerhardsson et al., 1995; Lundstrom et al.,

1997) have been observed in occupationally exposed workers. However, the actual compounds of lead, routes of exposure, and levels of lead that may cause cancer in humans are unknown. Furthermore, the potential for exposure to other carcinogens exists, particularly in lead smelters.

2.4 REPRESENTATIVE POPULATION

As described in the previous section, adverse health effects of lead exposure have been documented in people of all ages. Although occupational exposure to lead presents a serious hazard and the subsequent health effects are well-documented, infants and young children are more at risk from lead exposure than adults (USEPA, 1986; ATSDR, 1993). This intensified risk is due to children's increased oral activity (e.g., hand-to-mouth behavior) and ability to absorb lead, coupled with the susceptibility of their rapidly developing central nervous systems (Goyer, 1993; Bellinger, 1995).

The §403 regulations are intended to reduce the risk of childhood lead exposure through the reduction of residential lead levels. Estimation of the benefits of reducing lead exposure in children requires selection of an age group for characterizing the health risks of lead exposure. The health benefits of reducing lead exposure are estimated for children aged 1-2 years (12-35 months) in this risk assessment. The selection of this age group was based on the most appropriate age of child for the estimation of health effects, as described below.

The §403 standards are intended to protect all children, not just those aged 1-2 years. However, it is assumed that the number of children outside this age range with elevated blood-lead concentrations, who did not have such elevations at this age, is relatively small, and so the selection of children aged 1-2 years does not result in a gross underestimate of the health benefits of reducing lead exposure. To assess the impact of using this age group for the characterization of risk, an alternative age group of children aged 1-5 years is considered in the sensitivity analysis (Chapter 5).

Many lead exposure studies have been conducted on children aged 1-2 years, because blood-lead concentrations tend to peak in this period, hand-to-mouth activity is greatest, the level of cognitive ability is sufficiently developed for testing, and children are more cooperative for assessment. In addition, several mechanisms for lead's effect on the developing brain were identified in Section 2.2.2. These mechanisms provide a neurological basis for increased risk to fetuses, infants, and young children exposed to lead. One mechanism, the disruption, or delay, of synaptic development, suggests special concern for children aged 1-2 years. The synaptic density of the frontal cortex of the brain peaks at age 2. Developmental disruptions at this critical time could lead to permanent functional impairment in the brain. The effects of lead on the developing brain may be estimated through IQ test scores later in life. Strong relationships between blood-lead concentration in early childhood and IQ scores have been reported in four major longitudinal studies conducted in Boston, Cincinnati, Cleveland, and Port Pirie, Australia. Lower IQ scores at school-age are reported for children who had earlier exhibited elevated blood-lead levels.

In Boston, slightly elevated blood-lead levels at age 24 months (mean 6.5 μg/dL) were associated with intellectual and academic performance deficits at age 10 years (Bellinger, 1992). In fact, the correlation of IQ deficits at age 10 years was greatest with blood-lead concentration measured at age 24 months. This is particularly significant, as IQ measures tend to be relatively stable after age 10. Thus, in addition to age 2 years being an important developmental period, the long-term effects from lead exposure at this age appear to be particularly important.

In Cincinnati, postnatal blood-lead levels measured through age 3 years were inversely associated with IQ scores measured at age 5, although the effect was not statistically significant when adjusted for covariates (Dietrich et al., 1993). In Cleveland, a significant association was reported between blood-lead concentration at age 2 (mean 16.7 μg/dL) and IQ measured at 5 years (Ernhart et al., 1989). In Port Pirie, statistically significant associations were reported between IQ measured at age 7 and blood-lead levels from birth through age 7, with the strongest associations for blood-lead levels measured at 15 months to 4 years (Baghurst et al., 1992).

Three of these studies are included in the meta-analysis of Schwartz (1994), which is used in this risk assessment to quantify IQ point decrements resulting from lead exposure. For the longitudinal studies, Schwartz selected blood-lead concentration measures prior to age 3, because basic cognitive abilities develop in that period. Cross-sectional studies were also included in the meta-analysis. For those studies, the blood-lead concentration and IQ scores were measured at the same time. In a separate analysis, Schwartz concluded that the results reported by longitudinal and cross-sectional studies were similar, so that estimates from the various study designs could be combined.

A second meta-analysis considered blood-lead concentrations from five longitudinal studies, including the four described above (Pocock et al., 1994). Three measurements of blood-lead concentration, at birth, at approximately age 2, and the mean of all post-natal measurements, were related to IQ scores. This analysis determined that there was a strong relationship between IQ scores and blood-lead concentration measured at age 2, but not with the other measurements. Thus, the blood-lead concentration at age 2 may be used to predict the effect of lead on IQ scores later in life.

2.5 SELECTED HEALTH ENDPOINTS

The childhood lead poisoning problem encompasses a wide range of exposure levels, with varying health effects at different levels of exposure. As described in Section 2.3, even low-level exposure to lead can result in adverse health effects. At low levels, the health effects may not be severe or obvious, but a large number of children are affected. As the exposure level increases, the severity of the health effects increases, but the number of affected children decreases.

Both individuals and society as a whole are damaged by adverse health effects associated with lead exposure. In this section, several elevated blood-lead concentration and health effect endpoints are identified. These endpoints are used in the risk characterization in Chapter 5, and the risk management analysis in Chapter 6, to estimate the numbers of children who may benefit under the proposed §403 rule. Each endpoint may be used both to estimate the number of

children who will benefit under the proposed rule and also the economic benefit to society. While the health effect endpoints were selected because they are indicative of health effects from low exposures and the elevated blood-lead concentration endpoints are based on CDC's guidelines for lead levels that cause effects, the ability to quantitatively measure health risks was considered in selecting the health endpoints, as well. Economic benefits resulting from the rule will be estimated in the §403 RIA.

2.5.1 Elevated Blood-Lead Concentration

Although an elevated blood-lead concentration is not a health effect in and of itself, the relationship between blood-lead concentration and a range of adverse health effects is well-established. In addition, CDC guidelines on childhood lead poisoning prevention traditionally have been and currently are defined in terms of blood-lead concentrations. Table 2-1 summarizes CDC's recommended actions for children with elevated blood-lead concentrations (CDC, 1991). These actions include 1) more frequent rescreening, 2) parental education on reducing lead exposure, 3) nutritional counseling, 4) environmental assessment and remediation, 5) medical evaluation, and 6) chelation therapy. The extent and expense of the recommended interventions increases with blood-lead concentration. The classes defined in Table 2-1 were used to select the following two levels of elevated blood-lead concentration for which this risk assessment estimates the number and percentage of children exceeding these levels:

Table 2-1. Interpretation of Blood-Lead Concentration Categories and Follow-Up Actions Recommended by CDC.

Class	Blood-Lead Concentration (µg/dL)	Recommended Action
I	≤ 9	A child in Class I is not considered to be lead-poisoned.
IIA	10 - 14	Many children (or a large proportion of children) with blood-lead levels in this range should trigger communitywide childhood lead poisoning prevention activities. Children in this range may need to be rescreened more frequently.
IIB	15 - 19	A child in Class IIB should receive nutritional and educational interventions and more frequent screening. If the blood-lead level persists in this range, environmental investigation and intervention should be done.
III	20 - 44	A child in Class III should receive environmental evaluation and remediation and a medical examination. Such a child may need pharmacologic treatment of lead poisoning.
IV	45 - 69	A child in Class IV will need both medical and environmental interventions, including chelation therapy.
V	≥ 70	A child with Class V lead poisoning is a medical emergency. Medical and environmental management must begin immediately.

Source: Preventing Lead Poisoning in Young Children (CDC, 1991).

Incidence of blood-lead levels greater than or equal to 10 µg/dL: Adverse health effects have been documented at blood-lead concentrations as low as 10 μg/dL (USEPA, 1986, 1990a; ATSDR, 1993). This level is the lowest blood-lead level that is considered elevated by CDC. While extensive interventions are not always recommended, children with blood-lead concentrations at or above 10 μg/dL require more frequent rescreening at minimum, and may require environmental or medical interventions. In addition, if many children in a community have blood-lead concentrations above 10 µg/dL, community-wide intervention activities are recommended (CDC, 1991).

Incidence of blood-lead levels greater than or equal to 20 µg/dL: Medical and environmental interventions are recommended for all children with blood-lead concentrations at or above 20 μg/dL.

2.5.2 IQ Point Deficits

In this section, IQ based health endpoints are identified to represent the neurotoxicological effects of lead exposure. While tests that focus on a specific neurological effect might be more sensitive to the effects of lead than IQ tests, the selection of a representative effect is difficult. Differences in the level, timing, and route of exposure for individuals may result in differing effects of lead. For example, early exposure to lead (before age 2) may affect language skills, while later exposure is more likely to affect spatial-symbolic skills (Shaheen, 1984). In the absence of details of the exposure scenario, which are rarely available, exposure-related differences will be most apparent on tests, such as IQ tests, that measure performance over a range of neurological functions (Bellinger, 1995). The relationship between blood-lead concentration and IQ scores has been reported consistently in the literature and efforts have been made to quantify this relationship by meta-analysis (Schwartz, 1993; Pocock et al., 1994; Schwartz, 1994; Section 4.4; Appendix D). The following IQ-based health endpoints are used in the risk assessment to represent the neurotoxicological effects of lead exposure:

IQ Points Lost: This effect is used to represent the neurological loss due to low level lead exposure. Lower IQ scores are associated with a lower level of educational attainment and lower life-time earnings. The average IQ point loss in a child resulting from lead exposure is estimated, along with incidences of IQ point loss ≥ 1, ≥ 2, and ≥ 3 points. These levels were selected arbitrarily for presentation purposes. These small effects are not meaningful for individual children, as the standard deviation associated with IQ tests is usually 5 points. However, these effects may be estimated for the population of children and provide a useful illustration for this risk analysis.

Increased Incidence of IQ scores less than 70: This effect measures the increased likelihood of mental retardation resulting from lead exposure. An IQ of 70 is two standard deviations below the population mean score of 100 and is used as an indicator of mental retardation. Children who are mildly mentally retarded require special education classes in school. Children who are severely mentally retarded may require life-long institutional care.

2.6 HAZARD CHARACTERIZATION

Though lead causes a wide array of adverse health effects, particularly at high dose levels, lead is most known for its adverse effects on the central nervous system. Young children are most susceptible to adverse health effects associated with lead exposure due to their developing central nervous systems and their increased ability to absorb lead. Long-lasting impacts on intelligence, motor control, hearing, and neurobehavioral development of children have been documented at levels of lead in the body that are not associated with noticeable symptoms and were once thought to be safe. There is no apparent threshold in the level of lead associated with some of these subtle neurological effects. At higher levels, lead affects the hematological, gastrointestinal, renal, and reproductive systems. Severe cases of lead poisoning may result in delirium, convulsions, paralysis, coma, and death. Although the evidence is less conclusive, lead may also affect the immune system, thyroid function, growth and development in children, and vitamin D metabolism. Lead has been associated with hypertension, chromosomal aberrations, cancer, and increased risk of death due to cerebrovascular disease. The documented evidence on the adverse biological responses to lead is one of the major strengths of this risk analysis.

Typically, in studies assessing adverse health effects associated with lead exposure, relationships between health effects and exposure are established using a measure of internal rather than external exposure. A variety of direct measures (lead in blood, bones, teeth, and hair) and indirect measures (hemoglobin and EP levels) of lead exposure were identified in this chapter. Although some of these measures have desirable characteristics, blood-lead concentration is the most readily available and widely accepted measure of internal exposure. Thus blood-lead concentration was selected as the measure of body lead burden to quantify environmental lead exposure.

To provide an endpoint that represents neurological effects and because the neurological effects of lead are well-documented and generally accepted by the scientific community, two types of IQ-related health endpoints were identified: IQ score decrements (average, $\geq$1, $\geq$2, and $\geq$3 IQ points) and the increased incidence of IQ scores less than 70 due to lead exposure. In addition, incidences of elevated blood-lead concentrations above specified thresholds (10 and 20 μg/dL) were selected as surrogates for the wide array of non-IQ related health risks to both the central nervous system and other organs. The relationship between elevated blood-lead levels and adverse health effects is well-established. The blood-lead concentration thresholds selected for this risk analysis were among those established by CDC as levels of concern and are generally recognized by the scientific community. The neurotoxic and blood lead endpoints selected for this risk analysis have been used to support previous regulatory decisions. It is likely that if additional endpoints were included, the baseline risks to lead exposure would be larger and the potential risk reduction might be larger.

A potential weakness of this risk analysis lies in the selection of the age group for which health benefits are estimated. Children aged 1-2 years are targeted for estimation of health risks in this risk analysis for two reasons: 1) increased vulnerability of 1-2 year olds due to their rapidly developing central nervous system, and 2) both the normal hand-to-mouth activities of this age group and the pica tendencies observed in some children may put children aged 1-2 years most at

risk to lead exposure. While older children may also experience adverse health effects, it is assumed that few such children would not have been previously exposed to lead at age 1-2 years. If this is not the case, then the estimated health risks for children aged 1-2 years may underestimate the risks for all young children. It is also assumed that children who experience an acute increase in lead exposure while aged 1-2 years suffer the same health consequences as those whose exposure duration is longer. If this is not the case, then the health risks to this group may be overestimated. To assess the impact on selecting children aged 1-2 years versus a larger population, an alternative age group of children aged 1-5 years is considered in the sensitivity analysis for the risk characterization (Chapter 5).