# PUBLIC HEALTH GOALS FOR CHEMICALS IN DRINKING WATER

# LEAD

**April 2009**

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# Public Health Goal for Lead in Drinking Water



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**April 2009**

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# PREFACE

**Drinking Water Public Health Goals**
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This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances that may cause chronic disease shall be based solely on health effects and shall be set at levels that OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider potential adverse effects on members of subgroups that comprise a meaningful proportion of the population, including but not limited to infants, children, pregnant women, the elderly, and individuals with a history of serious illness.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. OEHHA shall consider additive effects of exposure to contaminants in media other than drinking water, including food and air, and the resulting body burden.
7. In risk assessments that involve infants and children, OEHHA shall specifically assess exposure patterns, special susceptibility, multiple contaminants with toxic mechanisms in common, and the interactions of such contaminants.
8. In cases of insufficient data for OEHHA to determine a level that creates no significant risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.

9. In cases where scientific evidence demonstrates that a safe dose response threshold for a contaminant exists, then the PHG should be set at that threshold.
10. The PHG may be set at zero if necessary to satisfy the requirements listed above in items seven and eight.
11. PHGs adopted by OEHHA shall be reviewed at least once every five years and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Public Health (DPH) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations or technical feasibility, drinking water standards adopted by DPH are to consider economic factors and technical feasibility. Each primary drinking water standard adopted by DPH shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By state and federal law, MCLs established by DPH must be at least as stringent as the federal MCL, if one exists.

PHG documents are used to provide technical assistance to DPH and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not intended to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA Web site at www.oehha.ca.gov.

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# PUBLIC HEALTH GOAL FOR LEAD IN DRINKING WATER

## SUMMARY

A revised Public Health Goal (PHG) of 0.2 ppb (or 0.2 μg/L) for lead in drinking water is established, on the basis of new studies relating neurobehavioral deficits to lower lead concentrations in the blood than previously reported. The existing PHG of 2 ppb for lead in drinking water was developed by the Office of Environmental Health Hazard Assessment (OEHHA) and published in December 1997. This value was also based on neurobehavioral effects of lead in children.

Lead is a metallic element which has been used primarily in piping, paints, cable coverings, bullets, radiation shielding material, and as a gasoline additive (tetraethyl lead). It is a widespread contaminant in the human environment and occurs in drinking water as a consequence of leaching from plumbing containing lead. Lead was reported as found in 1,481/11,471 drinking water sources in California in the Department of Health Services (now Department of Public Health) survey results for 1984-2001. Lead has multiple toxic effects on the human body. In particular, decreased intelligence in children and increased blood pressure in adults are among the more serious non-carcinogenic effects. Lead is also a carcinogen in animals and is a probable carcinogen in humans. Based on studies correlating blood lead levels with decreased IQ in children, a daily oral intake of 28.6 μg/day was used to derive the PHG in 1997. A no observed adverse effect level (NOAEL) was not found for this effect. The health-protective level for cancer (6 ppb) was not used to determine the PHG as the non-cancer value provided a greater level of health protection.

In the current document, OEHHA has completed an extensive review of the literature since publication of the first PHG (OEHHA, 1997a). The focus of this review was on new data regarding the potential carcinogenicity, neurotoxicity, and mechanism of action of lead. Based on the new studies relating neurobehavioral deficits to lower blood lead concentrations than previously reported, we established a PHG that is lower than the previous one by 10-fold. The calculation uses a lower level of concern of 2.86 μg/day, which is primarily based on the review and slope factor work done by Carlisle and Dowling (2006) and their analysis of Lanphear *et al*. (2005) (OEHHA, 2007), using a relative source contribution of 0.2, an uncertainty factor of 3 and a drinking water consumption rate of 1 L/day.

Both the U.S. Environmental Protection Agency (U.S. EPA) and California Department of Public Health (DPH) have an Action Level of 15 ppb lead in drinking water. This Action Level was established in 1991 by the U.S. EPA and in 1995 in California.

# INTRODUCTION

The purpose of this document is to review and evaluate the new data since 1997 regarding the toxicity of lead that are relevant to the estimation of a public health-protective level in drinking water, and establish any necessary changes in the previous risk assessment based on the new findings. This document is centered on updating the earlier OEHHA assessments for drinking water (OEHHA, 1997a, 2007). Lead is a widespread contaminant in the human environment and occurs in drinking water. Pipes and solder made with lead may corrode and leach lead into tap water used for drinking, food preparation, and other household uses. Lead has toxic effects on many systems of the body, particularly on the developing nervous system, the hematological and cardiovascular systems, and the kidney.

# CHEMICAL PROFILE

## *Chemical Identity, Properties, and Uses*

Lead is a bluish gray or gray-white metal with a bright silvery luster. It is soft, malleable and a poor conductor of electricity, but is resistant to corrosion (ATSDR, 2007). Lead is a metallic element, the 82nd element on the periodic table, with four stable isotopes (i.e., 204, 206, 207, and 208) and exists in three oxidation states [Pb(0), Pb(II), and Pb(IV)]. Small amounts of lead are produced by the decay of heavier radioactive elements, both natural and synthetic (ATSDR, 2007).

The melting point of metallic lead is 327.4°C; its boiling point is 1,740°C. The density of metallic lead is 11.34 $g/cm^3$ at 20°C. Metallic lead is soluble in nitric or sulfuric acid, but insoluble in water or organic solvents. Lead salts such as lead nitrate and lead acetate are soluble in water. The usual valence states of lead are 0, +2 and +4. Lead can easily be alloyed with antimony, tin or other metals. Common lead salts include: acetate, chloride, chromate, nitrate, oxide, phosphate and sulfate. Lead can also be part of organic compounds, and can be chelated by various ligands (ATSDR, 2007).

Lead is easily obtained from its most common ore, galena (PbS). The many commercial uses of lead follow from the physical and chemical properties described above. Lead has been used in piping, roofing and other structural uses because of the malleability (ATSDR, 2007). Lead is also used in making containers for corrosive liquids (ATSDR, 2007). Metallic lead and lead dioxide are used in storage batteries for automobiles and other applications (ATSDR, 2007). In the past, organolead compounds were used to boost octane (reduce knock) in gasoline, but this use has now been eliminated for car, truck, and boat fuel in the U.S. Lead and lead salts have been widely used in paints and pigments, and in glazes for ceramics. Cable coverings have been made from lead because of its electrical resistance and ductility. Lead is used to make bullets and shot. Because of its low melting point, lead is used (with other metals) to make solder. Lead is used for radiation shielding around diagnostic x-ray machines and other sources of radiation (ATSDR, 2007). In the past lead was included in a number of medicines such as antiseptics and astringents, but these are no longer recommended because of the

cumulative toxic effects of lead in the body. More recently, lead has been found in Mexican candy (U.S. FDA, 2004) sold throughout the United States. Overall, approximately 1.6 million metric tons of lead were used in the United States in 1997 (Smith, 1998).

## ENVIRONMENTAL OCCURRENCE

Lead is widely distributed in the environment. It is found in all media including air, water, food and soil.

### *Air*

Lead levels in the ambient air have been monitored and atmospheric lead concentrations vary widely. Smelters and refineries emit lead into the air; automobiles in the past emitted large quantities from use of leading gasoline. Over the past three decades, the amount of lead in the air has been greatly reduced by the introduction of unleaded gasoline (ATSDR, 2007). For example, lead at all sites monitored by the National Park Service and U.S. EPA in 1986 had a sharp decrease (18 percent) from the mean levels of 1982 (Eldred and Cahill, 1994). Across the United States, a decline of 97 percent in the ambient concentration of lead was reported between 1976 and 1995 (ATSDR, 2007). Although lead ambient concentrations have declined, U.S. EPA (1996a) indicates that the rate of decline has slowed. The national average of lead concentrations remained unchanged at 0.004 $\mu g/m^3$ between 1994 and 1995. The average level of lead in ambient air in California has been reported as 0.04 to 0.06 $\mu g/m^3$, mostly in particulate form (OEHHA, 1997b).

In general, lead concentrations are 0.3-0.8 times lower indoors than outdoors, with an average ratio of 0.5 (U.S. EPA, 1986). The median lead concentration outdoors was 8.84 $ng/m^3$ in 2002 (Bonanno *et al*., 2002). Bonanno *et al*. (2001) earlier reported a mean and median lead concentration for indoor air from 213 residences as 15.2 $ng/m^3$ and 6.17 $ng/m^3$, respectively. Lead concentrations are higher in homes where one or more residents smoke indoors or where the home is more dilapidated.

Lead in contaminated soil can also become airborne when soil particles are picked up by the wind, or when soil is disturbed by digging, grading, plowing or gardening.

### *Soil*

Contamination of soil by lead is widespread in California and elsewhere. Lead has been deposited in soil in a number of ways: atmospheric particulates from the emission of smelters or at one time, the combustion of leaded gasoline; lead paint deposited in soil, particularly around older homes; disposal of lead storage batteries. Some lead storage battery disposal sites have very high levels of lead contamination, up to a few percent of the soil.

A national survey of soil lead in the United States (U.S.) found levels ranging from 10 to 700 ppm, with an average of about 15 ppm (Shacklette *et al.*, 1971). Fifteen parts per million has also been given as the average naturally occurring soil lead level (Lovering, 1976). Lead concentrations in California soils analyzed by Bradford *et al*. (1996) ranged from 12 to 97 mg/kg (or ppm).

### *Water*

Levels of lead in surface water and groundwater throughout the United States typically range between 5 and 30 μg/L or ppb (U.S. EPA, 1986). The concentration of lead is dependent upon sources of pollution, lead content of sediments, and characteristics of the system (pH, temperature). In drinking water, the major source of lead is leaching from the plumbing and solder. Lead enters drinking water from lead in pipes and fixtures and from lead solder used to join pipes (Mahaffey, 1985). This is particularly troublesome in older homes. Older public buildings such as schools and theaters may also have problems with lead contamination of drinking water (Mahaffey, 1985). U.S. EPA (1988) estimated that 99 percent of the U.S. population using public water supplies were exposed to drinking water with levels of lead below 5 ppb and that about 2 million people are served by drinking water with levels of lead above 5 ppb. In California, analysis of over 15,000 drinking water and 1000 surface water sources found no sources with reportable levels of lead (greater than 5 ppb) between 1994 and 2004.

## METABOLISM, PHARMACOKINETICS, AND MECHANISM OF ACTION

Inorganic lead can be absorbed following oral and inhalation exposure, with minimal absorption following dermal exposure. When lead is ingested from drinking water or foods, a fraction of it is absorbed into the bloodstream via the gastrointestinal tract. Lead in the bloodstream becomes deposited in tissues, mainly in bone. Blood lead is excreted via the feces and urine, but also is lost during childbirth and breastfeeding. Once absorbed, lead can cause hematological, cardiovascular, renal, and neurobehavioral effects via several mechanisms: mimicking calcium, interference with specific neurotransmitter systems, direct effect on vascular smooth muscle and enzymes, and other pathways.

### *Absorption*

Absorption of lead deposited in the lungs is dependent on particle size, age-related factors that determine breathing patterns, airway geometry, and air-stream velocity within the respiratory tract (ATSDR, 2007). Particles below 1 μm are deposited in the alveolar region and absorbed after extracellular dissolution or ingestion by phagocytic cells. For larger particles (>2.5 μm), deposition is usually in ciliated airways, where particles can be transported to esophagus and swallowed. Approximately 95 percent of deposited inorganic lead (<1 μm size particles) that is inhaled will be absorbed, while absorption

rates for the larger particles are determined by rates of transport to and absorption from the gastrointestinal tract (ATSDR, 2007).

Oral ingestion also results in good absorption of lead and lead compounds. The rate is highly influenced by the physiological state of the exposed individual (e.g., fasting, pregnancy, age, nutrition) and physicochemical properties of the ingested material (e.g., particle size, mineralogy, and solubility) (ATSDR, 2007). For dermal absorption, inorganic lead was the least absorbed while organic compounds such as tetraethyl lead and lead naphthenate had a greater absorption across human skin or *in vivo* in rats (Bress and Bidanset, 1991; ATSDR, 2007). Absorption ranged from 0.002 percent of the applied concentration for inorganic lead to 0.17 percent for lead naphthenate (ATSDR, 2007).

Absorption of water-soluble lead following oral exposure appears to be greater in children than in adults. Children (2 weeks to 2 years of age) absorb about 40 to 50 percent of ingested lead, whereas adults absorb only 5 to 15 percent (Heard and Chamberlain, 1982; Ragan, 1983). Absorption of lead into the blood from the gastrointestinal tract appears to be low in humans compared to animals, although it is higher in children than in adults (Ragan, 1983). A similar pattern is observed in animal studies. Rat pups were reported to absorb 40-50 times more lead via the diet than adult animals (ATSDR, 2007). The difference in absorption may be one reason why children are more sensitive than adults to lead exposure by the oral route.

Blood lead concentrations have dropped in the last three decades from an average U.S. national level of 12.8 μg/dL (ages 1 to 74) to 2.8 μg/dL (ATSDR, 2007). Prevalence of children aged 1-5 years with a blood lead concentration of $\geq$ 10 μg/dL also dropped with time. In 1991 to1994, the prevalence was 4.4 percent with a geometric mean of 2.7 μg/dL while in 1999-2002 the prevalence was 1.6 percent with a geometric mean of 1.9 μg/dL (ATSDR, 2007).

## *Distribution*

Once lead is absorbed, the distribution of lead is essentially the same regardless of route of exposure or age of individual (ATSDR, 2007). The lead which is not eliminated in the urine or feces is distributed into the tissues of the body including the bone, brain and kidneys (Rabinowitz, 1991). However, a larger fraction of the lead body burden of adults resides in bone (93 percent) compared to children (73 percent) (ATSDR, 2007). The relatively large pool of lead in the bone can serve to maintain blood lead levels long after exposure has ended (Inskip *et al*., 1996; Smith *et al*., 1996; Fleming *et al*., 1997). The storage of lead in bone depends on the diet; higher levels of calcium and iron in the diet tend to protect against deposition of lead into the bone (Rabinowitz, 1991; Silbergeld, 1991). Lead accumulates in the bone with time, and lead levels in the bone generally increase with age (Rabinowitz, 1991).

Lead also distributes to soft tissues (i.e., liver, skeletal muscle, skin, fat, kidney, lung, aorta, and brain). The highest soft tissue concentration of lead in adults occurs in liver and kidney cortex. The residence time of lead in the soft tissues (brain and kidneys) is much shorter than in the bone. High blood lead levels may indicate recent exposure, or in

some cases they may reflect remobilization of lead from bone storage (Silbergeld, 1991). During pregnancy, lead is often remobilized from bone and may be transferred from mother to fetus (Silbergeld, 1991). Approximately 80 percent of lead in fetal cord blood appears to derive from maternal bone stores (Gulson *et al*., 2003). Maternal lead can also be transferred to infants during breastfeeding. Thus the developing fetus and young child will be exposed early. Graziano *et al*. (1990) reported a cord/maternal ratio to be relatively constant at 0.93 in 888 mother-infant pairs evaluated over a maternal blood lead range of 3-40 μg/dL.

## *Metabolism*

The formation of complexes with a variety of protein (e.g., albumin or ALAD) and non-protein ligands (e.g., non-protein sulfhydryls) are observed in the metabolism of inorganic lead (ATSDR, 2007). For the organic lead compounds, metabolism is primarily by oxidative dealkylation catalyzed by cytochrome P-450 in the liver. For example, tetraethyl lead is excreted in the urine as diethyl lead, ethyl lead, and inorganic lead (Turlakiewicz and Chmielnicka, 1985; Zhang *et al*., 1994; Vural and Duydu, 1995).

## *Excretion*

Independent of route of exposure, absorbed lead is excreted mainly through the urine and feces, but also in the bile, sweat, hair, fingernails and breast milk (Rabinowitz, 1991; ATSDR, 2007). Chamberlain *et al*. (1978) reported that approximately one-third of total excretion of absorbed lead occurs through the feces.

## *Pharmacokinetics*

Physiologically based pharmacokinetic (PBPK) models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species (ATSDR, 2007). These models are increasingly used in risk assessments in order to predict the target tissue dose of chemicals in humans who are exposed to environmental levels. Several pharmacokinetic models have been proposed for a broad application in lead risk assessment.

The latest models being considered incorporated some of the earlier work done by Rabinowitz *et al*. (1976) and Marcus (1985a,b,c). The Rabinowitz *et al*. (1976) model included a central compartment representing blood and other tissues in rapid equilibrium with blood, a shallow tissue compartment representing soft tissues and rapidly exchanging pools within the skeleton, and a deep tissue compartment representing slow exchanging pools of lead within bone. This model predicted pseudo-first order half-times for lead of approximately 25, 28, and 10,000 days in the central, shallow, and deep compartments, respectively. Marcus (1985a,b,c) expanded the model by adding more compartments after reanalyzing the data used by Rabinowitz *et al*. (1976). The Marcus model 1) included separate compartments for cortical bone (slow kinetics) and trabecular bone (fast kinetics); 2) had a more complex representation of lead deposition in bone; and

3) used nonlinear kinetics in the exchange of lead among plasma, protein-bound lead in plasma, a "fast kinetic" erythrocyte pool, and a "slow kinetic" erythrocyte pool. A curvilinear relationship between plasma and blood lead concentrations observed in humans was predicted with this model (ATSDR, 2007).

The more recent models being used or considered in the lead risk assessment are those developed by O'Flaherty (1993, 1995), U.S. EPA (1994a,b), and Leggett (1993). The O'Flaherty model, which simulates lead kinetics from birth through adulthood, relies more extensively on physiologically based parameters to describe volumes, flows, and composition, and metabolic activity of blood and bone. The other two models are more classical multi-compartmental models that use values of the age-specific transfer rate constants for lead based on kinetic data obtained from animal/human studies, and may not have precise physiological correlates. The Leggett model is also a lifetime model (infant to adult lead kinetics) like the O'Flaherty model. However, the U.S. EPA Integrated Exposure Uptake BioKinetic (IEUBK) model is not intended for use in predicting lead pharmacokinetics in adults. This model provides blood lead concentration distributions in populations of children ages 0-7 years (U.S. EPA, 1994a,b).

All three models provide an assessment of lead exposure and blood lead concentration, and represent the rate of uptake of lead as relatively simple functions of lead intake; the values/variables assigned in the calculation are age-specific or even environmental medium-specific (ATSDR, 2007). In addition, the three models were calibrated using physiological data from humans and animals, and blood lead concentrations reported for individuals and/or populations. The focus on the use of blood lead concentrations derives from the observations that high blood lead concentrations have been associated with various dysfunctions or health effects. Also, the most available data for calibrating and validating a model are the data relating exposure and/or lead intake to blood concentration.

Although the three models can predict a blood lead concentration, differences do exist in the representation of lead exposure, exchanges of lead between tissues, and how tissues are represented. Some of the differences are due to assumptions used for lead biokinetics and bioavailability (ATSDR, 2007). Predicted blood lead concentration can be up to 2 to 4 fold different depending on the model used and the age being considered. Smaller changes are predicted in blood lead concentration in adults with the O'Flaherty and Leggett Models due to the lower lead bioavailability used for adults compared to children.

Simpler alternatives to pharmacokinetic models to obtain medium-specific exposures and blood lead concentrations are the slope factor models. These models predict blood lead concentration or the change in blood lead concentration that is associated with a given exposure using a simple linear relationship between blood lead concentration and either lead uptake (biokinetic slope factor) or lead intake (intake slope factor) (Carlisle and Wade, 1992; Bowers *et al*., 1994; Stern, 1994, 1996; U.S. EPA, 1996b; Abadin *et al*., 1997). The models that use the biokinetic slope factor will include an absorption parameter to account for absorption. The models that use intake slope factors integrate both absorption and biokinetics into a single slope factor because they are based on ingested lead rather than absorbed lead (ATSDR, 2007). Also, the intake slope factor

models are derived from epidemiologic observations. Carlisle and Dowling (2006) recently used a slope factor model with the review of several datasets for the development of a reference blood concentration for school and preschool children of 1.2 μg/dL lead. The calculated slope, based on Lanphear *et al*. (2000, 2005), Canfield *et al*. (2003), and Emory *et al*. (2003), was a drop of 1 Intelligence Quotient (IQ) point for each 1.2 μg/dL increase in lead concentration. This work has been incorporated into the OEHHA report, "Development of health criteria for school site risk assessment pursuant to Health and Safety Code Section 901(g): Child-specific benchmark change in blood lead concentration for school site risk assessment" (OEHHA, 2007). The slope provided in the children's reference concentration document is 1 IQ point drop for each 1 μg/dL increase in blood lead.

## *Mechanism of Action*

Multiple potential mechanisms of action exist for lead that affect many enzyme systems and cellular processes throughout the body (ATSDR, 2007). The main areas of focus in this document are on the major concerns for lead toxicity: neurotoxicity, cardiovascular/renal toxicity, and hematological toxicity. The most abundant amount of research is in the area of mechanism for neurological effects. However, research into the remaining areas of concern has also been abundant.

### Cardiovascular Effects

For cardiovascular changes, lead affects important hormonal and neural systems that contribute to the regulation of peripheral vascular resistance, heart rate, and cardiac output (Carmignani *et al*., 2000; Vaziri and Sica, 2004). Lead can have a direct effect on vascular smooth muscle by inhibiting Na-K-ATPase activity, with an associated elevation of intracellular calcium levels (Watts *et al*., 1995; Hwang *et al*., 2001). Lead-induced hypertension in rats was associated with depletion of nitric oxide, which is involved in 1) regulating blood pressure; 2) down-regulation of the soluble guanylate cyclase enzyme which forms cyclic guanosine monophosphate (a mediator of nitric oxide-induced vasodilation); and 3) changes in the adrenergic system (i.e., increased central sympathetic nervous system activity, elevated plasma norepinephrine, and decreased vascular β-adrenergic receptor density) (Gonick *et al*., 1997; Vaziri *et al*., 1997, 1999a,b; Carmignani *et al*., 2000; Tsao *et al*., 2000; Vaziri and Sica, 2004; ATSDR, 2007). Chronic lead exposure stimulates the sympathetic nervous system, which results in the activation of the renin-angiotensin-aldosterone system (Carmignani *et al*., 1988). Alterations in the regulation of the kallikrein-kinin system and the production of associated vasodilatory hormones are also associated with lead-induced hypertension (Carmignani *et al*., 1999).

### Renal Effects

Oxidative stress appears to be involved in the development of renal toxicity. As reported by Carmignani *et al*. (2000), Gonick *et al*. (1997), and Vaziri *et al*. (1997, 1999a,b),

depletion of nitric oxide can contribute to hypertension in the rat and this can result in impairment of glomerular filtration and in lesions of the glomerulus. Intranuclear inclusion bodies are observed in the renal proximal tubules of lead-exposed animals, as a result of formation of a lead-protein complex (ATSDR, 2007). The mechanism for the formation of the protein-lead complex still remains unknown.

**Hematological Effects**

Hematological effects have been demonstrated in humans and animals following exposure to lead. The effects include increased levels of urinary porphyrins, coproporphyrins, δ-aminolevulinic acid, zinc proporphyrin, and erythrocyte protoporphyrin. These changes are the result of the alteration of three enzymes involved in heme biosynthesis: δ-aminolevulinic acid synthetase, δ-aminolevulinic dehydrase, and ferrochelatase (ATSDR, 2007). Associated with these changes is a reduction of the hemoglobin concentration in blood.

**Neurobehavioral Effects**

A brief summary of the key areas regarding the potential neurotoxicity mechanism of action is provided for lead. The reader is referred to the more recent literature reviews (Carpenter *et al*., 1994; Banks *et al*., 1997; Bressler *et al*., 1999; Gilbert, 1999a,b; Cory-Slechta 1995, 2003; Bouton and Pevsner, 2000; Zawia *et al*., 2000; Lasley and Gilbert, 2000, 2002; Nihei and Guilarte, 2002; Suszkiw, 2004; ATSDR, 2007) and references cited within for more detailed information. The key mechanisms for neurological effects are postulated to be: 1) mimicking of calcium action and/or disruption of calcium homeostasis (e.g., interactions with protein kinase C or calmodulin); 2) substitution for zinc in some enzymes and zinc-finger domains found in enzymes, channels, and receptors; and 3) interference with specific neurotransmitter systems in the brain (i.e., glutamatergic, dopaminergic, and cholinergic systems).

Because lead mimics calcium action and/or disrupts calcium homeostasis, many cellular neurological processes regulated by protein kinase C (several forms of which are calcium-dependent) or calmodulin can be affected by lead. For example, protein kinase C (PKC) is involved in the synthesis of neurotransmitters, ligand-receptor interactions, conductance of ionic channels, and dendritic branching. One of the several calcium-dependent forms of PKC, the γ-isoform, is neuron-specific and involved in long-term potentiation (LTP), spatial learning, and memory processes (ATSDR, 2007). By disrupting or mimicking the calcium action, lead can have an affect on all of these processes. Activation of PKC also tends to change the blood brain barrier. Immature brain microvessels will contain most of the PKC in the cytosol while in mature brain the PKC is membrane-bound. Upon activation of PKC, the distribution of PKC changes from cytosol to membrane. A similar response is observed in the immature brain microvessels following exposure to lead. The effect on the microvascular formation and function may account for the gross defects observed in the blood brain barrier (e.g., penetration of albumin, ions, and water) and result in edema and intracranial pressure.

Substitution of lead for zinc can result in alteration of the binding and transcription of the regulated protein to its specific DNA sequence. For example, lead alters the binding of the zinc-finger transcriptional regulator Sp1 to the DNA binding site. Sp1 regulates the myelin basic protein, proteolipid protein, and β-amyloid precursor protein genes. Many of the zinc-finger domains can be found in enzymes, channels, and receptors, which accounts for the multiple responses following lead exposure.

The third major path for neurotoxicity is interference with specific neurotransmitter systems in the brain (i.e., glutamatergic, dopaminergic, cholinergic, and other systems) (ATSDR, 2007). In the most studied system, the glutamatergic system, lead is purported to diminish LTP, which is important in memory consolidation, by increasing the threshold for inductions, reducing the magnitude of potentiation, and shortening the duration of LTP by accelerating its rate of decay. The end result is loss of the neurophysiological substrate for learning and storing information. LTP is more sensitive to injury during early development and such exposure can result in an impaired LTP in adult animals. Lead is also purported to impair regulation of dopamine synthesis and release, which results in cognitive dysfunction. Learning and memory processes can also be affected by lead when lead blocks evoked release of acetylcholine and diminishes cholinergic function.

# TOXICOLOGY

The document focuses on the non-carcinogenic effects of lead and the health effects observed in the most sensitive population, i.e., children and neonates. The primary effect observed in children or neonates is the neurobehavioral deficits that occur at low blood lead concentrations. For the general population, exposure to lead occurs primarily via the oral route whereas occupational exposure is primarily by inhalation. The toxicological data will not be separated out by route of exposure because the toxicity of lead is the same regardless of route of entry into the body. Articles that are relevant to the understanding of lead toxicity will be summarized below. A discussion is also provided on the carcinogenicity of lead, which is determined to be a less sensitive endpoint than the neurobehavioral deficits in children or neonates, based on our evaluation for the development of the lead PHG.

## *Toxicological Effects in Animals*

An extensive database on the effects of lead in animals is available and is too large to cite fully in this review. For a recent review, the publication by ATSDR (2007) is recommended to the reader. In general, the findings reported in the animal studies provide support for effects observed in human studies, although no animal model for the effects of lead equivalent to the subtle effects observed in humans is currently available. In addition, a large database concerning the dose-effect relationships in humans exists and is more suitable for health effects assessments than are the animal data.

**Acute Effects**

Mean lethal dose ($LD_{50}$) values for lead compounds were not found in the literature, however there are lowest lethal dose ($LD_{Lo}$) values ranging from 20,500 mg/kg for lead sulfate in guinea pigs to 191 mg/kg for lead acetate in the dog (Sax, 1984). These are the lowest doses expected to cause death. For reproductive toxicity effects, Kennedy *et al*. (1975) reported an increase in fetal resorptions, retarded skeletal development, and maternal toxicity in rats treated with acute oral lead acetate doses of 390 mg/kg-day.

*In vitro* assessment of changes to mammalian neurogenesis using a well-characterized cortical precursor model was reported by Davidovics and DiCicco-Bloom (2005) using a moderate level of lead acetate. Gestational day 14.5 rat cerebral cortical precursor cells were cultured in defined media. Cell number, precursor proliferation, apoptosis, and neuritic process outgrowth were assessed following exposure to a range of 1 to 30 μg/mL lead acetate. A concentration of 30 μg/mL lead acetate was acutely toxic to neurons while concentrations between 1 and 10 μg/mL increased cell number 10 fold by day 4, compared to control. The increase in cell number was not a result of increased proliferation, but rather due to reduced apoptosis (i.e., less programmed cell death). Additionally, neuritic process initiation and outgrowth increased in a concentration-dependent manner. Processes were four times as abundant on day 1 and twice as long on day 2. The results suggest that brief exposure to lead during neurogenesis directly affects cell survival and process development, potentially altering cortical arrangement.

Vargas *et al*. (2003) evaluated the effects of lead on renal function, lipid peroxidation, and expression of heme oxidation in rat kidney. A single injection of lead acetate (50 mg/kg) was given to rats. Thiobarbituric acid reactive substances (TBARS) levels increased in kidney cortex 24 hours after lead administration. These changes reported in the kidney were suggested to be due to oxidative stress, indicated by the increased TBARS, caused by the administration of lead. In kidney cortex, lead exposure affected the expression of HO-1, a renal protein associated with oxidative stress. HO enzymatic activity and HO-1 protein increased six and three hours after lead administration, respectively, and remained increased at 24 hours. HO inhibition by tin-protoporphyrin potentiated lead-induced increase in TBARS and prevented the lead-induced reduction in Na+ excretion.

The effects reported by Vargas *et al*. (2003) agreed with those reported earlier by Karmakar *et al*. (1986). A dose of 44 mg/kg for durations of 9, 15 or 30 days was evaluated in groups of five Sprague-Dawley rats. After nine days, mild shortening of the intestinal villi was seen in two of five rats and histological changes in the liver were observed in all rats. No renal abnormalities were observed at day 9. After 15 days, intestinal and liver abnormalities had progressed and affected more animals than at nine days; three of five rats showed histological kidney abnormalities.

Qian *et al*. (2000) reported that the synthesis of glucose regulated protein 78 (GRP78) was increased in a protective response to lead. The authors exposed cultured C6 rat glioma cells, an astroglia-like cell line, to 1 microM lead acetate for 1 week and found raised intracellular levels of two proteins, one of which was GRP78. For GRP78, accumulation started within 1 day and progressed with time of exposure.

More recently, Lasky *et al*. (2007) reported that exposure to lead caused a decrease in cerebral white matter in Rhesus monkeys exposed pre or postnatally. Different regions of the brain of 13 17-year old monkeys were measured with volumetric magnetic resonance imaging (MRI) techniques. Three animals had been exposed prenatally (conception to birth) through mothers treated with 8.6 mg/kg-day lead acetate in drinking water; four animals had been exposed postnatally (birth to weaning or ~5 months) while breastfeeding on females exposed to 9.1 mg/kg-day to lead acetate in water; and 8 animals had not been treated and served as controls. The median maternal blood lead level for the prenatal group during pregnancy was 62.0 μg/dL while the medium maternal blood lead level for the postnatal group was 97.8 μg/dL. The median prenatal treatment offspring blood lead level during nursing was 26.5 μg/dL while the median postnatal treatment offspring blood lead level during nursing was 55.1 μg/dL. The animals in the prenatal group were only exposed in utero and not during nursing. The median control offspring blood lead level during nursing was 4.5 μg/dL. Blood lead levels for all lead-exposed infant monkeys declined after weaning and were <10 μg/dL by 2.5 years postpartum and <5 μg/dL by 4.5 years of age. No differences were noted between treated animals and controls in total brain size, perhaps due to small sample size. Statistically significant differences ($p<0.05$) were noted among groups in size of lateral ventricles and cerebral white matter; animals treated prenatally had the largest lateral ventricles and the least cerebral white matter.

Lead is also known to affect blood pressure. Bagchi and Preuss (2005) recently reported that young Sprague-Dawley rats had systemic blood pressure changes and decreased bone mineral density following exposure to 1 percent lead acetate in drinking water for 40 days. Systemic blood pressure levels increased acutely but returned to normal with the continued treatment, only to rise again above control levels several months after the lead exposure had ceased.

**Chronic Effects**

Numerous experiments in laboratory animals have demonstrated that lead has a wide variety of toxic effects across many different organ systems. Lead can affect the cardiovascular, gastrointestinal, hemolymphatic, urinary, immune, nervous, and reproductive systems as well as cause developmental effects in the offspring of treated dams and tumors in laboratory animals (ATSDR, 2007).

The effects of lead acetate in drinking water on the reproductive systems of male and female rats have been studied by a number of investigators. The best studies relate the oral dose to the blood lead level produced. Chowdury *et al.* (1984) observed reduced sperm counts in male rats that had blood lead levels of 72 μg/dL. No effects were observed in male rats with blood lead levels of 54 μg/dL. Both male and female rats were studied by Hilderbrand *et al.* (1973). They observed irregular estrus cycles in female rats with blood lead levels of 30 μg/dL. Ovarian follicular cysts were produced in female rats with 53 μg/dL blood lead levels. They found increased prostate weight in male rats with 19 μg/dL of blood lead, and testicular damage in male rats with 30 μg/dL blood lead.

Cardiovascular effects in animals were recently reviewed by Vaziri and Sica (2004), who discussed the role of oxidative stress in lead-induced hypertension.

Lead acetate, given orally, has been demonstrated to cause cancer in animals (Azar *et al*., 1973). This study yielded a dose-dependent increase in the incidence of kidney tumors in rats (Table 1) and has been used to estimate the oral cancer potency of lead (OEHHA, 1997; ATSDR, 2007). In this experiment, rats were fed lead acetate in their diet for two years. Kidney tumors were produced in a dose-related manner.

**Table 1. Kidney Tumor Incidence in Rats Administered Lead Acetate in the Diet (Azar *et al.*, 1973).**

| Dose (mg/kg-day) | Number of Rats in Dose Group | Number of Rats with Kidney Tumors |
|---|---|---|
| 0.23 | 20 | 0 |
| 0.39 | 100 | 0 |
| 1.40 | 50 | 0 |
| 4.78 | 50 | 0 |
| 10.9 | 50 | 0 |
| 42.3* | 20 | 5 |
| 79.7* | 20 | 10 |
| 167* | 20 | 16 |

*Treatment was begun for the groups with only 20 rats per dose several months after the other dose groups, although all were treated for two years.

### Summary of Animal Toxicity

Lead can affect the cardiovascular, gastrointestinal, hemolymphatic, urinary, immune, nervous, and reproductive systems as well as cause developmental effects in the offspring of treated dams and tumors in laboratory animals. Since the neurobehavioral changes are the more sensitive effects, the review focused on these reports. In general, the findings reported in the animal studies provide support for effects observed in human studies. In addition, a large database concerning the dose-effect relationships in humans exists and is more suitable for health effects assessments than are the animal data.

## *Toxicological Effects in Humans*

Exposure to lead has been associated with a large variety of human toxicological effects. Lead is known to cause changes in the cardiovascular, hematological, musculoskeletal, renal, reproductive, neurological, and immunological systems. In addition, lead may cause an increased risk of lung and stomach cancer. A brief summary is provided below on the acute and chronic effects associated with exposure to lead. The main focus of the

literature review will be on the most sensitive population – children – and most sensitive endpoint – neurobehavioral effects (Lanphear *et al*., 2000; Canfield *et al*., 2003; Chiodo *et al*., 2004). Some recent articles describing the effects of lead to various systems are Borja-Aburto *et al*. (1999), Lopez *et al*. (2000), Luchini *et al*. (2000), Sallmen *et al*. (2000), Steenland and Boffetta (2000), Cheng *et al*. (2001), Bockelmann *et al*. (2002), Gemmel *et al*. (2002), Gerr *et al*. (2002), Hernandez-Avila *et al*. (2002), Nawrot *et al*. (2002), Rothenberg *et al*. (2002), Muntner *et al*. (2003), Selevan *et al*. (2003), Sun *et al*. (2003), Wright *et al*. (2003), Wu *et al*. (2003), and Tsaih *et al*. (2004).

**Acute Effects**

Following ingestion or inhalation, the principal acute effect in humans is colic. This is a painful condition involving cramps and gastrointestinal distress. The effect is observed at blood lead levels in the range of about 40 to 120 μg/dL in adults (Awad el Karim *et al*., 1986; Pollock and Ibels, 1986; Pagliuca *et al*., 1990). Colic occurs most frequently to workers exposed to lead in the workplace as lead-bearing dust or lead fumes from soldering or welding (Meiklehohn, 1963). Colic is also a symptom of lead poisoning in children. U.S. EPA (1986) reported a Lowest Observed Adverse Effect Level (LOAEL) of approximately 60 to 100 μg/dL of blood in children.

**Chronic Effects**

Chronic exposure to lead has been demonstrated to affect many systems of the body including the nervous, renal, cardiovascular and reproductive systems. The effects occur at different levels of exposure. In children, the lowest level at which each of the chronic effects is observed is illustrated by Figure 1. Reference will be made to the figure within each section described below. The focus of the summary will be on effects on children; primarily the neurobehavioral effects due to lead exposure.

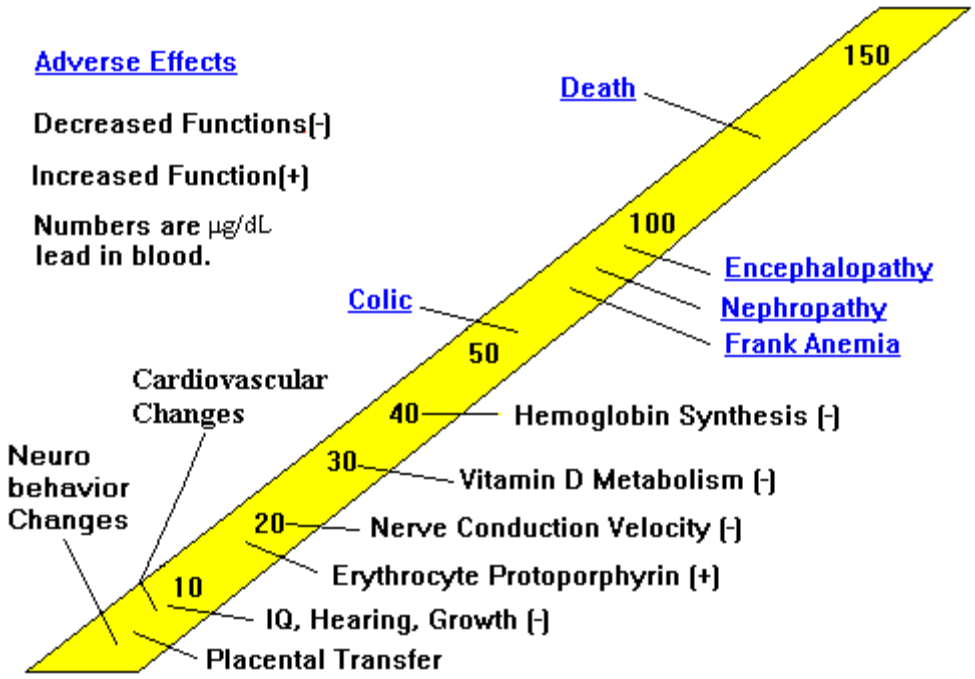


**Figure 1: Demonstrated Effect Levels of Inorganic Lead in Children.** The numbers in the diagram are blood lead levels at which studies have adequately demonstrated an effect, not necessarily the lowest level at which lead exerts the indicated effect.

*Cardiovascular Effects*

For humans, the greatest cardiological concern at low exposures and low blood lead levels is elevation in systemic blood pressure and decrements in glomerular filtration rate, which are mechanistically related. Schwartz (1991, 1995) earlier found that increased blood lead levels resulted in hypertension. Effects were observed in both children and adults, especially in middle aged males. Hypertension may also be caused in females or other age groups, but it has been most extensively studied in middle-aged males. Several authors have conducted meta-analyses of studies published between 1980-2001 (31 studies; Nawrot *et al*., 2002), 1984-1993 (23 studies; Staessen *et al*., 1994), and 1985-1993 (15 studies; Schwartz, 1994). An increase in systolic blood pressure of approximately 1–1.25 mm Hg can occur with each doubling of blood lead concentration (Schwartz, 1995; Staessen *et al*. 2000; Nawrot *et al*., 2002). Corresponding 95 percent confidence intervals (CI) reported were 0.5-1.5 mm Hg, 0.4-1.6 mm Hg, and 0.87-1.63 mm Hg, respectively. Mean blood lead concentrations reported were 1.9-7 µg/dL. Other cardiovascular changes include cardiac conduction and rhythm (Cheng *et al*., 2001; Bockelmann *et al*., 2002).

Nash *et al*. (2003) has reported an association between blood lead level and systolic and diastolic blood pressure in women aged 40 to 59 years, where the relationship is most pronounced in postmenopausal women. A small statistically significant adjusted change

in systolic and diastolic blood pressures was associated with changes in blood lead level quartile from the lowest (0.5-1.6 μg/dL) to the highest (4.0-31.1 μg/dL). Women with the highest exposures had increased risks of diastolic (>90 mm Hg) hypertension (Odds Ratio [OR] = 3.4; 95 percent CI = 1.3-8.7) and systolic (>140 mm Hg) hypertension (OR = 1.5; 95 percent CI = 0.72-3.2). The association in postmenopausal women was strongest with adjusted ORs for diastolic hypertension increasing with higher blood lead levels. The adjusted OR compared to the lowest blood level group was 4.6 (95 percent CI = 1.1-19.2) for quartile 2, 5.9 (95 percent CI = 1.5-23.1) for quartile 3, and 8.1 (95 percent CI = 2.6-24.7) for quartile 4 (the highest exposure group).

Epidemiological studies have also reported differences in cardiological effects between white and black Americans. Vupputuri *et al*. (2003) examined the relation between blood lead levels and blood pressure in a representative sample of 14,952 whites and blacks aged 18 years or older. For their multivariate analysis, co-variables were adjusted. The authors found that mean blood lead levels were significantly higher for black men and women (5.4 and 3.4 μg/dL, respectively) compared with white men and women (4.4 and 3.0 μg/dL, respectively). In addition, the authors reported that the higher blood lead was associated with a 0.82 mm Hg and a 1.55 mm Hg higher systolic blood pressure among black men (95 percent CI 0.19 to 1.44 mm Hg) and women (95 percent CI, 0.47 to 2.64 mm Hg), respectively. In contrast, Vupputuri *et al*. (2003) did not find an association between blood lead level and blood pressure among white men or women. The multivariate-adjusted odds ratio (95 percent CI) of hypertension associated with a one standard deviation higher level of blood lead was 1.08 (95 percent CI, 0.99 to 1.19) for black men and 1.39 (95 percent CI, 1.21 to 1.61) for black women. The earlier review of the dataset by Den Hond *et al*. (2002) did not find a consistent relationship between blood pressure and blood lead.

In a more recent review, Navas-Acien *et al.* (2007) also infer a causal association between lead exposure and increased blood pressure in adults. The authors identified about 3,100 studies from which only 62 met the author's criteria for inclusion in their review. Some studies indicated an effect below 5 μg/dL blood lead level while others did not, indicating overall no clear evidence of a threshold in the studies in their review.

The blood lead level at which the cardiovascular effects appear to begin is approximately 10 μg/dL in children (Schwartz, 1991). Similar or lower levels of blood lead are also associated with blood pressure changes in adults as observed in the epidemiological studies of Nawrot *et al*. (2002) and Navas-Acien (2007). Overall, the meta-analysis data suggest that there is an association between blood pressure and blood lead level in children and adults, where the effect in children is weaker than the one observed with male adults. However, the effects are being reported at blood lead levels below 10 μg/dL (Table 2) in both children and adults, which makes this a critical effect.

*Hematological Effects*

When lead levels are in the 50 to 100 μg/dL range, anemia may result. Anemia may be a consequence of several factors, including suppression of the heme synthesis pathway by altering σ-aminolevulinic acid dehydratase (ALAD) and ferrochelatase activity, leading

to shortage of hemoglobin and increased fragility of red blood cell membranes, which result in a shorter life span of red blood cells. The effect on the heme synthesis pathway leads to an increase in σ-aminolevulinic synthetase (ALAS) enzyme activity that leads to urinary porphyrins, coproporphyrin, and σ-aminolevulinic acid (ALA); increased blood and plasma ALA; and increased erythrocyte protoporphyrin (EP) levels. Threshold blood lead levels for decreased hemoglobin levels in adults and children are estimated to be 50 and 40 μg/dL, respectively (ATSDR, 2007). However, threshold lead blood levels for the ALAD and EP are much lower. The most sensitive endpoint, ALAD activity, was reported to be inversely correlated with lead blood levels of 3 to 34 μg/dL in the general population (Hernberg and Nikkanen, 1970; Chisolm *et al.*, 1985; ATSDR, 2007). Threshold blood lead for increased urinary ALA were 40 μg/dL and 30 μg/dL in adults and children, respectively, while the threshold for blood EP increases were 30 μg/dL and 15 μg/dL for adults and children, respectively (ATSDR, 2007).

*Renal Effects*

Lead exposure at doses intermediate between those that cause intelligence deficits and those that lead to encephalopathy may result in nephrotoxicity. Nephrotoxicity is characterized by proximal tubular nephropathy, glomerular sclerosis, and interstitial fibrosis (Diamond, 2005). This effect has been demonstrated in humans and animals. The mechanism involves structural changes in the kidney tissue that lead to blockage of the kidney tubules (Fowler and DuVal, 1991). Blood lead levels at which changes in renal parameters have been observed range from 6 to 100 μg/dL (ATSDR, 2007). For adults (>20 years of age; N ~ 5,000), the lowest blood lead levels reported to cause a change in serum creatinine or creatinine clearance was 5-10 μg/dL. In children (ages 4.6-13; N ~ 755), the lowest levels of blood lead reported to cause changes in renal function parameters were 12-34 μg/dL. Muntner *et al*. (2003) found a significant relationship between serum creatinine and blood lead levels when blood lead levels were below 10 μg/dL following adjustments for age and covariables contributing to glomerular disease. More recently, Ekong *et al.* (2006) found a decrease in creatinine clearance with blood lead levels below 5 μg/dL from the longitudinal studies reviewed.

*Reproductive Effects*

A potential association between occupational/environmental lead exposure and reproductive parameters in humans has been reported in men and women. The effects are associated with moderately high blood lead levels (ATSDR, 2007). In women, abortion and pre-term delivery are the effects reported (Borja-Aburto *et al*., 1999). In more recent studies, a decreased fertility was associated with longer exposures to lead and higher blood lead levels (Sallmen *et al*., 2000; Shiau *et al*., 2004). In these studies, abortion and pre-term delivery in women and decreased fertility in men were associated with blood lead levels above 12 and 30 μg/dL, respectively. However, other studies found no association with similar blood lead levels (Murphy *et al*., 1990; Apostoli *et al*., 2000; Joffe *et al*., 2003).

*Neurological and Neurobehavioral Effects*

Neurological and neurobehavioral effects have been reported to occur in children and adults. Children suffer encephalopathy at lower doses than adults. Encephalopathy during the 12 to 15 months after birth, during which the child's brain is developing, may lead to irreversible brain damage (Hutton, 1987; ATSDR, 2007). Lead encephalopathy is characterized by dullness, irritability, poor attention span, headache, muscular tremor, loss of memory and hallucinations. More severe cases exhibit delirium, convulsions, paralysis, coma and death (Kumar *et al.*, 1987). When children or fetuses receive high doses of lead (resulting in blood lead levels near 100 μg/dL) encephalopathy may result. For adults, encephalopathy has been reported to occur at blood lead levels of 40-120 μg/dL (ATSDR, 2007).

More recently, Dogu *et al*. (2006), in a case-control study, reported a relationship between higher lead blood levels in adults with an increased diagnosis of essential tremors (ET). The average blood lead level found in ET cases was 2.5 μg/dL compared to 1.5 μg/dL for controls ($p < 0.001$). The association in an unadjusted and adjusted logistic regression model was determined to be a four-fold increase of ET (OR = 4.01, 95 percent CI 2.53–6.37, $p < 0,001$). In addition, the authors reported that each 1 μg/dL increase in blood lead was associated with a four-fold increased odds of ET.

Shih *et al*. (2007) reviewed several environmental and occupational studies from 1996 to 2006 and found an association between acute or chronic exposure to lead in adults and neurobehavioral (i.e., cognitive function) outcomes. The authors reported that there was an association of lower cognitive function in populations with blood lead level as low as 4.5 μg/dL and mean tibia lead levels as low as 18.7 μg/dL. Blood lead level is a measure of current biologically active lead burden and measures acute effects, whereas the lead levels in bone are a measure of cumulative dose over decades.

Numerous studies have been conducted on the effects of low lead exposure on the intelligence of children in the U.S. and other countries. For some recent reviews, the reader is referred to Lidsky and Schneider (2003), Bellinger (2004), Koller *et al*. (2004), and Needleman (2004). Earlier, Needleman indicated that blood lead levels as low as 10 μg/dL may cause deficits in learning ability in very young children. Children who had umbilical cord blood lead levels at birth of 10 μg/dL or higher had poorer performance on intelligence tests and in school (Needleman, 1982). A four-year follow-up of these children showed that they had poorer classroom attention than the children with less lead exposure (Needleman, 1987).

Banks *et al*. (1997) also observed maladaptive behavior, slower reaction times, decreased nerve conduction velocity, and reduced Intelligence Quotient (IQ) scores, and reading, spelling, and mathematics performance, in pre-school and school-age children with increasing blood or tooth lead levels after reviewing epidemiological studies conducted in the 1970s and 1980s. The children examined generally had a minimum blood lead level in the range of 5-9 μg/dL and a maximum blood lead level in the range of 32-60 μg/dL. In reviewing some longitudinal studies done in the late 1980s and early 1990s, the authors found a significant inverse relationship between blood lead level for children exposed at birth to 5 years of age and one or more measures of linguistic ability, visual-

spatial relations, sensory-motor co-ordination, memory, motor skills, verbal, perceptual, or quantitative skills, or various measures of achievement (Banks *et al*, 1997). The blood lead levels in these children generally ranged from 1-8 μg/dL at the low end to 15 to 35 μg/dL at the high end.

Several recent studies have implied that there is no apparent threshold in the relationship between blood lead level and neurobehavioral functions. Lanphear *et al*. (2000) found an inverse association with four cognitive measures (arithmetic skills, reading skill, nonverbal reasoning, and short-term memory) and geometric mean blood lead levels after analyzing data obtained from 4,853 U.S. children, ages 6-16 years, as part of the NHANES III, 1988-1994. The geometric mean blood lead level of the population was 1.9 μg/dL and 2.1 percent exceeded 10 μg/dL. All end points were significantly affected when blood lead levels were below 10 μg/dL. When blood lead level was restricted to below 5 μg/dL, the inverse relationship was significant for two endpoints (arithmetic skills and reading skills) (Lanphear *et al*., 2000). Other studies have also found an association between low (<10 μg/dL) blood lead levels and decreased IQ (Schwartz, 1994; Shen *et al*., 1998; Schnaas *et al*., 2000, 2006; Al-Saleh *et al*., 2001; Gomaa *et al*., 2002; Bellinger and Needleman, 2004; Canfield *et al*., 2003, 2004; Carta *et al*., 2003; Emory *et al*., 2003; Chiodo *et al*., 2004; Chen *et al*., 2005). These results corroborate those of Lanphear *et al*. (2000) and further support the opinion that lead can have effects on cognition in some segments of the population at blood lead levels below 10 μg/dL. In fact, association with decreased attention, visual motor integration, social behavior and motor skills was observed in children with a blood lead level as low as 3 μg/dL (Chiodo *et al*., 2004). The mean blood lead level reported in Chiodo *et al.* (2004) was 5.4 μg/dL for a total of 237 children at 7.5 years of age.

A more recent study evaluating cognitive instead of aptitude outcomes found a robust relationship between cognitive outcome and blood lead level at low levels of lead exposure in children. Miranda *et al*. (2007) analyzed performance in end-of-grade (EOG) testing (i.e., reading and mathematics) from 2000-2004 in children from 7 counties in North Carolina using exploratory and multivariate statistical methods. The authors report a decline of 15 percent and 14 percent of the interquartile range in EOG reading and mathematic scores, respectively, at a blood lead level of 5 μg/dL. Lower blood lead levels of 2 μg/dL also showed a trend in decrease of EOG scores.

Recently, Lanphear *et al*. (2005) analyzed blood lead levels and full-scale IQ data from 1,333 children, ages 58 months to 10 years, in seven international population-based longitudinal cohort studies. The reanalysis of the pooled data included the seven following prospective lead studies: Ernhart *et a*l. (1989); Baghurst *et al.* (1992); Bellinger *et al.* (1992); Dietrich *et al*. (1993); Wasserman *et al*. (1997); Schnaas *et al.* (2000; 2006); and Canfield *et al*. (2003). The children were administered a version of the Wechsler Intelligence Scales for Children-Revised, Wechsler Intelligence Scales for Children-III, Wechsler Preschool and Primary Scales of Intelligence, or Wechsler Intelligence Scales for Children-Spanish version under uniform conditions within each study. The authors used concurrent blood lead levels as the exposure metric in all of their analyses because it was the most strongly related to IQ. After adjustment for the 5 covariates that significantly affected IQ, Lanphear *et al*. (2005) described a log-linear

model in which changes in blood lead level would correspond to decreases in IQ. With this model, a decline in IQ of 6.9 points (95 percent CI = 4.2-9.4) was associated with an increase in blood lead level from 2.4 to 30 µg/dL (the $5^{th}$ and $95^{th}$ percentiles, respectively). The model predicted decreases in IQ of 3.9 points (95 percent CI = 2.4-5.3), 1.9 (95 percent CI, 1.2-2.6), and 1.1 (95 percent CI, 0.7-1.5) with an increase in blood lead level from 2.4 to 10 µg/dL, 10-20 µg/dL, and 20-30 µg/dL, respectively. The authors concluded that maximal blood lead levels less than 7 µg/dL are associated with intellectual deficits.

Hornung (2005), a co-author in the Lanphear *et al*. (2005) study, fit a linear model to the blood lead level and IQ data for 703 children with concurrent blood lead levels below 10 µg/dL. The model estimates a slope of –0.47 with an upper end of the 97.5 percent CI ($UCL_{97.5}$) of –0.9 points per µg/dL. Jusko *et al.* (2008) have reported another study in 194 children showing similar correlations of IQ with blood lead levels from 6 months to 6 years of age.

Carlisle and Dowling (2006) reviewed the current literature and determined that a blood lead level increase of 1 µg/dL would be the lower-bound estimate to decrease IQ by 1 point. In their assessment, the studies of Lanphear *et al*. (2005) as well as Wang *et al*. (2002), Canfield *et al*. (2003), Emory *et al*. (2003), and Hornung (2005) were reviewed and found to provide evidence of neurobehavioral deficits at the lower blood lead level. In the end, the data from Lanphear *et al*. (2005) and re-analysis by Hornung (2005) were used by OEHHA to develop a draft child-specific health guidance value (HGV) for use in assessing risk at proposed or existing California school sites, which may include pre-school and day-care children (OEHHA, 2007). The study of Lanphear *et al*. (2005) was the basis for their assessment because the study reports on a sensitive endpoint (full-scale Wechsler IQ) in a large number of children (1,333; ages 58 months to 5 years), used appropriate measures of exposure, and evaluated appropriate covariates. The dataset provided sufficient statistical power to define the relationship between blood lead and cognitive function at lower blood lead levels within reasonably tight confidence limits.

Since the log linear model described by Lanphear *et al*. (2005) and the linear model described by Hornung gave a greater decrease in IQ at the lower blood lead level, OEHHA (2007) selected the 97.5 percent upper confidence limit ($UCL_{97.5}$) on the slope (-0.9 points per µg/dL) of the linear model as the basis for the child-specific benchmark change in blood lead concentration ($\Delta Pb_B$). The $UCL_{97.5}$ was used to account for variability and uncertainty in the data in order to be reasonably certain that the result is not an underestimate of the true slope. The linear model is expected to over-predict the drop in IQ at higher blood lead levels. OEHHA chose a model based on children in the lower half of the distribution because as population-wide blood lead levels continue to decline, more and more children will fall into this range. Also, OEHHA's mandate is to protect sensitive children, and these data suggest that children at the lower end of the exposure spectrum sensitive may exhibit a greater change in IQ for a given change in blood lead.

The child-specific benchmark change in blood lead concentration was calculated as follows:

$$BC_B = \frac{-1 \text{ IQ point}}{-0.90 \text{ IQ point per } \mu g/dL * (UF = 1)} = 1.1 \ \mu g / dL \ Pb_B$$, rounded to 1 µg/dL

An uncertainty factor (UF) of one was used because there is no interspecies or intraspecies extrapolation, since the data are based on sensitive humans, and the database was not considered deficient. This value was established as the new child-specific health guidance value for lead (OEHHA, 2007).

Based on these studies of IQ in children and blood lead levels from the U.S. and other countries, it appears that there is good evidence that very low blood lead levels (10 µg/dL or lower) can have a deleterious effect (a decrease of several IQ points) on the learning ability and intellectual development of young children. A decrease of only a few IQ points may be very significant on a population level in terms of increased need for remedial education (CDC, 1991). The work by Lanphear *et al*. (2005) and the analysis of the current data by Carlisle and Dowling (2006) demonstrate that the neurobehavioral effects (decrease in IQ) can occur much lower than 10 µg/dL. The new child-specific health guidance value for lead of 1 µg/dL is also used in the calculation of the new PHG.

*Genotoxic Effects*

The potential genotoxic effects of lead have been evaluated in lead workers. Wu *et al*. (2002) and Duydu *et al*. (2001) found an increase in sister chromatid exchanges in workers with blood lead levels around 32-36 µg/dL. Vaglenov *et al*. (2001) also reported an association with blood lead levels above 25 µg/dL and increases in micronuclei frequency in lead workers. Other occupational, environmental, and in vitro studies have evaluated the genotoxic potential (ATSDR, 2007). However, not all the studies have had consistent findings. There are several studies with negative results. In all, lead is considered a clastogenic agent due to the potential to induce chromosomal aberrations, micronuclei, and sister chromatid exchanges in peripheral blood cells (ATSDR, 2007).

*Cancer*

Most studies assessing the potential carcinogenicity of lead has involved exposure of inorganic lead in lead workers. Landrigan *et al*. (2000), Silbergeld (2003), Silbergeld *et al*. (2000), and Steenland and Boffetta (2000) have recently published reviews on the potential carcinogenicity of lead. Risk level reported by Steenland and Boffeta (2000) for lung cancer was an RR of 1.14 (CI of 1.04-1.73; 675 observed deaths) and for combined stomach cancers, RR of 1.34 (CI of 1.14-1.57; 181 observed). In general, the epidemiology studies provide some evidence of increased risk of lung and stomach cancer with little evidence of increased risk of kidney or brain cancer.

However, orally administered lead acetate has been demonstrated to cause cancer in animals (i.e., it increased the incidence of kidney tumors in rats) (Azar *et al*., 1973). This study has been used as the basis for estimating the cancer potency of lead (OEHHA, 1997; ATSDR, 2007). Lead is regarded by the International Agency for Research on Cancer (IARC) and the U.S. EPA as an animal carcinogen and probable human

carcinogen (IARC, 2004; NTP, 2005; U.S. EPA, 2005). Given that lead acetate is carcinogenic in rats (Azar *et al.*, 1973), other ionic salts would probably be carcinogenic as well.

**Summary of Chronic Health Effects in Humans**

The most significant health effects from the public health and regulatory point of view are the ones which occur at the lowest blood lead levels, because these affect the greatest part of the population. For children these are the effects on intelligence and behavior. For adults the most sensitive health effect is the increase in blood pressure and other cardiovascular effects. Both of these health effects are of concern below 10 μg/dL blood lead. Since measurable neurobehavioral effects in children for lead may occur with an increase of in blood lead of 1 μg/dL, this increase in lead level may be considered a shift of concern for both children and adults. Other health effects such as kidney and gastrointestinal effects occur at higher blood lead levels. See Figure 1 and Table 2 for a summary of these effects and the blood lead levels at which they occur.

## DOSE-RESPONSE ASSESSMENT

### *Noncarcinogenic Effects*

The most sensitive health endpoints for lead are intelligence deficits in children and hypertension (cardiovascular changes) in adults. The PHG was developed based on intelligence deficits in children, as this is the best-documented health endpoint that occurs at very low levels of exposure**.** The established public health-protective concentration will be applied to both children and adults.

Based on studies correlating blood lead levels with decreased IQ in children, the Centers for Disease Control (CDC) earlier identified 10 μg/dL as the lowest blood lead level of concern (CDC, 1991). Using an IEUBK model (Version 0.99d, 1994), OEHHA determined that for children between 12 and 24 months of age, a blood lead level increase of 0.35 μg/dL results from each increment in drinking water intake of 1.0 μg/day (OEHHA, 1997b). This was based on a calculation using the default values for exposure from dust, air, paint and other sources. Newer studies have demonstrated that neurobehavioral changes can occur at lower lead blood concentrations. Carlisle and Dowling (2006) found that an increase in blood lead levels of 1 μg/dL was correlated with a decrease of 1 IQ point based on the findings of Lanphear *et al*. (2005).

Therefore, the lead intake level that would correspond to the level of concern for children can be calculated as follows:

$$\text{Lead intake} = \frac{1\ \mu g/dL\ (blood)}{0.35\ \mu g/dL\ per\ \mu g/day} = 2.86\ \mu g/day$$

A daily lead intake from water ingestion of 2.86 μg/day corresponds to a 1 μg/dL increase in blood lead level. In other words, 2.86 μg/day can be used as a benchmark for daily oral intake from water that corresponds to a level of concern for neurobehavioral effects in children, designated as a decrease of 1 IQ point.

### *Carcinogenic Effects*

The best study for assessment of the carcinogenic effects of lead by the oral route is the study by Azar *et al.* (1973). This study was used to determine a public health-protective concentration for carcinogenic endpoints in the 1997 lead PHG document. Lead acetate was administered in the diet of rats for two years. From the dose-related kidney tumor data, a cancer potency $q_1$* (animal) and oral cancer slope factor (CSF) were calculated using the Global 86 software. A $q_1$* (animal) of $1.53 \times 10^{-3}$ $(mg/kg\text{-}day)^{-1}$ was obtained and converted to an equivalent human $q_1$* ($5.98 \times 10^{-3}$ $(mg/kg\text{-}d)^{-1}$). The $LED_{10}$ (the 95 percent lower-bound dose resulting in a 10 percent tumor incidence) of 68.8 mg/kg-day was obtained to calculate the rat CSF of $1.45 \times 10^{-3}$ $(mg/kg\text{-}day)^{-1}$. The CSF for the rat data was converted to a CSF for humans using the same body weight scaling ($3/4^{th}$ power) as described for the $q_1$*. This calculation yielded a CSF (human) of $5.68 \times 10^{-3}$ $(mg/kg\text{-}day)^{-1}$. Therefore, the CSF (human), which was approximately equal to the $q_1$* (human), was used to calculate a health-protective value based on carcinogenicity.

## CALCULATION OF PHG

### *Noncarcinogenic Endpoints*

A public health-protective concentration (C) for lead in drinking water can be calculated using the following equation for the most sensitive non-carcinogenic endpoint, which is a decrease in IQ in children:

$$C = \frac{\text{Level of Concern} \times \text{RSC}}{\text{UF} \times \text{L/day}} = \text{mg/L}$$

where,

Level of Concern = daily lead intake which results in a 1 μg/dL increase in blood lead level for children (2.86 μg/day);

RSC = relative source contribution of 20 percent (0.2);

UF = uncertainty factor of 3-fold;

L/day = daily drinking water consumption volume for a child (1 L/day).

There is some uncertainty as to whether the level of concern of 2.86 μg/day for children, used in the equation above, is protective for all children, because there are children in the

population whose blood lead levels are already above the concern level set by the CDC of 10 μg/dL (CDC, 2006). For these individuals any increase in blood lead level would simply add to an already adverse blood lead level. A threshold has not been observed for the non-carcinogenic effects (decrease in IQ points) of lead (Lanphear *et al.*, 2005; Schnaas *et al.*, 2006). In calculating the health-protective level for non-carcinogenic effects, an uncertainty factor of three is being applied to account for the uncertainty with regard to the degree of protection offered at this level, considering the lack of a threshold. The uncertainty factor of three also accounts for the extrapolation from the small sample size used in the main study of Lanphear *et al*. (2005) to the large, diverse population of children in California.

CDC's level of concern for lead in blood remains at 10 μg/dL, although CDC considers the actual level somewhat arbitrary because "there is no evidence of a threshold below which adverse effects are not experienced." However, the CDC level of concern has been consistently lowered over the last two decades, and may be lowered again in the future.

To calculate a health-protective level for non-cancer effects, children are assumed to consume 1 L of water/day. The drinking water contribution to children's lead exposure is estimated to range from 5 percent to over 50 percent (U.S. EPA, 1991) depending on the immediate environment in which the child lives. For children exposed to lead in paint, or lead in air and soil (e.g., living near roadways where lead deposits from engine exhaust still persist), U.S. EPA determined that drinking water exposure to lead would be on the lower end of this range. Therefore, in calculating a public health-protective concentration, we assume that drinking water exposures would contribute 20 percent of the total exposure to lead to account for exposures in children living in areas where high environmental concentrations of lead still persist.

Therefore,

$$C = \frac{2.86\ \mu g/day \times 0.2}{3 \times 1\ L/day} = 0.19\ \mu g/L = 0.2\ \mu g/L \text{ or } 0.2 \text{ ppb (rounded)}$$

## *Carcinogenic Endpoint*

A public health-protective concentration (C) for lead (in mg/L) in drinking water can also be calculated using the general equation for carcinogenic endpoints:

$$C = \frac{R \times BW}{CSF \times L/day} = mg/L$$

where,

R = *de minimis* theoretical excess lifetime cancer risk of $1x10^{-6}$;

BW = default adult body weight of 70 kg;

CSF = cancer slope factor calculated above [$5.68 \times 10^{-3}$ $(mg/kg\text{-}day)^{-1}$];

L/day = volume of daily water consumption for an adult (2 L/day).

Therefore,

$$C = \frac{1 \times 10^{-6} \times 70\ kg}{5.68 \times 10^{-3}\ (mg/kg\text{-}day)^{-1} \times 2\ L/day}$$

$$= 6.16 \times 10^{-3}\ mg/L = 0.006\ mg/L\ (rounded) = 6\ ppb$$

The public health-protective concentration for lead based on the carcinogenic endpoint is 6 ppb. This is higher than the public health-protective concentration of 0.2 ppb calculated for non-carcinogenic effects. Therefore, the PHG for lead in drinking water is 0.2 ppb (0.2 μg/L or 0.0002 mg/L) based on non-carcinogenic effects.

## RISK CHARACTERIZATION

The health risks of exposure to lead are well established by a large body of research. For the non-carcinogenic effects upon which the PHG is based (i.e., neurobehavioral effects in children), the research has been conducted on human populations. Therefore, there is no uncertainty in the calculation for extrapolation from animals to humans for these effects. The carcinogenic effect data are based on animal experimentation, which does introduce an uncertainty in extrapolating from animals to humans. The Azar *et al*. (1973) rat study, demonstrating kidney tumors after oral exposure to lead acetate, has the best available data for calculating a CSF.

Humans, especially children, may vary in their sensitivity to lead in drinking water because of differences in nutrition, exposure to lead from other sources and metabolic and genetic differences. Adults also may vary in their sensitivity to the hypertensive effects of lead.

The calculated PHG utilizes an RSC of 20 percent (0.2). This value is justified for certain subpopulations of children living in areas where lead in the environment still persists in moderate to high levels. Higher RSCs (up to 50 percent) might be justified for the general population because of the recent declines in relative contribution from air, water and food. The use of a higher RSC would increase the calculated PHG for non-carcinogenic endpoints for lead in drinking water.

## OTHER STANDARDS AND REGULATORY LEVELS

Lead is regarded by IARC and the U.S. EPA as an animal carcinogen and probable human carcinogen (IARC, 2004; NTP, 2005; U.S. EPA, 2005).

U.S. EPA has adopted a Maximum Contaminant Level Goal (MCLG) of zero for lead in drinking water, based on "occurrence of low level effects" and because U.S. EPA classifies lead as Class B2, a "probable human carcinogen" (Fed. Reg. 56:32112, July 15, 1991; U.S. EPA, 2008). U.S. EPA has not adopted a Maximum Contaminant Level (MCL) for lead in drinking water because they regard the development of such a level as "not feasible" and rely on the "treatment approach" described in the final rule (Fed. Reg. 56:32112, July 15, 1991) to achieve the objective of reducing exposures to lead. However, U.S. EPA has set an "action level" for lead in drinking water of 15 ppb (40 CFR 141, 142; Fed. Reg. 56:26461-26564). This is a level the U.S. EPA believes is feasible for public water systems to attain by such measures as adjusting the physical characteristics of the water (pH, hardness) which affect the corrosivity of the water.

The lead and copper rule is a Federal and State drinking water standard (Title 22 CCR, section 64672.3) that specifies requirements for lead in drinking water systems (measured at the customers' taps). The action level (15 ppb) is used to determine the treatment requirements that a water system must complete. The action level for lead is exceeded if the concentration of lead in more than 10 percent of the tap water samples collected during any monitoring period (conducted in accordance with 22 CCR sections 64682 to 64685) is greater than 15 ppb. Failure to comply with the applicable requirements for lead and copper is a violation of primary drinking water standards for these substances (22 CCR Chapter 17.5). Therefore, for all practical purposes the standard described in the lead and copper rule is equivalent to an MCL. U.S. EPA has set a National Ambient Air Quality Standard of 1.5 $\mu g/m^3$ (Fed. Reg. 43:41258, October 5, 1978).

Lead is listed as a carcinogen and as a reproductive and developmental toxic chemical under the Safe Drinking Water and Toxic Enforcement Act of 1986, "Proposition 65" (California Health and Safety Code, Chapter 6.6, section 25249.5 *et seq*.). Lead is listed as a reproductive and developmental toxic chemical because of its effects on IQ during development. Under this program the exposure level set for warning against possible reproductive and developmental effects is 0.5 μg/day for any one source of exposure.

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