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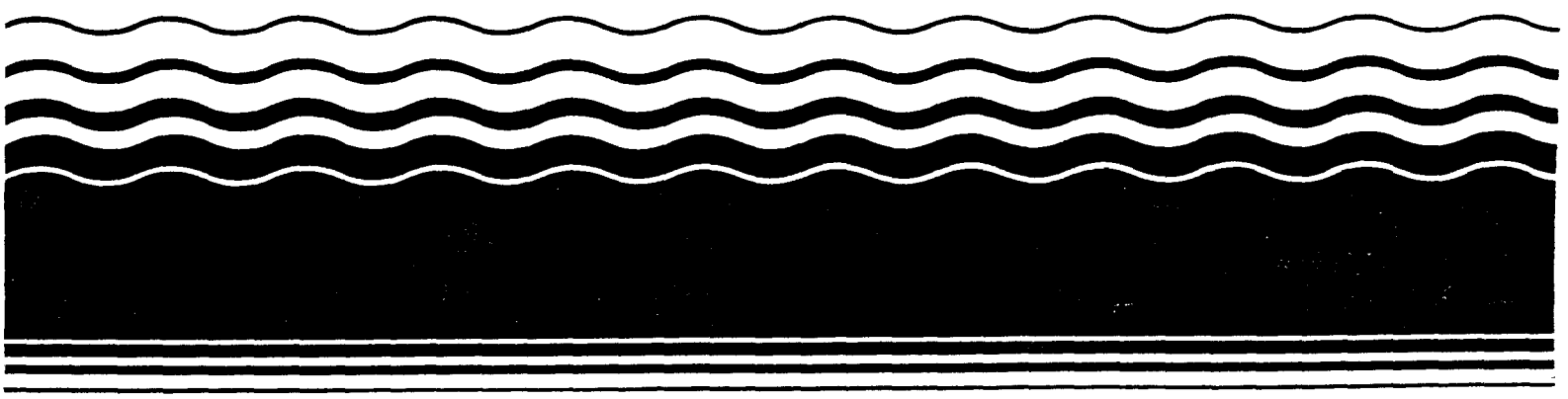
HEALTH EFFECTS ASSESSMENT FOR LEAD



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U.S. Environmental Protection Agency
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Office of Solid Waste and Emergency Response
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This report has been funded wholly or in part by the United States Environmental Protection Agency under Contract No. 68-03-3112 to Syracuse Research Corporation. It has been subject to the Agency's peer and administrative review, and it has been approved for publication as an EPA document. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with lead. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1977. Air Quality Criteria for Lead. U.S. EPA, ORD, Washington, DC. EPA 600/8-77-017.

U.S. EPA. 1980b. Ambient Water Quality Criteria for Lead. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-057. NTIS PB 81-117681.

U.S. EPA. 1983a. Reportable Quantity for Lead (and compounds). Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1984. Air Quality Criteria for Lead. Environmental Criteria and Assessment Office, Research Triangle Park, NC, OHEA. EPA 600/8-83-028B. NTIS PB 85-163996.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980a) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983b).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980a). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Lead is an extremely well studied compound. Despite the immense volume of data, or perhaps because of it, there is still uncertainty concerning "safe" exposure levels. As methods become increasingly sophisticated, effects are detected at lower levels. An underlying premise of the current air standard and ambient water quality criterion is that children are the most sensitive segment of the population and if blood lead levels in the majority of children are maintained $\leq$30 µg/dℓ, an adequate margin of safety for adverse effects will be achieved. However, the target level of 30 µg/dℓ is currently being reviewed. New guidelines may potentially be developed.

Another major problem associated with lead exposure is the ubiquitous nature of the compound. Unlike most other contaminants where exposure may be related to a specific route or situation, substantial "background" lead exposure occurs, primarily through food. This background exposure must be considered when guidelines for individual media or exposure routes are suggested.

The approach taken in the present document was to make use of the current air standard (1.5 µg/m^3) and information in the water quality criterion derivation (50 µg/ℓ) as the best available estimates at the present time. For reasons discussed in the text, AIC values in units of mg/day have not been estimated. A CS of 35 has been calculated for lead based on reduced survival of offspring in mice treated by inhalation.

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
ADP	Adenosine 5'-diphosphate
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
ALA	δ-aminolevulinic acid
ALAD	δ-aminolevulinic acid dehydrase
bw	Body weight
CAS	Chemical Abstract Service
CNS	Central nervous system
CP	Coproporphyrin
CS	Composite score
FEP	Forced expiratory pressure
GI	Gastrointestinal
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
PEL	Permissable exposure limit
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
STEL	Short-term exposure limit
TLV	Threshold limit value

1. ENVIRONMENTAL CHEMISTRY AND FATE

Lead is a metal in Group IVB of the periodic table. Elemental lead has a CAS Registry number of 7439-92-1. The inorganic chemistry of lead is dominated by compounds in the +2 valence state. The primary examples of lead in the 0 valence state are metal and alloys and the +4 valence state is dominated by organolead compounds. The most important organolead compounds are tetramethyl lead and tetraethyl lead. Selected physical properties of a few environmentally significant lead compounds are given in Table 1-1.

The environmental fate of lead has been extensively reviewed by U.S. EPA (1977) and Boggess and Wixson (1977). In this report, the environmental fate of lead will be discussed only briefly. In the atmosphere, lead is present primarily as particulate matter from exhaust of internal combustion engines using leaded fuel, coal or fuel oil combustion, from lead mining and refining operation and from welding of certain coated or uncoated steel (U.S. EPA, 1977; NIOSH, 1972). Small amounts of organic lead vapors (mainly tetramethyl lead vapors) have been reported in the vicinity of gasoline stations, garages and heavy traffic areas (U.S. EPA, 1977). These organic vapors are expected to undergo photodecomposition to form particulate matter, or the vapor may remain adsorbed on dust particles in the air (U.S. EPA, 1977).

Lead from different stationary and mobile sources is emitted as different chemical species in the atmosphere. Vehicular exhausts produce primarily emissions of PbBrCl (Boggess and Wixson, 1977). Emission from coal or fuel combustion consists primarily of PbO and $PbSO_4$. Smelting, mining and refining processes produce primarily PbS, $PbSO_4$ and elemental Pb (Boggess and Wixson, 1977); however, the major lead-containing atmospheric species

TABLE 1-1

Selected Physical Properties of a Few Lead Compounds[a]

Element/ Compound	Formula	Atomic Molecular/ Weight	Water Solubility	Vapor Pressure
Lead	Pb	207.19	insoluble	1 mm at 973°C
Lead chloride	$PbCl_2$	278.10	0.99 g/100 mℓ at 20°C	1 mm at 547°C
Lead bromide	$PbBr_2$	367.01	0.844 g/100 mℓ at 20°C	1 mm at 513°C
Lead oxide	PbO	223.19	1.7×10^{-3} g/100 mℓ at 20°C	1 mm at 943°C
Lead sulfide	PbS	239.19	8.6×10^{-5} g/100 mℓ at 25°C	1 mm at 852°C
Lead sulfate	$PbSO_4$	303.25	4.25×10^{-3} g/100 mℓ at 25°C	NA
Lead tetramethyl	$Pb(CH_3)_4$	267.33	15 mg/ℓ (Pb)[b]	22.5 mm at 20°C
Lead tetraethyl	$Pb(C_2H_5)_4$	323.44	0.8 mg/ℓ at 20°C	0.15 mm at 20°C

[a]Source: Weast, 1980; Verschueren, 1983

[b]Temperature not specified

NA = Not available

are $PbBrCl \cdot NH_4Cl$, $PbSO_4$ and $PbCO_3$ (Boggess and Wixson, 1977). Although little is known about the atmospheric interactions of lead species, it is obvious that some intractions must be responsible for the formation of prevalent lead-containing species in the atmosphere.

Chemical reactions of lead species in the atmosphere may cause transformation of one species to another, but these reactions do not remove lead from the atmosphere. Similarly, photochemical decomposition of tetramethyl lead and tetraethyl lead (U.S. EPA, 1977) may convert these species into the elemental form that may subsequently be oxidized to $PbSO_4$ or $PbCO_3$ in the presence of SO_2 and CO_2 in the atmosphere. This process, however, does not remove lead from the atmosphere. A more likely fate of atmospheric lead alkyls is sorption onto the surface of atmospheric particulates and subsequent conversion into inorganic lead compounds (Boggess and Wixson, 1977).

Lead is removed from the atmosphere through wet and dry deposition. Removal through rainfall (washout, the incorporation of a particle into precipitation below the cloud base) probably is insignificant compared to the rainout process which occurs within a cloud (Boggess and Wixson, 1977). Therefore, both the dry deposition and in-cloud rainout processes are principally responsible for the removal of lead from the atmosphere.

The atmospheric residence time for lead before its final removal through rainout and dry deposition is dependent predominantly on the particle size. It is estimated that 75% of the particulate lead emitted from automobiles is removed from the atmosphere in the immediate vicinity of traffic sources. Smaller particles from mobile sources and emission from tall stacks will remain airborne longer and be transported over greater distances. Submicron (<1 μm diameter) particles may remain in the atmosphere for ≥ 1 week (U.S. EPA, 1977).

Lead in aquatic media is primarily removed to bed sediments by two processes, precipitation as $PbCO_3$, PbS, $PbSO_4$ or adsorption onto organic materials, hydrous iron or manganese oxides. In some bodies of water, precipitation may be the most important process, but under most circumstances sorption may predominate. Biomethylation of lead by benthic microbes may cause some remobilization of lead from bed sediments. It should be emphasized that the removal of lead from aquatic media may be strongly pH dependent. In acidic pH ranges, lead may be more mobile than in alkaline pH ranges because of inherent higher solubility of precipitable lead salts and lower sorption characteristics of lead in solution (Callahan et al., 1979).

Lead in soil is expected to undergo speciation to more insoluble $PbSO_4$, $Pb_3(PO_4)_2$, PbS and PbO salts (U.S. EPA, 1977). Lead does not usually move downward in soil because of the relative insolubility of lead salts and the binding capacity of organic fractions that may be present in soils (Boggess and Wixson, 1977). Under certain circumstances, however, lead may be solubilized through complexation with organics present in soils (U.S. EPA, 1977). In the absence of suitable sorbents, the complexed lead may move downward in the soil. Page (1981) detected lead (1 µg/ℓ mean concentration) in groundwater samples in New Jersey at a frequency of ~100%.

Lead is bioconcentrated by aquatic organisms. The estimated bioconcentration factor for lead in edible bivalve molluscs may vary from 17.5-2570, whereas its value for edible fish may be ~42-45 (U.S. EPA, 1980b).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

It has been estimated that, in man, ~8% of the lead ingested daily is absorbed (Kehoe, 1961a; Rabinowitz et al., 1974). Absorption of lead consumed after a 6-hour fast was increased up to 8-fold as compared with lead consumed with food (Wetherill et al., 1974). Garber and Wei (1974) observed similar effects of dietary status in mice at a dose of 3 μg Pb/kg bw, but not at much higher doses (2000 μg Pb/kg bw).

Age also has a major influence on the extent of lead absorption from the GI tract. Forbes and Reina (1974) and Kostial et al. (1971) have observed that GI absorption of lead in infant rats was considerably greater than in adults. Similar results have been observed in humans. Alexander et al. (1973) and Ziegler et al. (1978) reported that ~50% of the dietary lead was absorbed by young children (3 months to 8.5 years old; majority <2 years old).

Numerous dietary factors influence the absorption of lead from the GI tract. Lead absorption has been demonstrated to be enhanced by low dietary Ca or Fe high dietary fat or low or high dietary protein (Sobel et al., 1938; Six and Goyer, 1970, 1972; Barltrop and Khoo, 1975). Absorption is decreased in animals receiving high mineral diets (Barltrop and Khoo, 1975). Ziegler et al. (1978) found an inverse relationship between dietary lead absorption and the Ca content of the diets of infants.

The GI absorption of lead is also influenced by the chemical nature of the lead consumed. Barltrop and Meek (1975) investigated the absorption of a wide variety of lead compounds by mature rats. They found that lead phthalate and lead carbonate were absorbed somewhat better than lead acetate. Lead naphthenate, lead octoate and lead sulfide were absorbed ~66% as

well as lead acetate; 180-250 μm diameter elemental lead particles were absorbed only 14% as well. Incorporation into paint films results in up to a 50% reduction in lead absorption (Gage and Litchfield, 1969; Kneip et al., 1974).

2.2. INHALATION

Randall et al. (1975) exposed four baboons to lead aerosols (Pb_3O_4) of varying particle size for 4 weeks. Absorption was faster for coarse particles (1.6 μm) than for fine particles (0.8 μm). High lead levels result in a reduction in the number of lung macrophages, resulting in prolonged residence times and increased absorption (Bingham et al., 1968; Beck et al., 1973; Bruch et al., 1973a,b). Pott and Brockhaus (1971) found that large doses of intratracheally administered lead bromide or lead oxide were retained as completely as were intravenous doses, but smaller doses were retained to a significantly smaller extent.

Kehoe (1961b,c,d) studied the deposition of combusted tetraethyl lead (Pb_2O_3) in volunteers. Thirty-six percent of particles with an average diameter of 0.26 μm and 46% of the particles with an average diameter of 2.9 μm were deposited. Nozaki (1966) reported inverse relationships between respiration rate, particle size and lung deposition. Chamberlain et al. (1975) reported a 35% deposition rate for lead from inhaled automobile exhaust at a respiration rate of 15/minute. For adult humans, the deposition rate of particulate airborne lead is ~30-50%. It also appears that essentially all of the lead deposited in the lower respiratory tract is absorbed so that the overall absorption rate is 30-50% (U.S. EPA, 1984). Respiratory uptake by children appears to be greater on a body weight basis. One report has estimated that a 10-year-old child has a deposition rate 1.6- to 2.7-fold higher than the adult on a weight basis (U.S. EPA, 1984).

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

Considerable data exist on the effects of lead exposure in humans, but these data are based on blood lead levels. In most cases, no estimate of exposure or the contribution of various routes of exposure are available. The available evidence suggests that effects of lead on the formation of hemoglobin and other hemo-proteins are detectable at lower levels of lead exposure than are effects on any other organ or system. The threshold for decreased hemoglobin levels is ~0.4 μg/mℓ blood in children (Betts et al., 1973; Pueschel et al., 1972) and 0.5 μg/mℓ blood in adults (Tola et al., 1973). Altered biochemical parameters, as indicated by increased urinary γ-aminolevulinic acid levels, are detectable at blood lead levels of 0.4 μg/mℓ in men and children and at somewhat lower levels in women (Selander and Cramer, 1970; Haeger-Aronsen et al., 1974; NAS, 1972; Roels et al., 1975).

Neurological effects in children appear to be another sensitive indicator of lead toxicity. Subtle neurobehavioral effects that do not result in clinical encephalopathy have been reported in children exposed to lead levels. U.S. EPA (1984) has summarized the evidence for health effects at low blood lead levels in non-overtly lead intoxicated children as follows:

> Among the most important and controversial of these effects are neuropsychological and electrophysiological effects evaluated as being associated with low-level lead exposures in non-overtly lead intoxicated children. Indications of peripheral nerve dysfunction, indexed by slowed nerve conduction velocities (NCV), have been shown in children down to blood lead levels as low as 30 μg/dℓ. As for CNS effects, none of the available studies on the subject, individually, can be said to prove conclusively that significant cognitive (IQ) or behavioral effects occur in children at blood-Pb levels <30 μg/dℓ. Rather, the collective neurobehavioral studies of CNS cognitive (IQ) effects can probably now be most reasonably interpreted as being clearly indicative of likely associations between neuropsychologic deficits and low-level lead

exposures in young children resulting in blood-Pb levels ranging to as low as 30-50 μg/dℓ. The magnitude of average observed IQ deficits appears to be approximately 5 points at mean blood lead levels of 50-70 μg/dℓ and about 4 points at mean blood lead levels of 30-50 μg/dℓ.

Certain additional recent studies have obtained results at blood lead values mainly in the 15-30 μg/dℓ range interpreted by some investigators as being indicative of small, but not unimportant, effects of lead on cognitive functioning, the ability to focus attention, appropriate social behavior, and other types of behavioral performance. However, due to specific methodological problems with each of these various studies, much caution is warranted that precludes conclusive acceptance of the observed effects being due to lead rather than other (at times uncontrolled for) potentially confounding variables. This caution is particularly warranted in view of other well-conducted studies now beginning to appear in the literature which did not find statistically significant associations between lead and similar effects at blood lead levels below 30 μg/dℓ. Still, because such latter studies found 1-2 point IQ deficits remaining after correction for confounding factors, lead cannot be totally ruled out as a possible etiological factor contributing to the induction of such effects in the 15-30 μg/dℓ range, based on existing published studies.

Also of considerable importance are studies which provide evidence of changes in EEG brain wave patterns and CNs evoked potential responses in non-overtly lead intoxicated children. The work of Burchfiel et al. (1980) indicates significant associations between IQ decrements, EEG pattern changes, and lead exposures among children with average blood lead levels falling in a range of 30-50 μg/dℓ. Research results provided by Otto et al. (1981, 1982, 1983) also demonstrate clear, statistically significant associations between electrophysiological (SW voltage) changes and blood-Pb levels in the range of 30-55 μg/dℓ and analogous associations at blood-Pb levels below 30 μg/dℓ (with no evident threshold down to 15 μg/dℓ or somewhat lower). In this case, the presence of electrophysiological changes observed upon follow-up of some of the same children 2 years and 5 years later suggests persistence of such effects even in the face of later declines in blood-Pb levels and, therefore, possible long-term persistence of the observed electrophysiological CNS changes. However, the reported electrophysiological effects in this case were not found to be significantly associated with IQ decrements.

The precise medical or health significance of the neuropsychological and electrophysiological effects found by the above studies to be associated with low-level lead exposures is difficult to state with confidence at this time. The IQ deficits and other behavioral changes detected at blood lead levels above 30 μg/dℓ, although statistically significant, are generally relatively small in magnitude as detected by the reviewed studies, but nevertheless may still impact the intellectual development, school

performance, and social development of the affected children sufficiently so as to be regarded as adverse. This would be especially true if such impaired intellectual development or school performance and disrupted social development were reflective of persisting, long-term effects of low-level lead exposure in early childhood. The issue of persistence of such lead effects, however, remains to be more clearly resolved, with some study results mentioned above suggesting relatively short-lived or markedly decreasing lead effects on neuropsychological functions over a few years from early to later childhood and other studies suggesting that significant low-level lead-induced neurobehavioral and EEG effects may, in fact, persist into later childhood. At levels below 30 μg/dℓ, observed IQ and other neuropsychologic effects are typically of even smaller magnitude, lead's etiological role in producing them is less clearly established, and their likely medical significant unclear (as is the case for electrophysiological changes observed at levels below 30 μg/dℓ).

Threshold blood lead levels for various endpoints in children and adults are presented in Table 3-1.

3.1. SUBCHRONIC

3.1.1. Oral. The effects of subchronic oral exposure of experimental animals to lead are summarized in Table 3-2. Six reproduction studies were located in which the effects of subchronic oral exposures could be evaluated. Three of these, Schroeder and Mitchener (1971), Schroeder et al. (1970) and Stowe and Goyer (1971) did not use doses sufficiently low enough to establish a threshold for effects.

In one study described in three separate reports (Kimmel et al., 1980; Grant et al., 1980; Fowler et al., 1980), groups of 60-90 21-day-old female CD rats were administered a semipurified, nutritionally adequate, virtually lead-free diet. Lead acetate was administered in deionized drinking water at concentrations of 0, 0.5, 5, 50 or 250 mg Pb/ℓ H_2O. The treated females were mated with untreated males after 6-7 weeks and were continued on treatment throughout gestation and lactation. The pups were continued on the same treatment as the dams from weaning through 6-9 months of age.

TABLE 3-1

Summary of Lowest Blood Lead Levels Associated with Observed Biological Effects in Various Population Groups*

LOEL (µg Pb/100 mℓ Blood)	Effect	Population Group
10	ALA-D inhibition	children and adults
15-20	erythrocyte protoporphyrin elevation	women and children
10-15	CNS electrophysiological deficits	children
10-30	vitamin D metabolism interference	children
25-30	erythrocyte protoporphyrin elevation	adult males
40	increased urinary ALA excretion	children and adults
40	reduced hemoglobin production	children
40-100	chronic nephropathy	adults
80-100	chronic nephropathy	children
80	frank anemia	adults
70	frank anemia	children
40-50	altered testicular function	adults
30-40	slowed nerve conduction	children
40	slowed nerve conduction	adults
40	coproporphyrin elevation	adults and children
40	cognitive (CNS) deficits	children
50	reduced hemoglobin production	adults
50-60	peripheral neuropathies	adults and children
80-100	encephalopathic symptoms	children
100-120	encephalopathic symptoms	adults

*Source: U.S. EPA, 1984

TABLE 3-2

Subchronic Oral Toxicity of Lead in Experimental Animals

Compound	Species/ Strain/Sex	Dose	Duration of Exposure	Effects	Reference
Lead acetate	rats/CD/MF	0, 0.5, 5, 50 or 250 mg Pb/ℓ H_2O	6-7 weeks pre-breeding until 609 months post-partum	Decreased maternal body weight at 50 and 250 mg Pb/ℓ. Delayed sexual maturation of female offspring at 50 and 250 mg Pb/ℓ and to a smaller extent at 25 mg Pb/ℓ. No teratogenic, fetotoxic or reproductive effects were observed. Delayed reflex maturation at 50 and 250 mg Pb/ℓ. Delayed locomotor development at 250 mg Pb/ℓ. Dose-related incidences of poor fur condition, tail-tip necrosis and sialodacryoadenitis. Histological changes in the kidneys at ≥5 mg/ℓ.	Kimmel et al., 1980, Grant et al., 1980; Fowler et al., 1980
Unspecified soluble salt	rats/NR/MF mice/NR/MF	25 mg/ℓ H_2O	3 generations	Delayed birth. Runting and excessive mortality among offspring before weaning. Decrease in male/female ratio. Decrease in number of pregnancies and litter sizes. The effects were more pronounced in mice than in rats.	Schroeder and Mitchener 1971; Schroeder et al., 1970
Lead acetate	rats/Sprague-Dawley/MF	10 g/kg diet	2 generations	Decreased pup weights. Decreased pups/litter.	Stowe and Goyer, 1971

NR = Not reported

There were no treatment-related differences in food or water consumption between the various treatment groups; however, body weights were depressed at the two highest doses. Sexual maturation, as measured by the time of vaginal opening, was delayed in a dose-dependent manner, with effects observed at a concentration $\geq$25 mg Pb/ℓ. No fetotoxic, teratogenic or reproductive effects were noted, although the mean body length of the female pups at 1 day of age was significantly decreased in the high dose groups. The most sensitive indication of lead toxicity in the offspring was histological changes in the kidney. Cytokaryomegaly of the tubular epithelial cells of the inner cortex was observed in males at concentrations as low as 5 mg/ℓ, and in both sexes at water concentrations of $\geq$25 mg/ℓ. Assuming that rats consume 35 mℓ of water each day and weigh 0.35 kg, the LOAEL of 5 mg/ℓ corresponds to a dose of 0.5 mg/kg bw/day.

No effects were reported in humans which could be unequivocally attributed to subchronic exposures.

3.1.2. **Inhalation.** Data regarding the effects of subchronic inhalation exposure to lead could not be located in the available literature.

3.2. **CHRONIC**

3.2.1. **Oral.** The chronic oral toxicity of lead in experimental animals is summarized in Table 3-3. Kopp et al. (1980a,b) reported that administration of lead acetate (5 mg Pb/ℓ H_2O) to female Long-Evans rats for 20 months produced slight effects on conduction tissue excitability, systolic blood pressure and cardiac ATP concentrations. This represents the lowest concentration at which chronic exposure to lead in the drinking water or diet has been demonstrated to produce adverse effects. Assuming that rats consume 35 mℓ of water each day and weigh 0.35 kg, this corresponds to a dose of 0.5 mg/kg bw/day.

TABLE 3-3

Chronic Oral Toxicity of Lead in Experimental Animals

Compound	Species/Strain/Sex	Dose	Duration of Exposure	Effects	Reference
Lead nitrate	rats/Long-Evans/ male	25 mg Pb/ℓ H_2O	lifetime	Decreased fasting blood glucose levels, increased incidence of glycosurea, weight loss and poor hair coats	Schroeder et al., 1970
NR	rats/NR/NR	25 mg Pb/ℓ H_2O	lifetime	Same as above, except diet not supplemented with chromium, decreased survival and longevity.	Schroeder et al., 1965
Lead acetate	rats/Long-Evans/ female	5 mg Pb/ℓ H_2O	20 months	Slight depression of conduction tissue excitability, sporadic slight increases in systolic blood pressure, decreased cardiac ATP concentrations and ATP/ADP ratios	Kopp et al., 1980a,b
Lead arsenate Lead carbonate Calcium arsenate	rats/NR/MF	597 mg PB/kg diet	2 years	The authors concluded that some of the effects of lead arsenate on the kidney were attributable to the lead moiety, and hemosiderin deposition in the spleen was due to the arsenate moiety. Lead arsenate was slightly more toxic than lead carbonate but slightly less toxic than calcium arsenate.	Fairhall and Miller, 1941
Lead arsenate	rats/Wistar/MF	0, 276 or 1104 mg Pb/kg diet	29 months	Decreased food consumption and body weight in high-dose group, decreased blood hemoglobin concentration and packed cell volumes in high dose males; enlargement of bile duct with dilatation and abscesses, marked bile-duct proliferation, pericholangitis, cholangiofibrosis and intranuclear eosinophilic inclusions in the kidneys; no effects in the low dose group	Kroes et al., 1974

NR = Not reported

U.S. EPA (1984) has reviewed the literature relating blood lead levels to lead exposure from food, water and dust/soil. They concluded that for adults, the best slope estimate for dietary intake in adults is 0.02 μg/dℓ per μg ingested. For children, the best slope estimate is higher, 0.16 μg/dℓ per μg ingested. For water, a slope estimate of 0.06 μg/dℓ per μg/ℓ is suggested. This estimate applies to water levels <100 μg/ℓ. In children, the increment of increase in lead levels in blood resulting from lead in dust and soil was estimated as 0.6-6.8 μg/dℓ per 1000 μg/g lead in dust.

3.2.2. Inhalation. Pertinent data regarding the chronic inhalation toxicity of lead in experimental animals could not be located in the available literature. From the many available studies addressing the relationship between lead inhalation exposure and blood lead levels, U.S. EPA (1984) has identified those most relevant to ambient exposures. These studies are shown in Table 3-4 which is adapted from U.S. EPA (1984). The median slope from the three population studies evaluating children is 1.92 μg/dℓ/μg/m³. U.S. EPA (1984) points out that the slope is not linear, but increases more rapidly in the upper range of air lead concentrations and that the slope estimate at lower air lead concentrations may not wholly reflect uncertainty about the shape of the curve at higher concentrations.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Pertinent data regarding the teratogenic effect of orally administered lead could be located in the available literature; however, postnatal developmental delays have been reported in pups from rats that received 50-250 mg lead/ℓ drinking water throughout gestation (Kimmel et al., 1976; Reiter et al., 1975). Other investigators reported decreased fertility and fetotoxic effects in a variety of species following higher

TABLE 3-4

Summary of Blood Inhalation Slopes (β)
(μg/dℓ per μg/m³)

Population	Study Type	N	Slope	Model Sensitivity[a] of Slope	Study
Children	population	1074	1.92	(1.40-4.40)[b,c,d]	Angle and McIntire, 1979
	population	148	2.46	(1.55-2.46)[b,c]	Roels et al., 1980
	population	879	1.52	(1.07-1.52)[b,c,d]	Yankel et al., 1977; Walter et al., 1980
Adult male	population	149	1.32	(1.08-1.59)[c,d]	Azar et al., 1975
	experiment	43	1.75	(1.52-3.38)[e]	Griffin et al., 1975
	experiment	6	1.25	(1.25-1.55)[b]	Gross, 1979
	experiment	5	2.14	(2.14-3.51)[f]	Rabinowitz et al., 1973, 1976, 1977

[a]Selected from among the most plausible statistically equivalent models; for nonlinear models, slope at 1.0 μg/m³
[b]Sensitive to choice of other correlated predictors such as dust and soil lead
[c]Sensitive to linear vs. nonlinear at low air lead
[d]Sensitive to age as a covariate
[e]Sensitive to baseline changes in controls
[f]Sensitive to assumed air lead exposure

oral doses of lead (Hilderbrand et al., 1973; Vermande van-Eck and Meigs, 1960; Hubermont et al., 1976; Maisin et al., 1975; Jacquet et al., 1975; Cole and Bachhuber, 1914; Weller, 1915; Der et al., 1976; Verma et al., 1974). Schroeder et al. (1970) reported a reduction in the number of offspring from rats and mice exposed to 25 mg Pb/ℓ drinking water, but only in animals receiving a chromium deficient diet.

Schroeder and Mitchener (1971) obtained marked effects on reproductive parameters in rats and mice in a 3-generation study with 25 ppm lead (from an unspecified soluble lead salt) in the drinking water. The semi-purified diet used was restricted in its content of trace metals (particularly chromium), and the animals environment was designed to minimize exposure to trace metals; these conditions may have contributed to the toxicity of lead (Schroeder et al., 1970). Rats and mice of both sexes (five pairs/species) were given 25 ppm lead in their drinking water from weaning and were allowed to produce litters through 6 months (mice) or 9 months (rats) of age. Pairs were selected randomly from F_1 litters and were allowed to produce an F_2 generation, and a similar procedure was followed for the production of an F_3 generation. F_1 and F_2 pairs were continued on the same treatments as their parents had received. In rats, results of lead treatment included a delay in birth of the first litter to the original parents, runting and excessive mortality ($p<0.05$) among the offspring before weaning, a decrease in the male/female ratio of the F_1 generation, and a decrease in pregnancies and litter size by the third generation. In mice, the effects were similar but more severe; by the second generation, the number of offspring was insufficient to continue the experiment.

3.3.2. **Inhalation.** The only data available on the teratogenicity of inhaled lead are derived from epidemiological studies. In most cases, reliable estimates of exposure are lacking. In high doses, lead compounds have been used to induce abortions (Tanssig, 1936). Oliver (1911) found that the miscarriage rate was elevated among British women occupationally exposed to lead (Table 3-5). Other investigators have related lead exposure, both before and during pregnancy, with increases in spontaneous abortions, premature delivery and early membrane rupture (Lane, 1949; Nozaki, 1958; Fahim et al., 1975; Rom, 1976).

3.4. TOXICANT INTERACTIONS

A large number of dietary factors have been demonstrated to alter the GI absorption, and thus presumably the toxicity, of orally administered lead (see Section 2.1.). The interrelationships between lead toxicity and the nutritional status of other metals is complex and has not been studied completely. High mineral diets inhibit the absorption of lead (Barltrop and Khoo, 1975) and diets low in calcium or iron enhance absorption (Sobel et al., 1938; Six and Goyer, 1970, 1972).

TABLE 3-5

Statistics on the Effect of Lead on Pregnancy*

Sample	Number of Abortions and Stillbirths/ 1000 Females	Number of Neonatal Deaths (first year)/ 1000 Females
Housewives	43.2	150
Female workers (mill work)	47.6	214
Females exposed to lead premaritally	86.0	157
Females exposed to lead after marriage	133.5	271

*Source: Oliver, 1911

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Data pertinent to the oral carcinogenic potential of lead to humans could not be located in the available literature.

4.1.2. Inhalation. The causes of death among people exposed to lead have been investigated in three epidemiological studies (Dingwall-Fordyce and Lane, 1963; Nelson et al., 1973; Cooper and Gaffey, 1975; Cooper, 1976, 1978). No association between lead exposure and cancer mortality was found in the two earlier studies, but in the study by Cooper and Gaffey (1975), a statistically significant elevation in deaths due to "all malignant neoplasms" and cancer of "other sites" was reported. Using different statistical tests, Kang et al. (1980) reanalyzed these data and calculated a statistically significant increase in deaths due to cancer of the digestive organs and cancer of the respiratory system for both lead smelter workers and battery plant workers. Deaths due to all malignant neoplasms were increased among lead smelter workers only.

4.2. BIOASSAYS

4.2.1. Oral. Several studies have associated specific lead salts with tumor formation in experimental animals. Dietary lead acetate at concentrations of 3-4 mg/day (Zawirska and Medras, 1968, 1972), 500-2000 mg/kg diet (Azar et al., 1973) or 1% in the diet (Boyland et al., 1962) have produced renal tumors in Wistar rats. Lead subacetate has produced renal carcinomas or adenomas in Swiss mice (Van Esch and Kroes, 1969) and in several strains of rats (Van Esch et al., 1962; Oyasu et al., 1970; Mao and Molnar, 1967; Shakerin and Paloucek, 1965; Shakerin et al., 1965; Hass et al., 1967; Ito et al., 1971; Ito, 1973), but not in golden hamsters (Van Esch and Kroes, 1969). Gliomas were also observed in many of these studies.

4.2.2. Inhalation. Data pertinent to the carcinogenicity of inhaled lead could not be located in the available literature.

4.3. OTHER RELEVANT DATA

Data pertinent to the mutagenicity of lead could not be located in the available literature.

4.4. WEIGHT OF EVIDENCE

IARC (1980, 1982) considered the evidence for carcinogenicity to humans to be "inadequate," the evidence for carcinogenicity to animals to be "sufficient for some salts" and evidence for activity in short-term tests to be "inadequate." Since humans are not environmentally exposed to the lead salts associated with tumors in animals, lead and lead compounds are most appropriately classified as Group 3-Possible Human Carcinogens, using the criteria for weight of evidence proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984). Those lead salts for which sufficient evidence of carcinogenicity in animals exists are most appropriately classified in Group B2-Probable Human Carcinogens.

5. REGULATORY STANDARDS AND CRITERIA

The ACGIH (1980) has established a TLV of 0.15 mg/m³ and a STEL of 0.45 mg/m³ for "inorganic compounds, dust and fume, as Pb." Separate TLVs were established for lead arsenate [0.15 mg/m³ as Pb_3 $(A_5O_4)_2$] and lead chromate (0.05 mg/m³ as Cr).

The Occupational Safety and Health Administration (Code of Federal Regulations, 1981) has defined an "action level" of 30 µg/m³ and a PEL of 50 µg/m³, averaged over an 8-hour period. For work periods of >8 hours, the maximum permissible limit is defined as 400 µg/m³ ÷ hours worked in the day.

The U.S. EPA (1980b) recommended an ambient water quality criterion for lead of 50 µg/ℓ. The ACGIH (1980) reported limits of 0.01 mg/m³ established by the USSR, 0.02 mg/m³ established by Hungary, 0.05 mg/m³ established by Czechoslovakia and Poland, 0.1 mg/m³ established by Romania, Sweden and West Germany and 0.15 mg/m³ established by East Germany, Finland and Yugoslavia.

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

6.1.1. Oral. No data regarding the effects of subchronic oral exposure of humans to lead were found in the available literature. One study in rats was located which could be used for the derivation of an AIS (Kimmel et al., 1980; Grant et al., 1980; Fowler et al., 1980). For the most sensitive parameter measured in this study, histological changes in the kidneys, the LOAEL was 5 mg Pb/ℓ H_2O and the NOAEL was 0.5 mg Pb/ℓ H_2O. Assuming that rats consume 35 mℓ of water each day weigh 0.35 kg, the corresponding doses are 0.5 and 0.05 mg/kg bw/day. The LOAEL will be used as the basis of the risk assessment. Applying uncertainty factors of 10 to convert from a LOAEL to a NOAEL, 10 for interspecies conversion and 10 to afford increased protection for more sensitive members of the population, results in an AIS of 0.5 μg/kg bw/day or 35 μg/day for a 70 kg man. This value is lower than estimates for chronic human exposure and therefore is not judged to be an appropriate estimate.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

Lead is a ubiquitous compound and, therefore, it would be inappropriate to suggest route specific exposure levels that do not reflect the contribution of other routes. Baseline exposures to lead in adults are primarily a function of food intake with food > water > dust > inhaled air. Lead in the diet is the result of atmospheric dust, lead solder from cans, metals used in grinding, crushing and sieving, and lead in water (U.S. EPA, 1984). In children, the greatest exposure occurs through food and dust. Consequently, control of air lead levels as the primary contamination route for food (except canned food) and surface dust would be a major factor in controlling overall lead exposure levels.

Previous estimates of acceptable lead exposure which were based on target blood lead levels of 30 μg/dℓ are currently being reevaluated. U.S. EPA (1984) presents a comprehensive and critical evaluation of recent data which suggest effects, especially in children, at blood lead levels below 30 μg/dℓ. If this target blood lead level is decreased, parallel decreases will be required in guidelines and standards delineating maximum lead levels in environmental media.

Until the uncertainty concerning target blood lead levels is resolved, it is suggested that the current air standard be used as a guideline for inhalation exposure (1.5 $\mu g/m^3$). Although the relationship between inhaled lead and blood lead has been established, it is suggested that estimation of absorbed dose in mg/day based on this air level would be inappropriate as a result of the substantial contribution of atmospheric lead to the food and dust exposure components.

In addition, it is proposed that water levels (water being the second major exposure category in adults) be targeted at the proposed criterion level (50 mg/ℓ).

Development of AIC values would be inappropriate since these values implicitly assume zero exposure by other routes. With many chemicals this is a reasonable assumption. In the case of lead, the general population is already accruing unavoidable background exposures through food, water and dust. As a result of substantial background exposure levels and because of uncertainty concerning "safe" exposure levels, any significant increase above present lead levels in air, water and soil represents a cause for concern in terms of human health endpoints.

6.2.1. Oral. As discussed in Section 6.2., an oral AIC for lead is not suggested at the present time. A criterion level for water of 50 µg/ℓ is suggested based on U.S. EPA (1980b). This level should be reevaluated when a consensus is reached concerning target blood lead levels. This water level, in conjunction with the current air standard should limit oral lead intake levels, assuming lead is not directly introduced into soils (as opposed to atmospheric deposition) used for agriculture.

An RQ for the decreased survival of offspring of mice in a 3-generation reproduction study treated with an unspecified soluble lead salt at 25 ppm lead in the drinking water (Schroeder and Mitchener, 1971) was calculated. The animal dose, 4.25 mg/kg/day, was calculated by assuming mice ingest water equivalent to 17% of their body weight/day. Multiplication of the animal dose by the cube root of the ratio of the body weight of mice (assumed: 0.03 kg) to that of humans (assumed: 70 kg) resulted in a human MED of 0.32 mg/kg/day or 22.4 mg/day for a 70 kg man. This human MED corresponds to an RV_d of 3.5. Decreased survival of offspring was assigned an RV_e of 10. A CS of 35, calculated as the product of RV_d and RV_e, resulted.

6.2.2. Inhalation. As discussed in Section 6.2., an inhalation AIC is not suggested at the present time. The current air standard of 1.5 µg/m³ is suggested as a maximum air level to limit inhalation, dietary and dust exposures. This level is currently being reviewed. The reader is referred to U.S. EPA (1984) for a detailed discussion.

6.3. CARCINOGENIC POTENCY (q_1*)

The potential role of lead in the etiology of human cancer is impossible to assess at this time. In their summary U.S. EPA (1984) states:

> "...at relatively high concentrations, lead displays some carcinogenic activity in experimental animals (e.g., the rat)...It is hard to draw clear conclusions concerning what role lead may play in the induction of human neoplasia. Epidemiological studies of lead-exposed workers provide no definitive findings...Also, since lead acetate can produce renal tumors in some experimental animals, it may be prudent to assume that at least that lead compound may be carcinogenic in humans."

This statement is qualified, however, by noting that lead has been observed to increase tumorigenesis rates in animals only at relatively high concentrations, and therefore does not appear to be an extremely potent carcinogen.

Additional data are needed concerning the potential role of lead in human carcinogenesis and available data need to be carefully assessed by an expert group.

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APPENDIX

Summary Table for Lead[a]

	Species	Experimental Dose/Exposure	Effect	Acceptable Intake (AIS or AIC)	Reference
Inhalation					
AIS	NA	NA	NA	ND	NA
AIC	human		decreased hemoglobin	1.5 μg/m³[b]	U.S. EPA, 1984
Maximum composite score	mice	25 ppm in drinking water, 4.25 mg/kg/day (RV_d=3.5)	decreased survival of offspring (RV_e=10)	35	Schroeder and Mitchener, 1971
Oral					
AIS	NA	NA	NA	ND	NA
AIC	human	NA	decreased hemoglobin	50 μg/ℓ[c]	U.S. EPA, 1980b

[a]429 μg/day has been estimated as a tolerable daily intake for an adult from all sources combined (WHO, 1977)

[b]Current air standard

[c]Suggested drinking water criterion level

NA = Not applicable; ND = not derived