DU PONT CENTRAL RESEARCH AND DEVELOPMENT
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CONFIDENTIAL

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DEVELOPMENT OF A TOXICITY CRITERION FOR LEAD

Attached please find documentation for our derivation of a lead toxicity criterion to be used in the "C Basin" remediation project. A level of 40 µg/L as total lead in water was derived and is expected to be protective of health effects that are related to blood lead. The EPA Biokinetic model, LEAD 0.4 was used to relate lead intake to blood lead levels. Assuming default background lead intake from sources other than drinking water, 40 µg/L in drinking water is predicted to result in mean blood lead levels in children below background levels (10 µg/dl to 15 µg/dl) in greater than 90 % of the population.

DERIVATION OF AN ORAL TOXICITY CRITERION FOR LEAD

SUMMARY

The toxicology of lead is reviewed with particular reference to the association of blood lead levels with developmental deficits in children. Since blood lead levels are predictive of toxicity in children, the EPA Biokinetic model was used to predict blood lead levels in children exposed to lead in drinking water and through background sources. Maximum blood lead levels were chosen to be 10 µg/dl to 15 µg/dl. Conservative parameters for lead uptake and bioavailability were used to account for potential exposure to both organic and inorganic forms of lead. A value of 40 µg/dl was derived and is predicted to be protective of greater than 90% of the population.

General Toxicity

The major route of exposure of workers to lead is by inhalation and ingestion of lead-bearing dusts and fumes. For the general public, the oral route (diet and drinking water) provides most of the lead intake with a small amount resulting from inhalation of airborne lead. However, reductions in the amount of lead in the environment have greatly reduced the amount of lead received from inhalation. Biological monitoring as a measure of occupational exposure to lead is most effectively determined by the measurement of blood-lead concentration (12).

Increased blood-lead levels above the normal range can occur without overt clinical symptoms or effects and biochemical changes can be detected within what is currently recognized as the normal range of blood-lead levels (< 35 ug/dL) (12).

Lead, like other chemicals, produces changes which range from those merely indicative of lead exposure, through those which are measurable but have no adverse impact on the organism, to those producing adverse effects. Lead has been extensively studied in both animal models and in man and support data for relating lead exposures to a wide variety of toxicity end-points can be found. However, many of these studies do not reliably allow precise definition of lead-induced toxicity with lead exposure (as measured by blood-lead levels). The discussion which follows

recognizes this and points out areas in which the relationship between toxicity and blood-lead levels has been more clearly demonstrated.

In adult populations, a number of target organs or systems have been identified as being adversely affected by lead. Changes in the hematopoietic system (decrease in delta-amino-levulinic acid dehydrase activity in the red-blood cells, increase in erythrocyte protoporphyrins, changes in pyrimidine-5-nucleotidase levels) have been associated with lead exposure. Nerve conduction velocity decreases and suggestions of neurologic symptoms have been detected. Increased systolic blood pressure has been associated with blood-lead levels of about 30 ug/dL (42). Associations between blood-lead levels and blood pressure have been reported in middle-aged men 40 to 59 years old, with no apparent threshold through < 10 ug/dL; e.g., as blood lead increases, systolic blood pressure increases slightly (12,33,34).

Renal changes associated with blood-lead levels ranging from 40 to > 100 ug/dL have been reported in lead workers. However, the blood-lead levels measured at the time of renal function testing may not fully reflect the exposure history that contributed to the development of these renal effects (12).

It is not possible to establish lead exposures (as measured by maternal blood-lead levels) at which no effects are produced in the fetus. Several studies have revealed potential developmental effects in the form of reduced birth weight, pre-term birth, decreased growth rate, and lowered learning abilities. Lower birth weights were associated with maternal blood-lead levels of 12 to 13 ug/dL (4,8,9). IQ deficits of -5 points in children, indicating neurobehavioral impairment, are associated with mean blood-lead levels of 50 to 70 ug/dL in the children (7,39); and IQ deficits of -4 points are associated with blood-lead levels of 30 to 50 ug/dL (31). A significant association between cognitive ability and the children's blood-lead levels, with no apparent threshold down to the lowest blood-lead levels of about 6 ug/dL has been shown in two populations of children (15,18). Additional evidence of IQ deficits in children with blood-lead levels below 25 ug/dL has been reported (17).

Carcinogenic Potential

Certain lead compounds, e.g., lead acetate (11) and lead naphthenate (1), have been shown to be carcinogenic in animals, but epidemiological studies of lead workers have shown equivocal evidence of carcinogenicity (6,12,40). In the study in rats with lead acetate, administration of 500 ppm (as lead) of lead acetate for two years produced an increased incidence of kidney tumors. The mean blood-lead level of these rats was 77.8 ug/dL. Another group administered 100 ppm (blood lead of 35.2 ug/dL) had no kidney tumors (11). Lead naphthenate also produced kidney tumors in mice dermally administered a 20% benzene solution, twice a week, for up to 569 days (1).

Lead chromate has been associated with lung tumors in epidemiology studies. However, the lung cancers seen in one study might be related to chromium, especially zinc chromate, which was also produced in this plant (14).

The studies in animals suggest that lead does produce kidney cancer generally following long-term, high-level exposures. The epidemiology studies do not readily yield the same kind of single-variable information and have been equivocal. It can be concluded that some lead compounds are weakly carcinogenic in rats and mice. No evidence for human carcinogenicity exists.

Genotoxic Potential

Tests for mutagenicity in microbial studies have yielded consistently negative results (10). Mammalian tests have given conflicting results, although the weight of evidence indicates lead may have clastogenic effects (2,38).

Developmental Toxicity

A number of animal studies have been conducted by the oral (5,16,19,21-23,25-27,29,30,36,37,41) and inhalation routes (35). Lead compounds do not appear to be teratogenic. Embryo- and fetotoxic effects suggest that the fetus is as sensitive, and maybe even more sensitive, to the effects of lead than the maternal animals.

In humans, prenatal exposure to lead produces toxic effects on the fetus including reductions in gestational age, birth weight, and mental development. However, no clear evidence of an association with congenital malformations was found (13,28,32).

Based on risk estimates, the risk of pre-term delivery increases four-fold as cord or maternal blood-lead levels increase from < 8 to > 14 ug/dL (28). A significant association between prenatal maternal blood-lead levels and birth weight has also been reported with the effect apparent at blood-lead levels as low as 12 to 13 ug/dL (4,8,9). IQ deficits of 4.8 points were detected in children 6 to 24 months old who had blood-lead levels at birth between 10 and 25 ug/dL (3).

Reproductive Toxicity

Sperm analysis indicates decreased fertility in occupationally exposed workers with blood-lead levels of about 50 ug/dL or more (24,43).

A group of 150 workers with long-term lead exposure was categorized by clinical and toxicological data into four groups: lead-poisoned (mean blood-lead level = 74.5 ug/dL), moderately-exposed (mean = 52.8 ug/dL), slightly-exposed (mean = 41 ug/dL), and physiologically-exposed (mean = 23 ug/dL). The lead-poisoned and moderately-exposed groups had significant decreases in fertility as measured by asthenospermia, hypospermia, and teratospermia (24). Effects on sperm were also observed in another group of lead-exposed workers with mean blood-lead levels of 44.6-46.1 ug/dL (however, these men had blood-lead levels of 50 ug/dL or more at least once prior to the study) (44).

Data from older literature indicate high-level exposure to lead may be related to abortion in women, but these studies had methodological problems and did not indicate a dose-response relationship (12). A higher incidence of miscarriage and stillbirth was reported among women living in a lead-smelter town than in women living outside of the town. However, maternal lead levels were lower in some cases of stillbirth than in cases of live birth (28).

Studies in rats indicate a NOEL for reproductive effects in females of 9 to 16 ug/dL and a lowest effect level of 18 to 29

ug/dL (16). In males, the NOEL is 19 ug/dL and the lowest effect level for testicular damage is 30 ug/dL (20).

Long-term, high-level exposure to lead can apparently interfere with the reproductive system of animals and humans. However, as mentioned above, these data do not permit any estimate of NOELs in women, and information on low-level exposures to lead and any potential effects on sperm or the testes is lacking. In animals, NOELs are below 30 ug/dL.

For women of childbearing capability, exposures above background (as reflected by blood-lead levels of less than 15 ug/dL) should be avoided. For others, while no one piece of evidence suggests significant health effects following exposure to lead resulting in blood-lead levels of 50 ug/dL, the data taken together suggest a prudent practice would be to have a program to reduce blood-lead levels to 35 ug/dL or below.

Development of a Toxicity Criteria

Lead toxicity has been shown to be closely related to blood lead levels and therefore a toxicity criterion should be based on blood lead. A method for relating lead intake to blood lead level is the EPA Lead 0.4 Biokinetic model (42). This model is a pharmacokinetic-based description of lead intake and distribution to six compartments within the body. The model has been verified against human lead intake/blood levels and appears to be suitable for this purpose. The Biokinetic model includes air, soil and dust, and water ingestion pathways and models uptake in children up to 7 years of age. This is appropriate for environmental exposure as children appear to be the most sensitive sector of the population. Default values for lead ingestion are available for each pathway.

Blood lead values were modeled using the default intake values for all exposure pathways except drinking water. For drinking water exposure, blood lead levels were modeled by modifying gastrointestinal bioavailability method, percent absorption, population geometric standard deviation of predicted blood lead levels, and drinking water lead concentration.

Two methods for gastrointestinal uptake of lead are available in the model. The default value models uptake as nonlinear active transport at low lead levels and as passive absorption at lead levels expected to saturate the active transport mechanisms. A more conservative approach is to model uptake using the second method, which models uptake as a passsive-linear process at all lead levels.

Differen forms of lead, organic versus inorganic, have varying degrees of bioavailability from the gastrointestinal tract based on the degree of adsorption to nonabsorbable materials. The model does not explicitly account for the absorption of inorganic versus organic lead. The default absorption value in the biokinetic value is 50%. Lead entirely in the form of organic lead is expected to be extensively absorbed and therefore, a higher absorption value could be argued. Thus, values of 50%, 80%, and 100% were run in the Biokinetic model.

The geometric standard deviation is a measure of the heterogeneity of the population around a population mean. A lower geometric standard deviation assumes a more homogeneous population. The default geometric standard deviation is 1.42. The Technical Support Document for the Biokinetic model states that values in the range of 1.30 to 1.52 is considered reasonable for children living near a point source. Values of 1.30 and 1.42 were tested.

Blood lead levels in the range of 10 to 15 µg/dl are considered to be background. Therefore, water lead levels were adjusted to meet target geometric mean blood levels of less than 15 µg/dl.

RESULTS OF LEAD UPTAKE BIOKINETIC MODEL

Drinking Water Conc. (µg/L)	% Absorption (all ages)	GI Bioavail. Method	Geometric Standard Deviation	Geometric Mean	% Population Below 10 µg/dl	% Population Below 15 µg/dl
100	50	NL/A-P*	1.42	9.58	56.9	90.4
80	50	NL/A-P	1.42	8.30	72.6	95.9
80	50	L	1.42	8.35	70.9	95.5
80	100	L	1.42	13.76	19.6	61.3
40	100	L	1.42	8.35	70.9	95.5
40	50	L	1.42	5.65	95.2	99.8
40	50	L	1.30	5.65	98.7	99.9
40	100	L	1.30	8.35	76.7	98.8
40	80	L	1.30	7.27	89.7	99.7

*NL/A-P = nonlinear/active-passive absorption model.
L = Linear passive absorption model.

The results of the lead modeling indicate that drinking water values in the range of 100 µg/L to 40 µg/L should provide an adequate margin of protection against blood lead-related health effects. All yielded mean blood lead levels below 15 µg/dl. At a drinking water concentration of 40 µg/L, the model predicts that 70.9% or 99.9% of the population will have blood lead levels below 10 µg/dl or 15 µg/dl, respectively depending on the method of absorption, the percentage of lead bioavailable, and the chosen geometric mean standard deviation. As a final value, 80% bioavailability was chosen as the lead in drinking water is likely to be comprised of both inorganic and organic forms. Because organic lead is expected to be readily absorbed relative to inorganic lead and uptake is unlikely to be saturable, the linear method of GI bioavailability was chosen. Finally, a geometric standard deviation of 1.30 was chosen because it is within the range of values acceptable to EPA and because the population of potentially exposed individuals is fairly well defined. Using these parameters, 40 µg/dl is expected to result in a geometric mean blood lead value below background (10 to 15 µg/dl) in greater than approximately 90% of the population.

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