FINAL

**Report on Carcinogens
Background Document for**

Lead and Lead Compounds

May 8, 2003

Prepared for the:
**U.S. Department of Health and Human Services
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FOREWORD

The Report on Carcinogens (RoC) is prepared in response to Section 301 of the Public Health Service Act as amended. The RoC contains a list of all substances (i) that either are known to be human carcinogens or may reasonably be anticipated to be human carcinogens and (ii) to which a significant number of persons residing in the United States are exposed. The Secretary, Department of Health and Human Services, has delegated responsibility for preparation of the RoC to the National Toxicology Program, which prepares the Report with assistance from other Federal health and regulatory agencies and nongovernmental institutions.

Nominations for listing in or delisting from the RoC are reviewed by a formal process that includes a multi-phased scientific peer review and several opportunities for public comment. The review groups evaluate each nomination according to specific RoC listing criteria. This Background Document was prepared to assist in the review of the nomination of lead and lead compounds. The scientific information in this document comes from publicly available peer-reviewed sources. Any interpretive conclusions, comments, or statistical calculations made by the authors of this document that are not contained in the original source are identified in brackets [ ]. If any members of the scientific peer review groups feel that this Background Document does not adequately capture and present the relevant information, they will be asked to write a commentary for this Background Document that will be included as an addendum to the document. In addition, a meeting summary that contains a brief discussion of each review group's review and recommendation for the nomination will be added to the Background Document, also as an addendum.

A detailed description of the RoC nomination review process and a list of all nominations under consideration for listing in or delisting from the RoC can be obtained by accessing the NTP Home Page at http://ntp-server.niehs.nih.gov. The most recent RoC, the Ninth Edition, was published in May 2000 and may be obtained by contacting the National Institute for Environmental Health Sciences Environmental Health Information Service at http://ehis.niehs.nih.gov (800-315-3010).

Executive Summary

Introduction

Lead can be used in its pure form as a metal, alloyed with other metals, or used in chemical compounds. Inorganic lead compounds usually consist of lead in the divalent state. Organic lead compounds were used in automotive gasoline additives in the United States until 1996. Lead and lead compounds were nominated by the National Institute of Environmental Health Sciences based on the 1987 finding by the International Agency for Research on Cancer (IARC) of sufficient evidence of carcinogenicity in experimental animals to identify lead and inorganic lead compounds as possibly carcinogenic to humans (Group 2B) and the subsequent publication of additional human and animal studies of lead and lead compounds.

Human Exposure

Use. In worldwide metal use, lead ranks behind only iron, copper, aluminum, and zinc. Its greatest use is in lead-acid storage batteries found in motor vehicles and general industry. Other common uses of lead metal include ammunition, cable covering, piping, brass and bronze, bearing metals for machinery, and sheet lead. Lead oxides are found in paint, glass, and ceramics. Organic lead was used in motor vehicle fuels as an anti-knock additive in the United States until 1996, when it was banned by the U.S. Environmental Protection Agency, following a phase-out initiated in the 1970s. Organic lead still is permitted for use in gasoline for aircraft and in fuels for racing vehicles and for non-road vehicles such as farm machinery, marine vessels, construction equipment, and recreational vehicles. Despite reductions in some lead applications and the legislated end to use of lead as a gasoline additive, the overall consumption of lead is growing, mainly due to increased production of lead-acid batteries.

Production. Lead is refined from mined ore. Lead ore occurs most frequently in the form of lead sulfide, also known as galena. As of 2000, 19 mines, employing approximately 1,000 workers, produced the vast majority of lead in the United States. Mined lead ore first is crushed and ground; then the various minerals are separated, resulting in a lead concentrate, which is shipped to a primary smelter for refining. At a primary smelter, lead concentrates are sintered, then roasted and subjected to a series of refining steps, resulting in lead metal that is 99.99% pure. In 2001, two primary lead smelter-refineries were operating, employing a total of approximately 400 people. Secondary smelters (recycling smelters) use scrap lead, mainly from used lead-acid batteries, as their supply. As of 2001, 26 secondary lead smelters were operating within the United States, employing approximately 1,600 workers. In 2001, the United States produced 1,375,000 tons of lead, used 1,687,000 tons of lead, and recycled 1,099,000 tons of lead.

Environmental exposure. Environmental exposure to lead results in absorption of lead into the body via inhalation (approximately 30% to 50% absorbed into the bloodstream), via ingestion (approximately 8% to 15% absorbed into the bloodstream) and, to a limited extent, through the skin. Air lead concentrations may be > 10 $\mu g/m^3$ near industrial sources such as smelters. A 1991 survey of lead levels in U.S. urban air revealed a maximum quarterly mean concentration of approximately 0.08 $\mu g/m^3$. Rural

concentrations typically are lower, bringing the estimated U.S. mean air lead concentration to 0.04 μg/m^3 in 1995. The average intake of lead by inhalation is estimated at 2 μg/day for an adult living in a U.S. urban setting. Lead concentrations in U.S. drinking water generally are below 5 μg/L. Lead also is found in food, cigarette smoke, and alcoholic beverages. In 1990, the estimated daily intake of lead from consumption of food, water, and beverages was approximately 4 μg/day for children 2 years of age and younger, 6 to 9 μg/day for children aged 14 to 16, 6 to 9 μg/day for adults aged 25 to 30, and 2 to 8 μg/day for adults aged 60 to 65. The most common source of environmental lead exposure for young children is direct ingestion of paint chips and leaded dusts and soils released from aging painted surfaces, which can contribute an additional intake of 5 μg/day for a toddler engaging in normal hand-to-mouth activity.

Occupational exposure. The most common route of occupational exposure to lead is inhalation of lead fumes or leaded dusts in air and absorption of lead through the respiratory system. Lead also may be ingested and absorbed in the gastrointestinal tract. The National Institute for Occupational Safety and Health has estimated that more than three million Americans potentially are occupationally exposed to some form of lead.

Many occupations have the potential for high exposure to lead. Occupations having frequent high exposure to lead include battery-production workers, battery-recycling workers, foundry workers, lead chemical workers, lead smelter and refinery workers, leaded-glass workers, pigment workers, and radiator-repair workers. Occupations with moderate frequency of high exposures include firing-range instructors, house renovators, lead miners, newspaper printers, plastics workers, rubber workers, and steel welders and cutters. Occupations with low frequency of high exposure include automobile-repair workers, cable-production workers, construction workers, demolition workers, firing-range participants, flame-solder workers, plumbers and pipe fitters, pottery-glaze producers, ship-repair workers, and stained-glass producers. Mean lead air concentrations in U.S. industries, as monitored by the Occupational Safety and Health Administration, ranged from 165 μg/m^3 (secondary smelters) to 200 μg/m^3 (storage-battery plants and brass, bronze, and copper foundries).

Human Cancer Studies
IARC reviewed lead and lead compounds in 1987 and concluded that the evidence available at that time, which was very limited, was inadequate to demonstrate human carcinogenicity. The number of epidemiologic studies on the potential role of lead exposure in cancer has expanded since the last IARC update; 17 case-control and 17 cohort studies have been published, as well as updates on previously studied populations and meta-analyses. Steenland and Boffetta (2000) calculated a fixed-effects rate ratio of 1.04 (95% confidence interval [CI] = 1.00 to 1.09) for all cancers combined (N = 1,911) based on eight cohort studies of highly exposed workers.

Lung cancer. Meta-analyses performed since the IARC review have reported significantly elevated relative risks (RRs) for lung cancer and lead exposure. Fu and Boffetta calculated RRs of 1.24 (95% CI = 1.16 to 1.33) based on 15 studies and 1.42 (95% CI = 1.05 to 1.92) based only on studies of battery and smelter workers, who were

considered to have the highest exposure. Steenland and Boffetta (2000) calculated an RR of 1.30 (95% CI = 1.15 to 1.46; 675 lung-cancer deaths) based on eight cohort studies in which lead was the predominant exposure. In Section 3.3.1 of this background document, 21 lead-exposed populations are evaluated; 15 of the 18 populations included in at least one cohort study had elevated risks of lung cancer, eight of which were statistically significant. Two of the three case-control studies of populations not included in cohort studies also reported weak associations between lead expsoure and lung cancer. Population-based cohort studies of environmental exposure to lead also have reported positive associations between lung cancer and blood lead levels. The addition of one environmental cohort study to the Steenland and Boffetta (2000) meta-analysis yielded an RR of 1.32 (95% CI = 1.16 to 1.50). Confounding by smoking or other occupational exposures, particularly to arsenic, may be partially responsible for the elevated risks seen in these studies. However, elevated risks also were observed in population studies that adjusted for cigarette smoking.

Stomach and general digestive cancer. Meta-analyses conducted since the 1987 IARC review have reported elevated risks for stomach cancer with lead exposure; Fu and Boffetta (1995) reported an RR of 1.33 (95% CI = 1.18 to 1.49) for lead exposure based on ten studies and an RR of 1.50 (95% CI = 1.23 to 1.83) for battery or smelter workers only, and Steenland and Boffetta (2000) reported an RR of 1.34 (95% CI = 1.14 to 1.57). In Section 3.2, 21 studies are evaluated, approximately half of which reported a positive association between lead exposure and stomach cancer.

Kidney cancer. Meta-analyses for kidney cancer were based on fewer studies and fewer cases or deaths among exposed individuals. Fu and Boffetta (1995) calculated an RR of 1.19 (95% CI = 0.96 to 1.48) based on five studies, and Steenland and Boffetta (2002) calculated an RR of 1.01 (95% CI = 0.72 to 1.42) based on seven studies. For the review in Section 3.3.3 of this document, Steenland and Simonsen calculated an RR of 1.22 (95% CI = 0.93 to 1.59) based on the same seven studies plus a recently published case-control study; because the recent study was large, it had a substantial effect on the RR. The low incidence of kidney cancer, resulting in a small number of cases, limits the evaluation of carcinogenicity. Of the four studies reviewed in Section 3.3.3 that had more than five cases in lead-exposed subjects, three reported a positive association between lead exposure and kidney cancer.

Bladder cancer. Fu and Boffetta (1995) reported an RR of bladder cancer from lead exposure of 1.41 (95% CI = 1.16 to 1.71) based on five studies. Of seven studies reviewed in Section 3.3.4, six reported a positive association between lead exposure and bladder cancer.

Other cancers. Other cancers with evidence linking them to lead exposure include cancers of the brain and central nervous system, liver, colon, and rectum, among which the evidence is strongest for brain and central nervous system cancers. The results of studies on paternal lead exposure and childhood cancer are conflicting and difficult to evaluate because of the limited number of studies and small sample sizes.

Summary. Overall, the evidence is consistent with the hypothesis that lead is carcinogenic to humans. This evidence is strongest for lung cancer, for which a largely consistent association has been demonstrated with occupations and industries entailing lead exposure, as well as with indices of individual lead exposure, including job history and biological monitoring of occupationally exposed and general populations. Evidence also suggests an association between lead and stomach cancer.

Where exposure-response assessment was attempted, the strongest association with lung cancer usually was seen in the highest exposure group, but a monotonic increase with duration, intensity, or overall amount of exposure was not always observed. Here, interpretation again is complicated by the general lack of adequate statistical power to evaluate multiple exposure levels while controlling for smoking, age, gender, and other potential confounders or effect modifiers. Also, workers who experience acute lead toxicity tend to drop out of the exposed worker population, which could lead to underestimation of the association between lead and cancer.

The observed associations, while consistent, generally are weak. The crude exposure measures used by most studies, such as treating whole plants or jobs as uniformly exposed, may have contributed to the modest size of most risk estimates. Confounding by lifestyle exposures, such as smoking for lung cancer or diet for stomach cancer, or by concomitant occupational exposures, such as arsenic, may partially explain these small associations. However, associations were also observed in studies that adjusted for potential lifestyle confounders or that were conducted in populations without systematic occupational exposures other than lead. Thus, confounding may not entirely account for the increase in cancer risk associated with lead exposure.

Studies in Experimental Animals
Lead acetate (soluble), lead subacetate (soluble), and lead phosphate (insoluble) were found to be carcinogenic in rats and/or mice, inducing tumors of the kidney (adenoma and adenocarcinoma) and, in some studies, increased incidences of cerebral glioma and lung adenoma. Renal tumors were observed in male and female rats and mice and were not always accompanied by chronic lead-induced nephropathy. The studies used a variety of exposure routes, including oral, subcutaneous, intramuscular, transdermal, transplacental, and translactational; however, no inhalation studies were reported. Many of the studies focused on kidney toxicity and carcinogenicity, and thus did not include complete histopathological exams. However, the few studies that did examine other tissues found little evidence that lead induced tumors. Lead subacetate co-administered with 2-acetylaminofluorene was reported to enhance liver and kidney tumorigenicity in one study but not in two others and was shown to promote renal tumors in Wistar rats administered *N*-ethyl-*N*-hydroxyethylnitrosamine. In other studies, lead acetate increased the incidence of viral-induced lymphocytic leukemia in mice and was co-carcinogenic when administered with *N*-(4'-fluoro-4-biphenyl)acetamide to F344 rats, but lead acetate did not increase tumor incidences in Sprague-Dawley rats when co-administered with ethyl urea and sodium nitrite.

Genotoxicity

Lead induced chromosomal aberrations in most studies in plants and in mammals *(in vitro* and *in vivo)* and DNA damage and fragmentation in mammals (*in vivo*; conflicting results were observed in *in vitro* studies) and cell-free systems (in the presence of hydrogen peroxide) and inhibited DNA and RNA polymerase in cell-free systems and mammalian cells (*in vitro*). Conflicting results were observed for sister chromatid exchange and micronucleus induction in mammalian studies (*in vitro* and *in vivo*). Lead was not mutagenic in bacteria, and conflicting results were observed in mammalian *in vitro* systems. Conflicting results may reflect differences in the model systems employed, the end points used to determine genotoxicity, and the lead compounds employed. In studies of humans occupationally exposed to lead, there is evidence to suggest that lead damages chromosomes or DNA; most studies were positive for induction of micronuclei, chromosomal aberrations, and DNA damage. Studies on sister chromatid exchange and studies in humans exposed environmentally to lead gave conflicting results. Studies in humans are sometimes difficult to evaluate, because little information is given on how the populations were selected for study and because of potential exposure to compounds from occupational or environmental sources that may act in conjunction with lead to increase its genotoxic potential. Likewise, personal habits such as smoking and alcohol consumption affect the genotoxic properties of various compounds, including lead. However, many of the more recent studies either controlled for smoking or reported an exposure-response relationship, suggesting that the genotoxic effects were due to lead exposure. Although lead(II) forms stable complexes with the nitrogenous bases and phosphate groups of purified DNA, it is unlikely that lead compounds are directly genotoxic. However, several mechanisms exist by which lead compounds could indirectly alter DNA replication, fidelity, and repair, resulting in genotoxicity.

Other Relevant Data

Absorption, distribution, and excretion. Lead absorption in humans and laboratory animals is affected by age, the chemical form of lead, and minerals in the diet (e.g., iron, calcium, and zinc). Gastrointestinal absorption declines with age, with children absorbing lead to a greater extent than adults. Dietary deficiencies in iron, calcium, and zinc increase lead absorption and retention, whereas a high-protein diet appears to reduce absorption. After absorption, lead is distributed to blood plasma, nervous system, and soft tissues. It subsequently is redistributed and accumulates in bone; approximately 75% to 90% of the lead body burden is found in bones and teeth.

Toxicity. The toxic effects of lead include neurotoxicity and developmental, reproductive, and cardiovascular effects. Lead is a potent neurotoxin affecting the central nervous system (CNS) and the peripheral nervous system (PNS), and high levels of exposure result in profound cognitive impairments. Exposure of children to lower levels of lead has been associated with impairment of neurocognitive and behavioral development, including impairment of attention and hearing.

Potential mechanisms of carcinogenicity. The mechanisms leading to the carcinogenic effects of lead are not understood. Lead compounds do not appear to be directly genotoxic but may cause genetic damage through several indirect mechanisms. These include inhibition of DNA synthesis and repair, oxidative damage, and interaction with

DNA-binding proteins and tumor-suppressor proteins. Interference with DNA synthesis and repair has been suggested as one possible explanation for the genotoxic and co-mutagenic properties of lead. It has been suggested that increased cell proliferation may play a role in lead's induction of renal cancer in rodents; however, the mechanisms have not been established. Although exposure to lead also induces cell proliferation in the liver, the data suggest that the liver is not as susceptible as the kidneys to the carcinogenicity of this effect. No studies have associated liver tumors with lead exposure, and several studies have shown that lead-induced proliferative mitogenesis does not promote the formation of liver foci or nodules from initiated hepatocytes, as observed during regenerative mitogenesis. An association of renal adenocarcinoma with cystic nephropathy has been suggested but is uncertain.

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Criteria for Listing Agents, Substances or Mixtures in the Report on Carcinogens

U.S. Department of Health and Human Services
National Toxicology Program

Known to be Human Carcinogens:

There is sufficient evidence of carcinogenicity from studies in humans, which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer.

Reasonably Anticipated to be Human Carcinogens:

There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible but that alternative explanations such as chance, bias or confounding factors could not adequately be excluded; or

There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors: (1) in multiple species, or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor or age at onset; or

There is less than sufficient evidence of carcinogenicity in humans or laboratory animals, however; the agent, substance or mixture belongs to a well defined, structurally-related class of substances whose members are listed in a previous Report on Carcinogens as either a *known to be human carcinogen, or reasonably anticipated to be human carcinogen* or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

Table of Contents

List of Tables

List of Figures

1 Introduction

Two lead compounds, lead acetate and lead phosphate, have been listed in the Report on Carcinogens (RoC) since 1981 as *reasonably anticipated to be human carcinogens* (NTP 2000). Lead and lead compounds were nominated by the National Institute of Environmental Health Sciences for possible listing in the RoC, based on the 1987 listing by the International Agency for Research on Cancer (IARC) of lead and inorganic lead compounds as possibly carcinogenic to humans (Group 2B) and the subsequent publication of additional human and animal studies of lead and lead compounds.

1.1   Chemical identification of lead

Elemental lead (Pb, atomic wt 207.2, CASRN 7439-92-1) is an odorless silver-bluish white soft metal that is insoluble in water. It also is known as C.I. 77575, C.I. pigment metal 4, KS-4, and lead (inorganic). Its melting point is 327.43°C, its boiling point is 1,740°C, and its appearance varies depending on the physical structure of the specific compound. Lead exists in the valence states of +2 and +4 and has four naturally occurring isotopes: 204, 206, 207, and 208. Inorganic lead compounds usually consist of lead in the divalent state (+2). The chemistry of divalent lead is similar to that of other Group 2 metals, which include beryllium, magnesium, calcium, strontium, and barium.

The major chemical forms of lead found in the environment, as well as in occupational exposures, are reviewed in this report. The U.S. Environmental Protection Agency (EPA) codes for lead and lead compounds are K005, K006, K007, K046, K061, K062, K069, U144, U145, U146, P110, and D008. The RTECS number for lead is OF7525000, and the shipping code is NA 1794 ORM-C.

1.2   Physical-chemical properties of lead

The physical structure of crystalline lead is cubic and close-packed, as illustrated in Figure 1-1. Lead is very soft, highly malleable, ductile, and a relatively poor conductor of electricity. It is very resistant to corrosion but tarnishes upon exposure to air. Lead alloys include pewter and solder. The physical and chemical properties of lead are listed in Table 1-1.
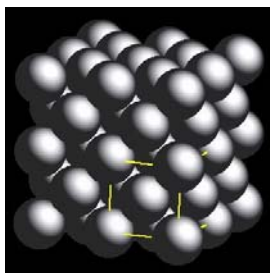
Source: WebElements 2000.

Figure 1-1. Physical structure of lead

Table 1-1. Physical and chemical properties of lead

Property	Information	Reference
Atomic weight	207.2	Budavari *et al.* 1996, ChemFinder 2000
Color	silver-bluish white	Budavari *et al.* 1996, CRC 1998, ChemFinder 2000
Odor	odorless	CRC 1998, HSDB 2002
Physical state	soft metal	Budavari *et al.* 1996, CRC 1998, ChemFinder 2000
Melting point (°C)	327.43	Budavari *et al.* 1996, CRC 1998, HSDB 2002
Boiling point (°C)	1,740	Budavari *et al.* 1996, CRC 1998, HSDB 2002
Density (g/cc at 20°C)	11.4	HSDB 2002
Vapor pressure (mm Hg at 1,000°C)	1.77	HSDB 2002
Crystal system	cubic close-packed	WebElements 2000
Young's modulus (GPa)	16	WebElements 2000
Solubility: water at 20°C nitric acid hydrochloric acid	insoluble insoluble as lead nitrate soluble as lead chloride	Budavari *et al.* 1996, CRC 1998, HSDB 2002, ChemFinder 2000

1.3   Chemical forms of lead

Lead is released into the environment in many different chemical forms. The chemical form of lead determines its water solubility, the types of chemical reactions that occur in the atmosphere, water, and soil, and the extent to which lead binds in soils (NSF 1977). The primary source of lead in the environment historically has been lead emissions from gasoline-containing lead additives. The use of leaded gasoline was banned in the United States after December 31, 1995, except for use in gasoline for aircraft and in fuels for racing vehicles and for non-road vehicles (ATSDR 1999) (see Section 2.1). Lead exposure from all chemical forms most commonly is measured in the body by

determining blood lead levels. The results are reported as micrograms of lead per deciliter of blood, and childhood blood lead levels of 10 µg/dL or higher are considered to present risks to children's health (see Sections 2.6 and 2.10). Exposure to various chemical forms of lead also may be measured in urine, plasma, bones, teeth, and hair (see Sections 2.3.6 to 2.3.10).

1.3.1 Inorganic lead compounds

Of the lead emitted from automobiles using leaded gasoline, 90% is in particulate form, and the remaining 10% exists as organic lead vapors (see Section 1.3.2). The particle size distribution varies with the engine operating conditions; however, generally, 20% to 30% of the lead particles are larger than 5 µm in diameter, 50% to 70% are in the 1- to 5-µm range, and 5% or fewer are smaller than 1 µm in diameter. Any particle less than 30 µm in diameter can be deposited in the nasopharyngeal region of the respiratory tract, and particles smaller than 5 µm can reach the bronchiolar region (Casarett *et al.* 1996). The majority of compounds detected consist of the lead halides: lead bromide ($PbBr_2$), lead chloride ($PbCl_2$), lead bromochloride (PbBrCl), and the alpha and beta forms of the double salt lead bromochloride ammonium chloride ($2PbBrCl·NH_4Cl$) (NSF 1977).

Studies have shown that 95% of the particles emitted from secondary lead-smelting operations are less than 5 µm in diameter. The chemical forms most often detected are lead sulfide (PbS), lead sulfate ($PbSO_4$), and elemental lead (NSF 1977). Another form emitted from mining operations and smelters is lead oxide·lead sulfate ($PbO·PbSO_4$) (ATSDR 1999).

Once these lead compounds are present in the atmosphere, they are converted through chemical reactions into a large number of additional lead compounds. Some of the lead compounds identified in the atmosphere are $2PbBrCl·NH_4Cl$, $PbSO_4$, lead carbonate ($PbCO_3$), $PbBr_2$, $PbCl_2$, lead oxide (PbO_x), lead hydroxychloride (Pb(OH)Cl), lead hydroxybromide (Pb(OH)Br), lead phosphate ($Pb_3(PO_4)_2$), lead oxide·lead sulfate ($3PbO·PbSO_4$), lead oxide·lead chloride ($2PbO·PbCl_2$), and lead oxide·lead bromochloride ($2PbO·PbBrCl$) (NSF 1977).

Inorganic lead compounds also are found in water and soil. The amount of lead in surface water depends on the pH and the dissolved salt content. In the environment, the divalent form (Pb^{2+}) is the stable ionic form of lead. The forms of lead most often found in soil are $PbSO_4$ and $PbCO_3$, the same compounds identified as primary forms found in the atmosphere (NSF 1977).

1.3.2 Organic lead compounds

The tetraalkyl lead compounds, specifically tetraethyl lead (TEL) and tetramethyl lead (TML), are the primary organic lead compounds used as automotive gasoline additives in the United States until 1996 and still used today in racing-car and aviation gasoline. The phaseout of tetraethyl and tetramethyl lead from automotive gasoline was initiated in the 1970s. These two compounds no longer are present in large amounts in the atmosphere; however, their degradation products still exist in the atmosphere. These compounds

decompose rapidly to trialkyl and dialkyl lead compounds when exposed to sunlight and eventually degrade to inorganic lead oxides (ATSDR 1999).

In water, the tetraalkyl lead compounds are subject to photolysis and volatilization. The more volatile compounds are lost to the atmosphere by evaporation. As in air, the degradation process consists of trialkyl lead compounds degrading to dialkyl lead and finally to inorganic lead. Triethyl and trimethyl lead are more water soluble than are tetraethyl or tetramethyl lead and therefore are more often detected in aquatic environments (ATSDR 1999).

Another source of organic lead in water is the conversion of inorganic lead to tetramethyl lead by microorganisms living in anaerobic lake sediments (Craig *et al.* 1980, ATSDR 1999). However, if the water over the sediments is aerobic, the tetramethyl lead will be oxidized, resulting in release of lesser amounts of tetramethyl lead to the water (ATSDR 1999).

In soil, organic lead compounds such as tetramethyl and tetraethyl lead may be converted to highly water-soluble compounds, such as the trialkyl lead oxides. These compounds could be subject to leaching from the soil (ATSDR 1999).

1.4   Physical-chemical properties of lead compounds

Tables 1-2 and 1-3 present the chemical formulas, synonyms, uses, and structures of the major lead compounds, and Tables 1-4 and 1-5 present the physical-chemical properties of these same compounds. The tables are organized according to whether compounds are relatively insoluble in water (Tables 1-2 and 1-4) or relatively soluble in water (Tables 1-3 and 1-5). Compounds are considered soluble or insoluble based on the following criteria: (1) If a solubility constant (K_{sp}) is available, a compound with a value greater than or equal to the K_{sp} for lead chloride (1×10^{-4}) is considered soluble. (2) If a K_{sp} is not available, a compound is considered soluble if more than 2 g of the compound dissolves in 100 mL of water. (3) If no numeric solubility data are available, the compounds are considered soluble or insoluble based on a general rule of solubility of chemical species, as outlined in McQuarrie and Rock (1984).

1.5   Lead ionization and bioavailabilty
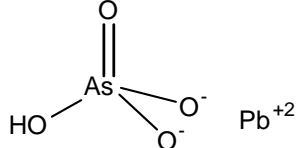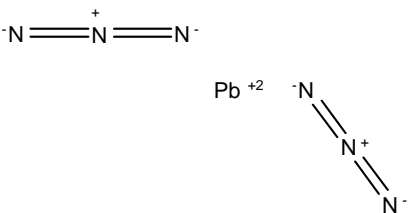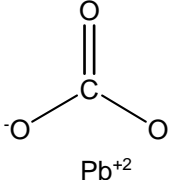
The physical-chemical properties of lead and lead compounds determine their availability to be absorbed into the body, as well as their other pharmacokinetic properties. Studies have shown that soluble lead compounds are more likely to be absorbed into the body than are insoluble compounds and that smaller inorganic lead particulates are absorbed to a greater degree than are larger particulates (Fleming 1998). The degree of absorption in the body also depends on the particular physical-chemical properties of the lead compound (see Section 6 for a discussion of the toxicokinetics of lead). In a study in which rats were fed lead in the diet, the percent absorption of metallic lead and several lead compounds was compared with that of lead acetate. The percent absorption was lowest for metallic lead (14%), followed by lead chromate (44%), lead naphthenate (64%), and basic lead carbonate (164%), for a 12-fold difference in absorption between metallic lead and basic lead carbonate (Barltrop 1975). In addition, studies of metals,
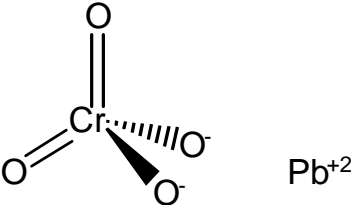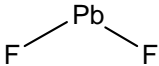
including lead, have emphasized the significance of chemical speciation, particularly ionization, in toxicity (Degawa *et al.* 1994, Ritchie *et al.* 2001).
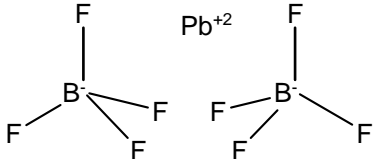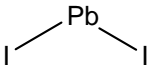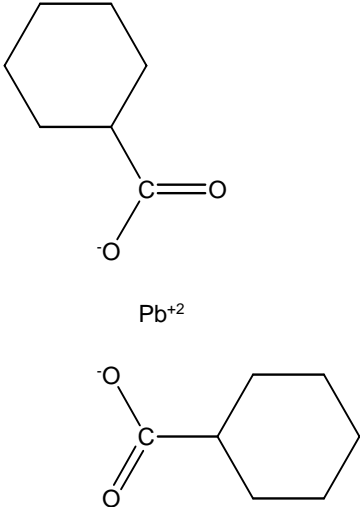
1.6   Identification of metabolites
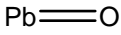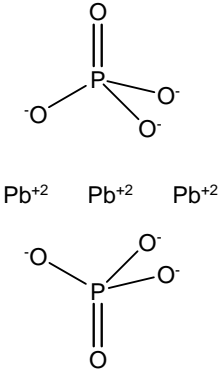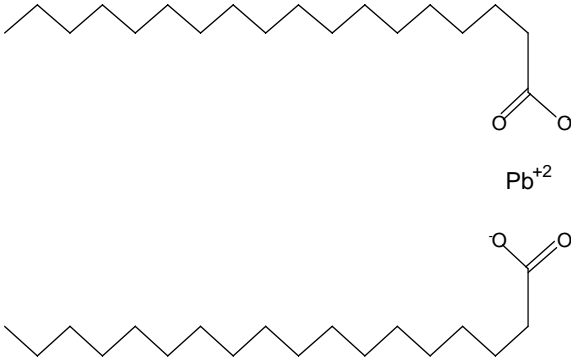
Metallic lead is not metabolized; however, metallic lead and lead compounds are transformed after entry into the body. These transformations are discussed in Section 6.
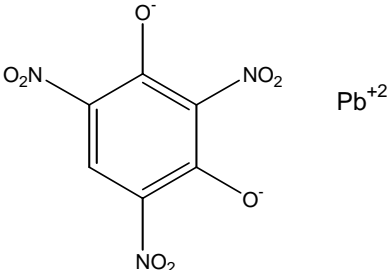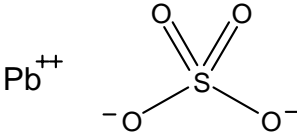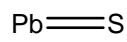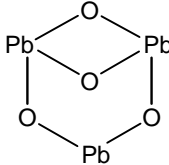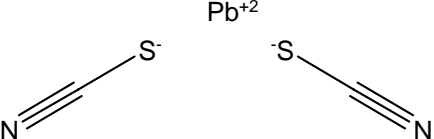
Table 1-2. Uses and structures of insoluble lead compounds
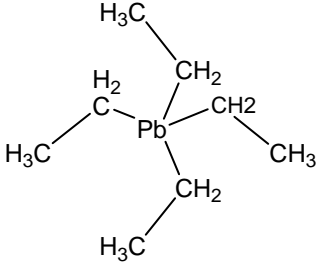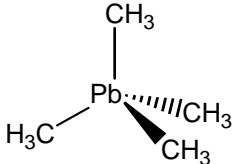
Compound, formula, mol wt	CASRN	Synonyms	Uses	Structure
Lead arsenate $PbAsHO_4$ 347.1271	7784–40–9	acid lead orthoarsenate, acid lead arsenate, arsenic acid lead (2+) salt, arsinette	formerly used as an insecticide and herbicide	
Lead azide PbN_6 291.2402	13424–46–9	initiating explosive	as an explosive	
Lead bromide $PbBr_2$ 367.008	10031–22–8	lead(II) bromide	(not available)	Br—Pb—Br
Lead carbonate $PbCO_3$ 267.2092	598–63–0	carbonic acid, lead (2+) salt (1:1), lead(II) carbonate, and lead carbonate, 99.999%	as a catalyst, in high-pressure lubricating greases, and as a photoconductor for electrolithography, and in coatings for thermographic copying, formerly used in paint	

Compound, formula, mol wt	CASRN	Synonyms	Uses	Structure
Lead chromate $PbCrO_4$ 323.1936	7758–97–6	lead(II) chromate; lead(IV) chromate; chrome yellow; plumbous chromate; crocoite; lead chromate (VI); chromic acid, lead(2+) salt (1:1); canary chrome yellow 40-2250; chrome green uc61; chrome green uc74; chrome green uc76; chrome lemon; chrome yellow g; chrome yellow gf; chrome yellow lf; chrome yellow light 1066; chrome yellow light 1075; chrome yellow medium 1074; chrome yellow medium 1085; chrome yellow medium 1298; chrome yellow primrose 1010; chrome yellow primrose 1015; chrome yellow 5g; chromium yellow; CI 77600; C.I. pigment yellow 34; cologne yellow; C.P. chrome yellow light; C.P. chrome yellow medium; C.P. chrome yellow primrose; crociote; dianichi chrome yellow g; leipzig yellow; lemon yellow; paris yellow; pigment green 15; pure lemon chrome l3gs	as a pigment in paints, rubber, and plastics	
Lead fluoride PbF_2 245.1969	7783–46–2	lead difluoride, lead(2+) fluoride, and plumbous fluoride	as a catalyst, in low-power fuses, in low-melting glasses, and in other electronic and optical applications	

Compound, formula, mol wt	CASRN	Synonyms	Uses	Structure
Lead fluoroborate PbB_2F_8 380.8072	13814–96–5	lead fluoborate, borate(1-), tetrafluoro-lead(2+), lead borofluoride, lead boron fluoride, and lead tetrafluoroborate	in electroplating, as a curing agent for epoxy resins, and as a catalyst	
Lead iodide PbI_2 461.009	10101–63–0	lead diiodide, lead(II) iodide, plumbous iodide	in photographic emulsions, aerosols for cloud seeding, asbestos brake linings, and thermoelectric materials	
Lead naphthenate $Pb(C_7H_{11}O_2)_2$ 461.5254	50825–29–1	cyclohexanecarboxylic acid and lead salt	as a varnish drier, catalyst, wood preservative, and insecticide	
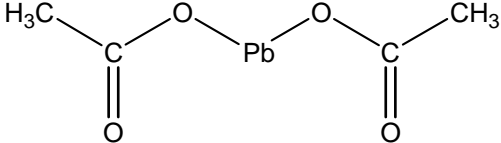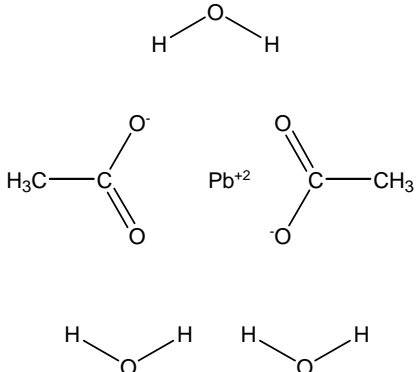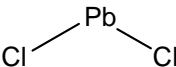
Compound, formula, mol wt	CASRN	Synonyms	Uses	Structure
Lead oxide PbO 223.1994	1317–36–8	lead(II) oxide, lead monoxide, lead oxide yellow, litharge, C.I. 77577, lead ocher, lead oxide(mono), lead protoxide, litharge yellow l-28, massicot, massicotite, pigment yellow 46, yellow lead ocher, plumbous oxide, lead(II) oxide yellow, and lead oxide, 99.99%	in paint, glass, and ceramic products, as a vulcanizing agent in rubber and plastics, and as an intermediate in the manufacture of pigments	Pb═O
Lead phosphate $Pb_3O_8P_2$ 811.54272	7446–27–7	lead orthophosphate, plumbous phosphate, trilead phosphate, perlex paste, trilead bis(orthophosphate), phosphoric acid lead(2+) salt (2:3), and lead(II) phosphate (3:2)	as a stabilizer for styrene and casein plastics and in special glasses	
Lead stearate $Pb(C_{18}H_{35}O_2)_2$ 774.1466	1072–35–1	lead distearate, lead(II) n-octadecanoate, and lead(II) stearate	as a stabilizer for plastics and rubber processing	
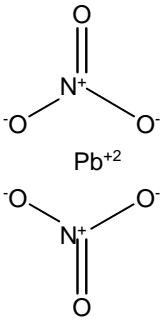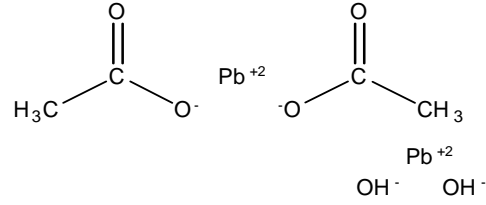
Compound, formula, mol wt	CASRN	Synonyms	Uses	Structure
Lead styphnate $PbC_6HO_2(NO_2)_3$ 450.2000	63918–97–8	initiating explosive lead styphnate, lead trinitroresorcinate, and styphnate of lead	in munitions manufacture	
Lead sulfate $PbSO_4$ 303.2576	7446–14–2	lead(II) sulfate, anglistlite, white lead, fast white, milk white, sulfuric acid lead (2+) salt (1:1), lead sulfate basic, lead sulfate 99.999%, and lead sulphate (lead(II) sulfate)	in photography, in lithography, in earth-fill dams, and roads, and with zinc in galvanic batteries	
Lead sulfide PbS 239.26	1314–87–0	galena, plumbous sulfide, lead(II) sulfide, lead monosulfide, lead sulfide 99.999%, and lead sulfide (1:1)	in ceramics, as a semiconductor, as a catalyst, as a mirror coating, and as a humidity sensor in rockets	
Lead tetraoxide Pb_3O_4 685.5976	1314–41–6	mineral red, lead oxide, red lead oxide, orange lead, and lead(II,III) oxide	in plasters, ointments, glazes, and varnishes, for coloring of rubber, in cement for glass, in storage batteries, and in paints	
Lead thiocyanate $Pb(SCN)_2$ 323.3554	592–87–0	isothiocyanic acid lead(2+) salt, lead dithiocyanate, lead(II) thiocyanate, lead isothiocyanate, and lead sulfocyanate	in manufacture of safety matches and cartridges	

Compound, formula, mol wt	CASRN	Synonyms	Uses	Structure
Tetraethyl lead $Pb(C_2H_5)_4$ 323.446	78–00–2	motor fuel anti-knock compound, lead tetraethyl, tetraethylplumbane, TEL, and tetraethyl lead (liquid)	as an antiknock additive in gasoline, banned since 1996 in motor vehicles in the U.S.	
Tetramethyl lead $Pb(CH_3)_4$ 267.3388	75–74–1	lead tetramethyl, TLM, tetramethylplumbane, TML, and toluene blend no.2	as an antiknock additive in gasoline, banned since 1996 in motor vehicles in the U.S.	

Sources: ChemFinder 2000, HSDB 2002.

Table 1-3. Uses and structures of soluble lead compounds

Compound, formula, mol wt	CASRN	Synonyms	Uses	Structure
Lead acetate $PbC_4H_6O_4$ 325.289	301–04–2	acetic acid, lead(2+) salt, sugar of lead, lead diacetate, lead(II) salt acetic acid, normal lead acetate, neutral lead acetate, lead dibasic acetate, and dibasic lead acetate	as a water repellant, for mildew prevention, as a coloring agent, and as a mordant in cotton dyes.	
Lead acetate trihydrate $PbC_4H_{12}O_7$ 379.3346	6080–56–4	salt of Saturn, lead acetate (II), trihydrate, acetic acid-lead(+2) salt trihydrate, bis(acetato)trihydroxy-trilead, lead diacetate trihydrate, and acetic acid-lead salt trihydrate	in varnishes, chrome pigments, and antifouling paints, in historical paint manufacture, and as an analytical reagent	
Lead chloride $PbCl_2$ 278.106	7758–95–4	lead(II) chloride and lead dichloride	in manufacture of organolead compounds, in asbestos clutch or brake linings, as a catalyst, and as a flame retardant	

Compound, formula, mol wt	CASRN	Synonyms	Uses	Structure
Lead nitrate PbN_2O_6 331.2098	10099–74–8	lead dinitrate, nitric acid-lead(2+) salt, lead(II) nitrate, and lead nitrate, 99.5%	in manufacture of matches and explosives, as a heat stabilizer in nylon, and as a coating on paper for photothermography	
Lead subacetate $Pb_2C_4H_8O_6$ 566.5036	1335–32–6	bis(acetato-O)tetrahydroxytrilead, basic lead acetate, bis(acetato)tetrahydroxytrilead, bis(aceto)tetrahydroxytrilead, bis(aceto)dihydroxytrilead, BLA, monobasic lead acetate, and subacetate lead	in sugar analysis and for clarifying solutions of organic substances	

Sources: ChemFinder 2000, HSDB 2002.

Table 1-4. Physical-chemical properties of insoluble lead compounds[a]

Compound, formula	Color and physical state	Melting point (^{o}C)	Boiling point (^{o}C)	Density or specific gravity	Solubility, reactivity
Lead arsenate $PbAsHO_4$	white powder or crystals	280	NA	5.94	insoluble in water; soluble in nitric acid and alkali
Lead azide PbN_6	white needles or powder	NA	explodes at 350	NA	230 mg/L at 18°C in water
Lead bromide $PbBr_2$	white crystalline powder	373	916	6.66	8,441 mg/L at 20°C in water; insoluble in alcohol
Lead carbonate $PbCO_3$	colorless rhombic crystals	315	NA	6.6	$K_{sp} = 1.1 \times 10^{-15}$; insoluble in water, ammonia, or ethanol; soluble in acid and alkali
Lead chromate $PbCrO_4$	yellow or orange yellow powder	844	decomposes	NA	$K_{sp} = 1.7 \times 10^{-14}$; insoluble in water, < 0.1 g/100 mL at 19°C
Lead fluoride PbF_2	colorless to white crystals	824	1,293	8.44 (orthorhombic) 7.75 (cubic)	insoluble in water, acetone, or ammonia; soluble in nitric acid
Lead fluoroborate PbB_2F_8	colorless crystalline powder	NA	NA	1.75	decomposes in alcohol
Lead iodide PbI_2	bright yellow crystals or powder	402	954	6.16	630 mg/L at 20°C; insoluble in alcohol
Lead naphthenate $Pb(C_7H_{11}O_2)_2$	yellow semi-transparent paste	100	NA	1.15	insoluble in water; soluble in ethanol
Lead oxide PbO	yellow or reddish-yellow crystals	888	1,470	9.53	insoluble in water or alcohol; soluble in alkali, ammonia chloride, acetic acid, and nitric acid
Lead phosphate $Pb_3O_8P_2$	white solid powder	1,014	NA	6.9	insoluble in water or ethanol; soluble in alkali and nitric acid

Compound, formula	Color and physical state	Melting point (^{o}C)	Boiling point (^{o}C)	Density or specific gravity	Solubility, reactivity
Lead stearate $Pb(C_{18}H_{35}O_2)_2$	white powder	NA	NA	NA	NA
Lead styphnate $PbC_6HO_2(NO_2)_3$	orange-yellow crystals	NA	NA	NA	NA
Lead sulfate $PbSO_4$	white heavy crystal powder	1,170	NA	6.2	$K_{sp} = 1.5 \times 10^{-8}$; soluble in sodium hydroxide; insoluble in alcohol
Lead sulfide PbS	metallic black cubic crystals	1,114	1,281	7.57–7.59	$K_{sp} = 1 \times 10^{-28}$; soluble in nitric acid; insoluble in alcohol, potassium hydroxide, or water
Lead tetraoxide Pb_3O_4	bright-red heavy powder	500	NA	9.1	soluble in hydrochloric and acetic acid; insoluble in water or ethanol oxidizing material
Lead thiocyanate $Pb(SCN)_2$	white crystals	190	NA	3.82	insoluble in water; soluble in alkali hydroxide, thiocyanate solutions, and lead sulfocyanate
Tetraethyl lead $Pb(C_2H_5)_4$	colorless liquid or dyed red, orange, or blue, with a slight musty odor	-136.8	200	1.659	$K_{sp} > 4 \times 10^{-15}$; insoluble (0.000021 g/100 mL) in water; soluble in benzene, ethanol, and diethyl ether flash point is 93°C
Tetramethyl lead $Pb(CH_3)_4$	colorless liquid or dyed red, orange, or blue, with a slight musty odor	-27.5	110	1.995	insoluble in water; soluble in benzene, ethanol, and diethyl ether flash point is 37.7°C

Sources: ChemFinder 2000, HSDB 2002.

NA = not available.

Table 1-5. Physical-chemical properties of soluble lead compounds[a]

Compound, formula, mol wt	Color and physical state	Melting point (^{o}C)	Boiling point (^{o}C)	Density or specific gravity	Solubility, reactivity
Lead acetate PbC$_4$H$_6$O$_4$	colorless or white crystals, granules, or powder	280	NA	3.25 at 20°C	K_{sp} = 2 x 10^{-2}; 1–5 g/100 mL water at 20°C; slightly soluble (< 0.1 g/100 mL) in ethanol; slightly soluble (1–5 g/100 mL) in DMSO; slightly soluble (< 0.1 g/100 mL) in acetone; soluble in glycerol
Lead acetate trihydrate PbC$_4$H$_{12}$O$_7$	white crystals	75	280	2.55	miscible in water; slightly soluble in ethanol and acetone; soluble in glycerol\n\nsensitive to air; reagent for neutralization of amino acids and hydrochlorides
Lead chloride PbCl$_2$	white crystalline powder	501	950	5.85	K_{sp} = 1 x 10^{-4}; soluble in water, dilute hydrochloric acid, and ammonia; insoluble in ethanol
Lead nitrate PbN$_2$O$_6$	colorless or white crystals	470	NA	4.53	K_{sp} = 2 x 10^{-2}; soluble in water, 43% ethanol, alkali, and ammonia; insoluble in nitric acid\n\noxidizing material
Lead subacetate Pb$_2$C$_4$H$_8$O$_6$	white heavy powder	75	decomposes	NA	soluble in water and ethanol\n\nsensitive to air

Sources: ChemFinder 2000, HSDB 2002.

NA = not available.

2 Human Exposure

2.1   Use

In worldwide metal use, lead ranks behind only iron, copper, aluminum, and zinc (Howe 1981). Lead may be used in its pure form as a metal, alloyed with other metals, or used in chemical compounds. The utility of lead may be derived from its low melting point (327°C), high density (11.4 g/cm^3), malleability, chemical stability, and resistance to acid corrosion (Howe 1981). The vast majority of lead used, both in the United States and internationally, is in lead-acid storage batteries found in motor vehicles and general industry. Other common uses of lead metal include ammunition, cable covering, piping, brass and bronze, bearing metals for machinery, and sheet lead (ATSDR 1999). In addition, lead-based metals are used in solders, shipping containers, radiation shielding, building construction, and metal cans. Lead oxides are found in paint, glass, and ceramics (Smith 2002a). However, in the United States, lead is no longer used as a solder in piping for drinking water, as a solder in food cans, or in house paints, because of environmental and health concerns (ATSDR 1999).

In the early 1970s, the U.S. EPA began to regulate the lead content in gasoline. Before that, approximately 250,000 tons of organic lead (tetraethyl and tetramethyl lead) were added to gasoline annually in the United States as an anti-knock additive. By 1988, a lead phase-down program had reduced the total lead usage in gasoline to less than 1% of that in 1970. In 1996, lead was totally banned as an additive to fuel in motor vehicles in the United States (ATSDR 1999). However, organic lead still is permitted for use in gasoline for aircraft and in fuels for racing vehicles and for non-road vehicles, such as farm machinery, marine vessels, construction equipment, and recreational vehicles (Smith 2000).

Lead also is used in folk remedies and cosmetics, particularly in developing countries (UNEP-UNICEF 1997). There is evidence that traditional cosmetics containing lead, such as the eye cosmetic kohl, have been purchased and used in the United States (Parry and Eaton 1991).

Despite reductions in some lead applications and the legislated end to use of lead as a gasoline additive, the overall consumption of lead is growing. From 1990 to 1996, the use of lead in the United States grew at an average annual rate of 3.3%. This trend was due primarily to increased production of lead-acid batteries. The proportion of lead used for this purpose increased from just below 80% to nearly 88% in this time span (ATSDR 1999). The vast majority of lead-acid batteries find application as starting, lighting, and ignition batteries in motor vehicles. The remainder are designed for various industrial motive power and stationary power battery applications (Smith 2000). Figure 2-1 shows the end uses of lead worldwide in 2000 (neither the data nor the percentages of the uses are provided in the reference).
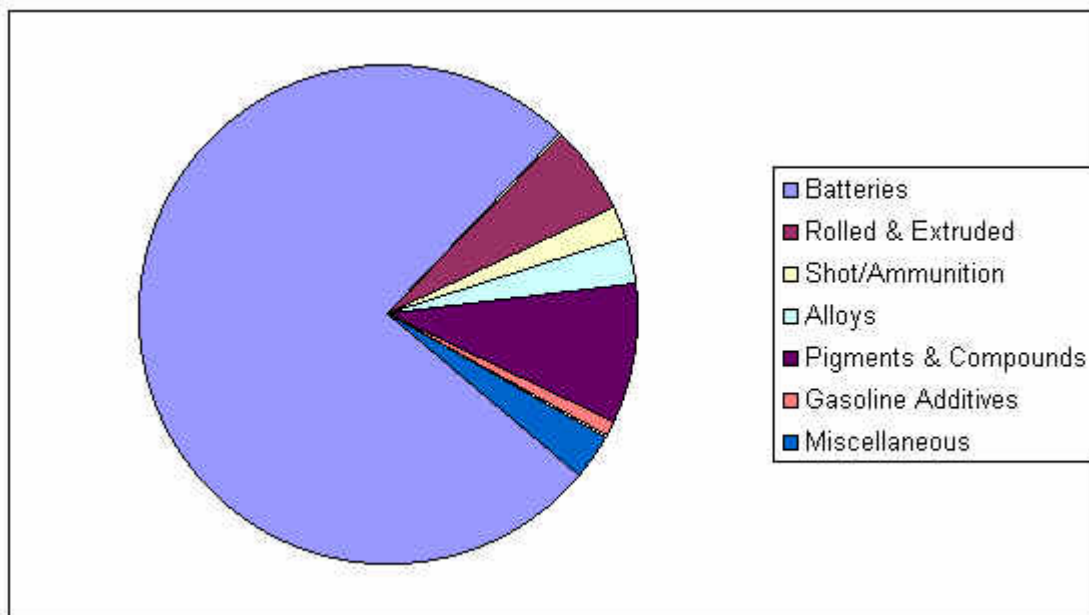
Source: LDA 2002.

Figure 2-1. Worldwide lead use by end consumption (2000)

2.2   Production

Lead is refined from mined ore. Lead ore occurs most frequently in the form of lead sulfide, also known as galena. Anglesite ($PbSO_4$) and cerussite ($PbCO_3$) are two other common ores (Howe 1981). In the United States, virtually all lead mines are underground, rather than open pits (ATSDR 1999). As of 2000, 19 mines produced the vast majority of lead in the United States (Smith 2000), employing approximately 1,000 workers (Smith 2002b). Mines were located in Alaska, Idaho, Missouri, Montana, Nevada, New York, and Tennessee, with over 90% of the total mining occurring in Missouri and Alaska (Smith 2000). Mined lead ore first is crushed and ground. The various minerals are then separated by differential flotation, resulting in a lead concentrate which is shipped to a primary smelter for refining. In 2001, two primary lead smelter-refineries were operating in Missouri and one primary lead smelter was operating in Montana, employing a total of approximately 400 people (Smith 2002b).

At a primary smelter, lead concentrates are sintered to remove sulfur dioxide and other volatile oxides, and the product is roasted with by-products and coke. Molten lead is formed in the blast furnace during the smelting process; impurities are collected in a slag. Drossing is performed to remove copper, lead oxide, and other compounds. Additional refining is performed to separate out minor quantities of silver, antimony, arsenic, copper, and bismuth. The resulting lead metal is 99.99% pure.

Secondary smelters (recycling smelters) use scrap lead, mainly from used lead-acid batteries, as their supply. Used batteries are passed through a separation unit that removes leaded materials and processes the battery acid. The remaining leaded materials are

passed through rotary, reverberatory, or blast furnaces, with an impure lead (or lead alloy) resulting (Howe 1981). The impure metal may then be refined, with its drosses submitted back for reprocessing. Lead recovery efficiencies of 98% may be achieved through secondary smelters. As of 2001, 26 secondary lead smelters were operating within the United States (Smith 2002b); approximately 98% of total lead recycling was carried out by seven companies operating a total of 15 plants in Alabama, California, Florida, Indiana, Louisiana, Minnesota, Missouri, New York, Pennsylvania, Tennessee, and Texas (Smith 2000). In total, secondary lead smelting employs approximately 1,600 workers nationwide (Smith 2002a). From 1990 to 1996, the share of total lead metal production coming from secondary smelters rose from just under 70% to 77% (ATSDR 1999). This trend toward secondary production is reflected in Table 2-1, which provides data on recent U.S. lead mining and smelting production (ATSDR 1999).

Table 2-1. Mine and smelter production of lead in the United States from 1990 to 1996 (thousands of metric tons)

	1990	1996	Percentage change
Mining	484	436	-10
Primary smelting	404	326	-19
Secondary smelting	922	1,100	+19

Source: ATSDR 1999.

Statistical data are available on lead mining in the United States going back over 100 years; in fact, there is information to indicate that lead was mined and smelted in North America as early as 1621. In the 1830s, annual U.S. production was reported at 2.7 million kg. In 1976, U.S. production of lead was reported at 550 million kg, with imports at 208 million kg in 1976 and 318 million kg in 1978. Exports were reported at 5.3 million kg in 1976, 9.0 million kg in 1977, and 8.0 million kg in 1978.

Lead acetate was first produced in the United States in 1944, with imports in 1978 reported at 112.7 kg (IARC 1980). U.S. production of lead acetate was approximately 300,000 kg in 1977 and 200,000 kg in 1980, with imports reported at approximately 52,000 kg in 1984 and 50,000 kg in 1985 (NTP 2000). Lead carbonate has been produced commercially in the United States since the 1600s; in 1976, U.S. production was 1.48 million kg, with imports in 1978 of 178,000 kg (IARC 1980). Commercial production of lead naphthenate in the United States was first reported in 1944. In 1969, production of lead naphthenate was 8.2 million kg, with production dropping to 2.2 million kg in 1977 (IARC 1980). Lead nitrate was first commercially produced in the United States in 1943, and imports of 480,000 kg were reported in 1978 (IARC 1980). U.S. production of lead oxide in 1976 was 120 million kg, with imports at 20 million kg (IARC 1980). Commercial production of lead subacetate was first reported in the United States in 1947 (IARC 1980); no production data are available. U.S. production of lead tetraoxide in 1976 was reported at 18 million kg, with imports at 800,000 kg in 1976 and 1 million kg in 1979. In 1977, approximately 1 to 15 million kg were exported (IARC 1980).

Tetraethyl lead was first produced commercially in the United States in 1923, with 266 million kg produced in 1964; production dropped in 1977 to 148 million kg. Imports of tetraethyl lead in 1978 were 17,000 kg (IARC 1980). Commercial production of tetramethyl lead in the United States began in 1960, with 54 million kg produced in 1977 and 13,800 kg imported in 1974 (IARC 1980).

Table 2-2 shows the number of U.S. suppliers of the lead compounds listed in Tables 2-2 and 2-3.

Table 2-2. Number of U.S. suppliers of lead compounds

Lead compound	Number of U.S. suppliers
Lead acetate	26
Lead acetate trihydrate	19
Lead arsenate	3
Lead azide	(not reported)
Lead bromide	13
Lead carbonate	20
Lead chloride	16
Lead chromate	13
Lead fluoride	17
Lead fluoroborate	15
Lead iodide	21
Lead naphthenate	(not reported)
Lead nitrate	44
Lead oxide	30
Lead phosphate	4
Lead stearate	10
Lead styphnate	(not reported)
Lead subacetate	15
Lead sulfate	8
Lead sulfide	17
Lead tetraoxide	9
Lead thiocyanate	10
Tetraethyl lead	3
Tetramethyl lead	2

Source: Chem Sources 2002.

Worldwide production data from 2001 show that the United States is the major producer, user, and recycler of lead, and that Australia mines more lead than any other country (see Table 2-3). Global statistics show that lead production and consumption increased fairly

steadily from 1964 to 2000, while worldwide mine production decreased slowly, remaining steady over the last few years (see Figure 2-2) [It is not stated in the reference whether these statistics are for metallic lead or lead compounds.].

Table 2-3. Key world lead production and consumption statistics[a]

	Lead (tons)
Top mining countries	
Australia	714,000
China	599,000
United States	459,000
Peru	289,000
Canada	154,000
Largest lead producers	
United States	1,375,000
China	1,172,000
United Kingdom	382,000
Germany	375,000
Japan	302,000
Major users of lead	
United States	1,687,000
China	650,000
Germany	403,000
United Kingdom	323,000
South Korea	314,000
Main recyclers of lead	
United States	1,099,000
Germany	218,000
United Kingdom	183,000
Japan	175,000
Italy	164,000

Source: LDA 2002.

*The statistics in this table do not include the amount of lead imported and exported; therefore the amount of lead produced is not equal to the amount of lead used by the countries cited in this table.
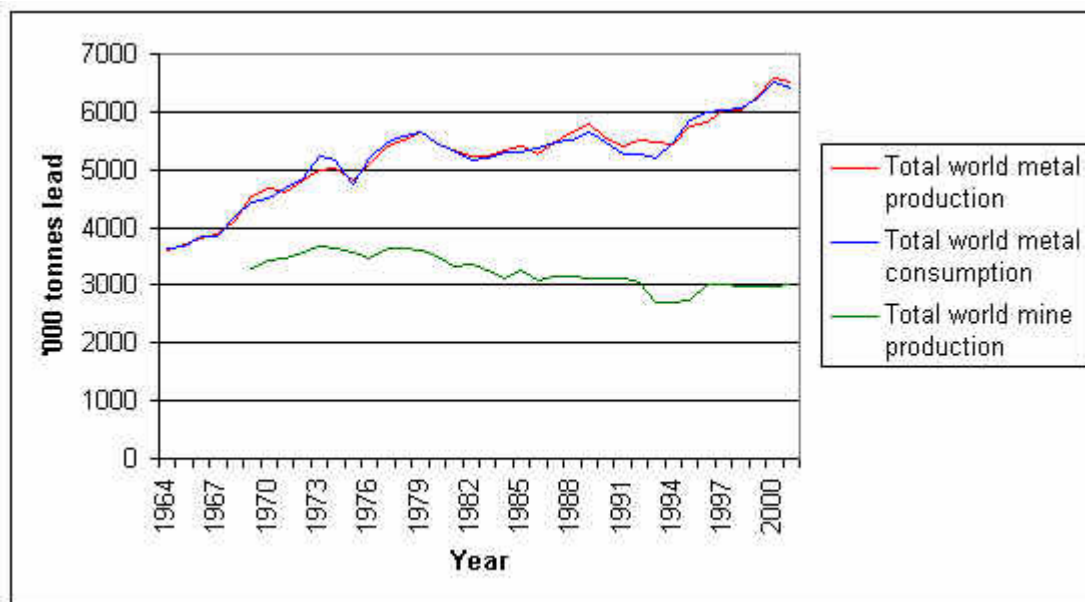
Source: LDA 2002.

Figure 2-2. Global lead mine production and consumption (1964–2001)

2.3 Analysis

The most common techniques for the analysis of lead in environmental or biological samples include atomic absorption spectrometry (AAS), graphite furnace atomic absorption spectrometry (GFAAS), particle-induced X-ray emission (PIXE), inductively coupled plasma mass spectrometry (ICP-MS), inductively coupled plasma atomic emission spectrometry (ICP-AES), and anode-stripping voltametry (ASV). Isotope-dilution mass spectrometry (IDMS) is the best technique for applications involving very low lead concentrations (NRC 1993) but is not commonly used because of its equipment requirements and reliance on technical expertise (ATSDR 1999). A brief overview of the methods for lead analysis in various media is presented below, along with summary tables for the methods most commonly used for environmental lead analysis (Table 2-4) and biological lead analysis (Table 2-5).

2.3.1 Air

Lead in air may be given as a concentration of lead in particulate or gaseous form, usually expressed as micrograms of lead per cubic meter. The most common methods for the analysis of particulate lead in air are AAS, GFAAS, PIXE, and ICP-AES. A filtering approach is used to isolate particulate lead. GFAAS has a lower limit of detection than AAS (approximately 0.25 ng/m^3 and 100 ng/m^3, respectively) but is more sensitive to spectral interference arising from the matrix (NRC 1993). Lead in gaseous form is organic lead and often is detected by GFAAS. Gas chromatography with AAS (GC-AAS), with a detection limit of approximately 0.2 ng/m^3, also may be used to distinguish among species of organic lead (De Jonghe *et al.* 1981).

22

Table 2-4. Common methods for the analysis of lead in environmental samples

Matrix	Preparation	Procedure	Detection limit	Reference
Air	Collect particulates onto membrane filter, digest with nitric acid and hydrogen peroxide, heat, dilute with distilled water.	GFAAS	$2 \mu g/m^3$ (particulate)	ATSDR 1999
	Collect particulates onto stretched-Teflon filter, mount into 3- mm slide frame.	PIXE	$0.6 ng/m^3$ (particulate)	Eldred and Cahill 1994
	Collect particulates onto cellulose nitrate filter, add ^{206}Pb spike to filter, dissolve in sodium hydroxide, acidify with nitric acid, separate lead by electrodeposition.	IDMS	$0.008 ng/m^3$ (particulate)	Völkening *et al.* 1988
	Filter gas, pass through iodine monochloride bubbler, convert lead compounds, extract with carbon tetrachloride solution, follow with acid extraction.	GFAAS	$0.25 ng/m^3$ (gaseous)	Birch *et al.* 1980
	Filter gas, trap gas cryogenically.	GC/GFAAS	$0.2 ng/m^3$ (gaseous)	De Jonghe *et al.* 1981
Water	Filter water through membrane filter, dissolve particulates by wet ashing.	AAS	$100 \mu g/L$ (particulate)	ATSDR 1999
	Filter water through membrane filter, dissolve particulates by wet ashing.	ICP-AES	$42 \mu g/L$ (particulate)	ATSDR 1999
	Filter water through membrane filter, dissolve particulates by wet ashing.	GFAAS	$1 \mu g/L$ (particulate)	ATSDR 1999
	Filter water, complex with sodium diethyldithiocarbamate, extract with pentane, run off water, butylate, extract sample with nonane.	GC/AAS	$2.5 ng/L$ (dissolved)	Chakraborti *et al.* 1984
Soil	Dry ash, digest with hydrochloric and nitric acids (3:1), dilute with water.	AAS	$2 \mu g/g$	Beyer and Cromartie 1987
	Dry sample and sieve, digest with nitric acid, agitate, centrifuge.	ICP-AES	$0.09 \mu g/g$	Schmitt *et al.* 1988
Food	Digest with sulfuric acid and dry ash, dissolve in hydrochloric acid, dilute with water.	GFAAS	$5 ng/g$ (bread)	Ellen and Van Loon 1990
	Dry ash sample; dissolve with nitric acid and water.	ASV	$1 ng/g$ (evaporated milk)	Capar and Rigsby 1989
	Dry ash sample with sulfuric acid; dilute with nitric acid and water.	DPASV	$0.4 ng/g$ (crops)	Satzger *et al.* 1982

Source: ATSDR 1999 (with additional references).

2.3.2   Water

Lead in water may be analyzed for concentration in particulate form or dissolved form, usually expressed as micrograms per liter or parts per billion. Techniques frequently used in the analysis of lead in water include AAS, GFAAS, and ICP-AES. ICP-MS is a more sensitive method, with a detection limit of about 1/1,000th that of ICP-AES (which is approximately 42 µg/L). For this reason, use of ICP-MS is becoming more widespread, not only for water lead analysis, but also for measurement of lead in other environmental and biological media. For dissolved lead analyses, GC-AAS can be used to separate organic lead into its various species (Chakraborti *et al.* 1984).

2.3.3   Soil

AAS, GFAAS, or ICP-AES may be used to determine lead concentrations in soil. Total lead or organic lead may be assessed. ICP-AES is the most sensitive technique in common application, with a detection limit of approximately 0.09 µg/g. As in analysis of other environmental media, GC-AAS may be used to distinguish among organic species of lead (Chau *et al.* 1979).

2.3.4   Food

Analyses of lead concentrations in food generally are similar to analyses of lead in soil. AAS, GFAAS, and ICP-AES are most common, although ASV and differential pulse anode-stripping voltametry (DPASV) have been introduced with good results (Satzger *et al.* 1982, Capar and Rigsby 1989). GFAAS has a detection limit of approximately 5 ng/g for measurement of lead in bread (Ellen and Van Loon 1990), and ASV has a detection limit of approximately 1 ng/g for measurement of lead in evaporated milk (Capar and Rigsby 1989).

2.3.5   Blood

Measurement of lead in whole blood is the most common biological means of monitoring exposure and is a routine occupational health procedure for many lead-exposed workers. Measurements of blood lead reflect exposure to all lead compounds (inorganic and organic) and all routes of exposure (inhalation, oral, and dermal). Blood lead gives information only about fairly recent absorption, since the half-life of lead in blood has been measured at 36 days (Rabinowitz *et al.* 1976) and 28 days (Griffin *et al.* 1975, as cited in ATSDR 1999). The most common approaches are AAS, ASV, GFAAS, and ICP-MS. The sensitivities of these methods, whose detection limits range from approximately 4 to 10 µg/L, are generally sufficient for either occupational or environmental lead exposure assessment.

2.3.6   Serum or plasma

Although lead more frequently is assessed in whole blood, it also is technically possible to analyze its concentration in serum or plasma, but with severe difficulties owing to the low lead concentrations. This analysis is desirable, since it is believed that the quantity of lead in blood plasma governs the amount available for distribution to tissue (Leggett 1993, O'Flaherty 1993). Analysis of lead in plasma or serum is becoming more common with improved techniques, primarily involving ICP-MS. Recent studies have shown that

lead in serum is 0.08% to 0.29% of that in whole blood, as measured by ICP-MS (Manton *et al.* 2001, Cake *et al.* 1996, Smith *et al.* 2002). As noted above for blood, lead concentrations in serum or plasma will reflect all routes of exposure to all lead compounds.

Table 2-5. Common methods for the analysis of lead in biological samples

Matrix	Preparation	Procedure	Detection limit	Reference
Blood	Digest with nitric, perchloric, and sulfuric acids (3:1:1), heat.	ICP-AES	10 μg/L	ATSDR 1999
	Wet ash, combine with dithizone, extract.	AAS	10 μg/L	Gerhardsson *et al.* 1995a
	Wet ash.	GFAAS	4 μg/L	Zhang *et al.* 1997
	Dilute with Triton X-100, nitric acid, and thallium internal standard; agitate.	ICP-MS	0.06 μg/L	Roberts *et al.* 2000
	Concentrate on mercury thin-film electrode, strip from electrode.	ASV	1 pg	NRC 1993
Serum or plasma	Dilute, add bismuth nitrate as internal standard.	ICP-MS	0.015 μg/L	Schütz *et al.* 1996
	Spike with lead isotope, heat in distilled nitric acid .	ICP-MS	0.015 μg/L	Manton *et al.* 2001
Urine	Wet ash with acid mixture and dissolve in perchloric acid.	ASV	4 μg/L	NIOSH 1977
	Extract with polydithiocarbamate resin and sodium hydroxide, agitate, filter, neutralize with sodium hydroxide, ash, heat, dilute with water.	ICP-AES	0.5 μg/L	ATSDR 1999
Soft tissues	Digest with sulfuric acid and dry ash, dissolve in hydrochloric acid, dilute with water.	GFAAS	5 ng/g (bovine)	Ellen and Van Loon 1990
	Ash, add nitric acid, stir solution.	GFAAS	2 ng/g (human)	Gerhardsson *et al.* 1995b
Bone	Excitation of lead with partially plane-polarized X-rays, characteristic lead L-shell X-rays detected.	LXRF	5 μg/g (*in vivo*)	Markowitz and Shen 2001
	Excitation of lead with ^{109}Cd γ-ray source, characteristic lead K-shell X-rays detected.	KXRF	6 μg/g (*in vivo*)	Todd *et al.* 2000, Hu *et al.* 1995

Source: ATSDR 1999 (with additional references).

2.3.7   Urine

Lead concentration in urine may be measured with good sensitivity by methods such as AAS, ASV, or ICP-AES. Detection limits for these methods range from approximately 0.5 to 4 μg/L. Usually, measurement of blood lead concentration is considered a more

direct biological approach to assessing current exposure. However, given the sampling limitations and the analytical difficulties of measuring lead in plasma, some researchers have used lead in urine as a proxy for lead in plasma that will provide an estimate of lead exposure from all routes and to all lead compounds (Tsaih *et al.* 1999, Gulson *et al.* 2000). Exposure to lead has on occasion been assessed by administration of a chelating agent, such as edetate calcium disodium (calcium disodium ethylenediaminetetraacetate dihydrate), followed by measurement of lead excreted in the urine.

2.3.8 Biomarkers

Biomarkers used to identify exposure to lead usually measure the level of total lead in tissues and fluids. Total lead measurements in the body reflect exposure to all lead compounds (inorganic and organic) from all sources of exposure (inhalation, oral, and dermal). Tetraalkyl lead compounds are the only lead compounds that may be measured in the breath, in addition to being measured in body tissues and fluids (ATSDR 1999).

A variety of biomarkers are available for monitoring lead exposure, effects, and susceptibility (NRC 1993). Some of the most commonly used biomarkers are those based on disturbance of heme synthesis by lead (see Table 2-6). One of these assays measures erythrocyte protoporphyrin (EP) or zinc protoporphyrin (ZPP) concentration in blood, and another measures the activity of δ-aminolevulinate dehydratase (ALAD; also known as porphobilinogen synthetase). EP and ZPP increase following lead exposure, while ALAD activity decreases (NRC 1993). However, EP measurements many not accurately reflect lead levels in populations that may be iron deficient, such as low-income children, because iron influences EP levels (Mahaffey and Annest 1986). EP has a sensitivity of 0.351 at blood lead levels of 15 μg/dL or higher, with sensitivity defined as the ability to detect a condition when it is present. This means that on average, the EP test will identify about 35% of children with blood lead levels of 15 μg/dL or higher and will fail to detect about 65% of these children. As the blood lead concentration increases, the EP test becomes more sensitive. For example, at blood lead concentrations of 30 μg/dL or higher, the sensitivity is approximately 0.87 (NRC 1993). Other biomarkers based on disturbance of heme synthesis are measurement of increased urinary δ-aminolevulinic acid (ALA) and the accumulation of coproporphyrin in urine.

In addition, a number of biomarkers of lead exposure are not based on heme-synthesis effects (see Table 2-6). One biomarker measures lead's inhibition of the enzyme pyrimidine-5'-nucleotidase (Py-5'-N), another measures decreased plasma concentrations of the hormonal metabolite 1,25-dihydroxyvitamin D, and a third measures inhibition of erythrocyte membrane Na^+,K^+-ATPase (NRC 1993).

Other biomarkers include measurement of lead in bones, teeth, and hair (see Section 2.3.10 for a discussion of lead in bone and teeth). Hair has been used in the past and is currently being used as a biomarker of lead exposure. However, use of hair analysis in a clinical setting poses many problems, including inaccuracy of measurements due to exogenous contaminants (such as sweat, dust, and beauty treatments), variable analytic procedures, and low interlaboratory reliability (Frisch and Schwartz 2002).

2.3.9   Soft tissue

The analysis of lead in soft tissue normally is limited to autopsy studies (Barry 1975, Gerhardsson *et al.* 1995b) and has included measurements in kidney, liver, brain, lung, testis, and spleen. Analysis methods include AAS, GFAAS, ASV, and ICP-AES, with detection limits of 2 to 5 ng/g (ATSDR 1999).

2.3.10 Bone and teeth

Because the half-life of lead in bone is on the order of years to decades (Gerhardsson *et al.* 1993), analysis of bone lead is more reflective of long-term than short-term exposure. The two main approaches to *in vivo* bone lead measurement are L-shell X-ray fluorescence (LXRF) and K-shell XRF (KXRF). The lower energies involved in the LXRF technique mean that this measurement samples a more superficial component of bone than does the KXRF approach (Todd and Chettle 1994). Common bone sites for measurements include the tibia, calcaneus, and patella. Lead content in teeth also may be assessed, either *in vivo* by XRF methods or, more commonly, by techniques such as IDMS (Gulson 1996) or ASV (Kim *et al.* 1996) with shed deciduous teeth.

Table 2-6. Biomarkers for lead exposure

Lead effect	Result	Marker threshold, lead concentration (μg/dL)	Comments
Heme synthesis disturbances biomarkers			
Inhibition of ALAD activity	accumulation of ALA in tissues and urine	5	sensitive for current population blood lead concentrations; problematic relation to tissue effects
Feedback stimulation of ALA synthetase activity	minor contribution to total ALA in urine	40	not a feasible marker
Accumulation of urinary ALA	--	20–40	useful for population screening; limited in individual predictability; not useful for childhood screening
Inhibition of heme formation from protoporphyrin IX	accumulation of erythrocyte protoporphyrin in blood	15–20 (children) 25–30 (adults)	most common screening marker for children and workers
Impaired use of coproporphyrin	accumulation of coproporphyrin in urine	40	supplanted in popularity by EP measurement
Non-heme synthesis biomarkers			
Inhibition of Py-5'-N activity in erythrocytes	accumulation of ribosomal fragments in reticulocytes	5–10	quite sensitive

Lead effect	Result	Marker threshold, lead concentration (μg/dL)	Comments
Inbition of Na$^+$, K$^+$-ATPase in erythrocyte membrane	potassium loss and net sodium gain in cells; altered cell survival	not established	studies in lead workers; direct measure of lead's presence; subject to contamination
Inhibited hydroxylation of 25-OH-vitamin D	reduction in hormonal metabolite 1,25-(OH)$_2$-vitamin D	10–15	important health effect, not appropriate for use as biomarker

Source: NRC 1993.

2.4 Environmental occurrence

Lead is a naturally occurring element found in the earth's crust in trace quantities of approximately 8 to 13 ppm (Rudnick and Fountain 1995, Taylor and McLennan 1995). Lead exists in the crust in a number of ores, predominantly as lead sulfide (galena). In the absence of human activity, small amounts of lead would reach the surface environment by natural weathering processes to create a baseline exposure, which in localized areas such as mineral provinces can be very high. The abundant and widespread presence of lead in our current environment is largely a result of anthropogenic activity. In this respect, lead has a long history; evidence exists that lead has been used for approximately 6,000 years (Hunter 1978). The ubiquity of lead in the environment has resulted in modern body burdens that are, by one estimate, 300 times those found in pre-industrial humans (Patterson *et al.* 1991).

2.4.1 Air

Lead is released to air by natural processes such as volcanic activity, forest fires, crustal weathering, and radioactive decay from radon. These natural contributions are of relatively minor consequence. The vast majority of lead in the atmosphere results from human activity. A major change in lead emission patterns in the United States resulted from the phasing out of tetraethyl lead as an anti-knock fuel additive. The overall emissions of lead to air dropped significantly beginning in the 1970s and continuing until a complete ban on lead in fuel went into effect in 1996. Nonetheless, as recently as the late 1980s, motor vehicle exhaust was the single largest source of lead emissions in the United States, resulting in the release of inorganic particulates (approximately 90% by mass) such as lead bromochloride and organic lead fumes (< 10% by mass) (ATSDR 1999).

Although numeric values are not available, it appears that the percentage of total lead in the atmosphere contributed by organic lead has dropped significantly as a result of the phase-out and the eventual ban of lead in fuel in 1996. When organic lead compounds are exposed to sunlight, they decompose rapidly to trialkyl and dialkyl lead compounds. These compounds eventually decompose to inorganic lead oxides, through a combination of photolysis and reactions with hydroxyl radicals and ozone. The half-lives of tetraethyl and tetramethyl lead in the summer are 2 and 9 hours, respectively, while in the winter, both compounds have half-lives up to several days (ATSDR 1999).

Investigators have measured long-range transport of lead from motor vehicle exhausts in populated regions to pristine areas by comparing ratios of stable lead isotopes in remote areas with the isotope ratios characteristic of lead from industrial sources in various regions. Rosman *et al.* (1994a) measured lead isotopes in preserved layers of snow deposited in Greenland between 1960 and 1988 and found ratios of $^{206}Pb/^{207}Pb$ of 1.16 in the early 1960s, 1.18 in 1976, and 1.16 in the mid 1980s. They concluded that the elevated ratio of ^{206}Pb to ^{207}Pb indicated transport of lead from U.S. sources, particularly lead in gasoline, and they speculated that the decrease in the 1980s was due to the switch to unleaded gasoline for motor vehicles. In another study, the ratios of lead isotopes in samples from Antarctica in the 1980s indicated that the lead probably was from South America (Rosman *et al.* 1994b).

Releases of airborne lead also occur during smelting, the manufacture of goods, and the incineration of municipal and medical wastes (ATSDR 1999). The largest of these sources is waste incineration; however, the contribution from this source is significantly less than the environmental release of lead to landfill (see Section 2.4.3). This is because the amount of lead in incinerated waste is less than that released to landfills and because not all of the lead in incinerated waste is released to air.

EPA's Toxics Release Inventory (TRI) estimated a release of 354,065 lb of lead from 832 facilities and 1,224,315 lb of lead compounds from 1,045 facilities to air in 1999 in the United States (TRI99 2001). However, the TRI data are not exhaustive and should be used with caution, as only certain types of facilities are required to report releases. The June 2000 edition of EPA's National Toxics Inventory (NTI) estimated that 5,253,736 lb of lead compounds were released into air in 1996 (EPA 2000). The NTI draws on data from the TRI, state and local agencies, and EPA databases.

2.4.2   Water

Lead enters groundwater from natural weathering of rocks and soil, indirectly from atmospheric fallout, and directly from industrial sources. In water, organic lead compounds undergo photolysis and volatilization. Degradation processes convert trialkyl lead to dialkyl lead and then to inorganic lead compounds (ATSDR 1999). EPA's TRI estimated that in 1999, 8,368 lb of lead from 832 facilities and 65,600 lb of lead compounds from 1,045 facilities were released to surface water in the United States (TRI99 2001). The TRI data should be used with caution, since only certain types of facilities are required to report releases. An additional and distinct hazard to the water supply is lead piping or lead solder in older plumbing systems. Areas with a supply of soft (acidic) water are more susceptible to release of lead from plumbing, which can result in levels of lead in drinking water high enough to have significant effects on human health (Lee *et al.* 1989).

2.4.3   Soil

The largest amount of lead released into the environment is released to land, predominantly to landfill sites. Lead-containing wastes result from ore production, household renovation and remediation of lead paint, use of lead in ammunition, solder, weights, and bearing metals, and production of iron and steel. Although lead is now

banned in motor fuels in the United States and several other countries, organic lead compounds continue to be present or actively deposited in the soil. Data suggest that tetraethyl and tetramethyl lead are converted to water-soluble lead compounds in soil (ATSDR 1999). EPA's TRI estimated a direct release of 10,411,207 lb of lead from 832 facilities and 311,467,762 lb of lead compounds from 1,045 facilities to land in 1999 in the United States. An additional 13,250 lb of lead and 8,142,009 lb of lead compounds were released in 1999 by underground injection (TRI99 2001). The TRI data should be used with caution, as not all types of facilities are required to report releases.

2.4.4   Paint

The release of lead from paint to the local environment deserves mention as an important source of environmental exposure. Leaded paints were most commonly used in the United States from approximately 1870 to 1940, although they persisted as recently as the late 1970s. Lead carbonate was the most frequently used lead pigment, and lead oxide and lead chromate also were common. Flaking or peeling of aging paint can be a major point source of environmental lead exposure, as well as sanding of painted surfaces during home renovation. By these processes, lead can become mobilized in dust to the air and soil. In a pooled analysis of 12 epidemiological studies, Lanphear *et al*. (1998) confirmed that lead-contaminated house dust was the major source of lead exposure in children. Additionally, young children may directly ingest chips of paint containing lead (ATSDR 1999).

2.5   Environmental fate

As an element, lead is not destroyed in the environment. When emitted into the atmosphere, tetraethyl and tetramethyl lead decompose via photolysis into trialkyl and dialkyl lead compounds and then to inorganic lead oxides and carbonates (ATSDR 1999). With restrictions on the use of lead in gasoline, industrial sources now produce the majority of lead emissions in the United States, and lead in the atmosphere is primarily in the form of lead sulfate and lead carbonate. Particulate lead is removed from the atmosphere by wet or dry deposition, resulting in its uptake by soil and water. Particle size is a determinant of atmospheric transport, with particles of diameter greater than 2 μm remaining close to the point of emission and smaller particles demonstrating greater mobility (ATSDR 1999).

The proportion of lead remaining in solution in surface water and groundwater generally is small, because of formation of the low-solubility compounds lead sulfate, lead carbonate, lead phosphate, and lead hydroxide. Lead is held strongly in soil and does not readily transport into groundwater, except in highly acid soil. Lead is bound within soil by ion exchange and specific adsorption (ATSDR 1999). However, in one study, metallic lead in soil from shotgun pellets deposited in a lime-deficient, acidic, sandy soil was detected 20 years later in small mammals. This study showed that metallic lead in the environment could be transformed to a biologically available form and transferred up the food chain (Ma 1989).

2.6   Environmental exposure

Environmental exposure to lead results in absorption of lead into the body via inhalation, via ingestion, and, to a limited extent, through the skin. The most efficient exposure route generally is inhalation; the proportion of inhaled lead absorbed into the bloodstream is believed to range from 30% to 50%, whereas approximately 8% to 15% of ingested lead is absorbed (O'Flaherty 1993, Staudinger and Roth 1998). Conditions favoring high solubility result in the absorption of greater proportions of inhaled or ingested lead into the bloodstream. Among the factors affecting the solubility of inhaled or ingested lead are the type of lead compound involved, particle size, site of contact within the body, acidity of the body fluid contacted, and physiologic status of the individual (Spear *et al.* 1998). Compared with typical pre-industrial populations, the contemporary U.S. population is exposed to high levels of lead (Patterson *et al.* 1991), but the levels are substantially lower now than they were 30 years ago.

The most common way to measure environmental lead in the body is by measuring blood lead levels. Venous blood is usually analyzed by AAS or ASV (see Section 2.3.5), and the results commonly are reported as micrograms per deciliter (NRC 1993). The relationship between environmental lead exposure, lead uptake, and blood lead levels is complex. Several models have been used to predict blood lead concentrations in individuals exposed to lead in the environment. One of these models, EPA's Integrated Exposure Uptake Biokinetic Model for Lead in Children (IEUBK), allows the user to input relevant absorption parameters, such as the fraction of lead absorbed from water, as well as intake from exposure to soil, dust, water, and air, and exposure rates. The IEUBK model calculates a complex set of equations to estimate the potential concentration of lead in the blood for a hypothetical child or population of children aged 6 months to 7 years. Because the Centers for Disease Control and Prevention (CDC) has determined that childhood blood lead levels at or above 10 μg/dL present risks to children's health (see Section 2.3.10), the IEUBK model calculates the probability that children's blood lead concentrations will exceed 10 μg/dL (EPA 2002). Figure 2-3 shows the decrease in lead used in gasoline and the substantial reduction in blood lead levels from 1976 to 1980 in the U.S. population, as measured in the Second National Health and Nutrition Examination Survey (NHANES II) (NRC 1993).
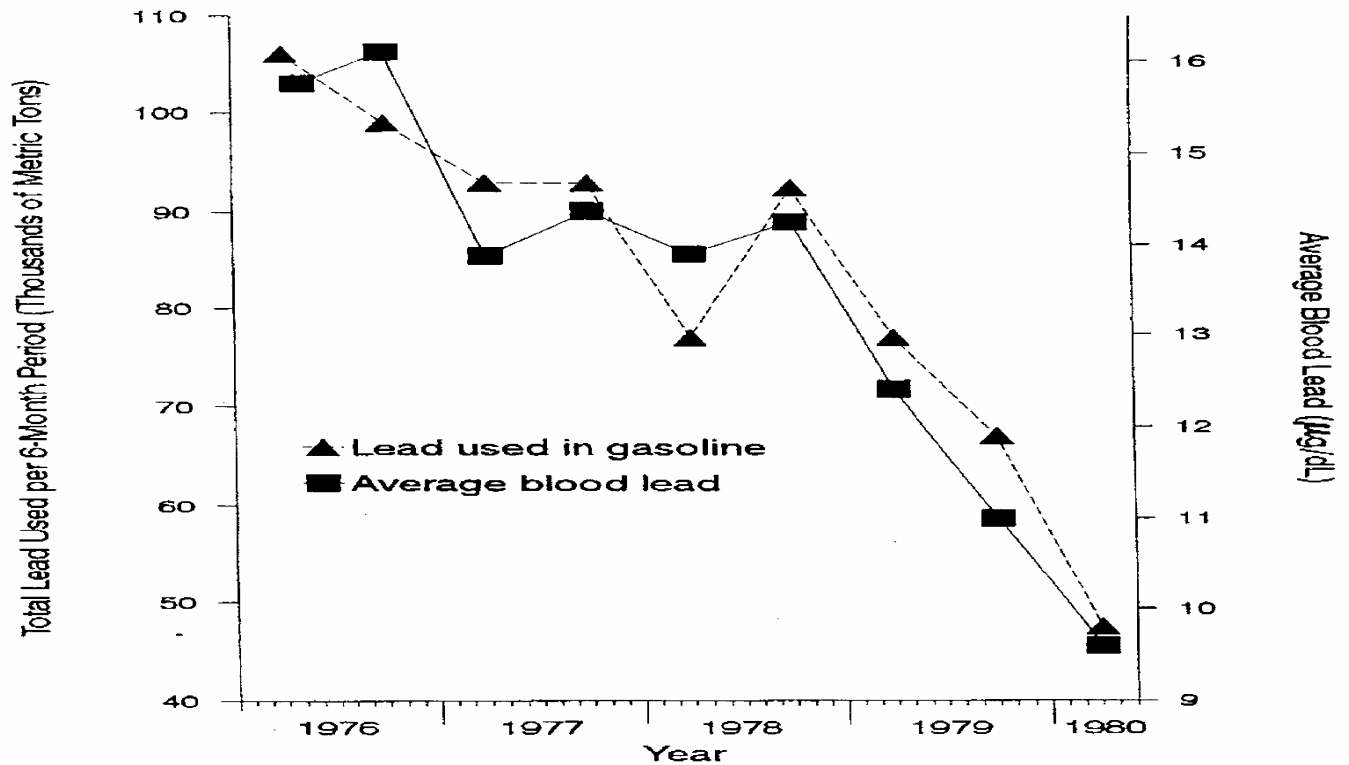
Figure 2-3. Lead used in gasoline and average blood lead levels measured in NHANES II

Source: NRC 1993.

Air lead concentrations may be high (> 10 μg/m^3) near industrial sources such as smelters (ATSDR 1999). A 1991 survey of lead levels in U.S. urban air revealed a maximum quarterly mean concentration of approximately 0.08 μg/m^3 (EPA 1996). Rural concentrations typically are lower, bringing the estimated U.S. mean air lead concentration to 0.04 μg/m^3 in 1995 (EPA 1996). Remote sites report air lead concentrations as low as 0.001 μg/m^3 (Eldred and Cahill 1994).

Lead concentrations in U.S. drinking water generally are below 5 μg/L (ATSDR 1999). Lead pipes or soldering in the presence of corrosive water can result in water lead concentrations above 500 μg/L under extreme circumstances (EPA 1989). For example, in a town in Scotland, drinking water samples showed lead levels greater than 1,000 μg/L due to leaching of lead from the plumbing system by acidified drinking water (Nordberg *et al.* 1985). The concentration of lead in foods can range from 0.002 to 0.6 μg/g (ATSDR 1999). The phaseout of lead-soldered cans (from 1979 to 1991) has virtually eliminated a previously significant source of dietary lead.

Cigarette tobacco contains lead at the level of 2 to 12 µg per cigarette, up to 6% of which may be inhaled (WHO 1977). Smoking a pack of cigarettes (20) per day, with 12 µg of lead per cigarette, and inhaling 6% of the smoke would result in daily exposure to 14 µg of lead. Relatively less common but potentially serious exposures are from alcoholic beverages held or served in leaded crystal, "moonshine" whiskey from leaded stills, food served or cooked in lead-glazed containers, and lead-containing folk medicine remedies and cosmetics.

The average intake of lead by inhalation is estimated at 2 µg/day for an adult living in a U.S. urban setting (ATSDR 1999). A smoker has an additional intake of approximately 6 µg/day, based on an estimated exposure of 14 µg/day and absorption of 30% to 50% of the inhaled lead into the bloodstream (O'Flaherty 1993). In 1990, the estimated daily intake of lead from consumption of food, water, and beverages was approximately 4 µg/day for children 2 years of age and younger, 6 to 9 µg/day for children aged 14 to 16, 6 to 9 µg/day for adults aged 25 to 30, and 2 to 8 µg/day for adults aged 60 to 65 (ATSDR 1999). The most common source of environmental lead exposure for young children is direct ingestion of paint chips and leaded dusts and soils released from aging painted surfaces (CDC 1997, Lanphear *et al.* 1998). This source can contribute an additional intake of 5 µg/day for a toddler engaging in normal hand-to-mouth activity, and significantly more for a child demonstrating pica behavior (ATSDR 1999).

2.7   Occupational exposure

The most common route of occupational exposure to lead is inhalation of lead fumes or leaded dusts in air and absorption of lead through the respiratory system. Lead also may be ingested and absorbed in the gastrointestinal tract. Absorption through the skin occurs with organic lead (Bress and Bidanset 1991) and possibly also with the more soluble species of inorganic lead (Stauber *et al.* 1994). The National Institute for Occupational Safety and Health (NIOSH) has estimated that more than 3 million Americans potentially are occupationally exposed to some form of lead (Staudinger and Roth 1998). The National Occupational Exposure Survey, conducted by NIOSH between 1980 and 1983, indicated that approximately 25,000 workers were exposed to tetraethyl lead, 57,000 to lead oxides, 4,000 to lead chloride, and 577,000 to other species of lead (ATSDR 1999).

Many occupations and job activities have the potential for relatively high exposures to lead (Fu and Boffetta 1995, ATSDR 1999). These occupations have been broadly divided into three lead exposure categories: (1) those having ongoing high exposure, (2) those having high exposure with moderate frequency or ongoing intermediate exposure, and (3) those having high exposure with low frequency or ongoing moderate exposure. Within these three categories, listed below, occupations are listed alphabetically, and asterisks indicate those that have been included in at least one epidemiologic study of lead exposure and cancer, as summarized in Section 3 of this document. The various occupations and job activities are described briefly below.

Category 1: High ongoing exposure

Battery-production workers*	Battery-recycling workers*
Foundry workers	Lead chemical workers*
Lead smelter and refinery workers*	Leaded-glass workers*
Pigment workers*	Radiator-repair workers

Category 2: High exposure, moderate frequency

Firing-range instructors	House renovators
Lead miners*	Newspaper printers*
Plastics workers*	Rubber workers
Steel welders and cutters	

Category 3: High exposure, low frequency

Automobile-repair workers	Cable-production workers
Construction workers	Demolition workers
Firing-range participants	Flame-solder workers
Plumbers and pipefitters	Pottery-glaze producers
Ship-repair workers	Stained-glass producers

Occupational exposure to lead may occur during the production of lead-acid batteries, in which grids are formed either by melting lead blocks and pouring molten lead into molds or by feeding rolled sheets of lead through punch presses. A lead oxide paste also is applied into grid spaces. Battery-recycling workers in secondary smelters are exposed as they convert used batteries and other leaded materials to lead of varying purity. Foundry workers may be exposed to lead through heating and casting operations or through the grinding and machining of components. This type of exposure may result from work with brass and bronze alloys, which contain some lead, mostly for ease of machining. Lead chemical production involves a wide range of end products, including the lead oxide used by the lead-acid battery industry. Production of tetraethyl and tetramethyl lead previously resulted in major occupational exposure, but tetraethyl lead has not been made in the United States since 1991 (ATSDR 1999). Lead smelter and refinery workers participate in operations such as sintering, roasting, smelting, and drossing, resulting in exposure to lead sulfide, sulfates, and oxides.

Leaded glassware is made by combining lead oxide compounds with molten quartz. This process results in lead fumes and dusts, and glassblowing is an additional avenue for potential contact with lead. Production of pigments can involve lead oxide, lead carbonate, and lead chloride. Chromate workers are also exposed to lead chromate, acetate, and nitrate, and lead acetate and naphthenate may be involved in leaded paint

production. Although the use of lead pigments has been reduced in recent years, workers continue to be involved in their production for specialty applications. Radiator repair workers are exposed to leaded dusts during radiator cleaning and to lead fumes during flame soldering. Exhaust ventilation control systems have been introduced into such repair operations with successful results (Tharr and Ed 1993).

Firing-range instructors, particularly in indoor ranges, are exposed to high levels of lead from both the lead projectile and lead styphnate used in the primer. Exposure is higher with non-jacketed pure lead bullets than with jacketed copper-coated bullets (Tripathi *et al.* 1990). The presence of leaded paints in homes built before 1978 continues to present a hazard to home renovators. Scraping, abrasive blasting, and heat-gun removal of paint in older homes can create leaded dusts. Lead miners and mine workers are involved in the extraction, crushing, grinding, and concentration of lead. The most commonly mined lead ore is galena (87% lead by weight), followed by anglesite (68%) and cerussite (78%). Miners of copper and zinc also are exposed to lead. In the past, newspaper printing has been associated with lead exposure, and this exposure is reflected in the epidemiologic studies summarized in Section 3. However, with the emergence of computerized printing techniques, lead exposure is no longer a significant concern in this profession. Workers in the plastics and vinyl industries may be exposed to lead when it is used as a stabilizing or coloring agent. Powdered pigments, such as lead chromate, are blended with plastic pellets and heated to form some plastic products. Similarly, lead has frequently been used in compounding rubber. Greater health awareness has led to reduction in applications of lead in plastics and rubber manufacture. Welders may be exposed to lead fumes resulting from gas-metal arc welding of structural steel (ATSDR 1999). Similar exposures occur for steel cutters.

Automobile-repair workers may be exposed to lead through work around batteries and other parts, engine reconditioning, solder, and, until recently in the United States and several other countries, leaded gasoline. Lead continues to find application in the production of cable sheathing because of its workability, durability, and resistance to corrosion. Construction and demolition workers are exposed to some lead through their interactions with pipes and traps, sheet lead, solder, and (in older buildings) paint. Firing-range participants are exposed to lead in the air, although generally in smaller quantities than firing-range instructors. Typical solders contain 60% lead, and the high temperatures involved in flame solder work volatilize some of this lead. Plumbers and pipefitters work with older lead pipes and copper pipes soldered with lead. Lead oxide and other lead compounds have been used in the making of pottery glaze, and lead chromate may be used in decorative coatings. Ship-repair workers involved with cutting and welding steel carry a risk of lead exposure. Additionally, leaded coatings and paints have been applied to ships to prevent corrosion and inhibit the growth of marine life. Stained-glass producers use lead strips (no longer pure lead, but alloys) to form joints, and soldering is a common procedure.

Air lead concentration may be monitored as a means of measuring occupational exposure in work areas. However, occupational exposure more frequently is inferred from measurement of blood lead concentration in individual workers. Less common methods include analysis of urinary lead concentration, ALA level, or coproporphyrin level. Other

biological indices that will likely become more prevalent in the future are measurement of serum or plasma lead concentration and *in vivo* bone lead concentration.

Various chemical forms of lead, or lead species, are present in occupational settings. In addition to the sheer quantity of exposure, the species of lead involved and the particle sizes encountered will influence how much lead ultimately is absorbed. In a primary smelter, for example, lead sulfide generally is dominant, with increasing quantities of lead sulfates and oxides near furnace areas (Spear *et al.* 1998). Lead sulfates and lead oxides are more soluble than lead sulfide and therefore more likely to be absorbed in the body. Likewise, smaller particles of leaded compounds in airborne dusts are absorbed more efficiently than larger particles. Particles less than 3 μm in diameter have a higher probability of reaching the deep lung (alveoli) and being absorbed into the bloodstream (Spear *et al.* 1998). Because speciation and particle size distribution usually are not available from conventional analyses of environmental media, these factors should be kept in mind when workplace lead exposure data are considered (Fleming 1998).

Table 2-7 summarizes levels of occupational lead exposure from a variety of industries, expressed as air lead concentrations, as determined from monitoring by the Occupational Safety and Health Administration (OSHA) (Froines *et al.* 1990). In a study of airborne lead exposures among janitorial and custodial workers, 23 (44%) of 52 personal air samples collected had no detectable lead. The highest exposures were during power sanding of a wooden door (36 μg/m^3), melting of lead in an open ladle for plumbing repairs (26 μg/m^3), removal of lead and oakum (a type of caulk) from a plumbing joint (13 μg/m^3), and removal and folding of the plastic sheeting used to contain dust during carpentry work (8 μg/m^3) (NIOSH 1997). More extreme examples reported in the literature include mean occupational air lead concentrations as high as 1,200 μg/m^3 for structural steel welding (Fu and Boffetta 1995), 4,470 μg/m^3 for smelting (Fu and Boffetta 1995), and 5,400 μg/m^3 within a storage battery plant (WHO 1977). Table 2-7 shows representative U.S. lead industry exposure conditions in recent years. Based on the mean air lead levels presented in Table 2-7 and assuming a human occupational default minute volume of 10 m^3/8 h (EPA 1994), estimated lead exposure levels ranged from 1,650 to 2,000 μg/day. These values are approximately 1,000 times greater than the average environmental lead exposure levels reported for adults living in U.S. urban settings (2 μg/day) (ATSDR 1999).

Table 2-7. Air lead concentrations in occupational settings, based on OSHA inspection data (1979–1985)

Industry	Inspections (samples)	% of Inspections w/ median air lead conc. > 50 ($\mu g/m^3$)	Mean conc. ($\mu g/m^3$)	Median conc. ($\mu g/m^3$)	Maximum conc. ($\mu g/m^3$)
Storage battery plants	87 (969)	57	200	120	35,000
Brass, bronze, and copper foundries	118 (822)	42	200	65	54,500
Primary lead smelters	5 (72)	40	195	80	5,650
Inorganic pigment plants	25 (143)	52	175	100	4,800
Secondary smelters	86 (718)	43	165	140	5,200

Source: Froines *et al.* 1990.

NIOSH (2001) summarized the results of its Health Hazard Evaluation and Technical Assistance program for occupational exposure to lead for the period 1994 to 1999. In this program, requests are received from employers, employees, or others, and site visits are conducted to determine whether a health hazard exists from exposure to a chemical or biological agent. Table 2-8 summarizes the lead concentrations measured in the personal breathing zone or in the general work area of workers evaluated in a number of industries.

Table 2-8. Air lead concentrations from NIOSH Health Hazard Evaluation and Technical Assistance Program (1994–1999)

Industry	Airborne lead concentration ($\mu g/m^3$)[a]
Law enforcement	ND to 5,910
Manufacturing and repairing	ND to 495
Lead abatement and lead-based paint	ND to 27,000
Abrasive blasting	ND to 1,800
Electric services	ND to 2,300
Other	7.4 to 280

Source: NIOSH (2001).

[a]ND = not detected.

2.8   Biological indices of exposure

Lead exposure may be assessed from a number of biological indices (see Sections 2.3.5 to 2.3.10). As discussed above (see Section 2.6), the most common means of monitoring recent exposure to lead is measurement of blood lead levels. The OSHA standard requires medical surveillance if a worker is exposed to lead in air at concentrations above the action level of 30 μg/m^3 for more than 30 days a year. Medical surveillance consists of testing of blood lead levels at least every six months after the initial blood lead test. If a worker's blood lead concentration exceeds 40 μg/dL, the monitoring frequency must be increased to at least every two months and may not be reduced until two consecutive tests indicate a blood lead level below 40 μg/dL. If a worker's blood lead level exceeds 60 μg/dL, the worker must be removed from the work environment until the blood lead level falls to 40 μg/dL (OSHA 2002). Table 2-9 shows blood lead concentrations measured during the 1990s in occupations with the potential for lead exposure (both high and low to moderate), as well as the average for the U.S. population, as estimated from NHANES III. If sufficient data are available for a given individual, cumulative exposure to lead may be estimated by integrating blood lead readings over time (Fleming *et al.* 1997).

Table 2-9. Blood lead concentrations from various occupations and the general population

Population	N	Average blood lead concentration (μg/dL)	Range (μg/dL)[a]	Reference
General lead industry workers, Korea (1997–1999)	798	32 (mean)	4–86	Schwartz *et al.* 2000
Primary smelter workers, Sweden	100	32 (median)	5.0–47.4	Gerhardsson *et al.* 1993
Battery factory workers, Finland	91	30 (mean)	NR	Erkkila *et al.* 1992
Radiator-repair workers, Colorado (1992)	63	29 (median)	6.6–94	Dalton *et al.* 1997
Primary smelter workers, Canada (1994)	381	23 (mean)	NR	Fleming *et al.* 1998
Carpenters, New Jersey (1991)	122	8.0 (mean)	NR	Smith 1995
Laborers, Iowa and Illinois (1994–1996)	80	7.6 (mean)	1.2–50	Reynolds *et al.* 1999
Painters, Iowa and Illinois (1994–1996)	83	5.9 (mean)	1.5–26.3	Reynolds *et al.* 1999
General population, U.S. (1991–1994)	13,642	2.3 (mean, ages 1 to ≥ 70) 2.1 (mean, ages 20 to 49) 3.1 (mean, ages 50 to 69)	NR	CDC 1997

[a]NR = not reported.

Since 1987, CDC has sponsored the Adult Blood Lead Epidemiology and Surveillance program, which tracks cases of elevated blood lead levels in the U.S. population. Based on data from 25 states reporting during 1998 to 2001, the overall annual mean state prevalence rate for adults with blood lead levels of 25 µg/dL or higher was 13.4 per 100,000 employed adults. In comparison, the overall rate for 1994 to 1997 was 15.2 per 100,000. Yearly rates were 13.8, 12.9, 14.3, and 12.5 for 1998, 1999, 2000, and 2001, respectively. For adults with blood lead levels of 40 µg/dL or higher, the overall prevalence rate for 1998 to 2001 was 2.9 per 100,000 adults, compared with 3.9 for 1994 to 1997. Yearly rates were 3.3, 2.5, 2.9, and 2.8, for 1998, 1999, 2000, and 2001, respectively (CDC 2002).

Bone lead concentration is another biological index of exposure, one that directly reflects long-term accumulation of absorbed lead. Upwards of 90% of an individual's lead body burden is contained in bone (Barry 1975). Noninvasive measurement of bone lead in occupationally exposed populations has some appeal, particularly where blood lead levels historically have not been well documented. Table 2-10 summarizes recent bone lead levels in various lead-industry and referent non-occupationally exposed populations, measured by Kα-XRF.

Table 2-10. Bone lead concentrations from various occupations and referent populations

Population	Bone site	N	Average bone lead conc. (µg/g)	Reference
Primary smelter workers, Canada, early hires (1994)	tibia	222	58 (mean)	Fleming *et al*. 1998
General lead industry workers, Korea (1997–1999)	tibia	798	37 (mean)	Schwartz *et al*. 2000
Battery factory workers, Finland	tibia	91	21 (mean)	Erkkila *et al.* 1992
Primary smelter workers, Canada, recent hires (1994)	tibia	159	19 (mean)	Fleming *et al*. 1998
Primary smelter workers, Sweden	tibia	100	13 (median)	Gerhardsson *et al.* 1993
Carpenters, New Jersey (1991)	tibia	122	9.4 (mean)	Smith 1995
Referents, Korea (1997–1999)	tibia	135	5.8 (mean)	Schwartz *et al.* 2000
Referents, Finland	tibia	26	3.5 (mean)	Erkkila *et al.* 1992
Referents, Sweden	tibia	41	3.4 (median)	Gerhardsson *et al.* 1993
Primary smelter workers, Canada, early hires (1994)	calcaneus	222	103 (mean)	Fleming *et al*. 1998
Primary smelter workers, Sweden	calcaneus	100	49 (median)	Gerhardsson *et al.* 1993
Primary smelter workers, Canada, recent hires (1994)	calcaneus	159	28 (mean)	Fleming *et al*. 1998
Referents, Sweden	calcaneus	41	12 (median)	Gerhardsson *et al.* 1993
Carpenters, New Jersey (1991)	patella	22	14 (mean)	Smith 1995

2.9 Regulations

A few of the key regulations on lead set by U.S. government agencies are summarized in Table 2-11, and a complete listing of lead regulations is provided in Appendix A.

Table 2-11. Key regulations on lead and lead compounds in the United States

Regulatory agency	Lead compound	Limit
OSHA	inorganic lead compounds	50 $\mu g/m^3$ in air, action level of 30 $\mu g/m^3$ in air Health protection goals: 40 $\mu g/dL$ blood, 30 $\mu g/dL$ blood (if intend to have children)
Consumer Product Safety Commission	all lead compounds	0.06% by weight in paints
Food and Drug Administration	all lead compounds	none used in can solders
	all lead compounds	0.5–3 $\mu g/mL$ (leaching standard for ceramicware), 0.5–7 $\mu g/mL$ (leaching standard for silver-plated hollowware)
EPA	tetraethyl lead	none added to gasoline (motor vehicles)
	inorganic lead compounds	none used in plumbing
	all lead compounds	1.5 $\mu g/L$ in drinking water (action level)

2.10 Guidance

In 1991, CDC issued new guidelines for childhood blood lead levels associated with toxicity. They lowered the action level from 25 to 10 $\mu g/dL$ and implemented a multi-tiered, graded response that depends on measured lead concentrations. Responses range from community-level actions to reduce lead exposure to emergency medical responses (NRC 1993).

The American Conference of Governmental Industrial Hygienists recommends threshold limit values for worker exposure to lead of 0.05 mg/m^3 for inorganic lead compounds and 0.15 mg/m^3 for lead arsenate, averaged over an 8-hour day and 40-hour workweek (ACGIH 1999). NIOSH has set a recommended exposure limit of 0.05 mg/m^3 for inorganic lead compounds and an immediately dangerous to life and health (IDLH) level of 100 mg/m^3 (NIOSH 1977).

3   Human Cancer Studies

Lead and lead compounds, in the form of inorganic lead, were classified as carcinogenic to animals by IARC (1987), but the evidence at that time was deemed inadequate to demonstrate human carcinogenicity. The epidemiologic literature on lead and cancer available to IARC was limited, but this literature has burgeoned in the interim. A meta-analysis of the literature was conducted in 1995 (Fu and Boffetta 1995), an overview of the evidence accompanied two new studies in 1997 (Vainio 1997), and a further meta-analytic review was conducted in 2000 (Steenland and Boffetta 2000). Continuing themes include accuracy of classification of lead exposure, simultaneous exposure to other substances that also may be carcinogens, and control for personal factors such as smoking. The cohort studies on workers provide a great deal of useful information; however, the ability to draw conclusions from these studies is limited by the fact that these workers almost always are exposed to multiple chemicals in the workplace. This section summarizes the findings and conclusions of the successive IARC Working Group evaluations of lead, reviews the wide body of relevant epidemiologic studies that have appeared since the 1987 IARC review, and summarizes their implications for the potential relationship between lead and human cancer.

3.1   IARC assessments

IARC has evaluated the evidence that lead exposure may cause cancer in a series of monographs published in 1972, 1973, 1976, 1980, and 1987.

Epidemiologic evidence on lead salts was scarce at the time of the first monograph (IARC 1972). One cohort and one case-control study were available for review. Dingwall-Fordyce and Lane (1963) compared the causes of death occurring among 425 male pensioners and employees from U.K. battery plants with cause-specific rates expected for the general population. Cancer deaths showed a nonsignificant elevation overall. When urinary lead measurements were used to divide the men into three exposure categories, however, no excess of deaths was observed in the highest exposure group (27 observed vs. 31 expected). Cerebrovascular events were more common among these workers, indicating that the absence of an association was probably not linked to a healthy worker effect. Jecklin (1956) found no significant differences in lead concentrations of postmortem lung tissue between five lung cancer patients and five control subjects dying of other causes.

Tetraethyl and tetramethyl lead were considered in a separate monograph (IARC 1973), but no epidemiologic evidence was cited. Similarly, no epidemiologic studies were reviewed in the monograph on lead carbamate (IARC 1976).

By the time of the 1980 IARC monograph, three additional studies of cancer in industrially exposed adults and three studies of childhood cancer in offspring of industrially exposed workers were available.

Cooper and Gaffey (1975) studied battery and lead production workers in the United States. The mortality of a group of 7,032 lead production facility and battery plant

workmen who had been employed for one or more years between 1946 and 1970, was followed through 1970. Although the lead absorption in many of these men greatly exceeded the accepted standards (as based on urinary and blood lead concentrations), their observed mortality by cause was comparable to that of the general population of United States males. Updated results for the same study population were summarized in a later IARC publication (Cooper *et al.* 1985), which is summarized in Section 3.2.1.1.

Robinson (1976) followed up 153 tetraethyl lead workers matched by age and years of employment to 139 workers with no known occupational lead exposure. The only cancers occurring in the study population were skin cancers. Seven cases of cancer occurred in the lead-exposed group, compared with four cases in the nonexposed group. The small number of cases among exposed workers, combined with the fact that workers who had terminated employment for any reason (potentially including development of cancer) were not included in the cohort, makes the results of limited utility.

Rencher *et al.* (1977) compared copper mine, smelter, and concentrator workers with the general population of the state of Utah or with workers in other operations. Workers in lead-exposed operations had triple the lung cancer risk of other workers; among workers in lead-exposed operations, those who developed lung cancer had higher estimated lead exposure than those who did not. Because workers with lung cancer had significantly higher estimated exposure to arsenic and sulfur dioxide, as well as lead, the observed lung cancer excess could not be directly attributed to lead.

The other three studies addressed paternal occupations and childhood cancer. Fabia and Thuy (1974) compared the occupational categories of parents of children dying of cancer with those of children dying of other causes. Hydrocarbon-related occupations, such as motor-vehicle mechanic, machinist, miner, and painter, and potential exposure to lead in the course of tetraethyl lead production were significantly associated with cancer in the workers' children.. A similar study by Hakulinen *et al.* (1976) found no association between hydrocarbon-related occupations and childhood cancer. Neither study measured lead exposure specifically and, thus, are not included in the summary table. Kantor *et al.* (1979) compared 149 Wilms' tumor cases with age, gender, and race-matched controls. More fathers of Wilms' tumor patients than of control subjects had lead-related occupations (22 vs. 6) or hydrocarbon-related occupations (22 vs. 10). Exposure assessment was derived from death certificate occupation listings; the IARC review concluded that the criteria used to identify lead-related jobs were questionable, potentially compromising the validity of all three studies.

IARC's 1987 update included a follow-up of one previous study and four new cohort studies of smelter, battery, or tetraethyl lead workers. Cooper *et al.* (1985) followed up 6,819 U.S. battery and lead production workers from 1947 to 1980, updating the earlier Cooper and Gaffey (1975) study. Compared with national rates, standardized mortality ratios (SMRs) were significantly elevated for all cancers (SMR = 1.13, 95% confidence interval [CI] = 1.02 to 1.26) and all respiratory cancers (SMR = 1.24, 95% CI = 1.03 to 1.49) in battery production workers. Among more site-specific cancers, significant excesses were found of stomach cancer (SMR = 1.68, 95% CI = 1.16 to 2.35) and lung, tracheal, or broncheal cancer (SMR = 1.24, 95% CI = 1.02 to 1.50). Nonsignificant

excesses of liver and laryngeal cancers were observed, whereas the SMR for kidney cancer was nonsignificantly depressed. Nephritis and "ill-defined conditions" also showed significant excesses. Among lead production workers, nonsignificant excesses occurred for digestive and respiratory cancer, and no excesses were noted for kidney, brain, or lymphopoeitic system cancer. Cancer mortality did not increase with duration of employment. Lack of detailed exposure information precluded quantitative evaluation except by years of exposure. Concomitant exposures to other compounds could not be controlled for, and these exposures are likely to be most intense among lead production workers. As lead production workers showed lower SMRs than battery workers, any bias resulting from lack of control for other exposures probably made it more difficult to observe an effect. No data on smoking, diet, or other potential non-occupational risk factors were available. Nevertheless, the large sample size made this study one of the most important studies of lead-exposed workers to date.

Malcolm and Barnett (1982) studied a cohort of 1,898 United Kingdom lead-acid battery workers. A non-significant excess of mortality from all cancers was mainly restricted to the most highly lead-exposed workers. The only significant excess in cancer at a specific site was for digestive cancers (21 observed, 13 expected) in non-exposed workers. The authors noted that blood lead monitoring indicated that by the end of follow-up, most of the difference between the moderate- and high-exposure groups had disappeared. However, the most critical exposure period would have been earlier in the period from 1925 to 1976, so the decline in exposure among the high-exposure group probably did not have much effect on the results. Sweeney *et al*. (1986) compared TEL-exposed workers at a U.S. chemical plant with the national population, observing an excess of respiratory cancer (15 observed vs. 11 expected) and brain cancer (3 observed vs. 1.6 expected) for white males. No excesses were observed for other cancers. The study was limited by its small size and the possiblity of a healthy-worker bias (total mortality = 131, vs. 167 expected).

Smelter workers were studied by Selevan *et al*. (1985) in the United States and Gerhardsson *et al*. (1986) in Sweden. As both studies have been updated in the interim, their results are addressed below.

Summarizing the evidence through its 1987 update, IARC cited the small excesses of respiratory cancer and potential confounding by smoking or exposure to other substances, such as arsenic, and again concluded that the epidemiologic evidence for carcinogenicity in humans was inadequate.

3.2   Studies published since 1987 or not included in the IARC update

Since the IARC update, an additional 17 case-control and 17 cohort studies of lead exposure and cancer have been identified (including analyses on new populations as well as extensions of follow-up or case-control investigations on previously studied populations), in addition to several subanalyses based on elements of these new studies. Seven new studies of parental lead exposure and childhood cancer also have been published. These additional works are discussed below, organized by study design and type of population investigated.

Most studies focus on exposure through occupational sources, where the most intense exposure to lead can be expected. This exposure predominantly involves inorganic lead species. Studies focused on occupations with the greatest potential for inorganic lead exposure are considered first. Among these are smelter and battery-plant workers, along with leaded-pigment workers. Glass workers also may experience considerable exposure in production of leaded glass or, to a lesser degree, in the manufacture of stained glass with leaded joints or lead-containing coatings. Lead miners have the potential for substantial lead exposure, but generally to a lesser degree than smelter, battery, pigment, or leaded-glass workers. Newsprint workers, particularly compositors and typesetters, have had substantial exposure potential in the past, although current printing technologies have largely eliminated lead exposure in these occupations. Many other occupations have not been the object of a specific study, despite the fact that they may entail some degree of inorganic lead exposure; foremost among these occupations are radiator-repair workers, followed by steel welders and cutters. Examples of other potentially exposed occupations include some plastic and rubber industry workers, firing-range instructors, and building renovation and construction workers. Finally, in contrast to most job-related exposures, the manufacture of tetraethyl lead provides a potentially major source of exposure to organic lead. Detailed information regarding sources and magnitudes of occupational lead exposure can be found in Sections 2.7 and 2.8.

Many occupations with potential for exposure to lead involve exposure to lead oxides but also are likely to involve exposure to multiple lead species (see Sections 1, 2, and 3.2). For the most part, good data on the relative contributions of different species or different particle sizes are not available for occupationally exposed individuals, and even when job exposure histories are available, classification into a few ordinal categories of exposure often is not entirely reliable. This limitation precludes assignment of risk estimates to specific inorganic lead species in the current review. Section 3.2.1 discusses studies not yet reviewed by IARC; these studies address cancers in adults in specific occupational groups exposed to inorganic lead. Groups are discussed in approximately descending order of potential exposure. Within these groups, cohort studies are described first, followed by case-control studies.

Section 3.2.2 discusses studies of mixed occupational groups, again progressing from cohort to case-control designs. Section 3.2.3 discusses studies of TEL workers. Section 3.2.4 discusses studies based on the general population, rather than on occupationally exposed persons. Finally, Section 3.2.5 discusses studies of childhood cancer in relation to parental lead exposure.

3.2.1   Studies of adult cancer focused on specific occupational groups

Although the ensuing discussion addresses studies not already reviewed by IARC, a comprehensive listing of studies addressing the association between lead and cancer is presented in Table 3-1 to provide an overview of the currently available literature. Studies are organized according to the occupational group of focus (e.g., smelter workers) in approximately descending order of exposure. For each grouping, all available studies conducted on a specific population are listed, subdivided by study design. Many populations have been the subject of more than one study. Thus, for example, workers at the same British battery factory have been the focus of two cohort studies (Dingwall-

Fordyce and Lane 1963, Malcolm and Barnett 1982) and one case-control study (Fanning 1988). Summaries of each of the studies identified in Table 3-1 are presented in three additional tables. Cohort studies addressing the association between lead and cancer are summarized in Table 3-4, case-control studies in Table 3-5, and studies of parental lead exposure and childhood cancer in Table 3-6.

Table 3-1. Human epidemiologic studies of lead exposure and cancer: published studies on specific populations, by study design

Study population	Study design		
	Cohort	Nested case-control	Case-control
Battery factory and/or smelter workers			
Lead-acid battery workers (U.K.)	Dingwall-Fordyce and Lane 1963, Malcolm and Barnett 1982		Fanning 1988
Battery and lead production workers (U.S.)	Cooper and Gaffey 1975, Cooper *et al.* 1985, Wong and Harris 2000	Cooper *et al.* 1989, Wong and Harris 2000 (same publication as cohort study)	
Copper workers (Utah, U.S.)	Rencher *et al.* 1977		
Zinc, cadmium, and lead smelter workers (U.K.)	Ades and Kazantzis 1988	Ades and Kazantzis 1988 (same publication as cohort study)	
Lead smelter workers (Idaho, U.S.)	Selevan *et al.* 1985, Steenland *et al.* 1992		
Copper and lead smelter workers (Sweden)	Gerhardsson *et al.* 1995a		
Copper and lead smelter workers (Sweden) (Lundström: full cohort; Englyst: sub-cohort)	Gerhardsson *et al.* 1986, Lundström *et al.* 1997, Englyst *et al.* 2001		
Lead and zinc smelter workers (Sardinia)	Cocco *et al.* 1996		
Lead and zinc smelter workers (Sardinia, but different from Cocco *et al.* 1996)	Cocco *et al.* 1997		
Pigment-plant workers			
Lead and zinc pigment plant workers (U.S.)	Sheffet *et al.* 1982		
Chromate (including lead-chromate) workers (U.K.)	Davies 1984a, 1984b		
Glass workers			
Glass workers (Italy)	Cordioli *et al.* 1987		
Glass workers (Finland)	Sankila *et al.* 1990		

Study population	Study design		
	Cohort	Nested case-control	Case-control
Glass workers (Sweden)	Wingren and Englander 1990	Wingren and Axelson 1985, 1987, 1993	
Miscellaneous workers potentially exposed to inorganic lead			
Lead and zinc miners: females only (Sardinia)	Cocco *et al.* 1994b		
Lead and zinc miners: male only (Sardinia)	Cocco *et al.* 1994a, Carta *et al.* 1994		
Newspaper plant workers (Italy)	Bertazzi and Zocchetti 1980		
Tetraethyl lead (TEL) workers			
TEL workers (U.S.)			Robinson 1976
TEL workers (U.S.)			Fayerweather *et al.* 1997
TEL workers (U.S.)	Sweeney *et al.* 1986		
Mixed worker populations			
Finnish workers via Cancer Registry	Anttila *et al.* 1995	Anttila *et al.* 1996	
Sample of deaths due to cancer vs. noncancer deaths (Illinois, U.S.)			Mallin *et al.* 1989
Population-based cases (Canada)			Risch *et al.* 1988
Specific cancers vs. all cancers (Canada)			Siemiatycki *et al.* 1991
Registry-derived liver cancer cases vs. stomach cancer or myocardial infarctions (Finland)		Kauppinen *et al.* 1992	
Brain cancer (U.S.)			Cocco *et al.* 1998a
Central nervous system cancer (U.S.)			Cocco *et al.* 1998b
Stomach cancer (U.S.)			Cocco *et al.* 1999
Gliomas vs. noncancer patients (China)			Hu *et al.* 1998
Meningiomas vs. noncancer patients (China)			Hu *et al.* 1999
Renal-cell cancer vs. population controls (Germany)			Pesch *et al.* 2000
NHANES II cohort mortality follow-up, general U.S. population	Jemal *et al.* 2002, Lustberg and Silbergeld 2002		

	Study design		
Study population	**Cohort**	**Nested case-control**	**Case-control**
Laryngeal cancer among persons with no history of lead exposure (Greece)			Kandiloris *et al.* 1997
Gall bladder cancer vs. gallstone patients (India)			Shukla *et al.* 1998
Parental exposure and childhood cancer			
Childhood acute nonlymphoblastic leukemia cases vs. population controls (U.S. and Canada)			Buckley *et al.* 1989
Wilms' tumor cases vs. population controls (U.S.)			Kantor *et al.* 1979, Wilkins and Sinks 1984a, 1984b, Olshan *et al.* 1990
Children of union printers (Norway)	Kristensen and Andersen 1992		

3.2.1.1   Smelter and battery workers

Smelter workers have a high potential for exposure to lead, much of it in the form of sulfides, in addition to highly absorbable sulfates and oxides. These workers also are typically exposed to other chemical species, such as arsenic and nickel, with well-established carcinogenic potential. Further, quantitative data adequate to differentiate between the magnitude of exposure to lead and these other potential carcinogens usually are not available. Battery plant workers share a high potential for lead exposure, and these plants often include smelter components.

Smelter workers: cohort studies
Ades and Kazantzis (1988) conducted a cohort study of lung cancer mortality among 4,393 U.K. zinc, lead, and cadmium smelter workers. The SMR for the smelter workers, compared with national rates, was 1.25 (95% CI = 1.07 to 1.44), based on 182 lung cancer deaths. Most of the study, however, was devoted to a nested case-control analysis in which workers who died of lung cancer were matched to worker controls by birth date, employment start date, and death date. Cadmium exposure levels were quantified based on job history to determine whether cadmium accounted for the increased mortality; significant exposure to lead and several other compounds also was identified from job histories. Cadmium exposure showed little association with lung cancer. Significant lead and arsenic exposures were associated with lung cancer mortality, whereas associations with zinc or other substances were much weaker. Potential effects of lead could not be separated from those of arsenic, nor could other exposures be simultaneously adjusted for, because of inadequate numbers. The results are thus consistent with lead and/or arsenic potentially contributing more than cadmium or other compounds to the elevated lung cancer mortality associated with lead smelting; however, the excess mortality could be due to exposure to lead only, arsenic only, or the combination of the two.

Steenland *et al*. (1992) monitored mortality among 1,990 U.S. male lead smelter workers employed from 1940 to 1965, with follow-up through 1988. A high-lead-exposure subgroup of 1,436 workers was identified based on air-monitoring records. The total cohort showed nonsignificantly elevated standardized mortality ratios (SMRs) for kidney, bladder, stomach, and lung cancer mortality. The excess for kidney cancer became statistically significant when the analysis was limited to the most highly exposed members of the cohort (SMR = 2.39, 95% CI = 1.03 to 4.71), but estimates for other cancers remained similar or fell (SMR = 1.33, 95% CI = 0.48 to 2.90 for bladder cancer; SMR = 1.28, 95% CI = 0.61 to 2.34 for stomach cancer; and SMR = 1.11, 95% CI = 0.82 to 1.47 for lung cancer). Although the excess mortality from kidney cancer was greater among workers with the highest intensity of exposure, it did not increase with duration of exposure. Where elevated risks were observed in the general cohort, they did not consistently increase among those most exposed. Neither smoking nor coexposure to cadmium or arsenic could be controlled for, but monitoring data from a 1975 NIOSH survey indicated that average exposures to these metals in air were much less intense than exposure to lead, which averaged 3.1 mg/m^3, compared with the current OSHA standard of 0.05 mg/m^3. For arsenic specifically, which has been linked to lung cancer in other studies, the cohort's average exposure was estimated at 14 µg/m^3 in 1975, compared with the current OSHA standard of 10 µg/m^3. A 1996 review of studies on arsenic-exposed worker cohorts concluded that no excess of lung cancer was found for arsenic exposures around the OSHA standard, and that where lung cancer excesses were observed, they appeared to occur in cohorts with much higher exposures (e.g., in the hundreds of micrograms per cubic meter) (Steenland *et al.* 1996).

Gerhardsson *et al*. (1995a) extended the follow-up of male Swedish lead smelter workers begun by Gerhardsson *et al.* (1986), tracing cancer morbidity among 664 lead-exposed workers from 1969 to 1989. Exposed workers were identified from records of routine blood lead monitoring, and cancer incidence was compared with that of the population of the surrounding county. The standardized incidence ratio (SIR) for all cancers was 1.27 (95% CI = 0.91 to 1.74), based on 40 tumors. SIRs for cancers at all specific sites except the brain were elevated, notably those for the respiratory system (SIR = 1.32, 95% CI = 0.49 to 2.88), stomach (SIR = 1.88, 95% CI = 0.39 to 5.50), and colon (SIR = 1.46, 95% CI = 0.30 to 4.28). Because of the small numbers of tumors (only 6, 3, and 3, respectively, even for the aforementioned sites), the reliability of estimates for most sites is limited. Workers in the highest quartile of lead exposure showed further elevation in SIR for total gastrointestinal cancer (SIR = 2.34, 95% CI = 1.07 to 4.45, 9 tumors), but not respiratory cancer. Availability of blood lead measurements to confirm exposure is a key advantage of this study, along with a worker population likely to have much more intense exposure to lead than to other metals. However, the cases were too few for detailed exposure-response analyses. Lack of data on smoking further restricts interpretation of the results.

Cancer-specific SMRs were calculated for 1,388 production and maintenance workers from an Italian lead and zinc smelter followed from 1950 to 1992 by Cocco *et al*. (1997). Deaths from lung cancer (31), stomach cancer (14), and all cancers (132) during 1965-1992 were not elevated over regional rates, but those from cancer of the kidney (4), bladder (12), and brain (4) were, yielding SMRs of 1.75 (95% CI = 0.48 to 4.49), 1.45

(95% CI = 0.75 to 2.53), and 2.17 (95% CI = 0.57 to 5.57), respectively. Risk of kidney cancer increased with years of exposure, whereas the relationship of lung cancer with years of exposure was inconsistent. Age, duration, and latency of exposure were addressed. The numbers of deaths were small for most cancers other than respiratory (33), and there was no control for smoking status. Although cadmium exposure was present, the levels of exposure to this metal were low. Direct lead exposure measurements were lacking, and job classifications were imprecise, but risk of reported lead toxicity did increase consistently with duration of employment. Lack of a strong association of lead exposure with mortality from lung cancer, despite the strong association of lead smelter work with pneumoconiosis and other respiratory disease (SMR = 4.47, 95% CI = 3.37 to 5.80 for national mortality rates), may reflect certificate-based misclassification of lung cancer deaths or other problems, since the excess of pneumoconiosis presumably reflected an excess of silicosis, which is thought to predispose individuals to lung cancer.

In a further analysis, Cocco *et al.* (1996) studied Italian lead and zinc smelter workers whose glucose-6-phosphate dehydrogenase (G6PD) phenotype had been measured. Among all the workers, lung-cancer mortality was lower than expected and stomach-cancer mortality higher, but these differences were based on few deaths (e.g., 2 observed vs. 0.6 expected for stomach cancer). Despite the thought that G6PD-deficient workers might be more vulnerable to the depletion of red blood cell glutathione associated with lead toxicity, mortality from cancer and from all causes was slightly lower among G6PD-deficient workers than among G6PD-normal workers.

Lundström *et al.* (1997) followed 3,979 Swedish smelter workers from 1928 to 1987. Workers were further subdivided into those with high cumulative blood lead scores (mean times years exposed > 10 μmol/L), and those exposed to "lead only" (excluding those from departments thought to have significant exposures to other potential carcinogens, such as arsenic, or little exposure to lead). The lung cancer SMR was 2.8 (95% CI = 2.0 to 3.8) for the total cohort, 2.8 (95% CI = 1.8 to 4.5) for the high-exposure subgroup, and reportedly similar for the subgroup exposed to lead only. With adjustment for a 15-year latency period, lung cancer SIRs likewise differed little between the total cohort and high-exposure subgroup; however, among workers with exposure to lead only, the SIR rose from 3.1 (95% CI = 1.7 to 5.2, 14 cases) for all workers to 5.1 (95% CI = 2.0 to 10.5, 7 cases) for those with the highest exposure. With a 15-year latency period, elevated SIRs also were observed for cancer of the brain and nervous system (SIR = 1.6, 95% CI = 0.4 to 4.2) and renal pelvis, ureter, or bladder (SIR = 1.8, 95% CI = 0.8 to 3.4) among the high-exposure subgroup. Non-respiratory cancers were too infrequent (5 total) in the high-exposure lead-only subgroup for meaningful analysis. This study's size, extensive follow-up, and ability to integrate blood-based and job-based exposure indices give it unusual power. The apparent increase in cancer risk with higher cumulative lead exposure that appeared when workers thought to be potentially exposed to other metals, such as arsenic and nickel, were excluded also appeared to strengthen the evidence for a specific link between lead and respiratory cancer. A subsequent study by Englyst *et al.* (2001), however, cast doubt on the efficacy of the "lead only" grouping.

Englyst *et al*. (2001) conducted additional analyses on one element of the Lundström *et al*. (1997) cohort. A total of 1,093 workers from the smelter's lead department was followed up through 1997. Significantly elevated lung cancer SIRs were observed in all subcohorts, including the subcohort who had never worked in arsenic-exposed areas (SIR = 3.6, 95% CI = 1.2 to 8.3, [5 cases]). This subcohort is the same as the "lead-only" subgroup evaluated by Lundström *et al*. A review of detailed job histories obtained for all workers with lung cancer, however, indicated that 13 of the 15 had "considerable" exposure to arsenic as well as lead, including all but 1 in the "lead only" subcohort.

Combined smelter and battery workers: cohort study
Wong and Harris (2000) presented a further update of the U.S. lead battery and smelter worker cohort last reported on by Cooper *et al*. (1985) and described in Section 3.1. [Lead production workers sometimes are referred to as smelter workers (Cooper *et al.* 1985)]. The updated study extended follow-up for an additional 15 years, through 1995, although employment history was not updated. The SMR for cancer of the lung, trachea, or bronchus among battery workers fell from 1.24 in the earlier analysis to 1.14 (95% CI = 0.99 to 1.30) in the update, narrowly missing statistical significance; among smelter workers, this finding was paralleled by change from a nearly identical SMR of 1.25 in the earlier analysis to 1.22 (95% CI = 1.00 to 1.47) in the update. The stomach cancer SMR remained significantly elevated at 1.53 (95% CI = 1.12 to 2.05) among battery workers and less elevated (SMR = 1.33, 95% CI = 0.75 to 2.20) among smelter workers. The only other cancer with a significantly elevated SMR was that of the thyroid for battery and smelter workers combined (SMR of 3.08; 95% CI = 1.33 to 6.07). Cancer mortality did not increase with earlier year of hire for lung, stomach, or thyroid cancer. Lung and stomach cancer mortality peaked among workers with 10 to 19 years of factory employment and declined with longer employment duration. Thyroid cancer mortality occurred exclusively among workers with 20 or more years of exposure. As noted regarding the earlier study of this cohort, concomitant exposures to other compounds could not be controlled for, but as these were likely to be most intense among lead production workers, whose SMRs were similar to or lower than those for battery workers, any bias resulting from such exposure probably was toward the null. No data were available to assess the possible role of smoking, diet, or other potential non-occupational risk factors in the results.

A nested case-control analysis of this cohort also was carried out for stomach cancer mortality at the largest battery plant (as discussed below). It found no evidence of increased lead exposure among workers who died of cancer and no consistent increase in ORs with increasing exposure. This finding argues against a truly causal role for lead in the SMR results, although the study did not adjust for potential confounders. Overall, the additional follow-up maintained evidence for a modest increase in lung cancer and stomach cancer risk among the lead workers, but found no association with duration of employment and, for stomach cancer, no indication that workers who died of cancer had higher estimated lead exposure than those who did not.

To explore the relationship with stomach cancer in more detail, a small nested case-control analysis also was conducted within the Wong and Harris (2000) cohort. Among workers employed at a Philadelphia lead battery plant, 120 controls were age-matched to

30 workers who died of stomach cancer. Job title histories were collected for each subject and used to estimate total duration of employment at the plant and cumulative exposure based on job-specific intensities of exposure. Neither duration of employment nor degree of estimated lead exposure was elevated among the workers who died of stomach cancer; in fact, these measures were higher among controls, although the differences did not approach statistical significance. No exposure-dependent associations were observed across quartiles of lead exposure, regardless of whether exposure was computed over a 10- or 20-year period before death. Apparently, few data were available on potential confounders. Italian and Irish immigrants were more common among case than control subjects. The authors speculated that in view of higher stomach cancer mortality rates among native Italians and Irish than the general U.S. population, confounding by immigrant status may have been at least partly responsible for the elevated SMR observed in the lead smelter and battery worker cohort. However, the proportions of immigrants in the lead battery plant were not compared with those expected in the corresponding general population. (A previous nested analysis, apparently including many of the same cases, with similarly negative findings, was published by Cooper *et al.* [1989]).

Battery and other workers: case-control study
Fanning (1988) studied deaths due to specific cancer types among battery and other factory workers in the United Kingdom from 1926 to 1985. High to moderate lead exposure resulted in ORs for lung and digestive cancer of 0.93 and 1.13, respectively, with the latter elevation due mainly to stomach cancer (OR = 1.34). No ORs reached nominal statistical significance, and no associations were noted for other cancer types. The excess of digestive cancer deaths was restricted to the 1926 to 1965 period, during which lead exposures would have been most intense. ORs for other cancers did not vary by period. Because each cancer case group was compared with a control group consisting of subjects who died from all other causes, including other cancers, ORs would have been biased downward if some of these other deaths also were lead-related. However, most deaths were due to nonmalignant respiratory or circulatory diseases other than hypertension, which mitigated the potential impact of such a bias.

3.2.1.2   Leaded pigment workers

Leaded pigment manufacture also carries great potential for exposure to lead compounds, which may include carbonates, nitrates, and acetates, among others. The key cohorts studied were involved in the manufacture of lead chromate, and thus were potentially coexposed to chromate, an established carcinogen.

Pigment workers: cohort studies
Sheffet *et al.* (1982) computed age- and calendar-year-specific SMRs for 1,946 workers at a U.S. lead and zinc chromate pigment plant vs. the national population. Lung, stomach, and pancreatic cancer SMRs for chromate workers were significantly elevated when persons of unknown vital status were assumed to be alive at the end of follow-up. When persons of unknown vital status were excluded, only the elevation for lung cancer remained significant (SMR = 1.6 in both whites and blacks, $P < 0.05$ in whites only). Nonsignificant elevations were found for stomach, rectal, pancreatic, and prostate cancer and Hodgkin's disease, and deficits in intestinal and laryngeal cancer were observed

among whites. Similar results for stomach, laryngeal, and pancreatic cancer were found in nonwhites. All but one of the lung cancers among workers of known smoking status occurred among smokers, indicating that if exposure to lead affects lung cancer risk, it does not do so independently of cigarette smoking. The relative degrees of lead and zinc chromate exposure were not determined, nor could coexposure to nickel and other compounds be controlled for. On the other hand, the presence of multiple coexposures would tend to make a true association with lead chromate harder to detect.

Davies (1984a) studied 1,152 U.K. chromate pigment factory workers. A significant excess of lung cancer deaths were observed among these workers, but only for the two factories with combined zinc and lead chromate exposure. Excess lung cancer deaths were noted among workers exposed to both lead and zinc chromate, but not among workers exposed to lead chromate only. In a follow-up of 57 pigment factory workers who had been diagnosed with non-fatal lead poisoning (Davies 1984b), a small excess of lung cancer deaths was found (RR 1.45), but the number of deaths (4) was too small for statistical significance.

3.2.1.3   Glass workers

Leaded-glass workers, particularly those involved in glassblowing, constitute another potentially heavily exposed group, with lead oxides and dust prominent among the species involved. As with smelter workers, however, arsenic is a common coexposure, and antimony, silica, or even asbestos exposure may occur as well.

Glass workers: cohort studies
Three European studies followed up cohorts of glass workers. Cordioli *et al*. (1987) studied 468 Italian glass workers. Workers producing low-quality glass containers were classified as being exposed to lead. A small elevation in mortality from all cancer (SMR = 1.3, 95% CI = 0.8 to 1.8) among glass workers was driven by significant excesses in lung cancer (SMR = 2.1, 95% CI = 1.1 to 3.6) and laryngeal cancer (SMR = 4.5, 95% CI = 1.2 to 11.4). The small number of deaths among exposed workers (28 total, 13 lung, and 4 laryngeal cancer) limited the study's statistical power. Sankila *et al*. (1990) compared the incidence of cancer in 1,803 male and 1,946 female Finnish glass workers with that of the national population. Glassblowers were considered to be a lead-exposed subgroup. Modest elevations in lung cancer risk were observed among glass workers for both men (SIR = 1.3, 95% CI = 1.0 to 1.7) and women (SIR = 1.1, 95% CI = 0.5 to 2.3); no increase was observed for other cancers, and the increased risk of lung cancer was not specific to glassblowers. In the final study, Wingren and Englander (1990) compared mortality in Swedish glass workers from work areas with airborne lead levels ranging from < 0.001 up to 0.110 mg of Pb/m^3, noting a significant elevation for pharyngeal cancer (SMR = 9.9, 95% CI = 1.2 to 36.1) and nonsignificant elevations for lung and colon cancer compared to national rates.

Glassworkers: case-control studies
Wingren and Axelson (1985, 1987, 1993) conducted a case-control analysis comparing stomach, colon, and lung cancer mortality among Swedish glass workers with that of the surrounding regional populations. A small early study of three parishes (Wingren and Axelson 1985) was expanded to include 11 parishes, thus encompassing most of the

Swedish glass-work industry (Wingren and Axelson 1987). For the final analyses (Wingren and Axelson 1993), total lead exposure was estimated, based on work histories, and characterized as "none," "low," or "high." Because of the complex pattern of exposure of glass workers to metals and other agents over time, data on the consumption of metals linked with any particular type of production were obtained by means of a questionnaire submitted to 13 glass works in operation at that time, 7 of which provided answers. These metals were antimony, arsenic, cadmium, chromium, copper, lead, manganese, nickel, selenium, and zinc.

ORs for mortality from cancer of the lung (OR = 1.7, 90% CI = 1.1 to 2.5), stomach (OR = 1.5, 90% CI = 1.1 to 2.0), and colon (OR = 1.6, 90% CI = 1.0 to 2.5) all were elevated among glass workers as a whole (Wingren and Axelson 1987). Among specific classes of glass workers, glassblowers had the highest ORs (2.3, 2.6, and 3.1 for lung, stomach, and colon cancer, respectively). When the data were analyzed according to estimated level of metal exposure, no consistent dose-response trend was found for lung cancer, and the association with stomach cancer was weaker for lead than for arsenic, copper, and other metals. Increasing exposure to either lead or antimony was associated with increased risk of colon cancer mortality; however, exposure to the two elements was strongly correlated. Elevated cardiovascular disease mortality in the population indicated a generally poor health experience. For all three cancers, the highest ORs were seen for glassblowers, who had potentially much higher inhalation exposure to manganese, chromium, and nickel than to lead. In addition to the presence of multiple exposures (e.g., chromium, nickel, and arsenic), the study did not control for other factors such as smoking and diet.

3.2.1.4   Miners: cohort studies

Lead miners obviously are subject to lead exposure, but copper and zinc miners also may experience secondary exposure to lead. The probability of exposure to other dusts and to radon greatly complicates the evaluation of potential associations between lead exposure and lung or other cancers in miners.

Three papers described studies on Sardinian lead-, zinc-, and silica-exposed miners. Carta *et al*. (1994) and Cocco *et al*. (1994a) followed 1,741 male workers from two mines. SMRs based on age- and calendar-year-specific regional rates were not increased for mortality from all cancers (SMR = 0.94, 95% CI = 0.83 to 1.05). A significant excess (SMR = 3.67, 95% CI = 1.35 to 7.98) was seen for cancer of peritoneal tissues, based on 6 deaths. Mortality from prostate, bladder, kidney, and nervous-system cancer and non-Hodgkin's lymphoma showed small excesses. All workers were subject to zinc exposure and either high silica or high radon-daughter exposure, and smoking was not controlled for. Among 526 female workers from the same mines, Cocco *et al*. (1994b) found a significant increase in liver cancer mortality (SMR = 5.02, 95% CI = 1.62 to 11.70) and a nonsignificant increase in lung cancer mortality (SMR = 2.32, 95% CI = 0.85 to 5.05). SMRs for other cancers were below unity. The excess lung cancer mortality was not restricted to workers with high radon-daughter or silica exposure, but was based on small numbers.

3.2.1.5   Newspaper plant workers: cohort study

Bertazzi and Zoccheti (1980) studied Italian newspaper plant workers, singling out compositors and stereotypers as having lead-exposed jobs. Mortality among workers from 1956 to 1975 was compared with national rates. Newspaper workers as a whole had elevated risk estimates for all cancer (SMR = 1.23, 95% CI = 0.92 to 1.62), digestive-system cancer (SMR = 1.20, 95% CI = 0.72 to 1.88), and respiratory-system cancer (SMR = 1.56, 95% CI = 0.91 to 2.50) and for lung cancer specifically (SMR = 1.48, 95% CI = 0.79 to 2.53). No elevated risks were observed for compositors and stereotypers, but these estimates were based on a total of only 4 deaths from cancer of any types.

3.2.2   Studies of mixed occupational groups

Summaries of the cohort and case-control studies described below are provided in Tables 3-4 and 3-5, respectively.

3.2.2.1   Mixed workers: cohort and nested case-control studies

Anttila *et al*. (1995) linked 20,700 Finnish workers whose blood lead was monitored during 1973 to 1983 by the Finnish Institute of Occupational Health to the Finnish Cancer Registry. Exposure was subdivided according to highest peak blood level measured: low (0 to 0.9 µmol/L [0 to 18.6 µg/dL]), moderate (1.0 to 1.9 µmol/L [20.7 to 39.4 µg/dL]), and high (2.0 to 7.8 µmol/L [41.4 to 161.6 µg/dL]). The total cohort showed no elevation in total or site-specific cancer mortality, based on an SMR analysis. Among male workers with moderate exposure, incidence of total respiratory cancer and lung cancer both were elevated (SIR = 1.4, 95% CI = 1.0 to 1.9 for both). Risks of total digestive, stomach, bladder, and nervous-system cancer also were modestly elevated. However, risks did not increase in the high-exposure group. Risks of mortality for all cancer for both men and women (RR = 1.4, 95% CI = 1.1 to 1.8) and lung or tracheal cancer (RR = 2.0, 95% CI = 1.2 to 3.2) were even stronger when a person-year analysis was applied to compare workers with moderate lead exposure to those with low exposure. Again, risks did not increase in the highest exposure group. This exposure group was smaller than the others, however, which limited the power of analyses specific for high exposure workers. Thus, for example, the numbers of lung or tracheal cancer deaths among men in the low-, moderate-, and high-exposure groups were 25, 34, and 11, respectively, for the person-year-based analyses.

It should be noted that for cancer, cumulative exposure, particularly during the earlier part of the follow-up period, might be more relevant than peak exposure, although the two were reportedly highly correlated (*r* = 0.8) in the Finnish workers (Anttila *et al.* 1995). Case-referent substudies of lung cancer used different exposure criteria (Anttila *et al.* 1995). ORs increased most consistently with increasing cumulative exposure to lead. Among histologic subtypes, significantly elevated risk for squamous-cell cancer of the lung (OR = 4.1, 95% CI = 1.1 to 15) for the highest blood lead group persisted after adjustment for smoking, although with additional adjustment for engine exhaust and solvent exposure, the risk declined (OR = 3.4, 95% CI = 0.9 to 13). Results for female workers are not considered, as too few cancers (3 total) occurred to permit meaningful conclusions. Although the follow-up period was relatively short, the lung cancer association was analyzed in much greater detail than in most studies, and smoking was

adjusted for. Although the association between lead exposure and lung cancer weakened with control for engine exhaust and solvent exposure, the OR remained well above 1. The highest OR of all was observed for estimated risk of lung cancer among workers with peak blood lead levels of at least 0.8 µmol/L [≥ 16.6 µg/dL] who were exposed to engine exhaust (OR = 14.9, 95% CI = 1.3 to 178, 11 cases). If engine exhaust was acting as an effect modifier, directly controlling for it might not have been appropriate. The exhaust could have served as a source of organic lead, as well.

Anttila *et al*. (1996) presented a nested case-control analysis of 26 Finnish male workers with central nervous system (CNS) cancer and 200 controls, using the same Finnish occupational cohort as in Anttila *et al*. (1995). Detailed occupational histories and data on other potential risk factors were obtained from cancer patients or next of kin. For CNS cancer incidence, ORs rose with increasing peak lifetime blood lead level; however, the trend was not statistically significant. An association with mortality was confined to glioma. ORs for glioma mortality rose consistently and significantly with increasing peak and mean blood lead level, as well as duration of and estimated cumulative lead exposure (e.g., for low, medium, and high cumulative lead exposure vs. no exposure, ORs = 2.0, 6.2, and 12, respectively, with a trend significant at $P = 0.02$). Adjustment for exposure to gasoline, cadmium, and other potential risk factors did not alter the results. Strengths of this study are the availability of blood lead measurements and control for reported cadmium and gasoline exposure. Limitations include the small number of cases (10 gliomas among workers with complete exposure information), short follow-up time (maximum of 15 years), potential selection bias due to low response rates (60% for cases, 56% for controls), and possible coexposures such as solvents or other metals.

3.2.2.2   Mixed workers: case-control studies

Mallin *et al*. (1989) used death certificates for Illinois males to compare deaths from seven specific cancers with a control group of 3,198 randomly selected deaths from other causes. Based on occupations from death certificates, the OR for cancer of the brain (3.0, $P < 0.05$) was significantly elevated in white male glass workers (as well as physicians and communications workers). No significant association was observed for other cancer sites, including lung and stomach. This isolated association is not consistent with the results for Swedish glass workers summarized above. No specific information on lead exposure other than the decedent's occupation was available, and the analyses were not controlled for other established or potential risk factors.

Risch *et al*. (1988) compared 826 Canadian men with histologically confirmed bladder cancer with 792 Canadian population controls. Reported occupational exposure to lead yielded a significantly elevated smoking-adjusted OR (2.0, 95% CI = 1.2 to 3.5) and a significant trend with duration of exposure. Of 17 other exposures examined, only one (tar and asphalt) was significantly associated with bladder cancer. Although these analyses relied on self-reported exposure, with the potential for inaccurate recall, this study design would be more likely to bias results toward the null than toward a positive association. The ability to control for smoking, education, ethnicity, and other factors are strength of the study; however, although no multivariate analyses adjusting for other occupational exposures were conducted.

Siemiatycki *et al*. (1991) conducted a case-control study in Canada using 3,730 cases of various histologically confirmed cancers. Occupational exposure to 293 substances, including lead, was estimated from interview data. Elevated ORs were noted for cancer of the lung (OR = 1.1, 90% CI = 0.9 to 1.4), stomach (OR = 1.2, 90% CI = 1.0 to 1.6), bladder (OR = 1.3, 90% CI = 1.0 to 1.6), and kidney (OR = 1.2, 90% CI = 1.0 to 1.6). Factors controlled for included age, smoking, income, ethnicity, and blue vs. white-collar occupation. No evidence for exposure-response relationships was presented. Significant strengths of this study are adjustment for smoking and other potential risk factors and reliance on interview-obtained exposure data, rather than estimation of exposure from death certificates. Limitations include potential confounding by the other 292 occupational exposures and low quantitative detail regarding lead exposure.

Kauppinen *et al*. (1992) conducted a nested case-control study in Finland, matching 344 primary liver cancer deaths by age and gender to 476 stomach cancer deaths and 385 myocardial infarct deaths. Exposures were assigned based on work histories. Workers estimated to have potential lead exposure showed no elevation in OR (0.91, 95% CI = 0.65 to 1.29). Few workers (4 in all) were deemed to have probable high cumulative exposure, limiting the power of the study, particularly in view of the potential-for exposure to metals, solvents, and welding fumes among the worker population. Although confounding due to alcohol intake was addressed, use of a control group with stomach cancer, which some other studies have linked to lead exposure, may have biased results toward a negative association.

The National Cancer Institute, NIOSH, and the National Center for Health Statistics have assembled a database that integrates industry, occupation, and cause of death information from death certificates in 24 states. This resource provides a very large sample size for case-control analyses of occupational exposures. Three studies using these data are summarized below. All analyses based on this database share the following primary limitations: (1) no information is available on occupations or industries other than the primary one listed on the death certificate; therefore, some truly exposed subjects will be classified as unexposed; (2) no information is available on the duration of employment in the listed occupation or industry; and (3) cause of death may be misclassified on the death certificate; in combination these limitations will hamper accurate quantification of exposure and linkage of that exposure to outcome status. The net effect of the exposure and outcome misclassifications arising from these limitations most likely would be underestimation of the strength of any true association.

Cocco *et al*. (1998a) matched all 27,060 brain cancer deaths occurring among persons aged 35 or older during 1984 to 1992 with four gender-, race-, age-, and region-matched deaths from non-malignant causes. A job-exposure matrix was used to assign subjects to low, medium, or high probability and intensity of exposure. Subjects were subdivided into four groups based on gender and race (white or African-American). Risk of brain cancer mortality increased consistently with rising intensity of lead exposure among African-American men but not among the other three race-gender groups. When probability of exposure alone was examined, no consistent association was observed for any group. However, among subjects with a high probability of exposure, risk increased with increasing intensity of exposure for all groups except African-American women,

who had only a single lung cancer death in the high exposure probability group. Analyses were adjusted for age, marital status, urban residence, and socioeconomic status. Work in industries associated with lead exposure, such as chemical manufacturing and metal fabrication, may involve exposure to many potential carcinogens in addition to lead, so confounding is a possibility.

Broadening the study to CNS cancer deaths, the same research team computed ORs for specific industries and occupations rather than particular substances (Cocco *et al.* 1998b). Notable elevations of CNS mortality risk were seen for the newspaper printing and publishing industry (OR = 1.4, 95% CI = 1.1 to 1.8, for white males; OR = 3.1, 95% CI = 0.9 to 10.9, for African-American males); for typesetting and compositing among white males (OR = 2.0, 95% CI = 1.1 to 3.8), white women (1.3, 0.4 to 3.8), and African-American women (OR = 4.2, 95% CI = 0.6 to 30.7); and for white male plumbers and pipefitters (OR = 2.4, 95% CI = 1.1 to 5.4). Among whites of both genders, positive associations also were found between CNS cancer and the petroleum refining and petroleum products industries. Results for groups lacking at least one significantly elevated OR ($P < 0.05$) were not presented; these groups included smelter, battery and paint manufacturing, parking-garage, and service-station workers.

In the third 24-state death-certificate study, 41,957 stomach cancer deaths were matched with 83,914 deaths due to non-malignant causes (Cocco *et al.* 1999). A job-exposure matrix was used to assign subjects to low, medium, or high probability and intensity of exposure to lead and 11 other chemicals. ORs were adjusted for age, ethnicity, marital status, urban residence, and socioeconomic status. Elevated ratios occurred among white women (OR = 1.53, 95% CI = 1.10 to 2.12), African-American men (OR = 1.15, 95% CI = 1.01 to 1.32), and African-American women (OR = 1.76, 95% CI = 0.74 to 4.16) with high probability of lead exposure. Risks in the moderate-probability group were elevated only for African-American women (OR = 1.37, 95% CI = 0.58 to 3.21), and risk was not elevated for any exposure group among white males. Risk showed no consistent increase with intensity of exposure in any group. The absence of any association with lead exposure among the largest race-gender group, white males, is notable, as is the general absence of association with intensity of exposure. More consistent elevations of ORs for stomach-cancer mortality were observed for inorganic dust and nitrosamines than for lead.

In a Chinese hospital-based case-control study, Hu *et al*. (1998) compared 218 patients with histologically confirmed primary gliomas with 436 patients with non-neurological, nonmalignant disease, matched by age, gender, and residence. Patients were interviewed to elicit details on occupational and chemical exposures for factory and farm occupations. An OR could not be calculated for occupational exposure to lead because no glioma patients reported such exposure.

In a parallel study, Hu *et al*. (1999) compared 183 patients with histologically confirmed primary meningiomas with patients with non-neurological, nonmalignant disease, matched by age, gender, and residence. Patients were interviewed to elicit details on occupational and chemical exposures for factory and farm occupations. Reported occupational exposure to lead was associated with risk of meningioma in both men

(OR = 7.20, 95% CI = 1.00 to 51.72) and women (OR = 5.69, 95% CI = 1.39 to 23.39). Results were adjusted for income, education, and consumption of fruits and vegetables, indicating that the increased cancer risk was not a consequence of lifestyle, but no attempt was made to control for other occupational exposures. Some elevation of ORs occurred in most of the 14 occupational exposures examined, including exposure to cadmium. Exposure to two or more agents, regardless of type, was a stronger predictor than exposure to any specific agent, suggesting that lead exposure may have been simply a surrogate for occupational chemical exposure in general.

Finally, Pesch *et al*. (2000) investigated occupational exposure to potential carcinogens among 935 Germans newly diagnosed with renal-cell cancer and 4,298 controls selected from regional population registries and matched by age, gender, and area of residence. Lifetime job histories and information on smoking habits and other potential risk factors were collected by interview. Cumulative exposure to lead, as well as cadmium, solder fumes, welding fumes, and metals in general, was estimated based on previously published job exposure matrices and grouped into four ascending categories; separate estimates of lead exposure were calculated based on British- and German-developed matrices. After adjustment for age and smoking, ORs for renal cancer were elevated in men (OR = 1.5, 95% CI = 1.0 to 2.3) and women (OR = 2.6, 95% CI = 1.2 to 5.5) with the highest lead exposure, compared with the low-exposure groups based on the British matrix. When exposure was based on the German matrix, the OR was less elevated among men (OR = 1.3, 95% CI = 0.9 to 2.0); no results for women were reported. Limited indications of increased risk with increasing exposure were reported for men but not for women. Strengths of the study are its size and population base. The primary limitation is uncertainty regarding the specificity of the results for lead. Significant associations also were noted for exposure to cadmium, solder fumes, and organic solvents among men, for example, but no analyses attempting to account for other exposures were reported. It is thus unclear how much of the observed risk associated with lead exposure may be secondary to exposure to cadmium or other agents (or, more generally, to what extent the true association may be obscured by confounding due to these exposures).

3.2.3   Studies of occupations exposed to organic lead: case-control study of TEL workers

Fayerweather *et al*. (1997) studied mortality in a U.S. TEL production plant. Cases included 735 cancer deaths during 1956 to 1987 among men identified by the company's cancer and mortality registries, excluding cases of bladder cancer deemed likely to have been due to benzidine or beta-naphthalamine exposure. Controls were time-, age-, gender-, and payscale-matched plant workers who died of causes other than cancer. Cumulative exposure to TEL was derived by summing yearly exposure over time to yield ranks of none, low, medium, high, and very high TEL exposure. TEL exposure was associated with digestive cancers in general; most of the association was limited to very high cumulative TEL exposure (OR = 2.2, 90% CI = 1.2 to 4.0), with a weaker association for high exposure (1.3, 90% CI = 0.7 to 2.7) and no association with lower exposures.

Among specific digestive cancers, rectal cancer showed a strong association with ever-exposure to TEL (3.7, 90% CI = 1.3 to 10.2). The risk of rectal cancer increased with

cumulative exposure; compared with no exposure, the OR was 1.7 (90% CI = 0.4 to 8.3) for low or medium exposure and 5.1 (90% CI = 1.6 to 16.5) for high or very high exposure. The authors reported that control for smoking habits and addition of a 10-year lag increased the strength of the association between lead exposure and rectal-cancer mortality. Colon cancer also showed a mild association with ever-exposure to TEL (OR = 1.3, 90% CI = 0.7 to 2.5), apparently limited to high or very high cumulative TEL exposure (OR = 1.7, 90% CI = 0.8 to 4.0). Adjustment for smoking and exposure to nitriles did not affect the results, but restriction to cancer of the sigmoid colon reportedly produced an exposure-response gradient (OR = 3.6, 90% CI = 0.5 to 28.0 for high exposure; no OR reported for low-to-medium exposure). TEL exposure also was associated with mortality from Hodgkin's disease (OR = 2.7, 90% CI = 0.6 to 12.0), although the small number of cases (8) precluded in-depth analysis. Results for other cancers were not presented, as they were judged to show no association with TEL exposure. Results were not sensitive to lag time and were unaffected by adjustment for smoking or exposure to aromatic amines, radioactive materials, or asbestos, eliminating confounding by these factors as a source of the observed association. Overall, the study found a significant relationship between TEL exposure and risk of digestive and particularly rectal cancer, not reported in previous studies of TEL-exposed workers, but did not find relationships with any of the cancers associated with TEL or lead exposure in previous studies. The absence of associations with other cancers could be a consequence of failure to include cancer deaths among pensioned workers or those who left employment early because of illness.

3.2.4 Cohort studies based on general population (environmental) exposures

Jemal *et al*. (2002) conducted the first biomarker-based general population cohort study of lead exposure and cancer. The study employed the subsample of 3,592 white U.S. participants in NHANES II (1976 to 1980) who had undergone blood lead level determinations at time of entry. Deaths among this population were enumerated through 1992 by linkage to the National Death Index (NDI) and Social Security Administration Death Master File, as part of the NHANES II Mortality Study.

Adjusted for age, smoking, drinking, region, year, and gender, risk of mortality from any cancer rose across quartiles of blood lead level, but this trend was not statistically significant. The trend across quartiles was not consistent in gender-specific analyses, although relative risks were elevated for the highest quartile of blood lead level in both men and women (RR = 2.0 for men and 1.6 for women). The RR for lung cancer based on comparison of subjects with blood lead levels above or below the median was 1.5 in the combined population, with higher risk observed among women (RR = 2.5, 95% CI = 0.7 to 8.4) than men. The highest risks were observed for cancer of the esophagus (RR = 3.7, 95% CI = 0.2 to 89), pancreas (RR = 3.6, 95% CI = 0.6 to 19.8), and stomach (RR = 2.4, 95% CI = 0.3 to 19.1); no elevations were noted for cancers of other sites.

The lack of statistically significant results reflects the small number of deaths during follow-up, which limited the study's power; of the nine major sites examined, the number of deaths ranged between 5 and 16 for all sites except the lung. Detailed exposure-response analyses were restricted to all cancers combined, although potential effects could have been strongly target-organ specific. In addition, the use of quartile cutpoints

based on the distribution of lead concentrations estimated for the total U.S. population resulted in relatively small numbers in the referent group (lowest exposure quartile) for males and in the high-exposure quartile for females. Use of a biomarker provided an objective measure of lead exposure. Nevertheless, reliance on a single blood lead measurement produces less reliable estimates than would be obtained through multiple measurements and precludes addressing temporal changes in lead exposure over the follow-up period. Lack of control for exposure to occupational carcinogens other than lead and potential residual confounding by duration and intensity of tobacco smoking also could have biased the results, especially for men.

Lustberg and Silbergeld (2002) carried out another biomarker-based general population study based on the same NHANES II mortality cohort used by Jemal *et al.* (2002). This study did not exclude non-whites, however (thus gaining 524 subjects) and employed more extensive adjustment for potential confounding factors than the Jemal *et al.* (2002) analyses (i.e., education, body mass index, and exercise were included in the regression models, although alcohol intake was not). In addition, persons with blood lead levels of 30 μg/dL or higher were excluded in order to restrict comparisons to levels below the OSHA standard for lead exposure. Persons with levels below 10 μg/dL served as the referent group. Survival analyses adjusted for potential confounders found a relative risk for cancer mortality of 1.5 (95% CI = 0.9 to 2.5) for those with blood lead levels of 10 to 19 μg/dL, compared with those with levels below 10 μg/dL, rising to 1.7 (1.0 to 2.8) for those with levels of 20 to 29 μg/dL. Separate analyses of lung-cancer and non-lung-cancer deaths yielded estimates of increased risk for moderate- or high-exposure groups, compared with the referent population, both for lung cancer and non-lung cancer. However, none of the estimates reached the *P* < 0.05 level of statistical significance, and the results for non-lung cancers showed no evidence of an exposure-response relationship.

As with Jemal *et al.* (2002), the use of a biomarker for exposure and the prospective design of the study are strengths. Its attempts to control for potential confounders were more extensive, and its choice of cutpoints for the referent category yielded more males in the referent group, although that group still included less than 20% of the study population. However, it is notable that blood lead levels rose significantly with smoking level. The models included terms for former smoking, current light smoking, and current heavy smoking (> 1 pack per day). Nevertheless, some degree of residual confounding due to smoking might have remained, which could have contributed to the estimated risk of lung cancer for the highest exposure category (RR = 2.2, 95% CI = 0.8 to 6.1). Such residual confounding would have had less effect on the results for non-lung cancer. As noted regarding the other NHANES-based study, however, mortality due to cancers of other sites was too uncommon to allow for reliable site-specific comparisons.

3.2.5   *Case-control studies based on general population (environmental) exposures*

Kandiloris *et al*. (1997) compared blood lead levels and aminolevulinic acid dehydratase activity in 26 laryngeal carcinoma patients with no history of lead exposure or toxicity and 53 patients with no history of cancer from the same hospital. Cases and controls reportedly had comparable demographic characteristics. Blood lead levels were similar,

but ALAD activity was significantly lower in cancer patients. As an indicator of subclinical lead toxicity, the lower ALAD activity in laryngeal cancer patients supports the authors' hypothesis that lead exposure at subclinical levels may contribute to laryngeal cancer risk. However, the small sample and the potential influence of the disease process on ALAD activity make this conclusion highly speculative.

Shukla *et al*. (1998) examined heavy metal content in bile drawn from 38 patients with newly diagnosed, histologically confirmed gall bladder cancer and 58 patients with gallstones diagnosed at the same surgical unit, matched by geographic area within India. Bile lead concentrations were markedly higher in patients with cancer of the gall bladder (mean ± standard error [SE] = 58.38 ± 1.76 mg/L) than in those with gallstones (mean ± SE = 3.99 ± 0.43mg/L). Cadmium and chromium levels also were elevated in bile from cancer patients, but not as much as lead levels. Exposure to metals was assumed to occur through the heavily contaminated waters common to the area. No attempt was made to control for the higher cadmium and chromium levels that accompanied elevated lead level. However, the fact that lead levels differed more dramatically than levels of other metals argues against cancer-induced perturbation of bile concentrations as the source of these results. No data on personal risk factors or potential occupational exposures to other carcinogens were collected; therefore, the possible contribution of such factors relative to lead could not be established.

3.2.6   Studies of paternal lead exposure and childhood cancer

Buckley *et al*. (1989) compared 204 children with acute nonlymphoblastic leukemia (ANLL) with randomly selected age- and gender-matched local population controls in the United States and Canada. During telephone interviews with the parents, a questionnaire on occupational exposures, including lead, was completed. Duration of paternal exposure to lead was categorized as 0, 1 to 1,000, or > 1,000 days. Paternal lead exposure was rare, with 1 to 1,000 days' exposure reported for 5 cases and 5 controls. However, all six paternal exposures of > 1,000 days occurred among cases. Also of interest is the strong association noted for paternal exposure to petroleum products (53 cases vs. 31 controls exposed > 1,000 days, OR = 2.4, 95% CI =1.3 to 4.1); however, TEL exposure was not directly assessed. The small number of paternal lead exposures limited the study's statistical power.

Olshan *et al*. (1990) matched 200 Wilms' tumor cases in children across the U.S. with population controls of the same age and area. Detailed job history data were collected from the fathers of these children via a self-administered questionnaire. A NIOSH job-exposure matrix was used to estimate occupational lead exposure. The results showed little evidence for association of occupational lead exposure with Wilms' tumor, although the OR for paternal lead exposure in the postnatal period was slightly elevated (OR = 1.3, 95% CI = 0.6 to 2.8). These results contradict the significant association with lead exposure reported by Kantor *et al*. (1979). It should be noted that IARC (1990) questioned the exposure assessment methodology used in the Kantor study.

Kristensen and Andersen (1992) traced the cancer incidence in 12,440 offspring of Oslo printers' union members through linkage with the Norwegian Cancer Registry. No elevation in cancer incidence was observed for children of printers as a whole or for those

with parental lead exposure. Because only 33 cancers of all types occurred, the analyses had little power and could not focus on specific rare cancers linked with lead exposure in some earlier studies, such as ANLL or Wilms' tumor (see Table 3-6 for a summary of the studies on childhood cancer and parental lead exposure).

3.3 Summary

The evidence for carcinogenicity is summarized below by cancer type. Where successive studies have been conducted on the same basic population, all studies of a particular cancer in those populations are considered as a whole. This summary also discusses results of meta-analyses by Fu and Boffetta (1995) and Steenland and Boffetta (2000). The studies included in the meta-analyses of Fu and Boffetta (1995) and Steenland and Boffetta (2000) and the cancer sites examined are summarized in Tables 3-2 and 3-3, respectively. It should be noted that Steenland and Boffetta (2000) calculated a fixed-effects rate ratio of 1.04 (95% CI = 1.00 to 1.09) for all cancers combined (N = 1,911) based on eight cohort studies of highly exposed workers. Given the potential site-specificity of lead, as well as other risk factors, however, this summary focuses on evaluating the evidence for the specific cancers that have been most strongly associated with lead exposure in published studies. Potential differences between the carcinogenic potentials of organic and inorganic lead are unclear, as is the possibility of different site-specificity for organic lead compounds. Since it is reasonable to consider the carcinogenicity of exposure to both inorganic and organic lead, studies of TEL workers are considered in this summary.

In addition to studies addressing the association between lead exposure and cancer directly, a number of investigators have assessed the relationship between occupational lead exposure and markers of genotoxicity. Sections 5.4 and 5.5 review the results of these studies in detail. About half of these studies found indications of increased chromosomal aberrations, sister chromatid exchanges, or other genotoxicity end points among lead-exposed workers.

Table 3-2. Studies included in the meta-analysis of Fu and Boffetta (1995).

Study	Study type	Cancer site			
		Lung	Stomach	Kidney	Bladder
Ades and Kazantzis (1988)	Case-control	4			
Bertazzi and Zocchetti (1980)	Cohort	4	4		
Cooper (1989)[a]	Case-control		4		
Cooper and Gaffey (1975)[a]	Cohort	4	4		
Cooper et al. (1985)[a]	Cohort	4	4	4	
Cordioli et al. (1987)	Cohort	4			
Davies (1984b)	Cohort	4			
Fanning (1988)	Case-control	4	4		
Gerhardsson et al. (1986)	Cohort	4	4		
Goldstein et al. (1970)	Cohort	4			
Michaels et al. (1991)	Cohort	4	4		4
Risch et al. (1988)	Case-control				4
Sankila et al. (1990)	Cohort	4	4	4	4
Selevan et al. (1985)[b]	Cohort	4	4	4	4
Sheffet et al. (1982)	Cohort	4	4		
Siemiatycki (1991)	Case-control	4	4	4	4
Steenland et al. (1992)[b]	Cohort	4	4	4	4
Wingren and Axelson (1987)[c]	Case-control	4	4		
Wingren and Axelson (1993)[c]	Case-control		4		
Wingren and Englander (1990)	Cohort	4			

[a]Three papers by Cooper and co-workers were based on the same study population.
[b]Papers by Selevan et al. and Steenland et al. were based on the same study population.
[c]Two papers by Wingren and Axelson were based on the same study population.

Table 3-3. Studies included in the meta-analysis of Steenland and Boffetta (2000).

Study	Cancer site			
	All cancers	Lung	Stomach	Kidney
Anttila *et al.* (1995)	4	4	4	4
Cocco *et al.* (1997)	4	4	4	4
Fanning (1988)	4	4	4	
Gerhardsson *et al.* (1995a)	4	4	4	4
Lundström *et al.* (1997)	4	4	4	4
Steenland *et al.* (1992)	4	4	4	4
Wong and Harris (2000[a])	4	4	4	4
Wong and Harris (2000[b])	4	4	4	4

[a] Battery workers
[b] Smelter workers

3.3.1　Lung and other respiratory cancers and occupational lead exposure

Lung cancer is both the most common type of cancer and the type that has been most studied with respect to lead exposure. Fu and Boffetta (1995) conducted a meta-analysis of 13 cohort and 4 case-control studies of lead exposure and lung cancer. For studies with compatible quantitative risk estimates, a weighted summary risk estimate across all studies was derived. Combining 15 studies (multiple papers based on the same study population were counted as one study), Fu and Boffetta derived a fixed-effects RR for lung cancer of 1.24 (95% CI = 1.16 to 1.33) for lead exposure. Fixed-effects models are based on the assumption of no significant heterogeneity of effect, however, and when this assumption is violated, they may produce invalid estimates of the statistical significance of a summary estimate of effect. To account for heterogeneity, random-effects models add an extra component of variance to the usual variance calculated for the summary relative risk in a fixed-effects analysis. Because of significant heterogeneity across studies of lung cancer, a random-effects RR also was calculated for the 12 studies with the requisite information for this approach, yielding a RR of 1.29 (95% CI = 1.10 to 1.50). A statistically significant association between lung cancer and lead exposure thus appeared when results from the available literature were pooled, and it was similar in magnitude regardless of whether all 15 available studies were included using a fixed effects approach or only the subset of 12 studies meeting the requirements for the more robust summary estimate provided by a random effects approach were included. A separate random-effects estimate also was generated from studies of just the subset of battery and smelter workers, who were considered to have the highest exposure to lead. This analysis yielded a RR for lung cancer of 1.42 (95% CI = 1.05 to 1.92), consistent with the idea that risk should be greatest among the worker populations with the most exposure.

A meta-analysis of eight occupational cohort studies on lung cancer was published in 2000 by Steenland and Boffetta, who argued that the occupational cohort studies

provided the clearest information, because high exposure generally was documented. Studies were limited to those in which lead was established as the predominant exposure, except for one smelter study (Lundström *et al.* 1997) in which arsenic exposure was appreciable and could have confounded the lead effect estimates (see the discussion of Englyst *et al.* 2001). The meta-analysis showed significant heterogeneity due to the relatively high risk estimate from Lundström *et al.* (RR = 2.9, compared with 1.14, 1.22, 1.19, 0.93, 0.82, 1.8, and 1.32 in the other seven studies). Use of a random-effects model to account for this heterogeneity yielded a combined RR across the eight studies of 1.30 (95% CI = 1.15 to 1.46, 675 lung-cancer deaths). Excluding Lundström *et al.* (1997) eliminated the heterogeneity while still yielding a significantly elevated combined RR of 1.14 (95% CI = 1.04 to 1.25) based on a fixed effects model. This parallels the findings of the earlier meta-analysis by Fu and Boffetta (1995) insofar as both random and fixed effects approaches yielded a statistically significant association between lung cancer and lead exposure. It may be argued in this instance that the random effects estimate is more meaningful since it is based on one additional study (Lundström *et al.* 1997) that could not validly be included in deriving the fixed effects estimate. Also of note is that the random effects RR of 1.30 is very similar in magnitude to the RR of 1.29 obtained in the earlier random effects analysis by Fu and Boffetta (1995), which had included a larger number of studies since it did not bar case-control designs. As a counter argument to this, the RR of 2.9 observed in the Lundström *et al.* (1997) study could be viewed as an outlier, in which case the fixed effects estimate based on the subset of 7 studies might better reflect the actual relative risk for cohorts of lead-exposed workers as a whole. For the overview in this background document, Steenland and Simonsen re-examined the Steenland and Boffetta (2000) meta-analysis; however, no occupational studies on lead exposure and lung cancer had been published since that analysis.

This review considers 36 publications of studies addressing occupational lead exposure and lung cancer risk in 21 different populations. Of the 18 populations included in at least one cohort study, elevated risk estimates for lead exposure were reported in 15, with the elevation reaching statistical significance in 8. Only one study reported a reduced risk (Cocco *et al.* 1997), which was not statistically significant. Of the three case-control studies of populations for which no cohort analysis was available, two (Fayerweather *et al.* 1997, Mallin *et al.* 1989) found no association between lead exposure and lung cancer, and one (Siemiatycki *et al.* 1991) found a weak association. The studies reviewed here include two based on TEL workers; one study found evidence of an association with respiratory cancer (Sweeney *et al.* 1986) and the other did not (Fayerweather *et al.* 1997); however, the findings did little to alter the basic thrust of the evidence. Overall, the picture is one of an association between lead exposure and lung cancer.

Characterization of lead exposure for assessment of a potential link between occupational exposure and cancer should be based on the most accurate assessment possible of each individual's exposure. The measures employed in one or more of these studies include biomarkers, ambient air measurements, job histories with or without the use of job exposure matrices, history of employment in a given factory, and simply last known or predominant occupation. In considering the relative strengths and weaknesses of these methods, their influence on the results of particular studies and whether the results vary

systematically with the measure used, this discussion focuses on studies of inorganic lead exposure and on the most recent analysis of each population.

Biomarkers such as blood and urinary lead levels reflect lead that has been absorbed and circulated to tissues, thus eliminating variability in the exposure received from a given ambient lead level due to the effects of individual physiology, protective gear, workstation ventilation, and other factors. However, although biomarkers offer the key advantage of demonstrating whether an individual has absorbed lead and to what degree, blood or urinary lead measurements may fluctuate over time even when actual lead absorption has not changed. Integration of multiple measurements over an individual's employment history reduces this problem.

Three occupational cohort studies (Gerhardsson *et al.* 1995a, Anttila *et al.* 1995, Lundström *et al.* 1997) used extensive blood lead concentration data. Geometric mean blood lead levels among the Swedish smelter workers in Gerhardsson *et al.* and Lundström *et al.* were roughly similar, declining from around 3.0 µmol/L (62.2 µg/dL) at the start to 1.6 µmol/L (33.2 µg/dL) at the end of both studies. Lead levels among the general Finnish worker population studied by Anttila *et al.* were lower, declining from 1.7 (35.2 µg/dL) to 0.7 µmol/L (14.5 µg/dL) over the study period. All three studies noted positive associations with lung cancer; this association was statistically weakest in the Gerhardsson *et al.* study, whose smaller size precluded reliable risk estimates when exposure was categorized beyond whether or not lead ever was detected in a worker's blood.

Dingwall-Fordyce and Lane (1963) and Wong and Harris (2000) assessed urinary lead levels, although only the former based exposure classification on this measure. Nearly half of the U.K. battery workers in the former study had levels exceeding 100 µg/L, consistent with the means of 130 and 170 µg/L observed among U.S. battery and smelter workers, respectively, in the latter study. The SMR for all cancers showed no consistent increase across ascending exposure categories in the U.K. study, which, among the biomarker-based studies, included the smallest number of monitored workers.

In the studies reviewed here, lead exposure most commonly was estimated from job histories. Detailed job histories allow estimation of exposure through application of a job-exposure matrix and/or rating of exposure probability by an industrial hygiene expert. In some studies, job histories were bolstered by ambient air monitoring data (Wingren and Englander 1990, Steenland *et al.* 1992). Other studies simply followed up workers employed in a factory or operation known to have high potential for lead exposure (e.g., the follow-up of lead and zinc pigment plant workers by Sheffet *et al.* [1982]). This approach was modified in one study that followed up pigment-factory workers diagnosed with lead poisoning (Davies 1984b). Use of only a general occupational history, without details regarding specific types of work performed, precludes categorization of workers by risk of exposure within a given occupation. Exposure estimates based on occupation as reported on death certificates can be expected to be the least reliable of the job-history-based methods, being subject to the use of nonstandardized classification criteria by the person entering the occupational data and to the potential for missing previous lead-exposed occupations (Mallin *et al.* 1989; Cocco *et al.* 1998a, 1998b, 1999). Further, one

of these studies (Mallin *et al*. 1989) computed estimates for each of 30 industry and 29 occupation groupings that were not designed specifically to capture lead exposure, and presented no quantitative estimates of risk for groups that did not show a statistically significant association with lung cancer.

The studies reviewed here generally found positive associations, of varying strengths, between lead exposure and risk of cancer; the exception was the one study based on occupation as reported on death certificates (Mallin *et al.* 1989). Studies using blood lead levels consistently observed positive associations between lead and lung cancer, with risk estimates ranging from 1.32 (Gerhardsson *et al.* 1995a) to 2.9 (Lundstrom *et al.* 1997). The study using urinary lead levels yielded no consistent dose-response pattern despite an overall cancer SMR of 1.2 for battery factory workers (Dingwall-Fordyce and Lane 1963). Relative risk estimates from studies using job history in combination with ambient air or other monitoring ranged from 1.1 (Steenland *et al.* 1992) to 1.40 (Wingren and Englander 1990). Use of job histories alone yielded estimates of 0.82 (Cocco *et al.* 1997) to 2.32 (Cocco *et al.* 1994a) from studies that provided quantitative risk estimates. The study relying on death certificate-derived occupation reported no association with lung cancer for metal or glass workers, although no specific risk estimate was provided for those groups (Mallin *et al*. 1989). The most consistent evidence of association thus was seen in studies based on blood lead levels, the most objective measure of exposure, whereas no significant association was seen in the study based on the exposure assessment method with the greatest potential for misclassification, a death-certificate-derived occupational characterization that was not specifically designed to separate lead workers from metal workers in general.

Despite the relatively consistent direction of results across studies, a number of factors complicate drawing of potential causal inferences from the available epidemiologic literature. Foremost among these complications are potential confounding of lead exposure with smoking status, concomitant exposure to other carcinogens and other potential risk factors, and insufficient data for assessment of exposure-response relationships.

The risk of lung cancer due to cigarette smoking dwarfs that which could be expected from lead exposure based on any available evidence. Most studies of lead exposure and lung cancer to date have lacked data on smoking status, and thus their results could be confounded by smoking if lead-exposed groups smoked more than unexposed groups. The potential effect of confounding by smoking depends upon the comparison being made. It has been estimated that the effect of confounding due to smoking in a comparison of lung cancer risk between occupational groups and the general population is likely to be on the order of a 20% increase, that is, enough to generate a relative risk of 1.2 or less (Siemiatycki *et al.* 1988, Axelson and Steenland 1988). However, when the number of persons classified as lead-exposed is small, as in many studies of lead and cancer, most or all of the exposed group could be smokers, resulting in a much greater effect on the relative risk. On the other hand, in studies that controlled for cigarette smoking, the association between lead exposure and lung cancer remained, suggesting that the observed associations between lead exposure and lung cancer across the studies as a whole were not due to confounding by smoking. No other known non-occupational

risk factors for lung cancer are potentially as important as smoking. In studies that have controlled for such factors, they have had little impact on observed association between lead exposure and cancer.

Concomitant exposure to other potential carcinogens is ubiquitous in lead-exposed populations. Improved study designs with better monitoring (e.g., use of biomarker data or detailed personal job history data to facilitate estimation of arsenic exposure) can address this issue to some degree, but ruling out the potential roles of other metals nonetheless remains a difficult problem. This problem was illustrated when part of the Swedish smelter cohort studied by Lundström *et al*. (1997) was reexamined; detailed examination of the job histories of lung cancer patients in one department revealed that 13 of 15 also had been significantly exposed to arsenic (Englyst *et al.* 2001). Estimation of the potential effect of confounding due to other occupational carcinogens thus presents a different situation than that for smoking. Although exposure to arsenic, for example, could not be expected to increase a worker's risk to the degree that heavy smoking does, it is possible that a large proportion of the workers in lead-exposed operations also are significantly exposed to arsenic, whereas such exposure might be much less common in most other operations in the same plant and, unlike smoking, would be relatively rare in the general population of most regions. This could result in lead-exposed workers having an estimated lung cancer risk approaching that of arsenic-exposed workers simply because of confounding by arsenic exposure. In addition, joint confounding by arsenic and other exposures could produce additive or even synergistic effects; such synergy has been proposed, for example, with smoking (Hertz-Picciotto *et al.* 1992).

In a review by Steenland *et al.* (1996), the relative risk of lung cancer was 3.7 for heavily arsenic-exposed workers from six cohorts compared with unexposed workers. Assuming that this risk reflects the effect of substantial exposure to arsenic in combination with smoking and possibly contributions by substances such as cadmium, it appears that confounding by arsenic and/or smoking could theoretically produce risk estimates of the magnitude commonly seen for occupational lead exposure. Countering this is the observation that lead exposure shows an association with lung cancer in many different exposure contexts, including ones with minimal potential for coexposure to arsenic, suggesting that the observed risk is to some degree due to lead exposure itself. A further consideration is the possibility that lead may act synergistically with other occupational carcinogens. Some evidence to support this hypothesis is available from animal studies (e.g., Shakerin *et al.* 1965, Tanner and Lipsky 1984, Hiasa *et al.* 1983; see Section 4.2.5 for details) and *in vitro* experiments with direct-acting genotoxic agents such as radiation (see Section 6.1.3.4). If so, one might expect much or all of any cancer excess resulting from lead exposure to be concentrated among persons co-exposed to other carcinogens, much as Englyst *et al*. (2001) observed with arsenic exposure.

Most studies of lead and cancer to date are limited by small sample size and the lack of good quantitative exposure data, which hinder assessment of exposure-response relationships and the ability to control for other exposures. Where exposure-response assessment was attempted, the strongest association with lung cancer usually was seen in the highest exposure group, but a monotonic increase with duration, intensity, or overall amount of exposure was not always observed. This could reflect the absence of a true

monotonic response, the use of quantitative exposure measures that may not accurately reflect the individual's true exposure, or inadequate adjustment for other risk factors. Here, interpretation again is complicated by the general lack of adequate statistical power to evaluate multiple exposure levels while controlling for smoking, age, gender, and other potential confounders or effect modifiers. Another factor potentially affecting exposure-response analyses is the possibility that workers who experience acute lead toxicity tend to drop out of the exposed worker population. This factor could lead to underestimation of the association between lead and cancer if such an association actually exists but is most pronounced at lead exposures near or above those that cause acute toxic effects. A related concept is that subgroups of the population that are more susceptible to lead-induced carcinogenesis because of metabolic or other differences may likewise be more susceptible to acute toxicity; thus, the higher the exposure level they encounter, the more likely they are to leave employment before the induced cancer occurs. Such a progressively greater loss of the most highly susceptible subpopulations at increasing exposure levels could blunt or distort the exposure-response curve for occupational lead exposure and cancer. The study that followed up a group of workers diagnosed with lead poisoning found an RR of 1.45 for lung cancer among that group, compared with the general population (Davies *et al.* 1984b), which exceeds the summary RRs of 1.14 to 1.30 obtained from meta-analyses of occupation cohorts (Steenland and Boffetta 2000). Nevertheless, the small numbers of lead-poisoned workers (57) and of lung cancers among those workers (4) prevent the difference between their estimated risk and that for exposed cohorts as a whole from approaching statistical significance.

Evidence from the totality of epidemiologic studies is consistent with a mild elevation in risk of lung cancer with lead exposure. In meta-analyses, either broadly inclusive of case-control and cohort studies (Fu and Boffetta 1995) or narrowly focused on studies of populations with the strongest documentation of significant lead exposure (Steenland and Boffetta 2000), the estimated increase in lung-cancer risk associated with lead exposure has reached statistical significance. However, the average magnitude of the increased risk observed across studies is small enough that the hypothesis of no effect cannot be definitively eliminated. It can be argued that given the modest estimated increase in risk, residual confounding due to smoking, exposure to additional occupational carcinogens, or other factors cannot be conclusively ruled out as the source of the elevated risk estimate. However, in the absence of an effect threshold, even a small real elevation of risk due to lead exposure would have a significant impact at the population level, given the ubiquity of low-level lead exposure.

3.3.2   Stomach and general digestive cancer

In their meta-analysis, Fu and Boffetta (1995) combined 10 studies with a quantitative estimate of risk to derive a fixed-effects RR of 1.33 (95% CI = 1.18 to 1.49) for lead exposure and stomach cancer. Because no significant heterogeneity was apparent across studies of stomach cancer, no random-effects RR was calculated. For battery or smelter populations, which were presumed to have the heaviest occupational exposure to lead, an RR of 1.50 (95% CI = 1.23 to 1.83) was obtained.

In their meta-analysis of eight cohort studies of highly exposed workers, Steenland and Boffetta (2000) found that a fixed-effects analysis was justified by the homogeneity of

risk estimates for lead exposure and stomach cancer across the studies (1.13, 1.43, 1.53, 1.33, 1.36, 0.97, 1.07, 1.88). They calculated a fixed-effects combined RR of 1.34 (95% CI = 1.14 to 1.57, N = 181).

This overview considers 21 studies that examined the relationship between lead exposure and stomach cancer or digestive cancer in general.

Seven case-control studies included stomach cancer. One large study focused entirely on stomach cancer (Cocco *et al.* 1999), using the U.S. 24-state death certificate registry and finding positive associations between lead-related occupations and stomach cancer for black men and women and white women, but not white men. A small case-control study of stomach cancer nested in a larger cohort found no association with exposure among battery production workers (Wong and Harris 2000). Five studies included stomach cancer as part of a series of case-control comparisons. Studies of U.K. battery workers (Fanning 1988) and Swedish glass workers (Wingren and Axelson 1993) and a large study of the Montreal population (Siemiatycki *et al.* 1991) found statistically significant elevations in stomach cancer with occupational lead exposure. Studies of Illinois males (Mallin *et al.* 1989) and U.S. TEL workers (Fayerweather *et al.* 1997) did not.

Discounting two small studies of glass workers (Cordioli *et al.* 1987, Wingren and Englander 1990) for inadequate case numbers, twelve cohort studies involving ten distinct populations addressed stomach or digestive cancer and lead exposure. Of the studies of smelter workers, three found positive associations (Steenland *et al.* 1992, Cocco *et al.* 1996, Wong and Harris 2000) and two found negative associations (Cocco *et al.* 1997, Lundström *et al.* 1997). A positive association was noted for U.S. (Sheffet *et al.* 1982) but not for U.K. (Davies 1984a, 1984b) pigment workers. A significantly elevated risk also was observed for a cohort of U.S. battery plant workers, compared with the general U.S. population (Wong and Harris 2000), although the nested study including cases and controls from the largest plant (discussed above) found no evidence of association with lead exposure (Wong and Harris 2000). A nonsignificant increase in stomach cancer risk was observed among Finnish glassblowers (Sankila *et al.* 1990) and Finnish workers with elevated blood lead levels (Anttila *et al.* 1995). No association was noted in Sardinian lead and zinc miners (Cocco *et al.* 1994a, 1994b). Results for stomach cancer thus are not as consistent as those for lung cancer. Interpretation of these results is subject to the same caveats discussed above with respect to lung cancer, and the issue of inadequate statistical power is exacerbated by the relative rarity of stomach cancer.

The strongest potential evidence for a link between lead and cancer would be provided by studies with clearly defined lead-specific exposures, relatively large sample sizes, and ability to evaluate exposure-response relationships. Cocco *et al.*'s (1999) case-control study is by far the largest available, with nearly 42,000 stomach cancer deaths and 84,000 noncancer deaths. It also is one of the few studies to include differing levels of lead exposure (based on death-certificate-listed occupation). Further, it is one of the only studies to adjust for socioeconomic status, which is inversely associated with stomach cancer. Although risks appeared elevated with high exposure among most age-race groups in this study, no elevation was observed for the largest group, white males. Anttila *et al.* (1995) employed blood-based exposure indices, which were used to construct a

large (20,700 worker) population-based cohort. In this study, lead exposure showed a positive, but not statistically significant, association with stomach cancer, with no consistent exposure-response pattern.

Surveying the epidemiologic evidence overall, approximately half of the relevant studies of lead and stomach cancer note a positive association of modest size. The small number of stomach cancers and infrequency of high lead exposure in most studies limited their statistical power; the positive associations observed within particular studies thus usually were not statistically significant. When studies were combined through meta-analysis, however, a statistically significant estimate of increased risk across the pooled study populations was obtained (Fu and Boffetta 1995, Steenland and Boffetta 2000). Evidence of consistent exposure-response patterns is lacking, as most studies have been unable to address this issue because of insufficient numbers and/or lack of detailed exposure data. Most studies did not include the information needed to adjust for socioeconomic status and dietary factors such as nitrosamine exposure, which are potentially significant confounders (nitrosamine exposure, for example, may reflect greater consumption of cured meats by blue-collar workers, who more likely to be lead-exposed, than by white-collar workers, who are less likely to be lead-exposed). Common to all studies of lead exposure is the problem of concomitant exposures to other potential carcinogens such as nickel and chromium, which few studies of stomach cancer have addressed and none has fully resolved.

3.3.3   Kidney cancer

In their meta-analysis of five studies of kidney cancer and lead exposure, Fu and Boffetta (1995) estimated a combined RR of 1.19 (95% CI = 0.96 to 1.48). The RR for heavy exposure rose only slightly, to 1.26 (95% CI = 0.70 to 2.26). They concluded that an effect of lead on kidney cancer risk could not be confirmed or ruled out based on the available evidence.

A meta-analysis of seven occupational cohort studies of lead exposure and kidney cancer was published in 2000 by Steenland and Boffetta. The results of the seven studies were not heterogeneous, and a fixed-effects meta-analysis yielded an RR of 1.01 (95% CI = 0.72 to 1.42) based on only 40 cancer deaths or cases. The RRs in the seven studies were 0.52, 0.93, 1.93, 1.75, 0.90, 0.72, and 0.80. Steenland and Simonsen recomputed this meta-analysis with the addition of the population-based case-control study by Pesch *et al.* (2000). For consistency with the rest of the studies, only workers from the highest category of estimated lead exposure ("substantial exposure" estimated from job exposure matrices) were included. Addition of these workers did not result in sufficient heterogeneity across the eight studies to preclude a fixed-effects analysis. The fixed-effects RR with the addition of 40 kidney cancers from Pesch *et al.* was 1.22 (95% CI = 0.93 to 1.59). It should be cautioned that the Pesch study, a large population-based case-control study, carried enormous weight in the meta-analysis, because it included as many highly exposed cases as the remaining seven studies, all occupational cohorts, combined. Despite the weight carried by this study, the confidence interval for the combined estimated RR again included 1.0.

The incidence of kidney cancer was too low to provide sufficient numbers of cases in most studies of lead exposure. Eight studies reported results for renal cancer. Among three cohort studies of smelter workers, Steenland *et al.* (1992) found a significantly elevated risk based on 8 cancers among the subcohort most heavily exposed to lead. Cocco *et al*. (1997) reported a positive association, but Lundström *et al*. (1997) did not; however, both studies' results were based on too few cases to be reliable. A mixed cohort of battery and smelter workers (Wong and Harris 2000) showed no increase in kidney cancer, but lead and zinc miners did (Cocco *et al.* 1994a), although lead exposure was not directly quantified in the latter group. Exposure to lead was associated with death due to kidney cancer in a case-control study based on the population of Montreal, Canada (Siemiatycki *et al.* 1991) and with incident kidney cancer in a German case-control study (Pesch *et al.* 2000); however, peak blood lead among a cohort of Finnish workers was not associated with increased risk of kidney cancer (Anttila *et al.* 1995). The Canadian results approached statistical significance (OR 1.2, 95% CI = 1.0 to 1.6), and the use of other cancer deaths as a control group may have biased this estimate downward. The German study was based on the highest number of cancers by far, 935, followed by 88 for the Canadian, 10 for the Finnish, and 8 for the lead-exposed smelter-worker study. Thus, of the four studies with more than 5 cases in the exposed group, three observed positive associations. Nevertheless, the German study also found elevated kidney-cancer risks for other exposures, including those to cadmium and solder fume, none of which were controlled for in the risk estimates for lead exposure.

The small number of kidney cancers available in most studies precluded statistically definitive results, clear demonstration of exposure-response relationships, or adjustment for potentially covarying metal or other occupational exposures.

3.3.4   Bladder cancer

In their meta-analysis of five studies on bladder cancer and lead exposure, Fu and Boffetta (1995) estimated a combined RR of 1.41 (95% CI = 1.16 to 1.71). No relative risk for heavy exposure was calculated, because not enough battery or smelter studies included results for bladder cancer. They concluded that while the combined risk estimate for the studies was statistically significant, the small number of studies reporting findings for bladder cancer may have indicated that negative findings were not being published, thus biasing the results toward a positive association.

Seven studies of bladder cancer are included in this overview. All three studies of U.S. smelter workers (Steenland *et al.* 1992), Sardinia (Cocco *et al.* 1997), and Sweden (Lundström *et al.* 1997) reported positive associations with lead exposure. Risk estimates ranged from 1.3 to 1.8, and deaths among the exposed from 6 to 12; no elevated risks were statistically significant, and no consistent exposure-response pattern was noted. Elevated risk of bladder cancer (SMR = 1.15) also was seen among lead and zinc miners (Cocco *et al.* 1994a). A borderline significant elevation (OR = 1.3, 95% CI = 1.0 to 1.6) was observed among French Canadians in a population-based Montreal case-control study, though the OR did not increase among those thought to have the most substantial exposure (Siemiatycki *et al.* 1991). A stronger association (OR = 2.0, 95% CI = 1.2 to 3.5) was noted in a second Canadian case-control study (Risch *et al.* 1988), including a significant trend with duration of exposure, and this study was able to adjust for smoking,

socieconomic status, and other personal risk factors. The lone exception to the pattern was provided by the lack of association of bladder cancer with peak blood lead measurements in a general cohort of Finnish workers (Anttila *et al.* 1995).

A positive association of lead exposure with bladder cancer thus was very consistent in studies published to date. It persisted when smoking was controlled for, and limited direct evidence was found for an exposure-response relationship, as well as indirect evidence of consistently elevated risks among smelter workers, with their potential for intense lead exposure. On the other hand, as suggested by Fu and Boffetta (1995), publication bias cannot be eliminated as a contributor to the preponderance of positive results. Further limiting the conclusiveness of the evidence is the limited size and low statistical power of most studies.

3.3.5   Childhood cancers

Five studies have examined the relationship of paternal lead exposure to childhood cancer. Three case-control studies focused on Wilms' tumor. The earliest of these studies (Kantor *et al.* 1979) reported a markedly elevated OR among children with fathers in lead-related industries. Two subsequent studies failed to replicate this finding (Wilkins and Sinks 1984a, 1984b, Olshan *et al.* 1990). IARC (1990) questioned the criteria used by Kantor *et al.* (1979) to assign lead exposure status to the paternal occupation listed on the childrens' death certificates. Olshan *et al.* (1990) obtained detailed job histories via questionnaire and assigned lead exposure status from a standard exposure matrix. Faulty exposure classification or a chance finding stemming from examination of multiple exposures in a small study may account for the discrepancy.

Buckley *et al.* (1989) linked fathers' occupational lead exposure of long duration to childhood nonlymphoblastic leukemia in a study of 204 cases and matched population controls. The association was striking, with 6 leukemia patients and no control subjects having exposed fathers. However, the statistical strength of these results is limited by the small number of paternal exposures.

A large cohort study of children of printers yielded an inconsistent association between estimated paternal lead exposure and development of cancer (Kristensen and Andersen 1992). The study was limited by the small number of casees, which made it necessary to combine all types of cancer, and by the absence of control for other potential risk factors.

Overall, the literature to date is characterized by a scarcity of studies and by small sample sizes, hampering the ability to draw firm conclusions from the available data (see Table 3-6).

3.3.6   Other adult cancers

Other cancers with some evidence linking them to lead exposure in the reviewed literature include cancers of the brain and central nervous system, liver, colon, and rectum.

Positive results were most common for brain and central nervous system cancers, with eight studies reporting evidence of an association with lead exposure. Based on seven

cohort studies of highly exposed workers, Steenland and Boffetta (2000) calculated a fixed-effects combined RR of 1.06 (95% CI = 0.81 to 1.40) for brain cancer (N = 69). A fixed-effects analysis was justified by the relative homogeneity of risk estimates across the seven studies (0.75, 0.75, 2.17, 1.10, 0.72, 1.14, 1.48, 1.23), taking into account their small sample sizes and wide confidence intervals. No additional relevant studies have become available since that meta-analysis was conducted. The positive associations observed in most studies is suggestive, although it is notable that a meta-analysis restricted to the cohorts with the most definitive lead exposure produced a nonsignificant risk estimate barely above 1.0. The fundamental problem is that the rarity of these cancers generally limits the statistical power of studies.

3.3.7   General population exposures and cancer

The population-based cohort studies of Jemal *et al*. (2002) and Lustberg *et al*. (2002) are a unique resource. The first study's findings are provocative in that they connect increased blood lead levels in the general U.S. population with mild elevations in risk of the same types of cancer, lung and stomach, most consistently associated with lead-exposed occupations. As discussed in Section 3.3.1, Steenland and Simonsen concluded that no relevant occupational studies of lead and lung cancer had been published since the Steenland and Boffetta (2000) meta-analysis. The only subsequent study involving populations with clearly established lead exposure was Jemal *et al.* (2002). With that study added to the meta-analysis, the data no longer exhibited sufficient heterogeneity to preclude a fixed-effects analysis even with Lundström *et al.* (1997) included. The expanded meta-analysis yielded a fixed-effects RR for lung cancer of 1.32 (95% CI = 1.16 to 1.50) over the nine cohorts, very similar to the random-effects RR obtained without Jemal *et al*. (2002). Inclusion of Jemal *et al.* (2002) must be accompanied by the caveat that the magnitude of lead exposure in the population-based cohort (whose exposure was defined as blood lead levels above the median observed in the general population) was not truly comparable to that expected in workers with substantial lead exposure. This cohort was not added to the revised meta-analysis for kidney cancer described in Section 3.3.3 because of inadequate numbers (only 5 cases in males) and the low exposure cutoff. Interpretation of the results of Jemal *et al.* (2002) is limited primarily by low statistical power, particularly for sites other than the lung, lack of adjustment for other risk factors (such as smoking) in the site-specific analyses, and the absence of data on exposure to other occupational carcinogens.

Lustberg *et al.* (2002) analyzed predominantly the same data as Jemal *et al*. (2002), using different techniques and analytical assumptions, yet reaching conclusions also linking cancer to lead exposure. Further, unlike Jemal *et al.*, Lustberg *et al.* limited the cohort to persons with blood lead levels below the OSHA standard for lead exposure. However, exclusion of persons with blood lead levels in the range typical of workers considered to be lead-exposed precluded inclusion of this study in the revised meta-analysis by Steenland and Simonsen. In considering the evidence provided by Lustberg *et al.* that lead could exert effects even at levels commonly found in the general population, it must be kept in mind that this study shares the limitations cited above for Jemal *et al.* (2002).

The case-control studies of Kandiloris *et al*. (1997) and Shukla *et al*. (1998) reported evidence mildly linking lead exposure with cancers of the larynx and gall bladder. These

studies' small sample sizes and lack of control for other potential risk factors limit the conclusions that can be drawn from them.

3.4   Conclusion

Many epidemiologic studies on the potential role of lead exposure in cancer have been published since the IARC (1987) update. The evidence is consistent with the hypothesis that lead is modestly carcinogenic to humans. This evidence is strongest for lung cancer, for which a largely consistent association has been demonstrated with occupations and industries entailing lead exposure, as well as with indices of individual lead exposure, including job history and biological monitoring. Evidence also suggests an association between lead and stomach cancer. However, the observed associations generally are sufficiently weak that they could be due at least partially to confounding by non-occupational risk factors, such as smoking in the case of lung cancer, or to effects of other occupational exposures that accompany lead exposure, particularly arsenic exposure. Such exposures are ubiquitous in smelting operations, battery manufacture, and other intense sources of lead exposure. Most studies to date have done little to control for non-occupational risk factors and occupational co-exposures, but more studies are beginning to do so, in most cases without weakening the observed association between lead exposure and cancer. Further, the crude exposure measures used by most studies, such as considering whole plants or occupations to be uniformly exposed, may have resulted in underestimation of risk, because individuals who truly had high lead exposure may have been combined with those who did not. Evidence from studies of human populations thus are compatible with mild increases in risk for lung cancer and, to a lesser degree, stomach cancer, although this evidence must be weighed against the potential for confounding by co-exposures.

Table 3-4. Studies of lead exposure and cancer: cohort

Reference	Study population	Exposure	Effects	Comments
Dingwall-Fordyce and Lane 1963	425 male employees drawing pensions from U.K. battery plants	Employees were compared with national population counterparts. Urinary lead excretion was also used to categorize workers by estimated exposure (none, light, or heavy): 80 lightly and 187 heavily (at least 100 µg/L) exposed.	SMR (95% CI); no. observed deaths *All cancer*: 1.2 (0.8–1.7); 267 no consistent increase in SMRs across categories of increasing lead exposure	*Potential confounders:* smoking, exposure to arsenic, other metals *Other limitations:* not cancer site-specific
Cooper and Gaffey 1975: see Cooper *et al.* 1985				

Reference	Study population	Exposure	Effects	Comments

Rencher *et al.* 1977	Utah copper workers (numbers not reported) employed in smelting, mining, or concentrator operations, followed from 1959–1969
	
	Mortality was compared with the state population and with workers in other operations.
	
	Cause of death was identified from death certificate.
		Exposure to lead, arsenic, amd other substances was estimated by operation type.
		
		Within smelter workers, cumulative exposure to lead (units not specified) was calculated for deceased workers.
			Age-adjusted respiratory cancer rates (per 10,000):
			
			  smelter workers 10.1
			
			  mine workers 2.1
			
			  state population 3.3
			
			Age-adjusted non-respiratory cancer rates (per 10,000):
			
			  smelter workers 16.6
			
			  mine workers 10.0
			
			Percentage of deaths from lung cancer:
			
			  smelter workers 7
			
			  mine workers 2.2
			
			Cumulative lead and arsenic exposure:
			
			  17 smelter workers dying of respiratory cancer 154.5 (Pb) 110 (As)
			
			  smelter workers dying of other respiratory causes 78.6 (Pb) 38.5 (As)
			
			  smelter workers dying of non-respiratory causes 93.4 (Pb) 47.0 (As)
				Potential confounders:
				
				arsenic, sulfur dioxide, sulfuric acid, other exposures, smoking

Reference	Study population	Exposure	Effects	Comments
Bertazzi and Zocchetti 1980	700 Italian newspaper plant workers employed for at least 5 years between 1940 and 1955 Mortality was compared with national rates.	Compositors and stereotypers were considered to be exposed to lead.	SMR (no. of deaths) *Lead-exposed workers:* all cancers 0.44 (4) digestive 0.59 (2) respiratory 0.42 (1) lymphatic 2.00 (1) no *P*-values < 0.05 *All newspaper workers:* all cancers 1.23 (51) digestive 1.20 (19) respiratory 1.56 (17) lymphatic 1.17 (3) no *P*-values < 0.05	*Potential confounders:* smoking, other occupational exposures *Other limitations:* scarcity of truly lead-exposed workers, small number of deaths
Sheffet *et al.* 1982	1,946 U.S. lead and zinc chromate pigment plant workers employed at any time from 1940–1969 Mortality was compared with age and calendar-year-specific national rates.	All workers were considered to be exposed to lead.	Lung, stomach, and pancreatic cancer risks significantly elevated (persons of unknown vital status assumed to be alive at end of follow-up) *Lung cancer SMR:* 1.6 (whites, blacks; *P* < 0.05 in whites only) *Whites:* nonsignificantly elevated risks for stomach, rectal, pancreatic, and prostate cancer, Hodgkin's disease; decreased risks of intestinal and laryngeal cancer *Nonwhites:* mildly elevated risks of stomach and pancreatic cancer; decreased risk of laryngeal cancer	*Potential confounders:* smoking, zinc, nickel, other occupational exposures

Reference	Study population	Exposure	Effects	Comments
Malcolm and Barnett 1982 (follow-up of Dingwall-Fordyce and Lane 1963)	1,898 U.K. lead-acid battery workers	High, medium, and no lead exposure were based on job history.	Proportionate mortality ratio (PMR) *All cancers:* 1.15 (136 deaths), $P > 0.05$ By exposure: no 1.02 medium 1.06 high 1.30 no significant excesses for individual cancer sites except for digestive cancer PMR of 1.67, $P < 0.01$, among non-exposed workers	*Potential confounders:* smoking, other occupational exposures *Other limitations:* difference in exposure for high vs. medium negligible by end of follow-up
Davies 1984a	1,152 U.K. chromate pigment factory workers employed for at least one year by 1975 Three factories: one lead chromate only, two lead and zinc chromate Mortality was compared with national rates.	High to moderate exposure to chromate dust was based on job history.	RR (no. of deaths) significant excess of lung cancer deaths among chromate-exposed workers with mixed zinc and lead chromate exposure: *Factory A:* entrants from 1932–1954 2.2 (21) no excess for entrants after 1955 *Factory B:* entrants from 1948–1960 4.4 (11) no excess among workers exposed only to lead chromate; no consistent increase with duration of service	*Potential confounders:* smoking, co-exposures (solvents, etc.) *Other limitations:* small numbers

Reference	Study population	Exposure	Effects	Comments

Davies 1984b (follow-up of Davies 1984a)	57 U.K. chromate pigment factory workers who had been diagnosed with lead poisoning between 1930 and 1945
	
	Mortality was compared with national rates.
		Workers ever clinically diagnosed with lead poisoning were considered to be exposed to lead.	RR (95% CI); no. of deaths
			Lung cancer:
			  1.45 (0.39–2.71) (4)
			All other cancers combined:
			  0.8 (3)
				Potential confounders:
				zinc, chromate, other occupational coexposures, smoking
				Other limitations:
				inadequate numbers

Cooper *et al.* 1985 (follow-up of Cooper and Gaffey 1975) (followed up by Wong and Harris 2000) (see also nested case-controls by Cooper *et al.* 1989 and Wong and Harris 2000)	U.S. battery (4,519) and lead production (2,300) workers employed for at least one year between 1946 and 1970
	
	Mortality was compared with national age- and gender-specific rates (SMR) and age-, gender-, and race-specific rates (PMR)
	
	Cause of death was identified from death certificate.
		(1) battery plant workers
		(2) lead production workers
		
		Workers also were stratified by cumulative years of employment (1–9, 10–19, 20+)
			SMR (95% CI)
			Battery plant workers:
			  all cancer 1.13 (1.02–1.26)
			  all respiratory 1.24 (1.03–1.49)
			  stomach 1.68 (1.16–2.35)
			  lung, trachea, bronchus
			            1.24 (1.02–1.50)
			  liver and laryngeal: nonsignificant excess
			  kidney: nonsignificant deficit
			Production workers:
			  digestive and respiratory: nonsignificant increase
			  kidney, brain, or lymphopoietic system: no excess
			PMR analyses controlled for race yielded similar results.
				Potential confounders:
				smoking, diet, coexposures

Selevan *et al.* 1985: see Steenland *et al.* 1992				

Reference	Study population	Exposure	Effects	Comments
Gerhardsson *et al.* 1986: see Gerhardsson *et al.* 1995				

Sweeney *et al.* 1986	2,510 male east Texas chemical plant workers employed 1952–1959
	
	Mortality compared with national rates.
		TEL was the major product from 1952–1959; thereafter, ethylene dibromide, inorganic lead, and vinyl chloride also were major products.	RR (observed vs. expected)
			Respiratory:
			  1.4 (15 vs. 11)
			Brain:
			  1.8 (3 vs. 1.6)
			Mortality from all causes:
			  0.8
			no excesses for other cancers
				Potential confounders:
				other occupational exposures
				Other limitations:
				small numbers, no detailed exposure data, healthy-worker effect

Cordioli *et al.* 1987	468 Italian glass workers employed for at least one year between 1953 and 1967	Workers producing low-quality glass containers were classified as lead-exposed.	SMR (95% CI); no. of deaths All cancer 1.3 (0.8–1.8); 28 Lung 2.1 (1.1–3.6); 13 Laryngeal 4.5 (1.2–11.4); 4	*Potential confounders:* smoking, exposure to arsenic and other metals, heat, and fumes

Reference	Study population	Exposure	Effects	Comments

Ades and Kazantzis 1988	4,393 male U.K. zinc, lead, and cadmium smelter workers followed up for lung cancer mortality
	
	Mortality was compared with national rates.
	
	Nested case-control analysis also was conducted that quantitatively assessed cadmium and, secondarily, arsenic, lead, and other metal exposures among 174 cases.
		Job histories were used to quantify cadmium exposure and assign ordinal ranks for exposure to lead and other metals.	SMR (95% CI); no. of deaths
			Cohort:
			   Lung 1.25 (1.07–1.44) (174)
			   increased significantly with duration of employment
			
			nested case-control analyses did not implicate any department or process, nor did cadmium, zinc, sulfur dioxide, or dust exposure account for the observed increase
			
			cumulative exposure to lead and to arsenic both showed positive associations with lung cancer, but the relative importance of these two exposures could not be determined
				Potential confounders:
				
				smoking, arsenic, other unquantified contaminants

Sankila *et al.* 1990	1,803 male and 1,946 female glass workers employed for at least 3 months at one of 2 Finnish glass factories in 1953–1971 or 1941–1977
	
	Cancer incidence was compared with age-, gender-, and calendar-year-specific national rates.
		Stomach, lung, and skin cancer rates also were compared separately for 201 male and 34 female glassblowers and non-glassblowers.	SIR (95% CI); no. of cases
			Lung cancer, all glass workers:
			   male 1.3 (1.0–1.7); 62
			   female 1.1 (0.5–2.3); 7
			lung cancer risk showed no specificity for glassblowers
			Skin cancer, M & F combined:
			   all workers 1.5 (0.8–2.7); 11
			   little difference between genders
			   glassblowers 6.2 (1.3–18.3); 3
			Stomach cancer, M & F combined:
			   glassblowers 2.3 (0.9–5.0); 6
			   no increase in other glass workers
			no increase in cancers of other sites
				Potential confounders:
				
				smoking, arsenic, cadmium, chromium, copper, nickel, zinc, silica, asbestos

Reference	Study population	Exposure	Effects	Comments
Wingren and Englander 1990 (same population as in case-control analyses of Wingren and Axelson 1985, 1987, 1993)	625 Swedish glass workers employed for at least 1 month between 1964 and 1985 Mortality was compared with national rates.	Workers from areas with airborne lead levels up to 0.110 mg Pb/m^3 were classified as exposed.	SMR (95% CI) *Pharyngeal:* 9.9 (1.2–36.1) *Lung:* 1.4 (0.5–3.1) *Colon*: nonsignificant	*Potential confounders:* coexposures, smoking, diet *Other limitations:* small numbers
Steenland *et al.* 1992 (follow-up of Selevan *et al.* 1985)	1,990 male workers employed for at least 1 year in a lead-exposed department at a U.S. lead smelter in Idaho during 1940–1965	High-lead-exposure subgroup consisted of 1,436 workers from departments with an average of least 0.2 mg/m^3 airborne lead or $\geq$ 50% of jobs showing 0.40 mg/m^3 or greater in a 1975 survey.	SMR (95% CI); no. of deaths *Total cohort:* nonsignificantly elevated RRs: kidney, bladder, stomach, and lung cancer *High-lead-exposure subgroup:* kidney 2.39 (1.03–4.71); 8 bladder 1.33 (0.48–2.90); 6 stomach 1.28 (0.61–2.34); 10 lung 1.11 (0.82–1.47); 49	*Potential confounders:* smoking, co-exposures, diet
Cocco *et al.* 1994a (expansion of Carta *et al.* 1994)	1,741 male Sardinian lead and zinc miners from two mines employed at least one year between 1931 and 1971 Mortality was compared with age- and calendar-year-specific regional rates	All miners were considered to be exposed to lead.	SMR (95% CI); no. of deaths all cancer 0.94 (0.83–1.05); 293 prostate 1.21; 16 bladder 1.15; 17 kidney 1.28; 7 nervous system 1.17; 8 oral 0.61; 8 lymphohemopoietic 0.91; 21 digestive 0.83; 86 peritoneum 3.67 (1.35–7.98); 6 no other *P*-values < 0.05	*Potential confounders:* silica, radon, other co-exposures, smoking, diet

Reference	Study population	Exposure	Effects	Comments
Cocco *et al.* 1994b	526 female Sardinian lead and zinc miners from the same mines as in Cocco *et al.* 1994a Mortality was compared with age- and calendar-year-specific regional rates	All miners were considered to be exposed to lead.	SMR (95% CI) liver　　　5.02 (1.62–11.70) lung　　　2.32 (0.85–5.05) other cancers showed nonsignificantly reduced rates	*Potential confounders:* coexposures *Other limitations:* small numbers
Gerhardsson *et al.* 1995a (follow-up of Gerhardsson *et al.* 1986)	684 male Swedish lead smelter workers with lead exposure, followed from 1969–1989 Incidence was compared with county rates.	Lead exposure was defined as a detectable blood lead level.	SIR (95% CI); no. of cases *All malignancies:* 　1.27 (0.91–1.74); 40 *Respiratory:* 　1.32 (0.49–2.88); 6 *All gastrointestinal:* 　cohort　　　　　　1.84 (0.92–3.29; 11 　highest quartile　　2.34 (1.07–4.45); 9 *Stomach:* 　1.88 (0.39–5.50); 3 *Colon:* 　1.46 (0.30–4.28); 3 SIRs for all other sites except brain were nonsignificantly elevated; too few cases	*Potential confounders:* smoking, diet *Other limitations:* small numbers, meaningful dose-response analyses not possible because of inadequate numbers for most cancer sites

Reference	Study population	Exposure	Effects	Comments

Anttila *et al.* 1995	20,700 Finnish workers with at least one blood lead measurement between 1973 and 1983 by the Finnish Institute of Occupational Health, linked to the Finnish Cancer Registry through 1988. No loss to follow-up.
	
	Cause of death was identified from death certificate.
	
	Mortality and incidence compared with gender-, 5-year age, and 4-year calendar-year matched national rates.
		Exposure was categorized according to the highest peak blood level measured:
		
		low: 0–0.9 µmol/L [0 to 18.6 µg/dL]
		
		moderate: 1–1.9 µmol/L [20.7 to 39.4 µg/dL]
		
		high: 2–7.8 µmol/L [41.4 to 161.6 µg/dL]
			Total cohort:
			  no elevation in total or site-specific cancer mortality
			
			Moderately exposed:
			  total respiratory and lung cancer: SIR = 1.4 (95% CI = 1.0–1.9) for both
			  total digestive, stomach, bladder, and nervous system: nonsignificant elevations
			
			Highly exposed:
			  no increase in risks
			
			All cancer:
			  RR = 1.4 (95% CI = 1.1–1.8)
			
			Lung or tracheal:
			  RR = 2.0 (95% CI = 1.2–3.2) no increase in high-exposure group
			
			no RRs reported for other cancers
			
			Case-referent substudies:
			  lung cancer ORs increased with increasing cumulative exposure to lead
			
			  highly exposed: squamous-cell lung cancer OR = 4.1 (95% CI = 1.1–15) after adjustment for smoking
				Potential confounders:
				coexposures
				
				Other limitations:
				short follow-up

Reference	Study population	Exposure	Effects	Comments
Cocco *et al.* 1996	1,222 male Sardinian lead and zinc smelter workers whose G6PD phenotypes had been determined, employed any time from 1973–1990 Mortality was compared with regional rates.	Workers were subdivided into G6PD-normal and -deficient groups.	SMR (no. of deaths) all cancer and lung cancer: lower than expected stomach cancer: higher (2 observed vs. 0.6 expected) G6PD-normal 0.26 (10) G6PD-deficient 0.18 (2) G6PD deficiency had little apparent effect on mortality: cancer and all-cause mortality was slightly lower among G6PD-deficient workers than among G6PD-normal workers	*Potential confounders:* co-exposures, smoking *Other limitations:* healthy worker bias (all-cause mortality 31 observed vs. 44 expected), brief follow-up, low proportion of older ages (mean age at entry 30, average follow-up less than 11 years), no cumulative exposure data
Cocco *et al.* 1997	1,388 male production and maintainance workers employed for at least 1 year at a Sardinian lead and zinc smelter between June of 1932 and July of 1971. Mortality was compared with age- and calendar-year-specific regional rates. National rates could not be used for comparison, because the regional population showed large departures from them, limiting the analysis to the period from 1965–1992 for which regional rates were available, instead of the entire 1950–1992 follow-up period.	All workers were considered to be exposed to lead.	SMRs vs. regional rates (95% CI); no. of deaths lung 0.82 (95% CI 0.56–1.16); 31 stomach 0.97 (0.53–1.62); 14 all cancers 0.93 (0.78–1.10); 132 kidney 1.75 (0.48–4.49); 4 bladder 1.45 (0.75–2.53); 12 brain 2.17 (0.57–5.57); 4 kidney cancer showed a significant trend toward increasing risk with increasing duration of exposure no significant trends were noted for lung or other cancers brain cancer excess was limited to workers employed for 10 years or less	*Potential confounders:* exposure in other jobs (e.g., silica from neighboring lead and zinc mine), smoking, co-exposure to zinc, arsenic, copper, other metals, silica *Other limitations:* no intensity of exposure, possible misclassification of cause on death certificates

Reference	Study population	Exposure	Effects	Comments
Lundström *et al.* 1997 (follow-up of Gerhardsson *et al.* 1986) (see also subcohort analyses of Englyst *et al.* 2001)	3,979 Swedish copper and lead smelter workers, subdivided into 1,992 belonging to departments exposed to lead only and 1,026 with high cumulative exposure Mortality and incidence compared with age-, year-, gender-, and county-specific rates	The lead-only group consisted of workers in lead-only departments; the high cumulative exposure group consisted of workers with blood lead levels ≥ 10 μmol/L [≥ 207 μg/dL], based on summing mean blood lead monitoring results for each year exposed.	SMR (95% CI); no. of deaths *Lung:* 　total cohort　　2.8 (2.0–3.8); 39 　highly exposed　2.8 (1.8–4.5); 19 SIR (95% CI); no. of cases *Lung with 15-year lag:* 　total cohort　　2.9 (2.1–4.0); 42 　highly exposed　3.4 (2.2.–5.2); 23 　lead-only　　　3.1 (1.7–5.2); 14 　lead-only highly exposed 5.1 (2.0–10.5); 7 *Other highly exposed (total cohort), with 15-year lag:* 　brain　　　　　1.6 (0.4–4.2); 4 　renal pelvis, ureter, bladder 1.8 (0.8–3.4); 9 　kidney　　　　0.9 (0.2–2.5); 3 　all cancer　　　1.1 (0.9–1.4); 83	*Potential confounders:* smoking, diet

Reference	Study population	Exposure	Effects	Comments
Wong and Harris 2000 (follow-up of Cooper *et al.* 1985)	U.S. lead battery plant (4,518) and smelter (2,300) workers followed from 1947 through 1995 follow-up of Cooper *et al.* 1985 with more detailed exposure data and nested case-control component for stomach cancer Mortality was compared with U.S. national age-, calendar-year-, and gender-specific rates. Cause of death was identified from death certificates (See entry under case-control studies for nested study of stomach cancer.)	(1) battery plant workers (2) lead smelter workers Workers also were stratified by cumulative years of employment (1–9, 10–19, 20+), date of hire (pre-1946 vs. 1946 on), and lag between exposure and cancer (< 20, 20–34, > 34 years).	SMR (95% CI) *Battery plant workers:* all cancer 1.05 (0.97–1.13) all respiratory 1.13 (0.98–1.29) stomach 1.53 (1.12–2.05), significant lung, trachea, bronchus 1.14 (0.99–1.30) thyroid, Hodgkin's: nonsignficant bladder 0.49 (0.23–0.90), significant depression *Smelter workers:* digestive, respiratory, thyroid: nonsignificant lung 1.22 (1.00–1.47) *Battery plant and smelter workers combined:* all cancer 1.04 (0.97–1.11) all respiratory 1.15 (1.03–1.28) stomach 1.47 (1.13–1.90) lung, trachea, bronchus 1.16 (1.04–1.30) thyroid/endocrine 3.08 (1.33–6.07), lung and stomach risks lower for pre-1946 hires; higher for workers employed 10–19 years than < 10, but lower for > 19 years; SMRs peaked with 20- to 34-year latency for lung, but < 20 years for stomach	*Potential confounders:* smoking, diet, coexposures *Other limitations:* no assessment of employment history after 1981

Reference	Study population	Exposure	Effects	Comments
Englyst *et al.* 2001 (follow-up and sub-analysis of Lundström *et al.* 1997)	Limited to 1,093 workers in the smelter's lead department, followed through 1997 Incidence was compared with county rates; age-specific SIRs with 15-year lag.	Workers were divided into Subcohorts I and II for ever and never worked in areas generally associated with exposure to arsenic or other known carcinogens (701 and 383 workers, respectively). Detailed individual assessment of arsenic exposure was made for all lung-cancer cases.	SIR (95% CI); no. of cases *Subcohort I (co-exposed):* lung 2.4 (1.2–4.5); 10 *Subcohort II (not co-exposed):* lung 3.6 (1.2–8.3); 5 subjects with lung cancer found to have history of "considerable" exposure to arsenic: 9/10 among Subcohort I, 4/5 among Subcohort II	*Potential confounders:* smoking, diet
Jemal *et al.* 2002 (same cohort as in Lustberg and Silbergeld 2002 except for inclusion criteria)	3,592 U.S. white participants from the 1976–1980 NHANES II health and nutrition survey who had blood lead measured at entry, followed through 1992 via NDI and SSADMF RRs were adjusted for age and smoking.	Blood lead (μg/dL) was measured by atomic absorption and used to classify subjects into exposure quartiles or groups above vs. below median exposure.	RR (95% CI); no. of deaths *Lung (above vs. below median):* Total cohort 1.5 (0.7–2.9); 71 M 1.2 (0.6–2.5); 52 F 2.5 (0.7–8.4); 19 *Stomach (above vs. below median):* Total cohort 2.4 (0.3–19.1); 5 M 3.1 (0.3–37.4); 4 F no deaths in referent group *All cancer:* total cohort by quartile (age-adjusted) 1.0, 1.2, 1.3, 1.5 (*P* for trend 0.16)	*Potential confounders:* occupational exposure, socioeconomic status, potential residual confounding by degree and duration of smoking (only controlled for never, former, current < 1, current 1+ pack/day)

Reference	Study population	Exposure	Effects	Comments

Lustberg and Silbergeld 2002
 	
(same cohort as Jemal *et al.* 2002 except for inclusion criteria)
	4,190 U.S. participants from the 1976–1980 NHANES II health and nutrition survey who had blood lead measured at entry and whose levels fell below 30 μg/dL. Followed up through 1992 via NDI and SSADMF.
	
	Age- and multivariate-adjusted relative risk.
		Blood lead (μg/dL) measured by atomic absorption and used to classify subjects into exposure groups:
		
		low: < 10
		
		medium: 10-19
		
		high: 20–19
			RR (95% CI)
			
			All cancer, vs. low exposure:
			    medium 1.5 (0.9–2.5)
			    high 1.7 (1.0–2.8)
			Lung, vs. low exposure:
			    medium 1.7 (0.6–4.8)
			    high 2.2 (0.8–6.1)
			Non-lung, vs. low exposure:
			    medium 1.5 (0.8–2.8)
			    high 1.5 (0.8–2.8)
				Potential confounders:
				
				potential residual confounding by degree and duration of smoking (only controlled for never, former, current < 1, current 1+ pack/day)
				
				Other limitations:
				
				small numbers for non-lung cancers.

Table 3-5. Studies of lead exposure and cancer: case-control

Reference	Study population	Exposure	Effects	Comments
Robinson 1976	*Cases:* 139 U.S. TEL workers with 20 or more years in exposed jobs *Controls:* 139 workers with no known occupational lead exposure, matched by age, gender, race, and years of employment	Workers were classified as TEL-exposed if they worked in exposed jobs for at least 20 years.	*Skin cancer:* 7 in lead-exposed, 4 in nonexposed group no cancers of other sites in either group	*Limitations:* inadequate size
Fanning 1988 (Cases overlap those occurring in the Dingwall-Fordyce 1963 and Malcolm 1982 cohorts)	*Cases:* 2,073 deceased males identified through pension records of battery and other factory workers in the U.K. *Controls:* workers dying from a specific cancer were compared with a control group consisting of workers dying from all other causes	High or moderate lead exposure vs. little or no exposure was based on job titles.	OR (95% CI) 76 lung cancer deaths 0.93 (0.8–1.1) 31 stomach cancer deaths 1.34 (1.10–1.17) no associations for other cancer types; elevations in stomach and total digestive cancers limited to the period before 1966	*Potential confounders:* metals and other occupational exposures, smoking *Other limitations:* potentially exposure-related deaths among controls

Risch *et al.* 1988	*Cases:* 826 Canadian men with histologically confirmed bladder cancer during 1979–1982
	
	Controls: 792 controls from Canadian population, matched on age, gender, and area
		Subjects were interviewed regarding length of occupational exposure to lead compounds, as well as 17 other substances.	OR (95% CI)
			
			61 men ever exposed to lead (smoking-adjusted):
			    2.0 (1.2–3.5)
			
			Trend per 10 years' duration of exposure:
			    1.45 (1.09–2.02)
			
			no other substances showed significant associations with bladder cancer
			
			adjustment for marital status, socioeconomic status, education, ethnicity, urban vs. rural origin had no effect on results
				Potential confounders:
				
				other occupational exposure
				
				Other limitations:
				
				low control interview rate (53%), potentially inaccurate recall

Reference	Study population	Exposure	Effects	Comments
Cooper *et al.* 1989 (based on cohort in Cooper *et al.* 1985) (succeeded by Wong and Harris 2000)	*Cases:* 39 male gastric cancer deaths from a Scandanavian battery and lead production worker cohort *Controls:* 120 controls from the same cohort	Exposure was categorized by duration of employment, in quartiles.	OR Second quartile vs. first: 0.3 Third quartile vs. first: 1.7 Fourth quartile vs. first: 0.4 increasing lead exposure showed no association with gastric cancer	*Potential confounders:* co-exposures, diet, socioeconomic status *Other limitations:* inadequate size
Mallin *et al.* 1989	*Cases:* random sample of 10,013 deaths from 7 specific cancers, identified from death certificates for Illinois males between 1979 and 1984 *Controls:* 3,198 randomly selected deaths from other causes	Exposure was based on ccupations abstracted from death certificates.	*Brain cancer, white male glass workers:* OR = 3.0, *P* < 0.05 no significant associations for other cancer sites	*Potential confounders:* no control for other factors *Other limitations:* poor specificity for lead exposure

Siemiatycki *et al.* 1991	*Cases:* 3,730 various histologically confirmed cancers
	 Controls: specific cancer types were compared with other cancers as a control group, excluding lung cancer
	 Separate subgroup analysis was restricted to French Canadians
		Occupational exposure to 293 substances, including lead, was estimated from interviews.
		 Exposure was classified as "any"; a subgroup with "substantial" exposure also was identified.
			<u>OR (90% CI); no. of cases</u>
			 Any exposure to lead:
			    lung 1.1 (0.9–1.4); 326
			    (French Canadians only)
			    stomach 1.2 (1.0–1.6); 126
			    bladder 1.3 (1.0–1.6); 155
			    (French Canadians only)
			    kidney 1.2 (1.0–1.6); 88
			 ORs rose in the "substantial" exposure subgroup for stomach and lung, but not for bladder or kidney cancer
				Potential confounders:
				 co-exposures
				 Strengths:
				 control for smoking
				
				 multiple testing for different risk factors

Kauppinen *et al.* 1992	*Cases:* 344 primary liver cancer deaths reported to the Finnish Cancer Registry in 1976–1978 or 1981 *Controls:* registry-reported stomach cancer (476) or myocardial infarction	Questionnaires regarding job history and personal habits were sent to the closest available relative. U.K. based job-exposure	OR (95% CI) *52 workers with potential lead exposure*: 0.91 (0.65–1.29) *11 women with potential lead exposure*:	*Limitations:* most controls had stomach cancer, small numbers of subjects rated probably exposed

Reference	Study population	Exposure	Effects	Comments
	(385) deaths in the same hospitals, frequency matched by age and gender	matrix was used to rate potential exposure to 50 substances, including lead compounds Industrial hygienists also inspected histories to identify those with highly probable exposure and rate it as high, low, or moderate (< 10 years high or 10+ years low exposure)	1.84 (0.83–4.06) *5 men with probable moderate exposure:* 2.28 (0.68–7.67) none had high exposure and only 1 had low exposure, whereas 4 controls had high exposure female controls appeared to underreport their job history	
Wingren and Axelson 1987, 1993 (update of Wingren and Axelson 1985, same basic cohort as in Wingren and Englander 1990)	*Source population:* 5,498 men aged 45 or older in 11 Swedish parishes, including 887 glass workers Cancer-specific nested case-control analysis: *Cases:* deaths due to stomach, colon, and lung cancer from 1950–1982 *Controls:* deaths due to causes other than cancer or cardiovascular disease	Glass workers were considered exposed. Occupations also were categorized as low, moderate, or high lead exposure based on job matrix.	OR (90% CI); no. of deaths *All glass workers:* lung 1.7 (1.1–2.5); 86 stomach 1.5 (1.1–2.0); 206 colon 1.6 (1.0–2.5); 79 *Glassblowers:* lung 2.3 stomach 2.6 colon 3.1 ORs for high or moderate vs. low exposure showed no consistent increase for lung or stomach cancer, mild upward trend for colon cancer	*Potential confounders:* smoking, co-exposures, diet

Reference	Study population	Exposure	Effects	Comments

Anttila *et al.* 1996	(See Anttila *et al.* 1995 for basic information on the source population.)
	
	Nested case-control analysis:
	
	Cases: 26 Finnish men with CNS cancer
	
	Controls: 200 Finnish men without CNS cancer
		Occupational history and other risk-factor data were obtained from patients or next of kin.
		
		Exposure based on peak blood lead levels was categorized as 0.1–0.7, 0.8–1.3, and 1.4–4.3 µg/L.
		
		Cumulative lead exposure as the sum of mean annual blood lead level was categorized as 0, 1–6, 7–14, or 15–49 µg/L.
			OR (no. of cases or deaths)
			
			CNS cancer incidence (26 cases):
			  rose with increasing peak lifetime blood lead measurements; not significant
			
			Glioma mortality (16 deaths):
			rose consistently and significantly with peak and mean blood lead level, duration of exposure, and cumulative exposure
			
			Mortality by cumulative exposure, controlled for cadmium, gasoline, and year monitoring began:
			
			  low (13 subjects) 2.0 (2)
			  medium (14 subjects) 6.2 (2)
			  high (16 subjects) 12.0 (5)
			
			1 death among 26 subjects with no exposure: test for trend significant at $P = 0.02$
				Strengths:
				
				complete follow-up and minimal disease misclassification, controlled for smoking and exposure to gasoline and cadmium

Kandiloris *et al.* 1997	*Cases:* 26 patients with histologically confirmed laryngeal carcinoma and no history of lead exposure or toxicity *Controls:* 53 patients with similar demographic profiles and no history of cancer from the same hospital	Blood lead levels and ALAD activity were measured.	blood lead levels were similar, but ALAD activity was significantly lower in cases than controls	*Potential confounders:* other risk factors or the disease process itself

Reference	Study population	Exposure	Effects	Comments

Fayerweather *et al.* 1997	*Cases:* 735 cancer deaths during 1956–1987 among male workers at a U.S. TEL production plant, identified by the company's cancer and mortality registries, excluding bladder cancers deemed likely due to benzidene or beta-napthalamine exposure
	
	Controls: time-, age-, gender-, and payscale-matched plant workers
		Exposure to lead was ranked as none, low, medium, high, and very high, with cumulative exposure derived by summing yearly exposure over time.	OR (95% CI)
			Digestive in workers ever TEL-exposed
			  very high 2.2 (1.2–4.0)
			  high 1.3 (0.7–2.7)
			no association for lower exposures
			Rectal:
			  ever 3.7 (1.3–10.2)
			  low or medium 1.7 (0.4–8.3)
			  high or very high 5.1 (1.6–16.5)
			Colon:
			  ever 1.3 (0.7–2.5)
			  high or very high 1.7 (0.8–4.0)
			  low or medium 0.8 (0.4–1.8)
			Hodgkin's disease:
			  ever 2.7 (0.6–12.0)
			other cancers showed no association with exposure
				Limitations:
				loss of cancer deaths among pensioners and those leaving work due to illness

Cocco *et al.* 1998a	*Cases:* all 27,060 brain cancer deaths occurring among persons aged 35 or older during 1984–1992, from U.S. 24-state death certificate registry *Controls:* 4 gender-, race-, age-, and region-matched controls per case selected from deaths due to non-malignant causes Subjects were subdivided into 4 groups by gender and race (white or African-American) for all analyses.	A job-exposure matrix was applied to death certificate-listed occupations to categorize persons as having low, medium, or high probability and intensity of exposure.	risk of brain cancer mortality increased consistently with intensity of exposure among African-American males, but not other race-gender groups probability of exposure alone was not consistently associated with risk in the high-probability group, risk increased with exposure intensity for all groups except African-American women (only 1 death in the high-probability group)	*Limitations:* death-certificate occupation only, incomplete job history, potential misclassification of cause of death

Reference	Study population	Exposure	Effects	Comments
Cocco *et al.* 1998b	*Cases:* all 28,416 CNS cancer deaths occurring among persons aged 35 or older during 1984–1992, from U.S. 24-state death certificate registry *Controls:* 4 gender-, race-, age-, and region-matched controls per case selected from deaths due to non-malignant causes Subjects were subdivided into 4 groups by gender and race (white or African-American) for all analyses.	Industry and occupation were identified from death certificates.	OR (95% CI) all occupations or industries with ORs above 1.0 and *P*-value < 0.05 in at least one race-gender group were reported *Newspaper printing and publishing industry:* white M $\quad$ 1.4 (1.1–1.8) black M $\quad$ 3.1 (0.9–10.9) *Typesetting and compositing:* white M $\quad$ 2.0 (1.1–3.8) white F $\quad$ 1.3 (0.4–3.8) black F $\quad$ 4.2 (0.6–30.7) no deaths among black males	*Limitations:* death-certificate occupation only, no direct measure of lead exposure, potential misclassification of cause of death

Reference	Study population	Exposure	Effects	Comments
Cocco *et al.* 1999	*Cases:* all 41,957 stomach cancer deaths occurring among persons aged 35 or older during 1984–1996, from U.S. 24-state death certificate registry *Controls:* 2 gender-, race-, age-, and region-matched controls per case selected from deaths due to non-malignant causes Subjects were subdivided into 4 groups by gender and race (white or African-American) for all analyses.	A job-exposure matrix was applied to death certificate-listed occupations to categorize persons as having low, medium, or high probability and intensity of exposure.	OR (95% CI) adjusted for age, ethnicity, marital status, urban residence, and socioeconomic status *Elevated ORs:* white F, high prob. 1.53 (1.10–2.12) black M, high prob. 1.15 (1.01–1.32) black F, high prob. 1.76 (0.74–4.16) highly exposed group included 1,503 white and 453 black men and 65 white and 10 black women; no pattern of increase across exposure levels intensity of exposure showed no association with stomach cancer except for black women: low 1.82 (1.04–3.18) moderate 1.39 high 1.25	*Potential confounders:* carcinogen coexposure(s) *Other limitations:* death-certificate occupation only, incomplete job history, potential misclassification of cause of death
Shukla *et al.* 1998	*Cases:* 38 patients with newly diagnosed, histologically confirmed gall bladder cancer cases assembled from an Indian surgical unit *Controls:* 58 patients with gall stones diagnosed at the same surgical unit, matched on by geographic area, served as controls	Heavy metal content was measured in bile drawn from the gall bladder at time of surgery.	*Bile lead content: mean (SE) (mg/L):* gall bladder cancer: 58.38 (1.76) gallstones: 3.99 (0.43) cadmium and chromium levels also were elevated in cancer patients, but less than lead	*Potential confounders:* coexposures to other metals and potential carcinogens, smoking

Reference	Study population	Exposure	Effects	Comments
Hu *et al.* 1998	*Cases:* 218 patients with histologically-confirmed primary gliomas occurring during 1989–1996 at 6 Chinese hospitals *Controls:* 436 patients with non-neurological, nonmalignant disease., matched by age, gender, and residence from the same hospitals except a cancer-only center	Patients were interviewed, and those with factory or farm occupations were further interviewed to identify exposure to lead (or other potentially toxic substances).	no occupational exposure to lead was reported for any glioma patients, but was reported for 4 controls	*Potential confounders:* coexposures to other potential toxic agents *Other limitations:* inaccurate recall
Hu *et al.* 1999	*Cases:* all 383 patients with histologically confirmed primary meningiomas occurring during 1989–1996 at 6 Chinese hospitals *Controls:* 366 patients with non-neurological, nonmalignant disease matched bu age, gender, and residence from the same hospitals except a cancer-only center	Patients were interviewed, and those with factory or farm occupations were further interviewed to identify exposure to lead (or other potentially toxic substances).	OR (95% CI); no. of cases *Occupational exposure to lead:* M 7.20 (1.00–51.72); 6 F 5.69 (1.39–23.39); 10 ORs adjusted for income, education, and fruit and vegetable intake, plus cigarette pack-years for the women	*Potential confounders:* coexposures to other metals *Other limitations:* recall bias

Wong and Harris 2000	Case-control study nested in Wong and Harris 2000 cohort
	
	Cases: the 30 stomach cancer cases occurring in a Philadelphia lead battery plant
	
	Controls: 120 age-matched cohort members
		Job titles were used to classify lead exposure as low, intermediate, or high; total months of any exposure, of intermediate or high exposure only, and of cumulative exposure, with months weighted by 1, 2, or 3 if spent in low-, intermediate-, or high-exposure job.	mean months of employment, of intermediate or high exposure, or of weighted exposure to lead were all nonsignificantly lower among cases
			OR for cumulative weighted exposure in the 10 years prior to death:
			  First quartile 1.00
			  Second quartile 0.62
			  Third quartile 0.82
			  Fourth quartile 0.61
			P for trend = 0.47; ORs showed no positive association with any index of exposure
				Potential confounders: unclear whether analyses were controlled for any potential confounders; diet, co-exposures

Reference	Study population	Exposure	Effects	Comments

Pesch *et al.* 2000	*Cases:* 935 renal-cell cancer patients in five German areas
	
	Controls: 4,298 region, age, and gender-matched controls from the surrounding population
	
	ORs were adjusted for age, center, and smoking,
		Exposure to cadmium, lead, and other potential carcinogens was estimated from detailed job histories and rated as low vs. medium, high, or substantial. British and German job-exposure matrices were used.	OR (95% CI); no. of cases
			
			Substantial lead exposure based on British matrix:
			    M 1.5 (1.0–2.3); 29
			    F 2.6 (1.2–5.5; 11
			
			Substantial lead exposure based on British matrix:
			    M 1.3 (0.9–2.0); 30
			    F not reported
				Potential confounders:
				coexposures to additional metals or other carcinogens

Table 3-6. Lead exposure and childhood cancer

Reference	Design	Study population	Exposure	Effects	Comments
Kantor *et al.* 1979	case-control	*Cases:* 149 Connecticut childhood Wilms' tumor cases from 1935–1973 *Controls:* 149 age-, gender-, and race-matched controls	Paternal occupation was identified from birth certificate as lead-related or, lead/hydrocarbon-related.	*Lead-related industry:* OR = 5.0 *Hydrocarbon- or lead-related industry:* OR = 3.4	*Potential confounders:* coexposures *Other limitations:* small numbers, no quantitative exposure
Wilkins and Sinks 1984a, 1984b	case-control	*Cases:* 62 Ohio childhood Wilms' tumor cases from 1950–1981 *Controls:* 62 matched controls	Paternal occupation was identified from birth certificate as lead-related or hydrocarbon-related.	OR "not significant for lead or for hydrocarbon-related occupations"	*Potential confounders:* coexposures *Other limitations:* very small numbers, no quantitative exposure
Buckley *et al.* 1989	case-control	*Cases:* 204 childhood ANLL cases from 1980–1984 *Controls:* 204 age-, gender-, area-matched controls identified by random-digit dialing	Cumulative paternal occupational exposure to lead was determined in telephone interviews with fathers and categorized as 0, 1–1,000, > 1,000 days.	*178 case-control pairs with occupational exposure data:* 1–1,000 days: OR = 1.0 (5 cases) > 1,000 days: not calculable; 6 cases, 0 controls exposed *P* for trend = 0.03	*Limitations:* *P* for trend was only 0.08 after exclusion of surrogate interviews, maternal exposures, and other paternal exposures (no multivariate models); no information on timing of exposure relative to gestation
Olshan *et al.* 1990	case-control	*Cases:* 200 histologically confirmed U.S. Wilms' tumor cases (less-common sarcomatous subtype excluded) occuring from 1984–1986 *Controls:* 200 age- and area-matched population controls	A self-administered questionnaire on job history was used to identify lead exposed jobs and the years worked.	OR (95% CI); no. of cases *Timing of paternal lead exposure:* preconception 1.1 (0.6–2.0); 37 pregnancy 1.1 (0.6–2.4); 24 postnatal 1.3 (0.6–2.8); 21	*Potential confounders:* coexposures *Other limitations:* control selection bias (52% response)

Reference	Design	Study population	Exposure	Effects	Comments
Kristensen and Andersen 1992	cohort	12,440 offspring of Oslo printers' union members, followed from 1965–1987	Union employment records were used to identify lead-exposed occupations (compositors, monotype casters, stereotypers) and lead- and solvent-exposed occupations.	SIR (95% CI); no. of cases *Cancer at age 0–14:* lead 0.8 (0.2–2.3); 3 lead & solvent 0.3 (0.0–1.4); 1 *Cancer at age 14+:* lead 1.4 (0.6–2.6); 9 lead & solvent 0.6 (0.2–1.4); 5	*Potential confounders:* no control for other risk factors *Other limitations:* cancer type not specified, inadequate power (very few cases)

4 Studies of Cancer in Experimental Animals

IARC reviewed the carcinogenic potential of lead and lead compounds administered to mice, rats, and hamsters and concluded that there was sufficient evidence that lead subacetate is carcinogenic to mice and rats and that lead acetate and lead phosphate are carcinogenic to rats (IARC 1980, 1987). Most of the available carcinogenicity studies of lead in experimental animals were published before 1980 and were included in the IARC review. A brief summary of the primary findings and data from these studies is presented below. Carcinogenicity studies that were not included in IARC's review are discussed in more detail.

Lead chromate compounds were not included in the IARC monographs for lead and lead compounds (IARC 1980, 1987) but were included in the monographs for chromium and chromium compounds (IARC 1973, 1990). Because the carcinogenic effects of lead chromates generally are associated with toxicity of chromium rather than lead, these compounds are not discussed in detail in the following sections.

4.1 Mice

Lead compounds have been administered to mice in the diet, by intraperitoneal (i.p.) injection, by subcutaneous (s.c.) injection, by skin application, and in drinking water. Most of these studies have investigated the carcinogenicity of lead administered to young adult mice; however, the two most recent studies investigated the effects of lead on chemical- and viral-induced tumors (Blakley 1987) or in prenatal and neonatal mice exposed during gestation and lactation (Waalkes *et al.* 1995). The compounds studied include lead subacetate, lead acetate, lead naphthenate, lead chromate, and tetraethyl lead. The results from these studies are presented below.

4.1.1 Lead acetate or subacetate

Van Esch and Kroes (1969) fed lead subacetate at 0.1% and 1.0% in the diet to groups of 25 male and female Swiss mice for two years. The 1.0% level was decreased to 0.5% beginning in the fourth month because of excessive toxicity; however, the authors reported that most mice in the high-dose groups "died before tumors could be induced." No renal tumors developed in the control group. Six male mice in the 0.1% group and one female mouse each in the 0.1% and 1.0% groups developed renal tumors (Table 4-1). Other tumors occurred but were not associated with lead exposure.

Groups of 20 male and female strain A/Strong mice were given i.p. injections of lead subacetate dissolved in tricaprylin for 5 weeks (for total doses of 30, 75, and 150 mg/kg body weight [b.w.]) and observed for up to 30 weeks (Shimkin *et al.* 1977, Stoner *et al.* 1976). The incidence of pulmonary adenoma was significantly higher in the high-dose group than in vehicle controls or untreated controls (Table 4-1).

Using strain A mice, Poirier *et al.* (1984) investigated the inhibition of lead subacetate-induced lung tumors by magnesium and calcium acetate. Lead subacetate dissolved in tricaprylin was injected i.p. at 10 mg/kg b.w. (0.04 mmol/kg) alone or in combination with calcium acetate or magnesium acetate. Calcium acetate and magnesium acetate were

administered at 1, 3, and 10 times the molar concentration of lead subacetate. Groups of 30 mice received three injections per week, for a total of 9 (magnesium acetate studies) to 20 (calcium acetate studies) injections. Lead subacetate induced a statistically significant increase in lung tumors in strain A mice; however, simultaneous treatment with either calcium acetate or magnesium acetate at all molar ratios significantly decreased this response (Table 4-1).

Blakley (1987) investigated the effects of lead on chemical- and viral-induced tumors in female Swiss mice. In the first experiment, lead acetate was given in the drinking water at 0, 50, 200, or 1,000 µg/mL for 15 weeks beginning at three weeks of age. At six weeks of age, mice in each group received i.p. injections of 1.5 mg/g urethan or saline. Incidences of lung adenoma were reported at the end of the exposure period. In the second experiment, 8-week-old mice, with the same genetic background as in the first study, were given lead acetate in drinking water at 0, 50, or 1,000 µg/mL for 40 weeks and examined for lymphocytic leukemia of thymic origin. These mice have a high incidence (approximately 50%) of spontaneous lymphocytic leukemia. No clinical manifestations of lead poisoning were observed in either experiment, and neither body-weight gain nor water consumption was affected. Lead exposure did not affect the number or size of pulmonary adenomas induced by urethan (Table 4-2). The spontaneous tumor incidence was less than 2 tumors per mouse in all treatment groups injected with saline. In the second experiment, lead exposure increased incidences of viral-induced lymphocytic leukemia and tumor-related deaths (Table 4-3). The authors concluded that the immunosuppressive effects of lead allowed for increased expression of the murine lymphocytic leukemia virus.

A dose-related increase in renal proliferative lesions (including atypical hyperplasia, adenoma, and adenocarcinoma) was evident in B6C3F$_1$ mice following gestational and lactational exposure to lead (Waalkes *et al.* 1995). Pregnant B6C3F$_1$ mice were given lead (as lead acetate) in the drinking water *ad libitum* at 0, 500, 750 or 1,000 ppm from gestation day 12 to four weeks postpartum. These drinking-water levels of lead were estimated to provide doses of 0, 100, 150, or 200 mg/kg b.w. per day, respectively. After weaning, the offspring were grouped by sex (23 to 25 per group) and observed for up to 112 weeks. Other groups of offspring received a tumor promoter (500 ppm sodium barbital) *ad libitum* in the drinking water for the balance of the study. Lead exposure did not affect litter size, growth of exposed offspring, or survival. A significant dose-related trend was noted in total renal proliferative lesions in male progeny mice exposed to lead alone ($P < 0.001$) or lead and sodium barbital ($P = 0.022$). In addition, male mice in the high-dose group showed a significantly increased incidence of renal tubular cell adenoma and renal tubular cell atypical hyperplasia (Table 4-4). Female progeny mice exposed to lead alone showed a significant dose-related trend ($P = 0.017$) in total renal proliferative lesions; however, lesion incidences were not significantly elevated at any dose level (Table 4-4). In the control groups, atypical tubular hyperplasia occurred in one male mouse, but no tumors were observed. Postnatal exposure of the mice to sodium barbital did not promote tumor development. The authors noted that the renal tumors observed in this study developed without evidence of concurrent lead-induced nephropathy (i.e., intranuclear inclusion bodies, interstitial fibrosis, or cystic hyperplasia).

Table 4-1. Summary of carcinogenicity studies of lead subacetate in mice

Strain and age	Exposure route and duration	Sex and no.[b]	Exposure group[c]	Tumor incidence (%)[a]				Reference
				Kidney		Lung		
				Adenoma	Carcinoma	Adenoma	Multiplicity[d]	
Swiss (5 wk)	diet for 2 yr	M (25)	0	0 (0)	0 (0)	3 (NR)	NR	van Esch and Kroes 1969
		M (25)	0.1%	2 (NR)	4 (NR)	1 (NR)	NR	
		M (25)	1.0% to 0.5%[e]	0 (0)	0 (0)	1 (NR)	NR	
		F (25)	0	0 (0)	0 (0)	3 (NR)	NR	
		F (25)	0.1%	1 (NR)	0 (0)	5 (NR)	NR	
		F (25)	1.0% to 0.5%[e]	0 (0)	1 (NR)	1 (NR)	NR	
Strain A (6–8 wk)	15 i.p. doses (3/wk), examined at 30 wk	M/F (19)	untreated	NR	NR	6 (31)	0.28 ± 0.07	Stoner et al. 1976
		M/F (18)	vehicle	NR	NR	8 (44)	0.5 ± 0.12	
		M/F (17)	30 mg/kg	NR	NR	6 (35)	0.35 ± 0.09	
		M/F (12)	75 mg/kg	NR	NR	5 (42)	0.5 ± 0.14	
		M/F (15)	150 mg/kg	NR	NR	11 (73)	1.47 ± 0.38*	

Strain and age	Exposure route and duration	Sex and no.[b]	Exposure group[c]	Tumor incidence (%)[a]				Reference
				Kidney		Lung		
				Adenoma	Carcinoma	Adenoma	Multiplicity[d]	
Strain A (6–8 wk)	20 i.p. doses (3/wk), examined at 30 wk	M/F (26)	vehicle	NR	NR	NR	0.35 ± 0.09	Poirier *et al.* 1984
		M/F (26)	vehicle + CA	NR	NR	NR	0.62 ± 0.17	
		M/F (20)	Pb (10 mg/kg)	NR	NR	NR	0.86 ± 0.20*	
		M/F (23)	Pb + CA (1:1)	NR	NR	NR	0.21 ± 0.10[†]	
		M/F (18)	Pb + CA (1:3)	NR	NR	NR	0.22 ± 0.10[†]	
		M/F (16)	Pb + CA (1:10)	NR	NR	NR	0.13 ± 0.09[†]	
	9 i.p. doses (3/wk), examined at 30 wk	M/F (21)	vehicle	NR	NR	NR	0.29 ± 0.11	
		M/F (29)	vehicle + MA	NR	NR	NR	0.45 ± 0.09	
		M/F (20)	Pb (10 mg/kg)	NR	NR	NR	1.65 ± 0.36*	
		M/F (1)	Pb + MA (1:1)	NR	NR	NR	NR[f]	
		M/F (13)	Pb + MA (1:3)	NR	NR	NR	0.08 ± 0.08[†]	
		M/F (18)	Pb + MA (1:10)	NR	NR	NR	0.28 ± 0.11[†]	

*$P < 0.05$ compared with vehicle controls.

[†]Significantly less ($P < 0.05$) than in the lead subacetate group.

[a]NR = not reported.

[b]The number of surviving animals except for van Esch and Kroes (1969), which reported only the initial number of animals.
M/F = male and female not given separately; total number of animals reported.

[c]Pb + CA = lead subacetate plus calcium acetate (molar ratio) ; Pb + MA = lead subacetate plus magnesium acetate (molar ratio)

[d]The average number of tumors per mouse ± S.E.

[e]Dosage decreased because of high mortality.

[f]Only one of 30 animals survived.

Table 4-2. Effects of lead acetate on body-weight gain and urethan-induced lung adenoma in female Swiss mice

Lead concentration (μg/mL)	Weight gain mean ± SE (g/day)	Tumors/mouse mean ± SE (No. of mice)	Tumor size mean ± SE (mm)
0	0.18 ± 0.006	36.0 ± 5.8 (22)	0.71 ± 0.03
50	0.18 ± 0.004	39.0 ± 6.0 (19)	0.67 ± 0.04
200	0.17 ± 0.006	49.6 ± 12.8 (24)	0.70 ± 0.04
1,000	0.17 ± 0.005	34.0 ± 4.9 (24)	0.68 ± 0.02

Source: Blakley 1987.

Table 4-3. Effects of lead acetate on mortality and spontaneous lymphocytic leukemia in female Swiss mice

Lead conc. (μg/mL)	Median survival time (days)	Mice surviving to the end of study[a]	Leukemia deaths (%)[a]	Other neoplasia-related deaths[b]	Survival probability[c]
0	223.5	20	24 (48)	2	0.007
50	170.6	13	34 (68)	0	0.0124[d]
1,000	165.5	10	38 (76)	1	0.0034[d]

Source: Blakley 1987.

[a]50 mice per group. One surviving animal in each group had evidence of leukemia at the end of the study.

[b]Mammary tumors (controls) and leukemia of non-thymic origin (high-dose group).

[c]Probability that the three treatment groups had the same survival distribution, based on the Lee-Desu statistic.

[d]Probabilities for lead-exposed groups are for pairwise comparison with the control group.

Table 4-4. Renal tubular cell proliferative lesions in B6C3F$_1$ mice following gestational and lactational exposure to lead acetate

Exposure group[a] (ppm)	No. of mice	Lesion incidence (%)			
		Atypical hyperplasia	Adenoma	Carcinoma	Total
Males					
0	23	1 (4)	0 (0)	0 (0)	1 (4)
500	25	3 (12)	0 (0)	1 (4)	4 (16)
750	25	5 (20)	0 (0)	1 (4)	6 (24)
1,000	25	7 (28)*	5 (20)*	0 (0)	12 (48)*
SB	24	2 (8)	0 (0)	0 (0)	2 (8)
500 + SB	25	2 (8)	1 (4.0)	0 (0)	3 (12)
750 + SB	25	5 (20)	1 (4.0)	1 (4)	7 (28)
1,000 + SB	25	2 (8)	5 (20.0)*	1 (4)	8 (32)*
Females					
0	25	0 (0)	0 (0)	0 (0)	0 (0)
500	24	0 (0)	0 (0)	0 (0)	0 (0)
750	25	0 (0)	1 (4)	0 (0)	1 (4)
1,000	25	4 (16)	0 (0)	0 (0)	4 (16)
SB	25	0 (0)	0 (0)	0 (0)	0 (0)
500 + SB	25	0 (0)	0 (0)	0 (0)	0 (0)
750 + SB	25	0 (0)	1 (4)	0 (0)	1 (4)
1,000 + SB	25	1 (4)	0 (0)	1 (4)	2 (8)

Source: Waalkes *et al.* 1995.

*$P < 0.05$, compared with appropriate controls.

[a]Concentrations of lead in the drinking water given to the dams; SB = Sodium barbital at 500 ppm in drinking water.

4.1.2   Lead naphthenate

Baldwin *et al.* (1964) tested the carcinogenicity of several engine oil additives, including lead naphthenate, in male albino mice. A 20% (v/v) solution of lead naphthenate in benzene was applied to the shaved backs of mice once or twice per week. The study was terminated at 648 days, for a total application of 6 mL. Lead naphthenate did not induce a significant carcinogenic response in mouse skin. Only 2 of 59 mice developed benign skin tumors. Marked kidney damage was reported; however, the nature and extent of damage was not specified. Four mice developed renal tubular adenoma, and one mouse developed a renal carcinoma. No controls were used.

4.1.3   Lead chromate

The IARC (1990) monograph included only one study of mice exposed to lead chromate. Two lymphomas and three lung adenocarcinomas were observed in 17 female NIH-Swiss weanling mice given intramuscular (i.m.) injections of 3 mg of lead chromate dissolved in trioctanoin

every 4 months for 24 months. Lymphomas occurred in 1 of 15 untreated controls and 2 of 22 vehicle-injected controls, while lung adenocarcinomas occurred in 1 of 15 untreated controls and 1 of 22 vehicle-injected controls.

4.1.4 Tetraethyl lead

Subcutaneous administration of tetraethyl lead to infant male and female Swiss mice resulted in significantly increased incidences of lymphoma in the females (Epstein and Mantel 1968). A single rangefinding dose of 2 mg on the first day of life was lethal to all 69 mice tested before weaning. Mice received four divided doses of tetraethyl lead dissolved in tricaprylin at a concentration of 1 mg/mL (109 mice, total dose of 0.6 mg) or 2 mg/mL (79 mice, total dose of 1.2 mg) between birth and 21 days of age. Both dose levels were toxic, resulting in 20% and 92% mortality in the low- and high-dose groups, respectively, before weaning. Malignant lymphomas were found between 36 and 51 weeks in 5 of 41 (12%) low-dose females, 1 of 26 (4%) low-dose males, 1 of 39 (3%) control males, and none of the female controls. No renal tumors or nephropathy were observed in the lead-exposed mice.

4.2 Rats

Lead compounds were administered to rats in the diet, by gavage, in drinking water, by injection, or through lactation. The compounds studied include lead subacetate, lead acetate, lead phosphate, lead chromate, lead arsenate, and lead powder. Several studies also investigated the modifying effects of other compounds (e.g., dietary calcium, tumor promoters, and other carcinogens) on lead carcinogenicity. The results from these studies are presented below.

4.2.1 Lead acetate and lead subacetate

The carcinogenicity of lead acetate and lead subacetate in rats was reported in the 1960s and 1970s (Boyland *et al.* 1962, van Esch *et al.* 1962, Shakerin and Paloucek 1965, Mao and Molnar 1967, Zawirska and Medras 1968, 1972, Ito *et al.* 1971, Ito 1973). The results from these studies are summarized in Table 4-5. Other researchers investigated the carcinogenic effects of lead compounds when co-administered with other compounds (see Section 4.2.4). In general, these early studies investigated only carcinogenic effects in the kidney; however, a few studies examined other tissues.

Table 4-5. Summary of carcinogenicity studies of lead subacetate and lead acetate in rats conducted before 1980

Strain and initial age	Compound, exposure route, and duration	Sex[b] and no.	Exposure group	Kidney tumor incidences (%)[a]			Comments	Reference
				Adenoma	Carcinoma	Total		
Wistar (10 wk)	lead acetate or sedormid, diet, 1 yr	M (20) M (20)	0.5% sedormid[c] 1.0% lead[c]	0 (0) 1 (6.3)	1 (5.9)[d] 14 (87.5)	1 (5.9)[d] 15 (93.8)	Percentages based on animals surviving at least 320 days (17 in sedormid group, 16 in lead group). No untreated control group.	Boyland *et al.* 1962
Wistar (weanling)	lead subacetate, diet, 24 to 29 mo	M/F (55) M/F (32) M/F (24)	0 0.1% 1%	0 (0) 8 (25) 7 (29.2)	0 (0) 3 (9.4) 6 (25)	0 (0) 11 (34.4) 13 (54.2)	Study duration of 29 months for 0.1% diet and 24 months for 1% diet. Tumors were approximately equally divided between males and females.	van Esch *et al.* 1962
Wistar (young)	lead subacetate, diet, 92 wk	NR (40) NR (40)	0 0.5%–1.0%	0 (0) NR	0 (0) NR	0 (0) NR	Data reported in a meeting abstract. Treated rats primarily developed adenomas beginning at six months increas in size and number thereafter. A few adenocarcinomas, hypernephromas, or undifferentiated carcinomas were observed.	Shakerin and Paloucek 1965
Wistar (NR)	lead subacetate, diet, up to 677 days	M (20) M (40)	0 1%	0 (0) NR	0 (0) NR	1 (5) 31 (77.5)	The tumor in the control group was a round-cell sarcoma. Tumor incidence was correlated with exposure duration. All 12 animals exposed to lead for 500 days or more developed tumors.	Mao and Molnar 1967
Wistar (NR)	lead acetate, diet, 18 mo	M/F (32) M/F (126)	0 3–4 mg/day	0 (0) 55 (43.7)	0 (0) 17 (13.5)	0 (0) 72 (57.1)	Leydig-cell tumors of the testicles were reported in 23/94 treated male rats, but the incidence in controls was not reported.	Zawirska and Medras 1968
Wistar (6–8 wk)	lead subacetate, diet, 48 wk	M (10)	1.5%	6 (60)	4 (40)	10 (100)	The carcinomas included one clear-cell carcinoma and three dark cell carcinomas.	Ito *et al.* 1971
Wistar (30 wk)	lead acetate, diet, 60–504 days	M/F (62) M/F (94)	0 3 mg/day	0 (0) 12 (12.8)	0 (0) 0 (0)	0 (0) 12 (12.8)	Other tumors included 10 cerebral gliomas and 17 pituitary, 11 thyroid, 5 parathyroid, 15 adrenal, 11 prostatic, and 8 mammary adenomas.	Zawirska and Medras 1972

Strain and initial age	Compound, exposure route, and duration	Sex[b] and no.	Exposure group	Kidney tumor incidences (%)[a]			Comments	Reference
				Adenoma	Carcinoma	Total		
Wistar (6–8 wk)	lead subacetate, diet, 23–48.5 wk	M (13) M (11) M (11)	1.5% 1.5% + neph[e] 1.5%	0 (0) NR NR	0 (0) NR NR	0 (0) 2 (18.2) 9 (81.8)	First two groups were treated for 23 weeks, and the third group was treated for 48.5 weeks. Rats in the second group were unilaterally nephrectomized. Of the 11 renal tumors, 7 were adenomas and 4 were carcinomas.	Ito 1973

[a]NR = not reported.

[b]M/F = male and female not given separately; total number of animals reported.

[c]After one year, surviving animals were placed on the basal diet and were sacrificed when they became ill or had a palpable tumor. Sedormid was used to test the hypothesis that porphyrinuria may be responsible for lead-induced renal tumors. Both lead and sedormid caused chronic cystic nephritis.

[d]Epidermoid carcinoma of the renal pelvis that was not likely related to treatment.

[e]neph = nephrectomized.

Kasprzak *et al*. (1985) investigated the interaction of dietary calcium with lead carcinogenicity in 4-week-old male Sprague-Dawley rats. Rats were divided into seven groups (30 per group) and fed diets containing 0 or 1% lead subacetate and 0, 0.3%, 1%, 3%, or 6% calcium acetate for 79 weeks. Body weight gains were significantly depressed in lead-exposed animals, and the depressive effect was enhanced with increasing exposure to calcium acetate. Exposure to lead and calcium acetate also increased the organ/body weight ratios for the liver and kidneys. Kidney tumors were not observed in the control or calcium-acetate-only groups. Renal tumors occurred in approximately 45% of the lead-only group and in 62.1% to 78.6% of the lead and calcium acetate groups (Table 4-6). Bilateral tumors occurred in 48% of the tumor-bearing rats. Primary tumors in other organs were not observed in the lead-only group but occurred in a few animals in the lead- and calcium-exposed groups (Table 4-6).

Table 4-6. Tumor incidence in male Sprague-Dawley rats fed lead subacetate (PbSA) and calcium acetate (CA)

Exposure group (%)	No. rats at risk[a]	Kidney tumor incidence (%)			Other tumors (no.)[b]
		Adenoma	Adeno-carcinoma	Total	
Control	30	0 (0)	0 (0)	0 (0)	schwannomas (2)
CA (3)	29	0 (0)	0 (0)	0 (0)	odontoma (1)
PbSA (1)	29	11 (37.9)	2 (6.9)	13 (44.8)	none
PbSA (1) + CA (0.3)	30	16 (53.3)	5 (16.7)	21 (70.0)	HCA (1), SCC (1), PAP (?)
PbSA (1) + CA (1)	29	11 (37.9)	7 (24.1)	18 (62.1)	PC (1), PAP (?)
PbSA (1) + CA (3)	30	15 (50.0)	7 (23.3)	22 (73.3)*	osteoma (1)
PbSA (1) + CA (6)	28	15 (53.6)	7 (25.0)	22 (78.6)*	none

Source: Kasprzak *et al.* 1985.

*$P < 0.05$ (compared to lead only group)

[a]Rats surviving at least 58 weeks.

[b]HCA, hepatocellular adenoma; SCC, squamous-cell carcinoma; PAP, papilloma; PC, pituitary carcinoma; (?), a total of three papillomas reported in groups 4 and 5 combined.

Bogden *et al.* (1991) also investigated the modifying effects of dietary calcium on lead tissue concentrations, blood pressure, and incidences of kidney tumors in rats. Forty-eight five-week-old male Wistar rats were randomly assigned to groups fed a low-calcium (0.2%) or high-calcium (4.0%) diet and given drinking water containing 0, 1.0, or 100 µg/mL lead for 31 weeks. Lead acetate trihydrate was used in the treatment groups, and sodium acetate trihydrate was used in the control groups. The lead concentrations were expected to produce blood lead concentrations similar to those found in individuals in the U.S. population with low or moderate exposure to lead. Tissue lead concentrations were not lower in groups on the high-calcium diet. All rats exposed to high calcium and high lead concentrations developed hyperplasia or transitional cell carcinoma in the kidney. These lesions were not observed in the other groups. The authors concluded that the high-calcium diet enhanced lead-induced renal carcinogenesis.

4.2.2   Lead phosphate

IARC (1980) reviewed three carcinogenicity studies of lead phosphate parenterally administered to rats (Zollinger 1953, Baló *et al.* 1965, Roe *et al.* 1965). No other studies with lead phosphate were identified. Renal tumors occurred in 36% to 66% of the albino rats given lead phosphate but were not observed in controls (Table 4-7).

4.2.3   Lead chromate

IARC (1990) reviewed several studies of lead chromates adminstered to rats by interbronchial implantation, intrapleural implantation, s.c. injection, or i.m. injection. Bronchial carcinomas were observed in a few rats (1% or less) administered various lead chromate compounds via interbronchial implantation, but the incidences were not statistically significant. Following intrapleural administration, implantation-site tumors (tumor type unspecified) occurred in 3 of 34 rats after 27 months, compared with 0 of 34 in the control group. In contrast, injection-site sarcomas were frequent in rats given a single s.c. injection of lead chromate (26/40, 65%), basic lead chromate (27/40, 67.5%), or molybdenum orange (a mixture of lead chromate, sulfate, and molybdate) (36/40, 90%), but were not observed in 60 control animals. Results from i.m. injection studies were inconsistent. Injection-site tumors were observed in 1 of 33 (3%) rats in one study and 31 of 47 (66%) in another. No injection-site tumors occurred in controls. In addition, renal-cell carinomas occurred in 3 of 23 (13%) rats injected i.m. with 8 mg of lead chromate once per month for nine months. The IARC (1990) Working Group noted that the renal tumors may have been attributable to the lead content.

4.2.4   Other inorganic lead compounds

Although studies with lead acetate, lead subacetate, and lead phosphate show clear evidence of carcinogenicity in rats, other lead compounds have not been associated with carcinogenicity. IARC (1980) reviewed the carcinogenicity of lead arsenate and lead carbonate administered in the diet, lead nitrate administered in drinking water, and lead powder administered by gavage or i.m. injection. These studies are summarized briefly below. No additional studies of these or other lead compounds were identified.

No tumors were found in 49 young male white rats fed 0.1% lead arsenate or in 55 rats fed 0.1% lead carbonate for two years. However, the authors reported kidney changes, including cytomegaly, vesiculation of nuclei, and accumulation of brown granules in the convoluted tubules (Fairhall and Miller 1941).

A study of male and female Wistar rats fed lead arsenate in the diet at a concentration of 463 or 1,850 ppm for two years did not provide clear evidence of carcinogenicity (Kroes *et al.* 1974). Eighty animals (40 of each sex) were included in the low-dose group and 48 (19 females and 29 males) in the high-dose group. No differences were observed between groups in the numbers of malignant or benign tumors. The incidence of malignant tumors was 1 of 28 (3.6%) in the high-dose group and 6 of 78 (7.7%) in the low-dose group, compared with 11 of 98 (11%) in controls. The authors suggested that the only tumors that may have been induced by lead arsenate were a renal cortical adenoma and a bile-duct carcinoma found only in the high-dose group.

Male Long-Evans rats exposed to lead (as lead nitrate) in drinking water at 25 µg/L from weaning until death did not show increased mortality or tumor incidence (Schroeder *et al.* 1970).

Tumors, unspecified with respect to location or type, were observed in 7 of 43 (16%) exposed rats and 10 of 50 (20%) controls.

Lead powder administered by i.m. injection or gavage did not increase tumor incidence in male or female F344 rats (Furst *et al.* 1976). Rats received nine monthly i.m. injections of 10 mg of lead powder, followed by three monthly injections of 5 mg. An injection-site sarcoma observed in one female rat was thought to be a random occurrence. The incidences of lymphoma or lymphocytic leukemia in exposed rats did not differ from those in controls. When lead powder was administered by gavage in corn oil (10 mg twice a month for 12 months), no tumors occurred in the gastrointestinal tract or kidneys. Lymphoma and leukemia occurred in both exposed and control animals; however, the incidences were not signficantly different.

4.2.5   Co-administration with other compounds

Three studies from the same laboratory (Shakerin *et al.* 1965, Hass *et al.* 1967, Oyasu *et al.* 1970) investigated the interaction of dietary lead subacetate with 2-acetylaminofluorene (2-AAF). Kidney, liver, urinary bladder, brain, and other tumors were reported; however, most of these occurred in rats given both 2-AAF and lead. Shakerin *et al.* (1965) reported a higher incidence of hepatic and renal carcinomas with metastasis to the lungs in rats fed both lead subacetate and 2-AAF than in groups fed either compound alone. Hass *et al.* (1967) reported that the combination of 2-AAF, lead subacetate, and linseed oil increased the anaplastic character of hepatocellular carcinomas but did not significantly increase their incidence. No other significant interactions were reported. However, lead subacetate was associated with kidney and brain tumors (Table 4-8).

Several studies published after the IARC (1980) review investigated the promoting or co-carcinogenic effects of lead administered to rats. Hiasa *et al.* (1983) investigated the promoting effects of lead subacetate in male Wistar rats treated with *N*-ethyl-*N*-hydroxyethylnitrosamine (EHEN). The animals were divided into six treatment groups that received diets containing: (1) no EHEN or lead subacetate (controls), (2) 500 ppm EHEN, (3) 1,000 ppm EHEN, (4) 1,000 ppm lead subacetate, (5) 1,000 ppm EHEN followed by 1,000 ppm lead subacetate, and (6) 500 ppm EHEN followed by 1,000 ppm lead subacetate. EHEN was given during the first two weeks of the study, lead acetate from week 3 to week 22, and the control diet from week 23 to week 32. Animals were sacrificed at 32 weeks and examined for kidney tumors. No tumors were observed in groups 1, 2, or 4. Exposure to lead subacetate significantly increased the incidence and size of renal-cell tumors induced by EHEN (Table 4-9). In addition, hepatocellular carcinomas were found in two rats in group 3 and one rat each in groups 5 and 6.

Table 4-7. Summary of carcinogenicity studies of lead phosphate in rats[a]

Strain[b]	Exposure route and duration	Sex and no.	Exposure group	Kidney tumor incidence (%)[a]			Comments	Reference
				Adenoma	Carcinoma	Total		
Albino	s.c., up to 16 mo.	NR (40)	0	0 (0)	0 (0)	0 (0)	Total doses ranged from 40 to 760 mg. Tumors in the renal cortex occurred in rats surviving more than 10 mo and receiving between 120 and 680 mg. Renal papilloma and cystadenoma also reported.	Zollinger 1953[c]
		NR (29)	20 mg/wk	NR	NR	19 (66)		
Albino	s.c., 18 mo.	NR (20)	0	0 (0)	0 (0)	0 (0)	The total dose was 1.3 g, and adenomas first appeared after 354 days.	Baló et al. 1965[c]
		NR (80)	20 mg/wk	29 (36)	0 (0)	29 (36)		
Albino Chester Beatty	s.c. and i.p., 34 wk	M (24)	0	0 (0)	0 (0)	2 (8)[g]	All groups began with 24 animals. Percentage is based on animals surviving at least 200 days. Treatment groups received 4 s.c. injections followed by 21 to 25 i.p injections with variable periods of no treatment during the study (see footnotes). Most of the tumors were cuboidal-cell, tubular, or papillary adenomas or adenocarcinomas arising in the renal cortex. Several non-renal tumors occurred but were not associated with lead.	Roe et al. 1965
		M (23)	29 mg[d]	0 (0)	0 (0)	0 (0)		
		M (23)	145 mg[e]	NR	6 (26)	14 (61)[h]		
		M (3)	450 mg[f]	2 (67)	0 (0)	2 (67)		

[a]NR = not reported.

[b]Ages not reported.

[c]As cited in IARC (1980). These papers were not published in English.

[d]Weekly injections of 1 mg: 4 s.c. injections + 7 i.p. injections + no treatment for 3 wk + 4 i.p. injections + no treatment for 2 wk, + 14 i.p. injections.

[e]Same as above except dose was 5 mg per injection.

[f]Four s.c. injections (25 mg) + 7 i.p. injections (25 mg) + no treatment for 9 wk, + 14 i.p. injections (12.5 mg).

[g]Includes one undifferentiated malignant tumor and one transitional cell carcinoma arising in the renal pelvis.

[h]Includes one undifferentiated malignant tumor and 13 adenomas or adenocarcinomas.

Table 4-8. Summary of carcinogenicity studies of lead subacetate co-administered with 2-AAF in rats[a]

Strain and age	Exposure route and duration	Sex[b] and no.	Exposure group[c]	Kidney tumor incidence (%)[a]			Comments	Reference
				Adenoma	Carcinoma	Total		
Wistar (NR)		(NR)	2-AAF (0.06%)	NR	NR	NR	Reported incidences of hepatic and renal tumors in combined group either lead subacetate or 2-AAF groups alone.	Shakerin *et al.* 1965
			Pb (1%)	NR	NR	NR		
		M (40)	Pb (1%)+ 2-AAF (0.06%)	NR	NR	NR		
Sprague-Dawley (6–8 wk)	diet, 30–52 wk (NR)	M (32)	2-AAF + indole	0 (0)	0 (0)	0 (0)	Lead acetate concentrations were 0.5% to 1% of the diet. Indole (1.6%) was added to counteract 2-AAF (0.06%) liver toxicity. Brain tumors (gliomas) occurred in 3, 2, 4, and 8 animals in the respective treatment groups (including interim sacrifice animals) but were considered spontaneous tumors.	Hass *et al.* 1967
		M (13)	Pb + indole	8 (61.5)	3 (23.1)	NR		
		M (11)	Pb + LO + indole	0 (0)	1 (9.1)	NR		
		M (32)	Pb + LO + indole + 2-AAF	10 (31.3)	11 (34.4)	NR		
	diet, 52–74 wk	M (32)	2-AAF + indole	0 (0)	0 (0)	0 (0)		
		M (11)	Pb + indole	11 (100)	8 (72.3)	11 (100)		
		M (39)	Pb + LO + indole	20 (51.3)	13 (44.8)	NR		
		M (42)	Pb + LO + indole + 2-AAF	19 (45.2)	14 (33.3)	NR		
Sprague-Dawley (6 wk)		M/F (325)	controls	0 (0)	0 (0)	0 (0)	Gliomas were observed in one control animal (0.3%) and in 11 of 130 (8.5%) rats in the lead treatment groups ($P < 0.05$). Gliomas occurred in 2, 3, and 6 rats in the Pb only, Pb + indole, and Pb + indole + 2-AAF treatment groups, respectively. Combining lead and 2-AAF did not increase tumor incidences.	Oyasu *et al.* 1970
		M (17)	Pb (1%)	NR	NR	13 (76.5)		
		M (41)	Pb + indole (1.6%)	NR	NR	25 (61.0)		
		M (72)	Pb + indole + 2-AAF (0.06%)	NR	NR	36 (50.0)		

[a]NR = not reported.

[b]M/F = male and female not given separately; total number of animals reported.

[c]LO = linseed oil containing a "lead drier" with 0.2% lead.

Table 4-9. The promoting or co-carcinogenic effects of lead acetate or lead subacetate in rats

Strain and age	Exposure route and duration	Sex and no.	Exposure group (ppm)[a]	Kidney tumors incidence (%)	Comments	Reference
Wistar (7 wk)	diet, 22 wk	M (24)	Control	0 (0)	Surviving animals were sacrificed at 32 weeks. Incidences of renal tumors > 3 mm in diameter were 0%, 0%, 10%, and 71% in tumor-bearing animals treated with EHEN alone, lead subacetate alone, 500 ppm EHEN plus lead, and 1,000 ppm EHEN plus lead, respectively.	Hiasa *et al.* 1983
		M (24)	EHEN (500)	0 (0)		
		M (18)	EHEN (1,000)	9 (50)*[b]		
		M (24)	PbSA (1,000)	0 (0)		
		M (17)	EHEN (1,000) + PbSA (1,000)	17 (100)*[c]		
		M (22)	EHEN (500) + PbSA (1,000)	10 (45)*[d]		
Sprague-Dawley (weanling)	drinking water, 76 wk	M (7)	Control	0 (0)	The first renal tumor was observed at 54 weeks. All animals in the groups treated with EU/NaNO$_2$ developed one or more tumor types (lymphosarcoma being the most common), but renal tubule carcinoma was the only tumor observed in the lead-only group.	Koller *et al.* 1985
		M (8)	EU/NaNO$_2$	0 (0)		
		M (7)	EU/NaNO$_2$ + PbA (26)	0 (0)		
		M (10)	EU/NaNO$_2$ + PbA (2,600)	6 (60)		
		M (16)	PbA (2,600)	13 (81)		

*$P < 0.05$.

[a]EHEN = *N*-ethyl-*N*-hydroxyethylnitrosamine; EU/NaNO$_2$ = ethyl urea and sodium nitrite; PbSA = lead subacetate; PbA = lead acetate.

[b]Compared with the control group (χ^2 test).

[c]Compared with the EHEN 1,000-ppm group (χ^2 test).

[d]Compared with the EHEN 500-ppm group (χ^2 test).

Koller *et al.* (1985) investigated the carcinogenic effects of lead acetate administered with sodium nitrite and ethyl urea to male Sprague-Dawley rats. The five treatment groups included the following: (1) untreated controls, (2) ethyl urea (EU) and sodium nitrite (NaNO$_2$) (3) ethyl urea, sodium nitrite, and 26 ppm lead as lead acetate, (4) ethyl urea, sodium nitrite, and 2,600 ppm lead, and (5) 2,600 ppm lead. Groups 1 through 4 had 10 animals and group 5 had 16 animals. Lead was administered in the drinking water for 76 weeks. Ethyl urea (6.36 g/kg) and sodium nitrite (2 g/kg) (precursors of the carcinogenic agent ethylnitrosourea) were mixed in the diet and administered for 20 weeks beginning 28 weeks after initiation of lead exposure. Early deaths from pneumonia reduced the effective group sizes to 7, 8, and 7 for groups 1, 2, and 3, respectively. At the end of the study, all rats fed ethyl urea and sodium nitrite (groups 2, 3, and 4) had tumors. Lymphosarcoma was the most prevalent, with an incidence of at least 50% in each of these groups. Only kidney tumors were observed in group 5 (lead only). No kidney tumors were detected among the controls, the EU+NaNO$_2$ group (group 2), or the low-dose lead and EU+NaNO$_2$ group (group 3). Renal tubular carcinomas were observed in both groups receiving lead at 2,600 ppm (Table 4-9). However, tumor incidences were not increased by co-administration of lead with urea and sodium nitrite.

Tanner and Lipsky (1984) studied the effects of lead acetate on induction of renal carcinogenesis by *N*-(4'-fluoro-4-biphenyl)acetamide (FBPA) in male Fischer-344 rats. Four groups of 50 rats each were used; however, mortality from acute toxicity was high in the treatment groups. Five to 10 rats were sacrificed in each group after 16, 24, 36, and 52 weeks of exposure and examined for kidney tumors. Group 1 (controls) was fed a semi-synthetic diet, group 2 was fed the control diet with 400 ppm lead as lead acetate, group 3 was fed the control diet with 10,000 ppm lead as lead acetate, and group 4 was fed the control diet with 400 ppm FBPA plus 10,000 ppm lead as lead acetate. No lesions were observed in the controls, but karyomegaly, hyperplasia, and microscopic nodules were seen in all lead-exposed groups. Renal adenocarcinoma occurred in groups 2, 3, and 4 after 36, 52, and 24 weeks, respectively. Kidney tumor incidence was higher in group 4 (lead acetate and FBPA) than in either the lead-only or FBPA-only group (Table 4-10). Exposure to lead acetate generally accelerated the onset and development of all renal lesions; however, karyocytomegaly was not correlated with the later appearance of hyperplasia, microscopic nodules, or adenocarcinomas. These researchers concluded that lead probably was acting synergistically with FBPA as a co-carcinogen by accelerating the neoplastic process in the proximal tubule epithelial cells.

Table 4-10. Co-carcinogenic effects of lead acetate administered with FBPA to male Fisher-344 rats

Treatment group (ppm)	No. of rats	Treatment duration (wk)	Renal lesion incidence (%)		
			Hyperplasia	Microscopic adenoma	Adeno-carcinoma
(1) Control[a]	5–10	16	0	0	0
	5–10	24	0	0	0
	5–10	36	0	0	0
	5–10	52	0	0	0
(2) FBPA (400)	7	16	4 (57)	0	0
	7	24	7 (100)	2 (29)	0
	7	36	5 (71)	3 (43)	4 [57]
	5	52	3 (60)	3 (60)	4 (80)
(3) PbA (10,000 as elemental Pb)	8	16	4 (50)	0	0
	8	24	4 (50)	0	0
	10	36	10 (100)	1 (10)	0
	5	52	3 (60)	1 (20)	1 (20)
(4) FBPA (400) + PbA (10,000 as elemental Pb)	8	16	8 (100)	3 (38)	0
	9	24	9 (100)	6 (67)	1 (11)
	5	36	5 (100)	5 (100)	4 (80)
	5	52	5 (100)	4 (80)	5 (100)

Source: Tanner and Lipsky 1984.

[a]The number of control rats sacrificed at each interval was not reported but was between 5 and 10.

4.3   Hamsters

In male and female golden hamsters (45 or 46 per group) fed control diet or lead subacetate at 0.1% and 0.5% in the diet for up to two years, lead exposure did not significantly increase the frequency of renal tumors, although pleomorphic cells and intranuclear inclusion bodies were found in the proximal renal tubules. The overall incidences of other tumors and hyperplasias in the low-dose, high-dose, and control groups were 25 of 46 (54%), 18 of 46 (39%), and 36 of 45 (80%), respectively (van Esch and Kroes 1969).

Four groups of Syrian golden hamsters (15 per sex) were given 10 weekly intratracheal injections of lead oxide (1 mg), benzo[a]pyrene (1 mg), or a combination of lead oxide and benzo[a]pyrene (1 mg of each). Animals were sacrificed when moribund or 60 weeks after the first treatment. The hamsters did not develop any lung tumors when administered either lead oxide or benzo[a]pyrene alone; however, lead oxide induced hyperplastic and squamous metaplastic foci in the alveolar region. Atypical epithelial proliferations in the lungs (11 adenomas, 1 adenocarcinoma) were observed only in animals given the combination of lead oxide and benzo[a]pyrene. The investigators

concluded that lead oxide exerted a co-carcinogenic effect with benzo[*a*]pyrene in the lungs (Kobayashi and Okamoto 1974).

4.4   Monkeys

Krugner-Higby *et al.* (2001) reported on a case of chronic myelocytic leukemia that may have been related to lead exposure in a juvenile female rhesus macaque. This monkey was part of a study that investigated the behavioral effects of subclinical neonatal exposure to lead. Lead acetate was administered in milk formula during the first six months postpartum (beginning on day 8). After weaning, lead acetate was given daily in a fruit-flavored vehicle for 1.5 years to achieve a blood lead level of 35 µg/dL. At 25 months of age, an increased white blood cell count and immature white blood cells were detected during a routine complete blood count. The animal was monitored and received chemotherapy treatments but was euthanized four months later because of deteriorating clinical conditions. No evidence of past or present viral infection or other risk factors for leukemia was observed. The authors concluded that the possible role of lead exposure in chronic myelocytic leukemia should be investigated.

4.5   Summary

Both soluble (lead acetate and lead subacetate) and insoluble (lead phosphate) lead compounds were found to be carcinogenic in rats and/or mice by a variety of exposure routes, including oral, subcutaneous, intramuscular, transdermal, and transplacental, and translactational. Inhalation carcinogenicity studies of lead compounds have not been conducted in experimental animals.

Other lead compounds found to be carcinogenic in experimental animals include lead chromates and tetraethyl lead. Exposure to lead chromates increased the incidence of injection-site sarcomas in rats, but these effects were likely due to chromate. However, renal-cell carcinomas were reported in one study of rats administered lead chromate by i.m. injection. Female infant Swiss mice administered tetraethyl lead by s.c. injection developed malignant lymphomas, but this effect was not observed in male Swiss mice.

Most of the studies of inorganic lead compounds focused on kidney toxicity and carcinogenicity; therefore, complete histopathological examinations were not conducted. However, the few studies that examined tissues other than the kidney found little evidence that lead induced tumors. The available data indicate that the primary target site for lead-induced neoplasia in experimental animals is the kidney (adenoma and adenocarcinoma), but increased incidences of cerebral glioma and lung adenoma were reported in some studies.

Lead subacetate was reported to enhance liver and kidney tumorigenicity of 2-AAF in one study but not in two others and was shown to promote renal tumors in Wistar rats administered EHEN. In other studies, lead acetate increased the incidence of viral-induced lymphocytic leukemia in mice and was co-carcinogenic when administered with FBPA to F344 rats. However, lead acetate did not increase tumor incidences in Sprague-Dawley rats when co-administered with ethyl urea and sodium nitrite.

Overall, renal tumors were observed in male and female rats and mice exposed to lead compounds, and were not always accompanied by chronic lead-induced nephropathy.

5 Genotoxicity

Numerous studies have been conducted to determine whether lead compounds are genotoxic and, if so, by what mechanism(s). Most of these studies were performed before 1990. A comprehensive review by the Agency for Toxic Substances and Disease Registry (ATSDR 1999) summarized their results, concluding that various inorganic lead compounds (lead acetate, chloride, and nitrate) were not genotoxic in microorganisms, with and without metabolic activation, based on various end points (mutations, DNA modification, and recombination). Conversely, *in vitro* assays using mammalian test systems (Syrian and Chinese hamster ovary cells) gave conflicting test results when cells were examined for chromosomal aberrations. *In vivo* studies using *Drosophila melanogaster* and various mammalian model systems also gave conflicting results concerning the genotoxic effects of lead acetate and lead nitrate. Evaluation of the genotoxicity of lead exposure in humans focused on *in vitro* and *in vivo* studies of chromosomal aberrations and sister chromatid exchange in lymphocytes from healthy individuals and from occupationally or environmentally exposed individuals. These studies also gave conflicting results. ATSDR concluded that the mechanism(s) of the genotoxicity of lead probably was indirect (see Section 6 for a discussion of lead's mechanism of action).

The literature through 1987 concerning the genotoxicity of lead compounds also was extensively reviewed by IARC (1972, 1973, 1976, 1980, 1987). The IARC reviews concluded that divalent lead compounds (lead acetate and lead chloride) reacted with purified DNA and decreased the fidelity of DNA replication *in vitro*, but were not mutagenic in bacterial test systems and did not enhance mitotic recombination in the *Saccharomyces cerevisiae* D3 assay. In plants, lead acetate (at concentrations of 20 to 30 mM) induced chromosome aberrations in *Allium cepa* root tips, and lead chloride (0.1 mM) was weakly mutagenic in rice seeds. *In vitro* and *in vivo* studies using mammalian systems yielded conflicting results for the genotoxicity of lead compounds.

Many factors contribute to the conflicting results concerning the genotoxic effects of lead. These factors include differences not only in model systems employed and end points used to determine genotoxicity, but also in the lead compounds used. As discussed in Section 1, lead is highly reactive and forms numerous compounds that have very different physical-chemical properties. One important property in biological systems is solubility. Lead compounds vary greatly in solubility: compounds such as lead acetate, lead chloride, and lead nitrate are extremely soluble in water, with solubility constants (K_{sp}) of 2×10^{-2}, 1×10^{-4}, and 2×10^{-2}, respectively, whereas other lead compounds, such as lead chromate and lead sulfide, are virtually insoluble in water (K_{sp} of 1.7×10^{-14} and 1×10^{-28}, respectively). Solubility affects the bioavailability of these compounds. Humans are occupationally and environmentally exposed to numerous lead compounds over the course of a lifetime. Likewise, personal habits such as smoking, alcohol, and drug intake can influence genotoxicity data obtained in human subjects, and it is difficult to account for the effects that these cofactors might have on lead genotoxicity. This section reviews relevant genotoxicity data reported since 1989.

5.1 Prokaryotic systems: Induction of mutations in *Salmonella typhimurium*, *Escherichia coli*, and *Serratia marcescens*

Maslat and Haas (1989) determined the mutagenic effects of lead bromide, a combustion product of the gasoline additives TEL and 1,2-dibromoethane, in *Serratia marcescens*, *Escherichia coli* KMBL 1851, and the *Salmonella typhimurium* tester strains TA 1535 (point mutations) and TA 1537 (frameshift mutations). *S. marcescens* mutants were scored on their inability to produce the pigment prodigiosin, *E. coli* mutants were scored for resistance to rifampicin, and *S. typhimurium* mutants were scored for histidine auxotrophy. Bacteria were exposed for various times (not reported) to concentrations of $PbBr_2$ ranging from 1.91 to 4.63 mM for *S. marcescens*, 1.91 to 3.27 mM for *E. coli,* and 0.5 to 68 µg/plate for *S. typhimurium.* The frequency of white colonies arising from *S. marcescens* exposed to $PbBr_2$ ranged from $0.42 \pm 0.01\%$ to 2.0 ± 0.10 % for exposure at 1.91 and 4.63 mM $PbBr_2$, respectively. The mutation frequency for non-exposed controls was 0.05%. The frequency of rifampicin-resistant mutants arising following exposure of *E. coli* to 3.27 mM $PbBr_2$ was $0.26\% \times 10^{-4}$ (non-exposed control $= 0.0066\% \times 10^{-4}$). The number of *S. typhimurium* TA 1535 revertants ranged from 0 to 977 after plating on $PbBr_2$ medium containing 0.5 and 34 µg of $PbBr_2$, respectively. No significant increase in revertants was seen with *S. typhimurium* strain TA 1537 (see Table 5-1).

5.2 Plants: *in vivo* assays

Reddy and Vaidyanath (1978) investigated the mutagenic activity of metallic salts, including lead chloride, on chlorophyll mutations in rice. Rice seeds were exposed to a 10^{-4} M aqueous solution of lead chloride for 24 hours. The pooled results of three replicates indicated mutant frequencies of 0.65% in the M1 and 0.04% in M2 generations. These values represent relatively weak mutagenic acticity compared with that reported for other metallic salts, including barium (6.36% in the M1 and 0.68% in the M2) and cadmium (5.23% in the M1 and 0.46% in the M2).

Sandhu *et al.* (1989) evaluated the clastogenicity of lead tetraacetate in the *Tradescantia* micronucleus assay, using *Tradescantia paludosa* clone 4430, as described by Ma *et al.* (1983). Plant cuttings were exposed for 30 hours by hypotonic uptake through stems, with no time for recovery. Results were expressed as micronuclei per 100 tetrads. Of the compounds tested (aldrin, arsenic trioxide, 1,2-benz[*a,h*]anthracene, dieldrin, heptachlor, lead tetraacetate, and tetrachloroethylene), lead tetraacetate was the most clastogenic, inducing 17.79 ± 8.56, 18.93 ± 2.90, and 13.07 ± 5.50 micronuclei/100 tetrads at concentrations of 0.44, 2.55, and 11.75 ppm, respectively. Micronucleus formation was significantly greater ($P < 0.05$) than in the solvent control (2.90 ± 2.0).

Table 5-1. Genotoxicity of lead compounds in prokaryotic systems

Species (test system)	End point	Results[a] With metabolic activation	Without metabolic activation	Compound	Concentration[b]	Reference
S. typhimurium *E. coli* *Bacillus subtilis*	mutation or DNA modification	–	–	lead acetate lead nitrate lead chromate lead chloride and acetate	NA 22–180 µM 0.2 mg 25 mM	Bruce and Heddle 1979[c], Dunkel *et al.* 1984[c] Kharab and Singh 1985[c] Nestmann *et al.* 1979[c] Nishioka 1975[c]
S. typhimurium (TA 1535) *S. typhimurium* (TA 1537) *E. coli* (KMBL 1851) *S. marcescens*	mutation	ND	+ – + +	lead bromide	0.5–68 µg/plate 0.5–68 µg/plate 1.91–3.27 mM 1.91–4.63 mM	Maslat and Haas 1989
S. cerevisiae	gene conversion or mitotic recombination	–	–	lead chloride lead nitrate lead chromate lead acetate	NA 22–180 µM 25 mM 5% (v/v)	Fukunaga *et al.* 1982[c] Kharab and Singh 1985[c] Nestmann *et al.* 1979[c] Simmon 1979a, 1979b[c]

Source: ATSDR 1999.

[a]ND = not determined.

[b]NA = not available.

[c]Not reviewed in the text; source: ATSDR 1999.

Ma *et al.* (1992) determined the synergistic effects of mixtures of lead tetraacetate, arsenic trioxide, dieldrin, and tetrachloroethylene on genotoxicity in the *Tradescantia* micronucleus assay. Lead tetraacetate (0.44 ppm) alone increased the frequency of micronucleus formation in plants exposed for 30 hours over that in the solvent controls.

Gill and Sandhu (1992) determined the genotoxic effects of arsenic trioxide, dieldrin, and lead tetraacetate alone and in combination in the *Tradescantia* micronucleus assay. The chemicals or their mixtures were either (1) mixed into soil, and exposure to the target cells was through the roots of intact plants grown in the soil, or (2) prepared as an aqueous solution, and exposure was by absorption through the stems of plant cuttings. Lead tetraacetate was tested at concentrations of 4 µg/mL in the aqueous test system and and 4 mg/kg in the soil test system. Soil-grown plants exposed to lead tetraacetate had significantly more ($P < 0.05$) micronuclei than did the controls (11.2 ± 2.3 vs. 5.1 ± 0.6 micronuclei per 100 tetrads, respectively). No difference was observed between the lead-exposed and control plants grown in aqueous media (2.9 ± 0.5 vs. 2.3 ± 0.1 micronuclei per 100 tetrads, respectively). The clastogenicity of lead tetraacetate was altered by the ratio of individual chemicals in the aqueous or soil media.

Lerda (1992) determined the effect of lead nitrate (at concentrations of 0.1, 1.0, 10, 50, 100, or 200 ppm) on root growth, cell proliferation, and chromosomal aberrations in *Allium cepa*. The effect of lead nitrate on root growth was determined by measuring the length of 10 to 20 roots per onion bulb at 24-hour intervals for 96 hours. Lead nitrate at a concentration of 100 or 200 ppm completely inhibited root growth. At lower concentrations, the rate of growth was reduced in a dose-dependent manner. Likewise, cell proliferation, which was determined at the root tip 12, 24, and 48 hours after exposure, was progressively reduced at high concentrations. However, this inhibition was transient; proliferation had recovered by 48 hours after exposure. No difference from controls was observed in cell proliferation at concentrations up to 10 ppm. At each exposure level, 5,000 cells were examined for chromosomal aberrations. The frequency of chromosomal aberrations in cells from onions exposed to lead nitrate at 0.1 or 1.0 ppm did not differ from that of the non-exposed controls. However, significantly ($P < 0.05$) more cells contained chromosomal aberrations in plants exposed at 10 ppm than in non-exposed controls (0.18 vs. 0 per 5,000 cells). The author stated that these results supported those of his previous studies demonstrating that lead compounds induced chromosomal aberrations in persons occupationally exposed to lead (Lerda 1992).

Minissi *et al.* (1998) examined the genotoxicity of sediments from the Tiber River and its tributaries in the urban area of Rome, using a micronucleus assay in *Vicia faba* root tips. All samples were collected in July 1992. Sediments were assayed for content of the 13 most important chemicals of the polycyclic aromatic hydrocarbon (PAH) group and for some heavy-metal ions (cadmium, chromium, copper, nickel, lead, and zinc). The lead concentration in the sediments ranged from 12.4 to 43.5 ppm. The frequency of micronuclei was significantly ($P < 0.01$) higher in plants exposed to sediment collected from 8 of the 10 sites than in the controls. These sites also contained significant amounts of PAHs and other metal ions (see Table 5-2).

Table 5-2. Genotoxicity of lead compounds in plants *in vivo*

Species	End point	Results	Compound	Concentration	Reference
Tradescantia clone 4430	micronucleus formation	+	lead tetraacetate	0.44 to 11.75 ppm in water; 4 µg/kg in soil	Sandhu *et al.* 1989, Ma *et al.* 1992, Gill and Sandhu 1992
Allium cepa	inhibition of root growth	+	lead nitrate	0.1, 1, 10, 50, 100, 200 ppm	Lerda 1992
	cell proliferation	+	lead nitrate	0.1, 1, 10, 50, 100, 200 ppm	Lerda 1992
	chromosomal aberrations	+	lead nitrate	0.1, 1, 10, 50, 100, 200 ppm	Lerda 1992
Vicia faba	micronucleus formation	+	lead with other metals	12.4 to 43.1 ppm	Minissi *et al.* 1998

5.3   *In vitro* studies using cell-free systems

Roy and Rossman (1992) reported that exposure of supercoiled plasmid DNA with lead acetate (1 mM) for 30 minutes at room temperature in a Tris-HCl buffer (pH 7.5) did not induce nicks or strand breaks in the DNA, as determined by agarose gel electrophoretic analysis. Addition of hydrogen peroxide (H_2O_2, 0.3 mM) to the reaction mixture induced the formation of nicks and double-stranded breaks in the DNA. The levels of DNA damage in the samples exposed simultaneously to H_2O_2 and lead acetate were greater than those observed in DNA exposed to either lead acetate or H_2O_2. The investigators suggested that lead(II) did not damage DNA directly, but caused damage indirectly by participating in a Fenton reaction to generate hydroxyl radicals in the presence of H_2O_2.

Calsou *et al.* (1996) investigated the ability of several heavy metal ions, including lead(II), to inhibit nucleotide excision repair *in vitro*. These investigators determined the effect of these metal ions on lesion recognition and strand incision/displacement steps in a whole-cell extract from HeLa cells. The incision assay was performed with ultraviolet- (UV-) treated pBluescript phagemid vector DNA, as described by Calsou and Salles (1994). Lesion recognition (UV damage) was tested in a mobility-shift assay, in which the protein-DNA complex was detected via electrophoresis. Lead chloride (0.1, 0.3, and 1.0 mM) inhibited incision repair activity in a dose-dependent manner, with approximately 50% of the activity inhibited at 1 mM. Likewise, lead chloride (1 mM) inhibited recognition of UV DNA damage by the cell extract. The investigators reported a good correlation between the inhibitory effects of several metal ions, including lead(II), on the excision activity of NER and a reduced protein-binding activity to damaged DNA.

Yang *et al.* (1999) reported that treatment of supercoiled plasmid DNA with lead acetate (0.3 mM) in HEPES buffer (10 mM, pH 6.8) at 37°C for 3 to 24 hours resulted in time-dependent DNA strand breakage. In studies with a 24-hour incubation period, the DNA strand breaks also were dose-dependent (over lead acetate concentrations of 0.1 to 0.3 mM), and DNA strand breakage also occurred in Tris-HCl buffer (1 to 10 mM, pH 6.8). To determine whether H_2O_2 was involved in the reaction, DNA was treated with 0.1 mM lead acetate for 1 hour at 37°C in the presence and absence of H_2O_2 (1 or 5 mM). Under these conditions, neither lead acetate nor H_2O_2 induced nicks or strand breaks in the plasmid, but treatment with lead acetate and H_2O_2 in combination increased the incidence of DNA strand breaks. Although the investigators stated that the effect of H_2O_2 was dose-dependent, no numerical data were reported to support this premise, and only two concentrations of H_2O_2 were employed. The singlet oxygen scavengers sodium azide and 2,2,6,6-tetramethyl-4-piperidone (TEMP) inhibited lead-induced DNA strand breakage more efficiently than did the hydroxyl radical scavengers, mannitol and 5,5-dimethyl-1-pyrroline-1-oxide. Deuterium oxide, a singlet oxygen enhancer, increased lead-induced DNA strand breakage, while catalase and superoxide dismutase did not protect the DNA from lead-induced breaks. Enhancement of lead-induced breaks by H_2O_2 was inhibited by sodium azide, TEMP, edetate calcium disodium, catalase, and glutathione, and was potentiated by superoxide dismutase and mannitol.

To further examine the potential role of reactive oxygen species-intermediates on lead-induced DNA damage, studies were performed to determine whether 8-hydroxydeoxyguanosine (8-OHdG) was formed in calf thymus DNA following its

exposure for 1 hour at 37°C to lead acetate (0.1, 0.5, and 1 mM) in the presence and absence of H_2O_2 (5 mM). Under these conditions, neither lead acetate nor H_2O_2 significantly increased the amount of 8-OHdG in DNA over that in non-treated controls (average 6.6 ± 0.7 8-OHdG per 10^5 deoxyguanosine residues). However, treatment of the DNA with lead acetate (1 mM) and H_2O_2 (5 mM) in combination resulted in a 14.4-fold increase in the amount of 8-OHdG (95.2 ± 10.8 8-OHdG per 10^5 deoxyguanosine residues). The investigators interpreted the data to suggest that lead(II) induced DNA damage through a Fenton-like reaction and that a singlet oxygen was the principal oxygen species involved in inducing the damage (see Table 5-3).

5.4   Mammalian systems

5.4.1   In vitro *assays*

5.4.1.1   *Lead acetate, lead chloride, lead nitrate, and lead sulfide*

Frenkel and Middleton (1987) reported that lead acetate did not inhibit DNA and RNA synthesis in HeLa cells even after exposure to 0.5 mM of lead acetate for 18 hours. Conversely, DNA and RNA synthesis were inhibited in intact nuclei (50% inhibition concentration [IC_{50}] = 150 and 80 µM, respectively). Likewise, HeLa DNA polymerase α and RNA polymerase II activities were inhibited by lead acetate (IC_{50} = 150 and 20 µM, respectively). *E. coli* DNA polymerase I was more sensitive to inhibition by lead acetate (IC_{50} = 10 µM) than was HeLa DNA polymerase α, but the sensitivity of the *E. coli* RNA polymerase was the same as that of the HeLa enzyme.

To investigate the genotoxicity of soluble and insoluble lead compounds, Zelikoff *et al.* (1988) used Chinese hamster ovary (CHO) cells (V79) as a model system to determine the mutagenic potential and the ability of the compounds to induce sister chromatid exchange (SCE) and Syrian hamster embryo (SHE) cells to determine their cell transformation potential. For the mutagenicity assays, V79 cells were treated with lead sulfide (insoluble) for 1 day or lead nitrate (soluble) for 5 days, and their resistance to 6-thioguanosine was determined. For the SCE assay, exponentially growing V79 cells were treated for 24 hours. Bromodeoxyuridine (5 µg/mL) was added for two cell cycles, followed by colcemid treatment. Two hours later, mitotic cells were collected by mechanical agitation, fixed, and stained using a modification of the technique described by Schneider *et al.* (1978). A minimum of 30 mitotic cells was counted, and the number of SCE per chromosome was determined. The cytotoxicity of lead acetate, lead nitrate, and lead sulfide to V79 cells was determined by clonogenic assay. The 50% lethal doses (LD_{50}) were 0.58, 2.55, and 2.95 mM for lead sulfide, lead acetate, and lead nitrate, respectively. Treatment of V79 cells with lead nitrate or lead sulfide increased the frequency of mutation of the *hprt* gene compared to non-treated controls. The increased mutation frequency was 6.2-fold higher in cells treated with 0.5 mM lead nitrate for 5 days. At higher concentrations, the mutation frequency decreased but remained 2-fold greater than background. Lead sulfide (376 µM, 24-hour treatment) induced a 5.5-fold increase in the mutation frequency. Neither lead nitrate nor lead sulfide induced a significant increase in the frequency of SCE, nor did they induce DNA single-strand

Table 5-3. Genotoxicity of lead compounds *in vitro* in cell-free systems (without metabolic activation)

Species or test system	End point	Results	Compound	Concentration	Reference
E. coli RNA polymerase and avian myeloblastosis DNA polymerase	inhibition of RNA or DNA biosynthesis	+	lead chloride	0.05–2 mM	Hoffman and Niyogi 1977[a]
		+	lead chloride	4 mM	Sirover and Loeb 1976[a]
DNA polymerase and RNA polymerase II in HeLa cell extracts	DNA and RNA polymerase inhibition	+	lead acetate	25–500 µM	Frenkel and Middleton 1987
Whole-cell (HeLa) extract	inhibition of DNA damage incision activity	+	lead chloride	0.1–1 mM	Calsou *et al.* 1996
Supercoiled plasmid DNA	DNA strand breaks		lead acetate	1 mM	Roy and Rossman 1992
	with H$_2$O$_2$	+			
	without H$_2$O$_2$	−			
Supercoiled plasmid DNA	DNA strand breaks		lead acetate		Yang *et al.* 1999
	with H$_2$O$_2$	+		0.1 mM (1 h)	
	without H$_2$O$_2$	−		0.1 mM (1 h)	
	without H$_2$O$_2$	+		0.3 mM (3–24 h)	

[a]Not reviewed in the text; source: ATSDR 1999.

breaks, as measured by alkaline elution. For the cell transformation assay, SHE cells isolated from embryos 12 to 24 days after gestation were treated with lead acetate for 24 hours, washed, and re-treated for an additional 24 hours. Fresh media was added, and plates were incubated for an additional 10 days or until colonies (> 50 cells) were observed. Lead acetate (10, 25, and 50 µM) induced cellular transformation of SHE cells in a dose-dependent manner. The investigators interpreted these results to mean that lead compounds were genotoxic by an indirect mechanism and to support the view that lead might be a carcinogen.

To determine whether the genotoxic effects of lead(II) were due to indirect effects rather than to direct DNA damage, Hartwig *et al.* (1990) used CHO (V79) and HeLa cells to examine the effects of lead acetate on DNA repair processes as they relate to genotoxicity. Cytotoxicity was determined by clonogenic assay. Survival values following treatment of V79 cells withlead acetate for 24 hours were 92.0%, 53.1%, 41.5%, 37.5%, and 32.1% at concentrations of 1, 3, 5, 10, and 25 µM, respectively. Lead acetate did not increase the frequency of *hprt* gene mutations in V79 cells, nor did exposure to lead(II) increase the frequency of SCE. Lead(II) also did not induce DNA strand breaks in HeLa cells, as determined by nucleoid sedimentation. However, for all the end points tested, lead ions interfered with the processing of UV-induced DNA damage. Mutation frequency in UV-irradiated CHO cells was increased by treatment with lead acetate (at 0.5, 1, 3, and 5 µM) for 20 hours prior to irradiation. Pretreatment of CHO cells with lead acetate (1, 5, and 10 µM) before UV irradiation also significantly increased ($P < 0.1$) the frequency of SCE. The investigators also concluded, based on nucleoid sedimentation assays with HeLa cells, that lead acetate inhibited repair of UV-damaged DNA.

Hartwig (1994, 1995) published two reviews concerning the relationship between inhibition of DNA repair processes by metal ions and their genotoxicity. In these reviews, she summarized previous studies concerning the genotoxicity of a variety of metal ions, including lead(II). With respect to lead(II), she concluded, based on research primarily with CHO (V79) cells, that the direct genotoxicity of lead(II) was weak and restricted to toxic concentrations. Lead(II) induced DNA strand breaks only at toxic levels (Roy and Rossman 1992), but not at lower concentrations, and it did not induce DNA protein crosslinks as determined by alkaline elution (Zelikoff *et al.* 1988) or nucleoid sedimentation (Hartwig *et al.* 1990). Hartwig concluded that the mutagenic potential of soluble lead compounds was low (Roy and Rossman 1992) and that lead acetate and lead sulfide did not significantly increase the frequency of SCEs in exposed V79 cells (Zelikoff *et al.* 1988, Hartwig *et al.* 1990). Hartwig also summarized data that she believed demonstrated that lead compounds acted as co-mutagens (Hartwig *et al.* 1990, Roy and Rossman 1992), possibly by inhibiting nucleotide excision repair (Hartwig *et al.* 1990). However, as she pointed out, this explanation was controversial even at that time, because studies in HeLa cells demonstrated that while lead chloride (250 µM) inhibited the recovery of DNA synthesis after X irradiation, suggesting inhibition of DNA repair (Skreb and Habazin-Novak 1977), lead acetate had no effect on the resealing of X-ray-induced DNA strand breaks (Snyder *et al.* 1989). Hartwig suggested interference with DNA repair processes as a possible mechanism for the genotoxicity of metal ions,

including lead(II), because these genotoxic effects were observed at low, nontoxic concentrations.

Using a transgenic CHO cell line (G12) derived from V79 cells, Roy and Rossman (1992) reported that exposure to lead acetate (1.7 mM) for 5 days increased the frequency of *gpt* recorder gene mutations approximately fivefold. Mutation frequency was not increased at lower concentrations of lead acetate (0.5 and 1 mM), nor at any concentration of lead nitrate (0.5, 1, 1.7 mM). However, pre-exposure of G12 cells for 24 hours to lead acetate at a nonmutagenic and slightly cytotoxic concentration (0.4 mM) increased the cytotoxicity and mutagenicity of *N*-methyl-*N'*-nitro-*N*-nitroguanidine and UVC light. The investigators concluded that lead(II) was weakly mutagenic and only at toxic doses ($LD_{50} = 1.7$ mM for lead acetate and 1.5 mM for lead nitrate), but that lead(II) might act as a co-mutagen at non-lethal concentrations.

Lin *et al.* (1994) reported that lead nitrate (1, 5, 20, 30 µM) was not overtly cytotoxic to CHO cells (cell line not stated) (18.5% to 19.6% decrease in viability, based on trypan blue staining) following treatment for 16 hours. However, low concentrations of lead nitrate (1 and 3 µM) significantly increased the mitotic activity of exposed cells. Higher concentrations of lead nitrate (10 and 30 µM) did not significantly increase the mitotic index of exposed cells (number of cells in division/total number of cells x 100). Genotoxicity was assessed with assays for micronucleus formation, chromosomal aberrations, and SCE frequency. None of the concentrations of lead nitrate tested induced micronuclei or significantly increased chromosomal aberrations. However, lead nitrate (3, 10, and 30 µM) did induce a significant increase (1.45- to 2.48-fold) in SCE. The investigators suggested that SCE may be the most sensitive end point for examining the genotoxicity of metal ions.

Yang *et al.* (1996) reported that exposure of CHO cells (*hprt*$^+$ cell line K1) to lead acetate (0.5 to 1.5 mM) for 24 hours increased the mutation frequency in a dose-dependent manner, ranging from a 3.36-fold increase at 0.5 mM to a 7.92-fold increase at 1.5 mM (the LD_{50}). Reverse-transcriptase-polymerase chain reaction (PCR) and genomic-DNA PCR analyses of cDNA and genomic DNA from mutants from the various exposure groups suggested that G:C base pairs might be the primary target sites for lead mutagenesis. Furthermore, molecular analyses indicated that G:C$\rightarrow$C:G transversions predominated in low-mutation-frequency populations and G:C$\rightarrow$A:T transitions in high-mutation-frequency populations. The authors suggested that lead might induce mutations by different mechanisms, possibly including interaction of the metal with DNA and subsequent reactive-oxygen-species- (ROS-) mediated damage and interference with DNA polymerase fidelity and DNA repair enzymes.

Using the CHO cell line AA8, Cai and Arenaz (1998) reported that lead nitrate was cytotoxic in a concentration-dependent manner to cells exposed for 3 or 12 hours. Four concentrations of lead nitrate (0.5 to 1 µM) were tested, and cytotoxicity was determined with a clonogenic assay. Cells were exposed to lead nitrate (0.1, 0.5, 1 µM) for 24 or 36 hours, and chromatids were differentially stained as described by Perry and Wolff (1974). A significant increase in SCE frequencies was observed at all lead nitrate concentrations tested, but there was no increase in the frequency of chromosomal aberrations.

Hwua and Yang (1998) examined the effect of 3-aminotriazole, an inhibitor of catalase, peroxidase, and cytochrome P450 2E1, on anchorage independence and on the mutagenicity of cadmium acetate and lead acetate in primary diploid human fibroblasts. Exponentially growing cells were treated with 80 mM 3-aminotriazole 1 hour before exposure to cadmium acetate and lead acetate for 24 hours. The concentrations of lead acetate used in these studies were 0.5, 1.5, and 2 mM. After removal of the metal ions, the cells were maintained in exponential growth for 7 or 9 days before mutation and anchorage-independence assays, respectively, were performed. The cytotoxicity of lead acetate was determined by clonogenic assay. The concentration required to reduce the survival of treated cells to 37% was 0.8 mM. Lead acetate exposure significantly induced anchorage-independent growth in a dose-dependent manner. The numbers of anchorage-independent colonies induced per 10^6 viable cells were 182.6 ± 16.9 at 1.5 mM and 262.7 ± 37.8 at 2.0 mM. Exposure to lead acetate did not increase the frequency of *hprt* gene mutations. Lead-induced anchorage independence and cytotoxicity were not affected by 3-aminotriazole cotreatment, but 3-aminotriazole did significantly increase lead uptake and accumulation in human fibroblasts. The investigators concluded that lead(II) might act as a tumor promoter, and that ROS were more important in cadmium- than in lead-induced cytotoxicity and anchorage independence.

In a series of studies using the transgenic CHO cell line AS52, Ariza and coworkers (Ariza and Williams 1996, 1999, Ariza *et al.* 1998) demonstrated that low, relatively nonlethal concentrations (0.1 to 1.0 µM) of lead chloride were mutagenic. At these concentrations, lead chloride was minimally cytotoxic to cells exposed for 1 hour (Ariza and Williams 1996). At the highest lead chloride concentration tested (1 µM), viability was reduced only by 28% in a clonogenic assay. Exposure of AS52 cells to lead chloride (at eight concentrations from 0.1 µM to 1 µM) for 1 hour resulted in a dose-dependent increase in the frequency of *gpt* transgene mutations. The increase in mutation frequency ranged from 2.5-fold at 0.1 µM to 6.2-fold at 1 µM.

Multiplex PCR and Southern blot analyses were used to examine 138 lead-induced, 29 ROS-induced, and 20 spontaneously arising mutants for point and deletion mutations in the *gpt* gene (Ariza and Williams 1999). Lead(II) induced significantly fewer point mutations (48%) than were observed in cells exposed to reactive oxygen intermediates (90%) or in spontaneous mutants (90%). Further examination of the data demonstrated that at lead chloride concentrations of 0.4 µM or lower, the majority of the mutations in the *gpt* gene were point mutations, while at higher concentrations, deletions (partial and complete) were predominant. These results are consistent with the hypothesis that soluble lead compounds induce mutations in eukaryotic cells by at least two distinct mechanisms (Yang *et al.* 1996, Ariza *et al.* 1998).

5.4.1.2 Lead chromate

Chromium metal salts, including lead chromate, have been classified as human carcinogens based on epidemiological and experimental data (IARC 1990). Several end points have been employed to assess the genotoxic potential of lead chromate, including enhancement of simian adenovirus transformation of SHE cells (Schechtman *et al.* 1986, Elias *et al.* 1989), morphological transformation of C3H/10T1/2 cells (Patierno *et al.* 1988, Patierno and Landolph 1989), morphological transformation of human

osteosarcoma cells (Sidhu *et al.* 1991), induction of mutation in CHO cells (Patierno and Landolph 1989), induction of DNA strand breaks and DNA-protein crosslinks in CHO cells (Xu *et al.* 1992), and clastogenic effects in CHO and human fibroblasts (Wise *et al.* 1992, 1993, Blankenship *et al.* 1997). However, these studies did not separate the genotoxic effects of lead from those of chromium; therefore, they are not considered in this review.

Wise *et al.* (1994), using CHO (AA8) cells, performed a series of studies designed to elucidate the relative roles of lead and chromium in the clastogenic activity of lead chromate. Cell-mediated extracellular dissolution of lead chromate resulted in intracellular accumulation of both lead and chromium. Accumulation of chromium was time- and concentration-dependent, and was maximal following a 24-hour exposure to lead chromate at 8 µg/cm^2. Accumulation of lead also was dose-dependent, but its time-dependency was more variable. Under these conditions, the intracellular concentration of chromium was 2.75 ± 0.3 mM, and the concentration of lead was 97 ± 58 µM. In similar studies with lead glutamate (500 µM), the maximum intracellular lead ion concentration was 834 ± 63 µM. The clastogenic activity of lead chromate was $21\% \pm 7\%$ at 0.8 µg/cm^2 and $66\% \pm 17\%$ at 8 µg/cm^2. These percentages were significantly greater ($P < 0.005$) than in the vehicle control ($3\% \pm 1\%$). Exposure of cells to sodium chromate (2 or 4 µM) resulted in a significant increase ($P < 0.005$) in chromosomal aberrations ($12\% \pm 2\%$ and $23\% \pm 8\%$). Lead nitrate (0.5 to 1 mM) did not induce chromosomal aberrations. Although lead glutamate at a concentration of 1 mM significantly increased the frequency of chromosomal aberrations (11%), this effect was not observed at lower (0.5 mM) or higher (2 mM) concentrations. Pretreatment of cells with vitamin E reduced sodium chromate- and lead chromate-induced clastogenesis 54% to 93%, respectively, but the vitamin had no effect on lead glutamate-induced clastogenesis. The authors concluded that although lead ion was weakly clastogenic, chromate ion was the major clastogen in lead chromate (see Table 5-4).

Table 5-4. Genotoxicity of lead compounds in mammalian systems *in vitro*

End point	Test system	Results	Compound	Concentration	Reference
Chromosomal aberrations	CHO cells	+	lead acetate	0.001–10 mM	Bauchinger and Schmid 1972[a]
Chromosomal aberrations	CHO cells	+	lead acetate	0.05–1 mM	Robison *et al.* 1984[a]
Chromosomal aberrations	CHO cells	+	lead nitrate	0.1, 0.5, 1 μM	Cai and Arenaz 1998
Chromosomal aberrations	CHO cells	+	lead nitrate	0.5, 1, 2 mM	Wise *et al.* 1994
Chromosomal aberrations	CHO cells	–	lead nitrate	3–30 μM	Lin *et al.* 1994
SCE	CHO cells	– –	lead nitrate lead sulfide	500–3,000 μM 133–938 μM	Zelikoff *et al.* 1988
SCE	CHO cells	–	lead acetate	1–25 μM	Hartwig *et al.* 1990
SCE	CHO cells	+	lead nitrate	1–30 μM	Lin *et al.* 1994
SCE	CHO cells	+	lead nitrate	0.1–1 μM	Cai and Arenaz 1998
Micronucleius formation	CHO cells	–	lead nitrate	3–30 μM	Lin *et al.* 1994
Micronucleus formation	Sprague-Dawley rat kidney cells	+	lead acetate	0.56–1.8 mM	Robbiano *et al.* 1999
Mitotic disturbance	CHO cells	+	lead acetate	0.001–10 mM	Bauchinger and Schmid 1972[a]
Mitotic disturbance	CHO cells	+	lead sulfate	10, 20, 40 μM	Costa *et al.* 1982[a]
Mitotic index	CHO cells	+	lead nitrate	3–30 μM	Lin *et al.* 1994

End point	Test system	Results	Compound	Concentration	Reference
Mutation in *hprt* gene	CHO cells	+	lead nitrate lead sulfide	50–2,000 μM 100–938 μM	Zelikoff *et al.* 1988
Mutation in *hprt* gene	CHO cells	+	lead acetate	0.5–2.0 mM	Yang *et al.* 1996
Mutation in *hprt* gene	CHO cells	–	lead acetate	1 to 25 µM	Hartwig *et al.* 1990
Mutation in *hprt* gene	primary diploid human fibroblasts	–	lead acetate	0.5 to 2 mM	Hwua and Yang 1998
Mutation in *gpt* gene	transgenic CHO cells	+	lead chloride	0.1–1 µM	Ariza and Williams 1996, 1999, Ariza *et al.* 1998
Mutation in *gpt* gene	transgenic CHO cells	+ –	lead acetate lead nitrate	500–1,700 µM 500–1,700 µM	Roy and Rossman 1992
Cell transformation	SHE cells	+	lead acetate	10, 25, 50 µM	Zelikoff *et al.* 1988
DNA strand breaks	CHO cells	– –	lead nitrate lead sulfide	500–3,000 µM 133–938 µM	Zelikoff *et al.* 1988
DNA strand breaks	HeLa cells	–	lead acetate	100–2,000 µM	Hartwig *et al.* 1990
DNA repair	CHO cells	+	lead acetate	0.05–1 mM	Robison *et al.* 1984[a]
DNA fragmentation	Sprague-Dawley rat kidney cells	+	lead acetate	0.56–1.8 mM	Robbiano *et al.* 1999
DNA damage	transgenic CHO cells	+	lead chloride	0.1–1 µM	Ariza *et al.* 1998
Inhibition of DNA and RNA synthesis	HeLa cells	–	lead acetate	500 µM	Frenkel and Middleton 1987

End point	Test system	Results	Compound	Concentration	Reference
Inhibition of DNA and RNA synthesis	intact nuclei of HeLa cells	+	lead acetate	80 μM (RNA) and 150 μM (DNA)	Frenkel and Middleton 1987
Inhibition of DNA and RNA polymerase	HeLa cells and *E. coli*	+	lead acetate	10–150 μM	Frenkel and Middleton 1987
Studies of lead as a co-factor or co-mutagen					
Mutation in *hprt* gene, SCE, and nucleoid sedimentation	CHO cells	+ increased genotoxicity[b]	UV irradiation pre-exposure to lead acetate	1–10 μM	Hartwig *et al.* 1990
Mutation in *gpt* gene	transgenic CHO cells	+ increased mutagenicity[c]	*N*-methyl-*N'*-nitro-*N*-nitroguanidine or UVC pre-exposure to lead acetate	0.4 mM	Robison *et al.* 1984

[a]Not reviewed in text; source: ATSDR 1999.

[b]The authors proposed that the genotoxic effects of pretreatment with lead acetate resulted from inhibition of DNA repair.

[c]The authors proposed an increase in DNA nicks due to inhibition of DNA ligase as a possible mechanism for the effects of lead acetate

5.4.2   In vivo *assays*

5.4.2.1   *Reproductive genotoxicity studies*

Nayak *et al*. (1989) determined the embryotoxicity and genotoxicity of lead nitrate using pregnant randomly bred ICR Swiss Webster mice (6 to 8 weeks old). Lead nitrate dissolved in normal saline was given intravenously (i.v.) at doses of 100, 150, or 200 mg/kg body weight on the ninth day of gestation. Fetuses were removed on the 18th day of gestation and used for cytogenetic and chemical studies. For cytogenetic studies, bone marrow cells were obtained from the femurs of three dams from each exposure group, and liver or lung tissues from three fetuses per dam. The cytogenetic studies included an analysis of numerical and gross cytogenetic changes in G-banded chromosomes, frequency of SCE, frequency of nucleolar organizing regions (NORs), and analysis of changes in G-banded karyotypes. The lead levels in maternal mice ranged from 0.04 ppm in non-exposed controls to 19.18 ppm in animals given 200 mg/kg of lead nitrate. The lead content in fetal tissue also increased (to a maximum 0.17 ppm in fetuses from dams given lead nitrate, compared with 0.07 ppm in fetuses from non-exposed controls). The percentage of resorptions was significantly higher ($P < 0.05$) in the lead-exposed animals than in non-exposed controls. The frequency of SCE also was significantly higher ($P < 0.05$) in dams given lead nitrate at either 150 mg/kg (4.87 ± 0.16 SCEs/cell) or 200 mg/kg (5.51 ± 0.17 SCEs/cell) than in the controls (3.40 ± 0.15 SCEs/cell). No significant difference was observed in the frequencies of SCE or NORs between fetuses from exposed animals and those from controls. The frequency of NORs per cell was significantly reduced ($P < 0.05$) at the two highest lead nitrate dose levels; the frequencies were 2.50 ± 0.39 at 150 mg/kg, 2.31 ± 0.23 at 200 mg/kg, and 4.1 ± 0.38 for controls. Aneuploidy was frequently associated with the lowest dose level of lead nitrate (100 mg/kg). Deletions also occurred frequently and involved several chromosomes.

Kristensen *et al.* (1993) performed dominant-lethal studies of lead chloride and cyclophosphamide to quantify the genotoxic effects of lead chloride in late spermatogenesis. Male mice (*Mus musculus* strain NMRI) were randomly assigned to four treatment groups (6 per group), and two groups received drinking water containing 1.33 g/L of lead chloride for six weeks. One week (seven days) before mating, one lead-exposed group received an i.p. injection of cyclophosphamide (120 mg). Blood lead concentrations (µmol/L [µg/dL]) at time of mating were as follows: control group, 0.03 ± 0.02 [0.6 ± 0.4]; lead group, 1.24 ± 0.24 [34.3 ± 5.0]; cyclophosphamide group, 0.01 ± 0.02 [0.2 ± 0.4]; and lead plus cyclophosphamide group, 1.15 ± 0.14 [23.8 ± 2.9]. After mating, female mice were examined for the number of implants, number of live implants, number of resorptions, number of late implant losses, and mortality. Although the frequency of resorptions was lower in females mated with lead-treated males, the difference was not statistically significant. The data suggest that inorganic lead does not influence the mutagenicity of cyclophosphamide in the dominant-lethal assay.

Foster *et al.* (1996) investigated the effect of chronic lead exposure on semen quality in healthy cynomolgus monkeys (*Macaca fascicularis*) aged 15 to 20 years with mean ($\pm$ SD) blood lead levels of 10 ± 3 µg/dL (range = 6 to 20 µg/dL, N = 4) and 56 ± 49 µg/dL (range = 22 to 148 µg/dL, N = 7) compared with a reference group with blood lead levels < 1.0 µg/dL (N = 8). Monkeys had been exposed to lead acetate (50, 100, 500, or 2,000

138

µg/kg body weight) since birth. Blood and semen samples were collected once from each monkey in five different months. Serum testosterone levels were determined by radioimmunoassay, and lead effects on chromatin structure were analyzed by flow cytometry. No effects of treatment were observed on circulating levels of testosterone or parameters of semen quality such as sperm count, viability, motility, or morphology. A single sperm sample from each monkey was analyzed for effects on chromatin structure (Evenson 1990). In the flow-cytometric-based assay, sperm with abnormal chromatin structure are defined as having an increased susceptibility to acid denaturation, resulting in a shift from green to red fluorescence, expressed as α_t and determined by the ratio of red fluorescence to total fluorescence. Sperm from lead-exposed monkeys had significantly different ($P < 0.03$) α_t values than that from the controls. Sperm quality also differed significantly ($P < 0.05$) among the lead-exposed groups. The authors concluded that chronic lead exposure altered sperm chromatin structure.

5.4.2.2   Genotoxicity studies in mammals

Dhir *et al.* (1993) determined the effects of *Phyllanthus emblica* fruit extract (PFE) and ascorbic acid on the ability of lead to induce SCE in the bone marrow of Swiss albino male mice (*Mus musculus*). The mice were 6 to 8 weeks old, weighed 25 to 30 g, and were divided into exposure groups of five animals each. Mice were treated with a single priming dose of PFE by oral gavage (685 mg/kg b.w.) or with ascorbate (16.6 mg/kg b.w.) for seven consecutive days before exposure to lead nitrate. Bromodeoxyuridine (BrdU) was implanted subcutaneously in the abdomen as described by Sharief *et al.* (1986). Immediately after, mice were injected i.p. with lead nitrate in saline at concentrations of 10, 20, or 40 mg/kg b.w. Mice were injected i.p. with colchicine 22 hours after BrdU implantation and sacrificed by cervical dislocation 2 hours later. Bone marrow cells were obtained from femurs, and differential staining was performed as described by Perry and Wolff (1974) and Giri *et al.* (1987). Sixty intact second-division metaphase cells per animal were scored for SCEs, for a total of 300 cells per exposure group. *In vivo* exposure to lead nitrate resulted in a significant ($P < 0.001$) dose-dependent increase in SCE frequency over that in the control group. The increase was 2.5-, 3.7-, and 4.2-fold for mice exposed to lead nitrate at 10, 20, and 40 mg/kg, respectively. No difference was noted in the proliferation index. Pretreatment with PFE or ascorbate significantly ($P < 0.001$) reduced the increase in SCE, compared with that observed in animals exposed to lead nitrate alone.

To determine the clastogenic effect of lead nitrate, Jagetia and Aruna (1998) employed the micronucleus assay. Swiss albino mice (either sex) were injected i.p. with lead nitrate at 0, 0.625, 1.25, 2.5, 5, 10, 20, 40, or 80 mg/kg b.w., and animals were sacrificed at 12, 24, or 36 hours post-treatment. Bone marrow cells from femurs were prepared as described by Jagetia and Jacob (1992). The frequencies of micronucleated polychromatic erythrocytes (MPCE) and micronucleated normochromatic erythrocytes (MNCE) at 12, 24, and 36 hours after treatment were significantly higher in exposed mice than in controls. The increase in frequency of micronuclei was not dose-related and was greater in male than in female mice. Lead nitrate exposure also resulted in increased erythropoiesis, as the ratios of polychromatic to normochromatic erythrocytes (P/N ratio) were significantly higher in lead-exposed mice than in controls at 12, 24, and 36 hours

post-exposure. The P/N ratio was significantly higher in females than in males at 12 and 24 hours post-exposure.

Robbiano *et al.* (1999) examined five chemicals, including lead acetate, that are known to induce tumors in rats; these chemicals induce DNA damage and micronuclei formation in primary cultures of rat and human kidney cells and in the kidneys of intact rats (Sprague-Dawley male albino rats). DNA damage was tested with the comet (single-cell gel electrophoresis) and micronucleus assays. Primary cells were exposed to lead acetate (0.56, 1, or 1.8 mM) for 20 hours and immediately used for the comet assay or were cultured for a total of 48 hours for the micronucleus assay. Cytotoxicity was determined following 20 hours of exposure to the compound, and relative survival was based on trypan blue exclusion. The relative survival of primary rat and human kidney cells ranged from 84% to 96%. Data from the comet assay, based on cells pooled from three different rats and cells from three different human donors, demonstrated that lead acetate induced a dose-dependent increase in both tail length and tail moment, indicating DNA fragmentation. DNA fragmentation was significantly ($P < 0.05$) greater than in vehicle controls. Similar results were obtained with the micronucleus assay. Lead acetate induced a 3.7- to 6.4-fold increase in micronucleated primary rat cells and a 3.6- to 7.1-fold increase in micronucleated primary human kidney cells; these increases were statistically significant ($P < 0.05$). Consistent with the results observed *in vitro*, statistically significant increases in the average frequency of both DNA breaks and micronucleated cells were detected in the kidneys of rats given a single dose of lead acetate (0.5 LD_{50}) or three successive daily doses (0.33 LD_{50}). DNA fragmentation, based on the Comet assay, increased 5.3-fold at a lead acetate concentration of 107 mg/kg (three successive daily doses). The frequency of micronucleated cells increased 3.2-fold in animals given a single dose of lead acetate (160 mg/kg b.w.) and 3.8-fold in animals given three successive daily doses of 107 mg/kg b.w.

To determine whether lead enhanced the genotoxic effect of the pyrethroid cypermethrin [(*RS*)-α-cyano-3-phenoxybenzyl(1*RS*)-*cis,trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate], an insticide, Nehez *et al.* (2000) administered cypermethrin to outbred male Wistar rats (30 days old) by gavage for 4 weeks, five times per week, at 5.54, 11.08, or 22.16 mg/kg b.w. (1/100, 1/50, or 1/25 LD_{50}) alone or in combination with 10 mg/kg lead acetate at the 1/100 and 1/50 LD_{50} dose levels. Following treatment, animals were sacrificed, and bone marrow cells were obtained from the femur. Twenty metaphases from 10 animals per group were evaluated for the number of aberrant cells, numerical aberrations (chromosome number under or over 42), and structural aberrations (gaps, iso gaps, breaks, iso breaks, chromatid exchange, acentric fragments, dicentric and ring chromosomes, deletions, and translocations). Exposure to lead acetate significantly increased the frequencies of aberrant cells (18% vs. 5.5% for vehicle control; $P < 0.01$) and numerical chromosomal aberrations (16% vs. 6% for vehicle control; $P < 0.05$) but did not affect the frequency of structural chromosomal aberrations (1% in control and exposed groups). The combination of cypermethrin and lead acetate significantly increased the frequency of aberrant cells (21.5% at a cypermethrin concentration of 5.54 mg/kg; $P < 0.01$; 25% at a cypermethrin concentration of 11.08 mg/kg; $P < 0.001$) over that in vehicle-treated cells (10%). The frequency of numerical aberrations was not significantly increased by cypermethrin and

140

lead acetate in combination. However, the frequency of structural chromosomal aberrations was significantly increased (7.0% at a cypermethrin concentration of 5.54 mg/kg; P <0.05; 11.5% at a cypermethrin concentration of 11.08 mg/kg; P < 0.001). The authors concluded that the co-administration of lead increased the genotoxic effect of cypermethrin (see Table 5-5).

Table 5-5. Genotoxicity of lead compounds to mammals *in vivo*

End point	Results	Species	Compound	Concentration[a]	Reference
Reproductive genotoxicity studies					

SCE
    fetuses
 	
    dams
	–
	
	+
		ICR Swiss Webster mice: pregnant mice exposed and genotoxicity measured in maternal bone marrow and fetal liver and/or lung cells	lead nitrate	100, 150, 200 mg/kg b.w.
				
				150, 200 mg/kg b.w.
					Nayak *et al.* 1989

NORs
    fetuses
 	
    dams
	–
	
	+
		ICR Swiss Webster mice: pregnant mice exposed and genotoxicity measured in maternal bone marrow and fetal liver and/or lung cells	lead nitrate	100, 150, 200 mg/kg b.w.
				
				150, 200 mg/kg b.w.
					Nayak *et al.* 1989

Chromosomal aberrations
    fetuses
 	
    dams
	+
	
	+
		ICR Swiss Webster mice: pregnant mice were exposed and genotoxicity was measured in maternal bone marrow and fetal liver and/or lung cells	lead nitrate	100 mg/kg b.w.
				
				100, 150, 200 mg/kg b.w.
					Nayak *et al.* 1989

Fetal resorptions in unexposed females mated with lead-exposed males	–	male NMRI mice exposed before breeding	lead chloride	1.33 g/L in water	Kristensen *et al.* 1993
Sperm morphology	–	male White New Zealand rabbits	lead acetate	0.25, 0.5 mg/kg b.w.	Willems *et al.* 1982[b]
Abnormal chromatin structure in sperm	+	Cynomolgus monkey sperm cells	lead acetate	50, 100, 500, 2,000 μg/kg b.w.	Foster *et al.* 1996

End point	Results	Species	Compound	Concentration[a]	Reference
Animal genotoxicity studies					
DNA fragmentation	+ (both doses)	male albino Sprague-Dawley rat kidney cells	lead acetate	117 mg/kg (1 dose) 78 mg/kg (3 doses)	Robbiano *et al.* 1999
Chromosome loss or nondisjunction	–	*Drosophila melanogaster*	lead nitrate	200 ppm in corn meal-agar substrate	Ramel and Magnusson 1979[b]
Structural chromosomal aberrations or chromatid gaps	+ aberrations – gaps	C57B1 mouse bone marrow	lead acetate	0.5% in food	Deknudt and Gerber 1979[b]
Structural chromosomal aberrations or chromatid gaps	– aberrations + gaps	A/sw mouse leukocytes	lead acetate	1% in food	Muro and Goyer 1969[b]
Structural chromosomal aberrations or chromatid gaps	– aberrations + gaps	female C57B1 mouse bone marrow	lead acetate	0.50%, 1% in food	Jacquet *et al.* 1977[b]
Structural chromosomal aberrations or gaps	+	Sprague-Dawley rat bone marrow	lead acetate	10.4, 51.8, 77.6, 103.5 mg/kg b.w.	Tachi *et al.* 1985[b]
Chromosomal aberrations	+	male Wistar rats bone marrow	lead acetate	10 mg/kg b.w.	Nehez *et al.* 2000
Structural chromosomal aberrations or gaps	+	Cynomolgus monkey lymphocytes	lead acetate	1.5, 6, 15 mg/day in water	Deknudt *et al.* 1977[b]
Structural chromosomal aberrations or gaps	+	Cynomolgus monkey lymphocytes	lead acetate	1, 5 mg/day	Jacquet and Tachon 1981[b]
Micronucleus formation	+	Sprague-Dawley rat bone marrow	lead acetate	10.4, 51.8, 77.6, 103.5 mg/kg b.w.	Tachi *et al.* 1985[b]
Micronucleus formation	+ (both doses)	male albino Sprague-Dawley rat kidney cells	lead acetate	117 mg/kg (1 dose) 78 mg/kg (3 doses)	Robbiano *et al.* 1999
Micronucleus formation	+	Swiss albino mouse bone marrow	lead nitrate	0.625, 1.25, 2.5, 5, 10, 20, 40, 80 mg/kg b.w.	Jagetia and Aruna 1998
Micronucleus formation	–	C57BL/6 x C3H/He F$_1$ mice	lead acetate	125, 250, 500, 1,000 mg/kg b.w.	Bruce and Heddle 1979[b]
Micronucleus formation	–	male rabbit bone marrow erythrocytes	lead acetate	0.25, 0.5 mg/kg b.w.	Willems *et al.* 1982[b]
SCE	–	male rabbit peripheral blood lymphocytes	lead acetate	0.25, 0.5 mg/kg b.w.	Willems *et al.* 1982[b]

End point	Results	Species	Compound	Concentration[a]	Reference
SCE	+	male Swiss albino mouse bone marrow	lead nitrate	10, 20, 40 mg/kg b.w.	Dhir *et al.* 1993
Cellular proliferation	–	male Swiss albino mouse bone marrow	lead nitrate	10, 20, 40 mg/kg b.w.	Dhir *et al.* 1993

[a]The concentration reported is the dose level at which treatment-related effects were observed.

[b]Not reviewed in text; source: ATSDR 1999.

5.4.2.3   *Human genotoxicity studies*

Summary of ATSDR review

ATSDR (1999) reviewed genotoxicity studies of humans exposed to lead *in vivo* (mainly from occupational studies) published through 1994 and concluded that although the results were somewhat contradictory, they did suggest that lead might have an effect on chromosomes. Occupational exposure to lead was associated with increased mitotic activity or effects on cell division. Most, but not all, studies reported higher frequency of chromosomal aberrations in workers exposed to lead, and mixed results were reported for SCE. ATSDR noted that a common problem in these occupational studies was the possibility of confounding by occupational co-exposures. These studies and others published since 1994 (discussed below), are summarized in Table 5-6.

Current studies

Rajah and Ahuja (1995) examined the *in vivo* genotoxic effects of smoking and occupational lead exposure in printing press workers. The study population contained 29 males, including 13 printing-press workers and 16 individuals from the general population. Previous studies had indicated that atmospheric lead levels from the printing press were three times as high as background levels. A questionnaire was used to obtain data on age; duration of lead exposure; smoking; alcohol, coffee, and drug consumption; and recent illnesses. The subjects were divided into four groups: nonsmoking controls (N = 9), smoking controls (N = 7), lead-exposed nonsmokers (N = 7), and lead-exposed smokers (N = 6). Mitotic index and SCE were determined in peripheral blood lymphocytes. Lead-exposed smokers had the lowest mitotic index (0.78), compared with smoking controls (1.24) and lead-exposed nonsmokers (1.26); however, significance testing was not reported for the difference between lead-exposed smokers and smoking controls. The lead-exposed nonsmokers also had a significantly ($P < 0.05$) lower mitotic index than did nonsmoking controls. Smokers in the control and lead-exposed groups had significantly ($P < 0.05$) higher frequencies of SCE than did the nonsmoking controls (5.66 ± 1.52/cell for smoking controls, 5.37 ± 2.53/cell for lead-exposed smokers, and 3.22 ± 0.47/cell for nonsmoking controls). The frequency of SCE in the lead-exposed nonsmokers (3.75 ± 0.58/cells) did not differ significantly from that in the non-smoking controls (3.22 ± 0.47/cell). The authors concluded that the combination of smoking and lead exposure increased the frequency of SCE and inhibited mitosis, but that lead exposure did not appear to increase genotoxic damage beyond that caused by smoking alone. [The ability to separate the effects of lead from those of smoking or to evaluate any possible interactions between lead and smoking was limited by small numbers in

each exposure category (N = 6 or 7) and by the lack of quantitative information on smoking and lead exposure. Individuals smoking 10 or more cigarettes per day for more than a year were considered smokers; thus, the "smoker" groups included both light and heavy smokers, and it is not known whether the degree of smoking was similar between the lead-exposed smokers and the smoking controls.]

Vaglenov *et al.* (1997) correlated micronucleus formation in lead smelter workers with lead air concentrations at the work site, blood lead levels, employment period, and smoking habits. A total of 73 male workers were grouped by occupation: millers (N = 23), assembly workers (N = 21), plate-stacking workers (N = 20), and formation workers (N = 9). Controls were 23 males from administration and maintenance staff of the same plant who were never in direct occupational contact with lead. The total exposed group and controls also were subdivided into smokers and nonsmokers. The frequency of micronucleated cells per 1,000 binucleated lymphocytes was measured in peripheral blood lymphocytes. The mean concentration of lead in the air at the work sites was 0.7 ± 0.5 mg/m^3 for mill workers, 0.38 ± 0.3 mg/m^3 for assembly workers, 0.23 ± 0.2 mg/m^3 for plate-stacking workers, and 0.19 ± 0.1 mg/m^3 for formation workers. The mean air lead concentration for controls at the same factory was 0.06 ± 0.02 mg/m^3.

Mean blood lead concentrations for 65 of the 73 workers were over the "dangerous" level of 1.92 µmol/L [40 µg/dL], which is associated with biological effects. Elevated micronucleus frequencies were observed in lead-exposed workers from the four groups, and micronucleus frequency was correlated with external exposure (air lead concentrations) and internal exposure (blood lead levels). The micronucleus frequencies per 1,000 binucleated cells for the groups were 51.1 for mill workers, 46.5 for assembly workers, 37.3 for plate-stacking workers, and 35.2 for formation workers, for an average of 44.0 for the lead-exposed group, compared with 20.1 for the control group. The number of cells containing micronuclei also was significantly higher in the lead-exposed group than in the control group. For the whole group, analysis of variance showed that lead exposure, but not age and smoking, was correlated with micronucleus formation. The genotoxic effect was linearly dependent ($P < 0.001$) on the internal exposure, supporting an association between lead exposure and micronucleus formation. Micronucleus frequency did not differ significantly ($P > 0.05$) between lead-exposed smokers and nonsmokers, but did differ significantly between the control-group smokers and nonsmokers. [Strengths of this study include quantitative assessment of lead exposure (both external and internal); larger numbers of smoking (44) and nonsmoking (29) lead-exposed workers; evaluation of effects of different variables, such as smoking, age, and lead exposure; greater power to detect an effect, due to the high lead-exposure levels; and the finding of an exposure-response relationship. Limitations included the small number of controls and small subsets of smoking (10) and nonsmoking (13) controls and the lack of reported quantitative information on smoking habits.]

Bilban (1998) analyzed the incidence of cytogenetic damage in peripheral blood leukocytes of miners working in a lead and zinc mine in Slovenia (N = 120 males; 52% smokers), housewives living in the immediate vicinity of the mine, but not occupationally exposed (control group 1: N = 57 females; 17% smokers), and an independent control group (control group 2: N = 100; 86 males, 14 females; 58% smokers). Workers were

144

exposed to metals, including lead, cadmium and zinc, and radon. The blood lead concentration in the lead-exposed miners averaged 28 μg/dL, but 16% of these miners had blood lead concentrations greater than 40 μg/dL (the permissible value recommended by the World Health Organization in 1980). The blood lead concentration in the control groups averaged 7.2 μg/dL. Peripheral blood leukocytes were examined for structural chromosomal aberrations, SCE, and micronucleus formation.

The frequencies of chromosomal aberrations, SCE, and micronuclei were significantly higher in the miners than in the control groups. The mean percentages of cells with chromosomal aberrations were 4.09% (21,600 cells examined) in miners, 1.43% (11,400 cells) in control group 1, and 1.88% (20,000 cells) in control group 2. The mean frequencies of SCE were 7.97 per cell (5,800 cells examined) in miners, 6.17 (2,850 cells) in control group 1, and 6.63 (3,050 cells) in control groups 2. The frequency of micronucleated cells was 13.00 ± 3.55 per 500 cytokinesis cells (60,000 cells examined) for miners and 6.40 ± 2.12 (29,000 cells) in control group 2. Blood lead concentration and years worked in the mine were significantly correlated ($P = 0.012$). SCE frequency was significantly dependent on blood lead concentration ($P = 0.001$), as well as smoking. Chromosomal aberrations, but not SCE, were significantly dependent on radiation dose (radon). Moreover, smoking and the frequency of micronucleated cells were significantly correlated ($P = 0.001$). The purpose of this study was to detect cytogenetic damage in the miners; the authors cautioned that it was not possible to separate the individual effects of the different occupational exposures, as well as any effects from smoking. [The strongest evidence of lead-induced cytogenetic damage probably was for SCE, because SCE frequency depended on blood lead levels and not on radon dose. Strengths of this study include larger numbers of exposed workers, measurements of blood lead levels and other occupational exposures, and smoking information. Limitations include the lack of a relevant control group (that is, workers not exposed to lead) and the lack of analysis to control for confounders (occupational or lifestyle).]

Donmez *et al.* (1998) examined SCE frequencies in 32 male workers in a lead and zinc powder-producing factory in Turkey. The controls were 20 male sugar-refinery workers matched for age, smoking habits, and alcohol consumption. Metal-exposed workers had statistically significant higher blood lead levels than the controls ($P < 0.0001$), but the differences in blood zinc levels between groups were not significant ($P > 0.05$). Peripheral blood lymphocytes were evaluated for SCE; for each subject, the frequency of SCE was determined in 30 metaphases. The frequency of SCE was significantly higher in lead- and zinc-exposed subjects ($P < 0.01$) than in the controls (mean SCE per cell = 8.55 in exposed subjects vs. 7.55 in controls), and was significantly higher in nonsmoking lead- and zinc-exposed subjects than in nonsmoking controls ($P < 0.01$). SCE frequency also was significantly higher ($P < 0.01$) in control smokers than in control non-smokers (8.74 vs. 7.16). [Strengths of this study included matching of controls by age, smoking, and alcohol consumption, which minimized possible confounding by these variables. Although the study population was small, significant differences were observed; however, the further stratification of the small number of workers and controls into smokers and non-smokers could result in spurious associations.]

Vaglenov *et al.* (1998) monitored the genotoxic effects of lead in 22 male workers from a starter-battery plant in Bulgaria who were heavily exposed to lead (0.45 ± 0.5 mg/m^3 lead in air at the workplace, which exceeded the threshold limit value of 0.1 mg/m^3). Two control groups were included: an internal control group of 19 male workers from the same plant without direct lead exposure (control group 1) and an external control group of 19 male workers from the administrative staff of another factory in the same town (control group 2). A questionnaire was used to obtain data on smoking and alcohol consumption habits. Blood lead levels were 0.88 ± 0.03 µmol/L [18.23 ± 0.62 µg/dL] for control group 2, 1.33 ± 0.08 µmol/L [27.56 ± 1.66 µg/dL] for control group 1, and 2.94 ± 2.15 µmol/L [60.92 ± 44.55 µg/dL] for the lead-exposed workers.

The frequency of micronucleated cells per 1,000 binucleated lymphocytes was determined from peripheral blood lymphocytes. The lead-exposed workers had a higher frequency of micronucleated cells (61.95 ± 3.31) and larger numbers of binucleated cells containing one or more micronuclei (53.09 ± 2.36) than did the internal controls (26.47 ± 2.71 micronuclei and 23.74 ± 2.34 binucleated cells containing micronuclei) or the external controls (19.68 ± 2.14 micronuclei and 18.84 ± 2.09 binucleated cells containing micronuclei). [Strengths of this study were good exposure assessment of lead (both air concentrations and blood levels were measured) and the lack of any apparent occupational exposure to other genotoxic agents. Limitations included the small number of subjects and the lack of exposure-response analyses; however, the numbers may have been too small for the latter.] Although the authors assessed and reported smoking (cigarettes per day) for each individual, they did not appear to use this information in their analyses. The lead-exposed group included a higher percentage of smokers (77%) than did either control group 1 (58%) or control group 2 (63%), but the average cigarettes per day in the lead-exposed group (13.2) was intermediate between the averages for the two control groups (11.1 for control group 1 and 15.7 for control group 2). [Percent smokers and average cigarettes per day were calculated from data reported in the publication. Because micronucleus formation was two- to three-fold higher in the lead-exposed workers than in the control groups, and the difference in smoking between the exposed and control groups did not appear to be substantial, it seems unlikely that smoking confounded these results.]

To explore the possible relationship between lead exposure and DNA damage and oxidative stress in Chinese secondary lead smelter workers, Ye *et al.* (1999) correlated DNA damage as measured by the comet assay with concentrations of blood lead, urinary lead, and urinary α-aminolevulinic acid. Malondialdehyde (MDA) concentrations and superoxide dismutase (SOD) activity in plasma also were determined. Information was obtained by questionnaire concerning gender, age, duration of work, job type, cigarette smoking, and alcohol consumption. Heparinized blood and urine were obtained from 66 secondary lead smelter workers (41 male and 25 female) (46 used for the comet assay) and 28 controls (18 male and 10 female). Subjects were divided into four groups based on blood lead concentrations (< 13, 13 to 27, 27 to 37, and > 37 µg/dL). SOD activity and MDA concentrations were significantly higher in females in the three highest blood lead groups than in the lowest blood lead group, and SOD activity was higher in males with the highest blood lead levels; smoking and alcohol consumption did not significantly

affect MDA concentrations or SOD activity. A positive correlation was observed between the blood lead concentration and DNA damage, which was statistically significant ($P < 0.05$) for blood lead concentrations greater than 27 µg/dL. Amounts of DNA damage differed significantly between lead-exposed workers with the same smoking levels or alcohol consumption but different lead levels, except for nonsmokers and the low-lead-exposure group. DNA damage also increased with increasing smoking levels at the same blood lead levels. [Strengths of this study were the finding of an exposure-response relationship between lead exposure and DNA damage and attempts to separate genotoxic effects of lead exposure from those of cigarette smoking. Another strength was measurement of MDA concentrations and SOD activity, which are markers of oxidative stress; elevated levels were consistent with potential mechanisms of lead-induced DNA damage. A potential limitation of the study was the stratification of a small number of subjects on many different variables (i.e., gender, smoking status, and lead exposure), resulting in very small numbers in each subgroup, which can yield spurious results.]

Restrepo *et al.* (2000) investigated the relationship between lead exposure and DNA damage and repair in 43 Colombian battery-factory workers and 13 controls who were not occupationally exposed to lead. Individuals completed a questionnaire on smoking habits, age, and medical and occupational histories. Workers were highly exposed to lead; 74% of the exposed workers exhibited clinical symptoms of lead toxicity, including headache, abdominal colic, metallic taste, and paresthesia. The average blood lead concentration of the lead-exposed workers (98.5 ± 25.3 µg/dL) was much higher than that of the non-exposed group (5.4 ± 3.6 µg/dL). Lead-exposed workers and controls were subdivided into four groups according to classification of their blood lead concentrations by Colombia's National Institute of Health: (1) lower than 40 µg/dL (normal), (2) 41 to 80 µg/dL (acceptable), (3) 81 to 120 µg/dL (excessive), and (4) greater than120 µg/dL (dangerous). [The normal blood lead group consisted of the 13 controls, who had blood levels of less than 15 µg/dL.] Approximately 70% of the workers had blood lead levels classified as excessive or dangerous. DNA damage was measured by the comet assay, using whole blood, and DNA repair capacity was assessed by measuring DNA damage before and after *in vitro* exposure of the cells to X rays, after various incubation times. A statistically significant ($P < 0.05$) difference in both the level of basal DNA damage (before irradiation) and level of DNA damage induced by X radiation was observed between the lowest and highest categories of lead exposure. Multiple regression analysis, in which variables included length of employment, age, and blood lead concentrations, showed that lead concentration was the main factor contributing to sensitization to genotoxic damage (that is, the difference in DNA damage before and immediately after irradiation). No significant differences in DNA repair capacity (as measured by DNA damage following incubation after irradiation) among the different blood level groups were observed. The comet assay under alkaline conditions mainly detects single-strand breaks, whereas X rays induced both single- and double-strand breaks; thus, repair of double-strand breaks was not measured in this study. Only 9% of the population smoked, and the authors stated that smoking habits had no effect on DNA damage. [Strengths of this study included measurement of blood lead concentration and the ability to control for smoking.]

Wu *et al*. (2002) evaluated SCE frequencies in 57 lead-exposed workers and 30 workers not occupationally exposed to lead (controls) at a storage-battery manufacturer in Taiwan. Blood lead levels were measured, and lead-exposed workers were divided into a high-blood-level group ($\geq$ 15 µg/dL; mean = 32.5 µg/dL; N = 23) and low-blood-level group (< 15 µg/dL; mean = 9.3 µg/dL; N = 34). The mean blood lead level in controls was 4.2 µg/dL. Zinc protoporphyrin also was measured and was significantly higher in both the high- and low-blood-level groups than in controls. [As discussed in Section 2, zinc protoporphyrin is a biomarker of effect, arising from the disturbance of heme synthesis by lead.] SCE, high-SCE frequency cells (HFCs) and DNA–protein crosslinks were measured by fluorescence spectrophotometry in peripheral blood lymphocytes collected from the subjects. An HFC was defined as a cell having a SCE frequency over the median 95% value from the 19 nonsmoking control subjects. SCE frequencies and percentages of HFCs and DNA–protein crosslinks were significantly higher in the high-blood-level group (6.1 SCEs/cell, 11% HFC, and 1.5% crosslinks) than in the controls (5.2 SCEs/cell, 3% HFC, and 1.0% crosslinks). Moreover, frequencies of SCE and percentages of HFCs and DNA–protein crosslinks also were significantly higher in both smoking and nonsmoking workers with high blood lead levels than in smoking and nonsmoking controls. Multiple linear regression analysis showed that smoking and blood lead levels but not age and gender were significantly associated with the percentage of DNA–protein crosslinks and SCE frequency. [A strength of this study was the use of multiple linear regression models to adjust for age, gender, and smoking.]

Table 5-6. Genotoxicity of lead compounds *in vivo* in humans

End point	Results	Blood lead level[a] (µg/dL)	Exposure (country)	Reference
Chromosomal aberrations in peripheral blood lymphocytes	+	37.7	lead-exposed workers	Schwanitz *et al.* 1970[b,c] Schwanitz *et al.* 1975[b,c]
Chromosomal aberrations in peripheral blood lymphocytes	+	38 to 64	storage-battery plant workers (Italy)	Forni *et al.* 1976[b]
Chromosomal aberrations in peripheral blood lymphocytes	+	> 50	lead-exposed smelter workers (Sweden)	Nordenson *et al.* 1978[b]
Chromosomal aberrations in peripheral blood lymphocytes	+	38 to 96	storage-battery plant workers (Iraq)	Al-Hakkak *et al.* 1986[b]
Chromosomal aberrations in peripheral blood lymphocytes	+	22 to 48	storage-battery plant workers (China)	Huang *et al.* 1988[b,d]
Chromosomal aberrations (also significantly dependent on radiation dose) in peripheral blood lymphocytes	+	27.9	lead and zinc mine workers, also exposed to metals and radon (Slovenia)	Bilban 1998
Chromosomal aberrations in peripheral blood lymphocytes	+/−	40 to > 120	shipyard workers (Scotland)	O'Riordan and Evans 1974[b]
Chromosomal aberrations in peripheral blood lymphocytes	−	average 48.7	lead smelter workers (Finland)	Maki-Paakkanen *et al.* 1981[b]
Chromosomal aberrations in peripheral blood lymphocytes	−	> 30	children living near lead plant (Germany)	Bauchinger *et al.* 1977[b]
Chromosomal aberrations	−	NA	lead manufacturing industry (The Netherlands)	Schmid *et al.* 1972[b,c]
Chromosomal aberrations in peripheral blood lymphocytes	−	40	volunteers who ingested lead acetate (49 days) (The Netherlands)	Bijlsma and de France 1976[e,f]
SCE in peripheral blood lymphocytes	+	22 to 48	storage-battery plant workers (China)	Huang *et al.* 1988[b,d]
SCE in peripheral blood lymphocytes (exposure-response with blood lead levels)	+	27.9	lead and zinc mine workers, also exposed to metals and radon (Slovenia)	Bilban 1998

End point	Results	Blood lead level[a] (µg/dL)	Exposure (country)	Reference
SCE in peripheral blood lymphocytes	+	13.81	lead and zinc powder factory (Turkey)	Donmez *et al.* 1998
SCE in peripheral blood lymphocytes High-SCE-frequency cells	+ +	32.5	battery manufacturer (Taiwan)	Wu *et al.* 2002
SCE in peripheral blood lymphocytes	+/–[g]	average 48.7	lead smelter workers (Finland)	Maki-Paakkanen *et al.* 1981[b]
SCE in peripheral blood lymphocytes	+/–[h]	29 to 75	storage-battery plant workers (Denmark)	Grandjean *et al.* 1983[b]
SCE in peripheral blood lymphocytes	–	29 to 63	children living near lead smelter (Italy)	Dalpra *et al.* 1983[b]
SCE in peripheral blood lymphocytes	–	NA	battery factory workers (Mexico)	Leal-Garza *et al.* 1986[b]
SCE in peripheral blood lymphocytes	–	NR	printing-press workers (India)	Rajah and Ahuja 1995
Micronuclei in peripheral blood leukocytes	+	67.55	lead smelter workers (Bulgaria)	Vaglenov *et al.* 1997
Micronuclei in peripheral blood leukocytes	+	27.9	lead and zinc mine workers, workers also exposed to metals and radon (Slovenia)	Bilban 1998
Micronuclei in peripheral blood leukocytes	+	60.92	starter-battery plant (Slovenia)	Vaglenov *et al.* 1998
Micronuclei in blood lymphocytes	+	40	metal-powder producing workers (lead, zinc, cadmium) (Turkey)	Hamurcu *et al.* 2001
DNA-protein crosslinks in peripheral blood lymphocytes	+	32.5	battery manufacture workers (Taiwan)	Wu *et al.* 2002
DNA damage (comet assay) in peripheral blood lymphocytes significant relationship at blood levels > 27 µg/dL	+	four groups: < 13 13 to 27 27 to 37 > 37	lead smelter workers (secondary) (China)	Ye *et al.* 1999

End point	Results	Blood lead level[a] (µg/dL)	Exposure (country)	Reference
DNA damage (comet assay) in peripheral blood lymphocytes		41 to >120	battery factory workers (Colombia)	Restrepo *et al.* 2000
basal level	+			
sensitivity to X rays	+			
DNA damage (comet assay)	+	39	battery factory workers (Italy)	Fracasso *et al.* 2002
DNA repair capacity (comet assay) after exposure to X rays in peripheral blood lymphocytes	–	41 to > 120	battery factory workers (Colombia)	Restrepo *et al.* 2000
Higher mitotic activity in peripheral blood lymphocytes	+	40	volunteers who ingested lead acetate (49 days) (The Netherlands)	Bijlsma and de France 1976[b,e]
Decrease in mitotic index in peripheral blood lymphocytes	+	NR	printing press workers (India)	Rajah and Ahuja 1995
Increased mitotic activity	+	NA	lead-exposed workers (Germany)	Schwanitz *et al.* 1970[b,c]
Effects on cell division	+	NA	(not available)	Sarto *et al.* 1978[b,c]

[a]NA = not available; NR = not reported.

[b]Not reviewed in text; source: ATSDR 1999.

[c]Foreign-language publication, not reviewed here; results are those reported by ATSDR 1999.

[d]Incorrectly listed in ATSDR (1999) as environmentally exposed children and as reporting negative results for SCE; no papers by Huang and genotoxicity in environmentally exposed children were found.

[e]Incorrectly listed in ATSDR (1999) as Bulsma.

[f]Study was reviewed in ATSDR (1999) (see mitotic index), but chromosomal aberrations were not reported.

[g]SCE frequency was higher in lead-exposed smokers than in non-exposed smokers, but not higher in lead-exposed nonsmokers than control non-smokers.

[h]ATSDR (1999) also reported a slight positive correlation with duration but not level of exposure.

5.5   Summary

Lead induced chromosomal aberrations in most studies in plants and in mammals *(in vitro* and *in vivo*) and DNA damage and fragmentation in mammals (*in vivo*; conflicting results were observed in *in vitro* studies) and cell-free systems (in the presence of hydrogen peroxide) and inhibited DNA and RNA polymerase in cell-free systems and mammalian cells (*in vitro*). Conflicting results were observed for SCE and micronucleus induction in mammalian studies (*in vitro* and *in vivo*). Lead was not mutagenic in bacteria, and conflicting results were observed in mammalian *in vitro* systems. Conflicting results may reflect differences in the model systems employed, the end points

used to determine genotoxicity, and the lead compounds employed. In studies of humans occupationally exposed to lead, there is evidence to suggest that lead damages chromosomes or DNA; most studies were positive for induction of micronuclei, chromosomal aberrations, and DNA damage. Studies on SCE and studies in humans exposed environmentally to lead gave conflicting results. Studies in humans sometimes are difficult to evaluate, because little information is given on how the populations were selected for study and because of potential exposure to compounds from occupational or environmental sources that may act in conjunction with lead to increase its genotoxic potential. Likewise, personal habits such as cigarette smoking and alcohol consumption affect the genotoxic properties of various compounds, including lead. However, many of the more recent studies either controlled for smoking or reported an exposure-response relationship, suggesting that the genotoxic effects were due to lead exposure. Although lead(II) forms stable complexes with the nitrogenous bases and phosphate groups of purified DNA, it is unlikely that lead compounds are directly genotoxic. However, several mechanisms exist by which lead compounds could indirectly alter DNA replication, fidelity, and repair, resulting in genotoxicity.

6 Other Relevant Data

This section is divided into three subsections: (1) absorption, distribution, and excretion of lead in humans, (2) other toxic effects of lead compounds, and (3) mechanistic studies relevant to lead carcinogenicity. In all subsections, the majority of the discussion focuses on human studies, since these are extensive.

6.1   Absorption, distribution, and excretion of lead in humans

6.1.1   Inorganic lead

6.1.1.1   Absorption

Inorganic lead can be absorbed by inhalation of fine particles and by ingestion. Before lead is absorbed by the lungs, a fraction of the inhaled lead is deposited in the respiratory tract. In adults, the rate of deposition of airborne lead is approximately 30% to 50%. This rate is dependent on the size of the particles and the ventilation rate of the individual. Smaller particles (< 1 μm) have been shown to have greater deposition and absorption rates than larger particles (ATSDR 1999).

Ingestion of inorganic lead results in gastrointestinal (GI) absorption in humans and rodents. Although GI absorption is influenced by chemical species, no inorganic lead compound studied to date is completely unavailable, as demonstrated in studies of rats by Dieter *et al.* (1993). GI absorption of lead also is age-dependent in humans and rodents. It is estimated that young children absorb 4 to 6 times more lead than do adults. Dietary constituents, also may influence GI absorption, as shown in Table 6-1. Deficiencies in iron, calcium, and zinc appear to increase the GI absorption of lead, while a high-protein diet appears to reduce absorption (Hammad *et al.* 1996).

Lead also can be absorbed through the skin, as demonstrated by a study in which 4.4 mg of lead (as lead acetate or lead nitrate) was applied to the skin under a covered plastic patch on the forearms of human subjects; 1.3 mg of lead was not recovered from washing of the skin and was detected in sweat, blood, and urine within 6 hours of the application (Stauber *et al.* 1994).

Table 6-1. Effects of nutritional elements on gastrointestinal lead absorption in animals

Element	Species	Index of effect	Interactive effect
Calcium	rat	lead in tissues and severity of effect at low levels of dietary calcium	low dietary calcium (0.1%) increases lead absorption and severity of effects
Calcium	rat	lead retention	calcium deficiency increases retention
Calcium	rat	lead in tissues at high levels of dietary calcium during pregnancy	high dietary calcium reduces release of lead from bone
Calcium	pig	lead in tissues at low levels of dietary calcium	low dietary calcium increases lead absorption
Calcium	horse	lead in tissues at low levels of dietary calcium	low dietary calcium increases lead absorption
Calcium	lamb	lead in tissues at low levels of dietary calcium	low dietary calcium increases lead absorption
Calcium	chick	lead absorption and retention	calcium deficiency increases lead absorption and retention
Iron	rat	tissue levels and relative toxicity of lead	iron deficiency increases lead absorption and toxicity
Iron	rat	lead absorption in everted duodenal sac preparation	reduction in intubated iron increases lead absorption; increased levels decrease lead uptake
Iron	rat	*in utero* or milk transfer of lead in pregnant or lactating rats	iron deficiency increases both *in utero* and milk transfer of lead to sucklings
Iron	mouse	lead retention	iron deficiency has no effect on lead retention
Protein	rat	body lead retention	low dietary protein either reduces or does not affect lead retention in various tissues
Protein	rat	tissue levels of lead	casein diet increases lead uptake, compared with soybean meal
Protein	rat	lead uptake by tissues	both low and high dietary protein increase lead absorption
Milk components	rat	lead absorption	lactose-hydrolyzed milk does not increase lead absorption, but ordinary milk does
Milk components	rat	lead absorption	lactose in diet increases lead absorption, compared with glucose
Zinc	rat	lead absorption	low-zinc diet increases lead absorption
Zinc	rat	lead transfer *in utero* and in milk during lactation	low-zinc diet of mother increases lead transfer *in utero* and in maternal milk
Zinc	rat	tissue retention	low-zinc diet increases brain lead levels

Sources: Fullmer 1997 (chick), ATSDR 1999 (all others).

6.1.1.2   Distribution and PBPK models

The mean-life of lead in blood is approximately 30 days. In blood, lead is partitioned between red cells and plasma. The relationship between whole-blood lead and plasma lead is linear at lower concentrations, but at higher concentrations, levels in plasma are higher than would be expected based on a linear relationship (Manton *et al.* 2001) (see Figure 6-1).
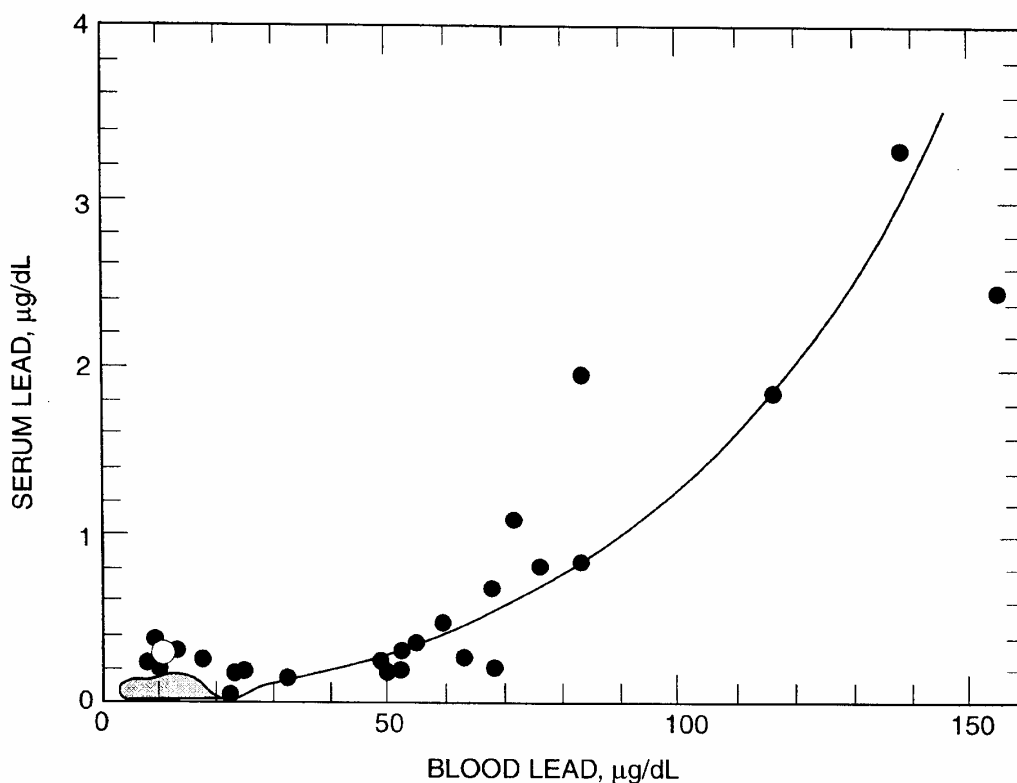
Source: ATSDR 1999.

Figure 6-1. Curvilinear relationship of human serum lead to blood lead

Note: Crosshatched area represents several overlapping data points.

Extensive physiologically based pharmacokinetic (PBPK) modeling has been conducted on inorganic lead in both adults and children (O'Flaherty 1993, 1995). The skeleton is a major compartment for inorganic lead deposition in mammals; between 75% and 90% of the body burden of lead is found in bones and teeth. In humans, bone lead levels gradually increase over the lifespan, as demonstrated in a series of autopsy and biopsy studies by Aufderheide *et al.* (1992). The half-life of lead in bone depends on bone type; it is estimated that the half-life of lead in cortical bone may be as long as 25 years (Marcus 1985). For this reason, analyses of teeth and bone provide an integrated biomarker of previous lead exposure, which has been used in several important studies of lead toxicity in both children and adults. Lead also is transferred across the placenta and

is excreted in breast milk. Some evidence indicates that the fetus accumulates lead in both the skeleton and soft tissue (ATSDR 1999).

6.1.1.3 Mobilization

Skeletal lead can be mobilized under normal and pathophysiological conditions that affect bone mineral metabolism. For example, lead is mobilized from the skeleton during pregnancy and lactation, as demonstrated in a series of elegant studies using stable isotope analysis to distinguish skeletal lead from environmental lead in Australian women (Gulson *et al.* 1997). In women, lead also is released from bone stores at menopause (Silbergeld *et al.* 1988), which can result in significant elevations of blood lead that may be associated with increases in blood pressure and other toxic effects (Hertz-Picciotto and Croft 1993). Pathophysiological conditions that favor bone resorption, such as Paget's disease, hypothyroidism, and prolonged bed rest, also increase blood lead concentrations; this occurrence has been interpreted as a redistribution of bone lead into blood (Silbergeld *et al.* 1993).

Mobilization of maternal lead during pregnancy was studied in female Sprague-Dawley rats (Buchet *et al.* 1977). Treatment regimens included controls (group 1), rats given 1 mg/L of lead as lead nitrate in drinking water for 150 days before mating, over gestation, and for three weeks after parturition (group 2), rats given 1 mg/L lead in drinking water for 150 days before mating, discontinued on day 1 of pregnancy (group 3), and rats given 1 mg/L lead in drinking water for 150 days, but discontinued 50 days before mating (group 4). On day 21 after delivery, lead concentrations and free porphyrins were measured in blood and various tissues. The results are summarized in Table 6-2. It was concluded that lead stored in the organism could be mobilized during gestation.

Lead also has been measured in a variety of tissue samples in humans. In one study investigating levels of inorganic chemicals in brain tumors, Al-Saleh and Shinwari (2001) measured concentrations of lead, as well as cadmium and mercury, in samples of tumors from 23 patients with malignant and 21 patients with benign brain tumors who were undergoing treatment at a Saudi Arabian hospital. Lead levels were somewhat higher in malignant than in benign tumors (0.65 vs. 0.61 µg/g); however, the authors noted that these concentrations were much higher than reported for brain tissue in a non-Saudi population. In addition, the lack of any biomarker surveyed in nondiseased tissue or other indices of cumulative lead exposure and the absence of a true control group for comparison preclude reliable inference from this study.

Table 6-2. Mobilization of lead during gestation in Sprague-Dawley rats

Exposure group	Concentration of lead on day 31 after delivery		Concentration of free porphyrins in brain on day 31 after delivery
	Blood (μg/L)	Brain (ng/mg of protein)	(ng/mg of protein)
Group 1 (controls)			
Mothers	30	0.5	1.0
Offspring	20	0.02	0.8
Group 2 (exposed before mating, over gestation, and after parturition)			
Mothers	18	0.2	0.7
Offspring	9	0.02	0.7
Group 3 (exposed before mating)			
Mothers	11	0.2	0.9
Offspring	6	0.02	0.8
Group 4 (exposed until 50 days before mating)			
Mothers	49	0.7	1.6
Offspring	36	0.23	1.1

Source: Buchet *et al.* 1977.

6.1.1.4   Excretion

Excretion of lead does not depend on the route of exposure (ATSDR 1999). Dietary lead excreted in the feces includes both lead that was not absorbed by the GI tract and lead that was excreted in the bile. The major routes of excretion of absorbed lead are urinary and biliary clearance, and excretion of lead in the feces generally is greater than excretion in the urine. In rats, fecal excretion of lead due to biliary clearance may still exceed urinary excretion even for lead administered i.v. Excretion in rats, dogs, and mice is a multiphasic process. In rats, excretion of lead following i.v. administration is biphasic, with half-lives of 21 hours for the fast phase and 280 hours for the slow phase. In dogs, a triphasic process with half-lives of 12, 184, and 4,951 days has been reported. The terminal phase of the biphasic elimination curve observed for mice had a half-life of 110 days. In humans, the total excretion rate may be lower in infants than in adults, resulting in retention of a larger percentage of the total amount of lead absorbed.

6.1.2   Organic lead compounds

Organic lead compounds are toxicokinetically distinct from inorganic lead compounds in terms of absorption and distribution. Eventually, organic lead compounds are dealkylated by hepatic metabolism and stored in the body as inorganic lead. Owing to their greater lipophilicity, organic lead compounds are rapidly partitioned into soft tissues, as demonstrated by average lead levels in major viscera (i.e., lung, brain, liver, kidney, spleen, and heart tissue) of approximately 7 to 100 mg/kg in rats and 7 to 30 mg/kg in

dogs following inhalation exposure to lethal doses of tetraethyl lead (12 to 46 mg/m^3) or tetramethyl lead (4 to 63 mg/m^3) (Davis *et al.* 1963).

It has been shown that inhalation of TEL results in much higher levels of lead in the brain than does exposure to inorganic lead. Boudene *et al.* (1977) exposed 40 female Wistar rats to an aerosol of gasoline containing 0.6 g/L of tetraethyl lead and enhanced with organic ^{210}Pb chelated with dibenzoylmethane. Animals were placed in a box and breathed the gasoline aerosol for 30 to 45 minutes. Lead was rapidly cleared from the lungs, with less than 10% remaining after 48 hours. Six days after exposure, 40% of the dose was eliminated in the feces and 15% in the urine; 40% was fixed in the bones, 4% was distributed among soft tissues, and 1% remained in the lungs. In another inhalation study (nose-only exposure), ^{203}Pb-labelled TEL was administered over 40 to 60 minutes (Morgan and Holmes 1978). Approximately 20% to 25% of lead particulates generated from engine exhaust was deposited in the lungs of 12 male albino rats, and at least half of the deposited lead was absorbed, with a half-life of less than one hour. Less than 2% remained in the lungs after 7 days.

Organic lead compounds also have been shown to be rapidly and extensively absorbed through the skin of rats and rabbits (ATSDR 1999). One study showed that 0.75 mL of TEL applied to the abdominal skin of rabbits resulted in 1.06 mg of lead being detected in the carcass after 0.5 hours and 4.41 mg after 6 hours of exposure. However, these measurements did not include the contents of the intestinal tract, which were inadvertently discarded. Following dermal application of 0.75 mL of TEL to three other rabbits, 7.9 to 9.3 mg of lead was detected in the carcasses after 4 hours of exposure (Kehoe and Thamann 1931).

Excretion of organic lead differs from that of inorganic lead (see Section 6.1.1.4, above). A major route of elimination of inhaled tetraalkyl lead compounds is exhalation (ATSDR 1999).

6.2 Other toxic effects of lead compounds

The toxicity of lead compounds to humans has been extensively studied. For the last 100 years, considerable attention has been focused on the neurotoxic effects of lead compounds in young children, following reports of the exposure of children to lead-based house paint. Because of the very large amount of published literature on lead toxicity, this section will provide only a brief review, with references to major reviews and government documents.

Human exposure to lead is regulated in the occupational and non-occupational environments (see Section 2.9 and Appendix A for lists of lead regulations). Several end points of concern have been associated with human exposure to lead and lead compounds; end points identified in adults, children, and/or fetuses include (but are not limited to) neurotoxicity, nephrotoxicity, hematoxicity and anemia, reproductive toxicity, developmental toxicity, and cardiovascular toxicity. The end points are discussed briefly below.

6.2.1   Neurotoxicity

By the 1930s, it was increasingly recognized that exposure to lead compounds (inorganic, lead carbonate based, and lead chromate and oxide pigments) was a frequent cause of encephalopathy in children. Under conditions of chronic exposure, the neurotoxic effects of exposure to lead in paint included loss of speech, seizures, and coma (McKhann 1932). Children who survived these severe events frequently were retarded intellectually and in their motor skills (Silbergeld 1997). Reviews of several large prospective studies of children's neurocognitive and behavioral development reached a consistent conclusion that "subencephalopathic" exposures to inorganic lead, i.e., at doses associated with blood lead levels as low as 10 µg/dL, are significantly associated with poor outcomes in neurocognitive and behavioral development and with impairments in attention, hearing, and school attainment (ATSDR 1999, Silbergeld 1997).

Although the CNS toxicity of lead in children became the critical end point in pediatrics, inorganic lead compounds also can affect both CNS and peripheral nervous system (PNS) function in adults. Neurotoxic manifestations depend on both dose and duration of exposure. High levels of exposure cause disabling impairments in PNS function, described as "painter's wrist" or "foot drop" in the 18th and 19th centuries, as well as profound mental changes and cognitive impairments, which were observed in workers in lead industries in the 19th century. In the 1920s, when production of TEL began in the United States, cases of acute psychosis and hallucinations in workers were reported. Some recent reviews (Stewart *et al*. 2002, Kamel *et al*. 2002) have suggested that adult lead exposure may be associated with increased risks of neurodegenerative disease in aging, specifically, amyotrophic lateral sclerosis and dementias.

6.2.2   Nephrotoxicity

The renal toxicity of lead has been well described for over 100 years. Acute nephrotoxicity has been described in lead-intoxicated children (Loghman-Adham 1997). The evidence in both humans and experimental animals indicates that thresholds exist for lead nephropathy. In rodents, proximal tubular injury occurs at blood lead levels of 60 µg/dL. Observations in humans indicate that blood lead levels greater than 60 µg/dL for up to 12 years are required for nephropathy. Increased risk of end-stage renal failure has been reported in lead workers long after cessation of exposure.

6.2.3   Hematoxicity and anemia

Lead inhibits the biosynthesis of heme through highly specific interactions with one of the rate-limiting enzymes in this pathway, ALAD. As a consequence of this effect, levels of some heme precursors are elevated (by feedback deregulation), and heme levels are decreased (Silbergeld 1987). These effects have been widely used as biomarkers for lead exposure, but they also represent toxic effects of lead and may play a role in target organ responses. Inhibition of heme production, along with toxic effects on globin synthesis and erythrocyte integrity, is associated with anemia at high levels of exposure (> 40 µg/dL).

6.2.4   Reproductive toxicity

Lead is toxic to sperm and can alter endocrine function in adults. Decreases in spermatologic parameters were reported in men exposed to inorganic lead compounds in battery plants and were associated with blood lead levels as low as 40 μg/dL, which are well within current occupational standards; in some cases, these deficits were ameliorated when lead exposure and blood lead levels were reduced (Sallmen 2001). No specific effects of lead have been reported on female reproduction; however, lead is toxic to fetal development, and these effects sometimes are misinterpreted as effects on pregnant women or women of childbearing age.

6.2.5   Developmental toxicity

Lead crosses the placenta and is accumulated in fetal organs, including the brain. High exposure to inorganic lead can induce intrauterine death and stillbirth. At lower levels, prenatal exposure to lead, indicated by cord blood lead level obtained at parturition, is associated with a range of adverse effects, including decreased growth in stature and delays in early infant development. If no further elevated lead exposure occurs after birth, development generally, but not always, normalizes, as demonstrated in longitudinal studies in which the subjects were enrolled prior to birth (Bellinger *et al.* 1992).

6.2.6   Cardiovascular toxicity

Several studies have reported significant associations between blood lead level and blood pressure in adult men and women (Hertz-Picciotto and Croft 1993, ATSDR 1999). In both of the NHANES surveys (II and III) of lead exposure and health status in the United States, blood lead level was positively associated with blood pressure, in a dose-related fashion. It was estimated that the effects of lead exposure on blood pressure contribute significantly to risks of hypertensive heart disease and stroke in the U.S. population.

6.2.7   Other effects in rodents

It is important to note that all of these toxic effects of lead described in human populations have been observed in rodent models at similar blood lead levels. Lead induces both PNS and CNS toxicity; affects CNS development in young animals, resulting in impaired learning performance and hyperactivity; inhibits heme biosynthesis; affects intrauterine growth; affects auditory-evoked responses; impairs reproductive function in males; and induces hypertension.

6.3   Mechanisms of lead carcinogenesis

Knowledge of the mechanisms by which metals cause cancer remains uncertain, even for those metals for which the evidence of human carcinogenicity is considered adequate. At high concentrations, lead can bind to DNA and change its conformation (Smirnov and Shafer 2000), break nucleic acids (Brown *et al.* 1983, Wedrychowski *et al.* 1986), and induce cell proliferation, measured by increased mitotic indices or increased thymidine incorporation (Calabrese and Baldwin 1992). However, the exposure levels used in these studies are well above the levels associated with other severe toxic effects of lead, including tissue damage and cytotoxicity. Because lead can cause tumors in experimental

animals at exposure levels that are not associated with tissue damage (Waalkes *et al.*
1995), these events probably are not relevant to mechanisms of carcinogenesis.

6.3.1 Possible mechanisms of genotoxicity and carcinogenicity

Even though lead has been intensely studied for many years, the mutagenic, clastogenic,
and carcinogenic properties of lead and lead compounds are not well understood. IARC
(1980, 1987) has determined that there is sufficient evidence to conclude that lead and
inorganic lead compounds cause cancer in experimental animals, but that sufficient
evidence in humans is lacking. Several possible mechanisms have been examined to
better understand the carcinogenic properties of lead and the conditions required for this
effect. These include mitogenesis, chronic nephropathy, effects on gene transcription, and
various indirect mechanisms of genotoxicity.

6.3.1.1 Mitogenesis

Increased cell proliferation (40-fold) was noted in the proximal tubular epithelium of
adult female Sprague-Dawley rats following a single i.p. injection of lead acetate at 40
mg/kg b.w. No renal pathology was noted in lead-exposed rats. A similar increase in the
mitotic index (45-fold) was observed in the proximal and distal epithelium of the renal
cortices of adult female CD-1 mice given a single dose of lead acetate at 5 mg/kg b.w. As
in the rat study, no detectable microscopic lesions were observed in the renal tubules
(Choie and Richter 1972). A similar proliferative mitogenic response, but of lesser
magnitude, was observed in the liver of adult male Wistar rats following administration
of a single dose of lead acetate at 100 µmol/kg b.w. Lead acetate caused a significant
enlargement of the liver, with a 30-fold increase in DNA synthesis as measured by
labeled thymidine incorporation (Columbano *et al.* 1983). In this context, several other
studies were conducted to determine whether mitogen-induced cell proliferation in the
liver supported the formation of foci.

A series of studies used diethylnitrosamine to initiate hepatocytes in male Wistar rats
(Columbano *et al.* 1990, Ledda-Columbano *et al.* 1992, Coni *et al.* 1993a, 1993b).
Regenerative mitogenesis was stimulated by partial hepatectomy and carbon
tetrachloride, whereas proliferative mitogenesis was stimulated by i.v. injection of 100
µmole/kg of lead nitrate and other mitogenic chemicals. Both types of treatment induced
cell proliferation primarily within zone 1, produced a similar labeling index (65% to
70%), and stimulated serum growth factors capable of inducing DNA synthesis in
primary hepatocyte cultures. However, the initiated hepatocytes did not respond to lead
nitrate but did respond to regenerative mitogenic stimuli. Therefore, DNA synthesis alone
apparently is not a sufficient condition for cancer development. Some possible
explanations include differences in the genes involved in the growth signal transduction
and growth factors induced, elimination of altered hepatocytes by apoptosis during
regression after proliferative mitogenesis, or differences in the subpopulation of cells
responding (ploidy state).

Coni *et al.* (1993b) provided evidence of differences in patterns of mRNA expression for
growth factors following regenerative mitogenesis and proliferative mitogenesis.
Following partial hepatectomy or carbon tetrachloride administration, increased

expression of *c-fos, c-jun,* and *c-myc* were noted; however, following lead nitrate administration, only expression of *c-jun* increased. Furthermore, studies by Ledda-Columbano *et al.* (1994) demonstrated that a single injection of lead nitrate induced a rapid increase in tumor necrosis factor-α (TNF-α). Inhibition of TNF-α resulted in an inhibition of liver cell proliferation, suggesting that TNF-α is involved in triggering proliferative mitogenesis in the liver. This finding is in contrast to observations on regenerative mitogenesis, in which the primary growth factors involved are hepatocyte growth factor, transforming growth factor-α, and transforming growth factor-β (Kinoshita *et al.* 1989, Lindroos *et al.* 1991). These studies suggest that proliferative mitogenesis induced by chemical exposure, unlike regenerative mitogenesis, does not have a significant role in initiation or promotion of hepatocarcinogenesis. Although the mechanism by which lead induces renal tumors in rodents has not been established, mitogenesis may be a contributing factor. Furthermore, marked differences in organ-specific susceptibility to this response are consistent with observations of renal but not liver tumors in animals (Calabrese and Baldwin 1992).

6.3.1.2   Nephropathy

Because the kidney is a frequent target for lead-induced cancer, studies have been undertaken to test the hypothesis that renal cancers are a consequence of renal pathology due to lead exposure. Goyer (1993) reviewed several current issues in regard to lead toxicity, including nephropathy and cancer. As described above, the toxic effects of lead on the kidney in both humans and experimental animals begin with morphologic changes in tubular endothelial cells, which may slowly progress to a chronic irreversible nephropathy after years of heavy exposure (Fowler 1993). The role of nephrotoxicity in renal carcinogenesis remains unclear. In rodents, progression from acute reversible nephropathy to chronic irreversible nephropathy to renal adenocarcinoma has been demonstrated; however, the evidence in humans is less clear. No evidence indicates that lead induces male-specific nephropathy or hyaline-droplet nephropathy. As noted in Section 4, lead can induce tumors in female and male mice, as well as rats, and at exposures that do not induce frank renal toxicity.

A characteristic histologic finding of early or acute lead-induced nephropathy is the appearance of intranuclear inclusion bodies in renal proximal tubule cells (Vicente-Ortega *et al.* 1996). These bodies contain lead complexed with acidic proteins, which may include human lead-binding protein or similar proteins; in this complex, lead is bound in a nondiffusible form (Moore and Goyer 1974, Saryan and Zenz 1994). Inclusion bodies are thought to represent a defense mechanism by which the cytoplasmic concentrations of lead are lowered. Furthermore, since they are excreted in the urine, inclusion bodies would provide the kidneys with a method for eliminating surplus lead without destroying the viability of the tubular lining cells (Saryan and Zenz 1994). Few or no nuclear inclusion bodies are observed in chronic lead nephropathy (ATSDR 1999). The presence of intranuclear inclusion bodies in the kidney is used as a primary biomarker of effect for lead (ATSDR 1999).

Following *in vivo* lead exposure, lead inclusion bodies commonly are found in the cytoplasm and the nuclei of osteoclasts, but not of other bone cells (Pounds *et al.* 1991).

These inclusion bodies may contain high-affinity binding proteins and may sequester lead, but also may indicate a potential for modulation of gene expression. High-affinity cytosolic lead-binding proteins also have been identified in the kidneys and brain. These high-affinity zinc- and lead-binding proteins are thought to moderate the inhibition of ALAD by lead through chelation of lead and donation of zinc; these proteins subsequently translocate lead to the nucleus, where it may influence gene expression. In the rat kidney, the high-affinity lead-binding protein was found in intranuclear inclusion bodies and was associated with nuclear chromatin. Similar lead-binding proteins have been found in human kidney, liver, and brain cytosol. In rats, the brain lead-binding protein is not the same as that found in the kidney and is developmentally regulated. Only traces of this protein were detected in neonatal rats, but protein concentrations increased to adult levels within 2 weeks; the increased protein levels also resulted in increased resistance to lead-induced encephalopathy. Development of this resistance is hypothetically related to the formation of lead-protein inclusion bodies in the astroglia, which, as they mature, develop the ability to sequester lead (ATSDR 1999).

6.3.1.3   Clastogenicity

Exposure of mice to lead causes chromosomal damage (Winder and Bonin 1993, Johnson 1998). More recently, Valverde *et al.* (2002) administered lead to mice by inhalation at a concentration of 0.0068 µg/cc (equivalent to 6.8 mg/m^3) for 60 minutes twice per week; they reported induction of DNA damage, detectable by electrophoresis, in many organs, including liver, kidney, brain, and lung. Yuan and Tang (2001) reported detection of DNA damage in the comet assay in the second and third generations of mice exposed to lead in drinking water at 1 or 0.25 mg/L. Consistent with these findings in experimental systems, researchers have reported chromosomal aberrations, micronuclei, and increased SCE in studies of lead-exposed workers (Gebhart 1984, Johnson 1998). However, these effects were not found consistently and generally were reported in occupational cohorts (Vaglenov *et al.* 2001) with blood lead levels in excess of the current OSHA standard (30 µg/dL).

6.3.1.4   DNA repair

The strongest evidence that lead may be permissive rather than initiating in its carcinogenic effects comes from studies of co-exposures to lead and directly genotoxic agents. As discussed in Section 5.3.1, lead *in vitro* can increase mutations in cells exposed to UV radiation (Hartwig 1994), X rays (Fischer and Skreb 2001), or the chemical mutagen *N*-methyl-*N´*-nitrosoguanidine (Roy and Rossman 1992). Similar *in vivo* interactions between lead and sensitivity to genotoxic agents were suggested by Restrepo *et al.* (2000), who exposed lymphocytes from battery workers to X rays *in vitro*. These effects may be due to lead's ability to decrease the accuracy of DNA polymerase and the fidelity of RNA synthesis. As reported by Zelikoff *et al.* (1988), lead affects DNA synthesis fidelity in CHO V79 cells. Hartwig *et al.* (1990) reported that lead interferes with repair of UV-induced DNA damage *in vitro*, which appears to be the same mechanism by which several toxic heavy metals act to prevent closure of single-strand DNA breaks (Snyder *et al.* 1989).

6.3.1.5 Oxidative damage

A general mechanism for metal toxicity involves generation of free radicals, either through depletion of cellular antioxidants, such as glutathione, or production of ROS (Klein *et al.* 1991). Lead has been shown to increase hydrogen peroxide production in cells (Ariza *et al.* 1998, Yang *et al.* 1999) (see Sections 5.3.1 and 5.4). In the presence of exogenously added hydrogen peroxide, lead increases the formation of the DNA adduct 8-OHdG (Yang *et al.* 1999). Fracasso *et al.* (2002) reported that significantly elevated levels of DNA breaks in lymphocytes of lead-exposed battery plant workers were significantly and positively correlated with ROS production and negatively correlated with glutathione levels. In addition, both the increase in ROS and the decrease in glutathione levels differed significantly between lead-exposed and unexposed controls. Another mechanism of adduct formation may involve δ-aminolevulinic acid, the heme precursor whose levels are elevated by lead exposure through feedback disinhibition of the enzyme ALA synthase (Silbergeld 1987). ALA can generate free radicals (Hermes-Lima *et al.* 1991) and has been shown to cause oxidative damage to DNA in CHO cells *in vitro* through the formation of 8-OHdG (Yusof *et al.* 1999). The role of oxidative damage to DNA in human lead toxicity also is supported by a recent study of 7,8-dihydro-9-oxoguanine adducts in lymphocytes collected from persons exposed environmentally to metals, including lead, chromium, cadmium, and nickel (Merzenich *et al.* 2001).

6.3.1.6 DNA-binding proteins

Lead is known to bind to several DNA-binding proteins, including protamines and histones, as well as transcription regulators such as stimulatory protein-1 and transcription factor IIA (Hanas *et al.* 1999, Petering *et al.* 2000, Zawia *et al.* 2000, Quintanilla-Vega *et al.* 2000, Silbergeld *et al.* 2000). In fact, many, if not all, zinc-binding nuclear proteins probably also can bind lead, and thus potentially dysregulate gene expression, as first suggested by Sunderman and Barber (1988). The critical role of zinc in conferring appropriate conformational structure has been well demonstrated for the zinc finger proteins, many of which are transcription regulators, such as the glucocorticoid receptor (O'Halloran 1993, Searles *et al.* 2000). Quintanilla-Vega *et al.* (2000) reported that lead could bind at a sulfhydryl and a nonsulfhydryl site to human protamine (HP2), a DNA-associated protein that regulates the condensation of sperm DNA. Several lines of evidence, including spectroscopy, nuclear magnetic resonance, and circular dichroism analysis, indicate that protein configuration is changed when lead is bound (Quintanilla-Vega *et al.* 2000, Razmiafshari *et al.* 2001). When HP2 is bound to lead, its subsequent binding to consensus sequences in DNA is significantly reduced (Quintanilla-Vega *et al.* 2000, Silbergeld *et al.* 2000).

Because one of the functions of protamines and histones, analogous somatic-cell nuclear proteins, is to protect DNA (Mirsky and Silverman 1972), genetic material may become more vulnerable to damage from other sources in the presence of lead-containing protamines or histones. Liang *et al.* (1999) reported that when nickel or copper was bound to HP2 in place of zinc, single- and double-strand DNA breakage increased, as well as oxidative damage to both purine and pyrimidine bases of DNA. These authors suggested that the DNA damage induced in the presence of HP2 and metals was related

to interactions of HP2 with DNA, as well as to the redox properties of HP2–metal complexes.

6.3.1.7   Tumor suppressor proteins

A final potential mechanism for lead carcinogenicity involves its interactions with tumor-suppressor proteins, at the pre- and post-translational level. The tumor-suppressor protein p53 is a zinc-binding protein. It has been shown that when p53 is exposed to cadmium, the protein is structurally altered, with functional consequences similar to those resulting from mutation of the *p53* gene (Hainaut and Milner 1993, Hainaut and Mann 2001). Other proteins related to tumorigenesis have been identified in studies of gene expression. Although these analyses were undertaken to identify novel targets related to lead neurotoxicity, some of the results are relevant to mechanisms of carcinogenicity. Bouton *et al*. (2001) undertook a broad analysis of lead-induced alterations in gene expression, using immortalized rat astrocytes exposed to 10 µM lead acetate or 10 µM sodium acetate (as control). Extensive controls were run to ensure reproducibility of the results. In the Clontech array (which contains a set of 418 genes), expression of 48 genes was upregulated and expression of 12 genes was downregulated. For instance, lead exposure downregulated expression of the gene for the tumor suppressor DCC (deleted in colon cancer) precursor protein. In the InCyte microarray (which included 282 genes also represented on the Clontech array), expression of 34 genes was upregulated and expression of 18 genes was downregulated. Among these, lead significantly affected the expression of genes for zinc-binding transcription factors (not further identified). In a more limited analysis of gene expression in astrocytes, Li and Rossman (2001) reported that exposure of glioma cells in culture to lead (at concentrations as low as 100 µM) resulted in downregulation of expression of the gene for thrombospondin 1, which has been considered to be a tumor-suppressor protein. These data suggest the importance of further research on the interaction of lead with expression of genes involved in tumorigenesis.

6.3.2   Indirect mechanisms

Glutathione transferase P (GST-P) is increased in rat kidney and liver following exposure to lead, and overproduction of GST-P is known to be a marker for hepatocarcinogenesis in the rat (Suzuki *et al.* 1996). These effects offer a possible explanation for the ability of lead to induce cancer without being a potent direct-acting mutagen (Johnson 1998). Oberley *et al.* (1995) demonstrated marked induction of specific GST isoforms in specific kidney cell types in female Sprague-Dawley rats and their pups following chronic administration of lead acetate in drinking water. Increases in GSTs preceded irreversible renal damage; however, the authors concluded that the observed renal damage was not related to neoplastic events. In another study, Daggett *et al.* (1998) determined that glutathione depletion and oxidative stress were not responsible for changes in the production of GSTs in rat kidney or liver. Sprague-Dawley rats were injected with lead acetate at 114 mg/kg b.w. and examined at 0.5, 1, 3, 6, and 12 hours after the injection. Two other exposure groups received injections on three successive days and were examined at 72 hours and 7 days after the first injection. Lead exposure resulted in increased levels of most GSTs in the kidney but decreased levels of most GSTs in the liver. GST-P1 was the only subunit increased in the liver. GST increases in

the kidney were independent of glutathione depletion or malondialdehyde (MDA) production. MDA was used as a marker for lipid peroxidation. In contrast, increased GSTP1 in the liver did correlate with glutathione depletion and MDA production. Histopathological effects were noted in the kidneys but not in the liver. Although these observations suggest an adaptive response to lead toxicity, they do not indicate that oxidative stress is a primary mechanism of toxicity. One possible explanation is that lead reduces the activity of glutathione in the kidney without depleting it (Daggett *et al.* 1998).

6.4   Summary

Lead absorption in humans and laboratory animals is affected by age, the chemical form of lead, and minerals in the diet (e.g., iron, calcium, and zinc). Inorganic lead can be absorbed by inhalation of fine particles and by ingestion. In adults, the rate of deposition of airborne lead in the respiratory tract is approximately 30% to 50% and is dependent on the size of the particles and the ventilation rate of the individual. Ingestion of inorganic lead results in GI absorption in humans. GI absorption declines with age, with children absorbing 4 to 6 times more lead than adults. Dietary deficiencies in iron, calcium, and zinc increase lead absorption and retention, whereas a high-protein diet appears to reduce absorption. Lead also can be absorbed through the skin. After absorption, lead is distributed to blood plasma, nervous system, and soft tissues. In humans, the relationship between whole-blood lead and plasma lead levels is linear at lower concentrations, but at higher concentrations, levels in plasma are higher than would be expected based on a linear relationship.

The skeleton is a major compartment for inorganic lead, as approximately 75% to 90% of the lead body burden is found in bones and teeth. In humans, bone lead levels gradually increase over the lifespan. The half-life of lead in bone depends on bone type. Lead analyses of teeth and bone provide an integrated biomarker of previous lead exposure. Lead also is transferred across the placenta and is excreted in breast milk. Some evidence indicates that the fetus accumulates lead in both the skeleton and soft tissue. Skeletal lead can be mobilized under normal conditions, such as pregnancy, lactation, and menopause, and under pathophysiological conditions, including Paget's disease, hypothyroidism, and prolonged bed rest; this mobilization affects bone mineral metabolism and increases blood lead concentrations.

Excretion of lead does not depend on the route of exposure. Dietary lead excreted in the feces includes both lead that was not absorbed by the GI tract and lead that was excreted in the bile. The major routes of excretion of absorbed lead are urinary and biliary clearance, and excretion of lead in the feces generally is greater than excretion in the urine. In humans, the total excretion rate for lead may be lower in infants than in adults, resulting in retention of a larger percentage of the total amount of lead absorbed.

The toxic effects of lead include neurotoxicity, nephrotoxicity, hematoxicity and anemia, and reproductive, developmental, and cardiovascular effects. These end points have been identified in adults, children, and/or fetuses. Lead exposure was a frequent cause of encephalopathy in children. Chronic exposure of children to lead in paints resulted in neurotoxic effects including loss of speech, seizures, and coma. Children who survived these severe events frequently were retarded intellectually and in their motor skills. In

adults, lead is a potent neurotoxin affecting the CNS and the PNS, with neurotoxic manifestations dependent on dose and duration of exposure. Recently, reviews have suggested that adult lead exposure may be associated with increased risks of neurodegenerative disease in aging, specifically, amyotrophic lateral sclerosis and dementias. Acute nephrotoxicity has been described in lead-intoxicated children. Exposure to lead also results in anemia and hematopoietic disturbances. Additionally, lead is toxic to sperm and can alter endocrine function in adults. Lead crosses the placenta and is accumulated in fetal organs, including the brain. Several studies have reported positive exposure-related associations between blood lead level and blood pressure in adult men and women. It was estimated that the effects of lead exposure on blood pressure contribute significantly to risks of hypertensive heart disease and stroke in the U.S. population. It is important to note that all these toxic effects of lead described in human populations have been observed in rodent models at similar blood lead levels.

The mechanisms leading to the carcinogenic effects of lead are not understood. Lead compounds do not appear to be directly genotoxic but may cause genetic damage through several indirect mechanisms. These include inhibition of DNA synthesis and repair, oxidative damage, and interaction with DNA-binding proteins and tumor-suppressor proteins. Interference with DNA synthesis and repair has been suggested as one possible explanation for the genotoxic and co-mutagenic properties of lead.

It has been suggested that cell proliferation may play a role in lead's induction of renal cancer; however, the mechanisms have not been established. Although exposure to lead also induces cell proliferation in the liver, the data suggest that the liver is not as susceptible as the kidneys to the carcinogenicity of this effect. No studies have associated liver tumors with lead exposure, and several studies have shown that lead-induced proliferative mitogenesis does not promote the formation of liver foci or nodules from initiated hepatocytes, as observed during regenerative mitogenesis. An association of renal adenocarcinoma with cystic nephropathy has been suggested but is uncertain.

7 References

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Appendix A: Lead Regulations

Table A-1. CPSC regulations

Regulatory citation	Regulatory action
16 CFR 1303 - PART 1303 - BAN OF LEAD-CONTAINING PAINT AND CERTAIN CONSUMER PRODUCTS BEARING LEAD-CONTAINING PAINT. 1978.	Bans paint or any other similar surface coating that contains more than 0.06% lead.

The regulations in this table have been updated through the 2001 Code of Federal Regulations 29 CFR, July 1, 2001.

Table A-2. EPA regulations

Regulatory citation	Regulatory action
40 CFR 50 – PART 50 – NATIONAL PRIMARY AND SECONDARY AMBIENT AIR QUALITY STANDARDS. Promulgated: 36 FR 22384, 11/25/71. U.S. Codes: 42 U.S.C. 7409, 7601(a).	National primary and secondary ambient air quality standards for lead and its compounds, measured as elemental lead, are 1.5 $\mu g/m^3$, maximum arithmetic mean averaged over a calendar quarter.
40 CFR 60 - PART 60, SUBPART L - STANDARDS OF PERFORMANCE FOR SECONDARY LEAD SMELTERS. Promulgated: 42 FR 37937, 7/25/77. U.S. Codes: 42 U.S.C. 7401-7601.	Standards for particulate matter for secondary lead smelters are: < 50 mg/dscm (0.022 gr/dscf) for blast (cupola) or reverberatory furnace and < 20% opacity.
40 CFR 60 - PART 60, SUBPART P - STANDARDS OF PERFORMANCE FOR PRIMARY COPPER SMELTERS. Promulgated: 41 FR 2338, 1/15/76. U.S. Codes: 42 U.S.C. 7401-7601.	Standards for particulate matter have been set for primary copper smelters.
40 CFR 60 - PART 60, SUBPART R - STANDARDS OF PERFORMANCE FOR PRIMARY LEAD SMELTERS. Promulgated: 41 FR 2340, 1/15/76. U.S. Codes: 42 U.S.C. 7401-7601.	Standards for particulate matter for secondary lead smelters are: < 50 mg/dscm (0.022 gr/dscf) for blast furnace, dross reverberatory furnace, or sintering machine discharge, < 20% opacity, and < 0.065% by volume sulfur dioxide.
40 CFR 60 - PART 60, SUBPART CC - STANDARDS OF PERFORMANCE FOR GLASS MANUFACTURING PLANTS. Promulgated: 36 FR 24877, 12/23/77l U.S. Codes: 42 U.S.C. 7401-7601.	Standards for particulate matter have been set for glass manufacturing plants.
40 CFR 60 - PART 60, SUBPART KK - STANDARDS OF PERFORMANCE FOR LEAD-ACID BATTERY MANUFACTURING PLANTS. Promulgated 47 FR 16573, 4/16/82. U.S. Codes: 42 U.S.C. 7401-7601.	Standards for lead are: < 0.40 mg/m^3 of exhaust (0.000176 gr/dscf) for grid casting facilities, <1 mg/m^3 of exhaust (0.00044 gr/dscf) for paste mixing facilities or three-process operation facilities, <5.0 mg/kg lead feed (0.010 lb/ton) for lead oxide manufacturing facilities, < 4.50 mg/m^3 of exhaust (0.00198 gr/dscf), 1.0 mg/m^3 of exhaust (0.00044 gr/dscf) for any other lead-emitting operation, 0% opacity for affected facilities other than lead-reclamation facilities, < 5% opacity for lead reclamation facilities.

Regulatory citation	Regulatory action
40 CFR 60 - PART 60, SUBPART VV - STANDARDS OF PERFORMANCE FOR EQUIPMENT LEAKS OF VOC IN THE SYNTHETIC ORGANIC CHEMICALS MANUFACTURING INDUSTRY (SOCMI), Promulgated 48 FR 48335, 10/18/83. U.S. Codes: 42 U.S.C. 7401-7601.	Standards of performance have been set for equipment leaks for facilities in the Synthetic Organic Chemicals Manufacturing Industry producing tetraethyl lead and tetramethyl lead.
40 CFR 60 - PART 60, SUBPART NNN - STANDARDS OF PERFORMANCE FOR VOC EMISSIONS IN THE SYNTHETIC ORGANIC CHEMICALS MANUFACTURING INDUSTRY (SOCMI) DISTILLATION OPERATIONS, Promulgated 55 FR 26942, 6/29/90. Codes: 42 U.S.C. 7401-7601.	Standards of performance have been set for VOC emissions for facilities in the Synthetic Organic Chemicals Manufacturing Industry, distillation operations, producing tetraethyl lead and tetramethyl lead.
40 CFR 60 - PART 60, SUBPART NNN - STANDARDS OF PERFORMANCE FOR VOC EMISSIONS IN THE SYNTHETIC ORGANIC CHEMICALS MANUFACTURING INDUSTRY (SOCMI) REACTOR PROCESSES, Promulgated 58 FR 45962, 8/31/93. Codes: 42 U.S.C. 7401-7601.	Standards of performance have been set for VOC emissions for facilities in the Synthetic Organic Chemicals Manufacturing Industry, reactor processes, producing tetraethyl lead and tetramethyl lead.
40 CFR 63 - PART 63, SUBPART RRR - NATIONAL EMISSION STANDARDS FOR HAZARDOUS AIR POLLUTANTS FOR SOURCE CATEGORIES. Promulgated: 57 FR 61992, 12/29/92. U.S. Codes: 42 U.S.C. 7401 et seq.1.	Hazardous waste incinerators must not discharge lead and cadmium > 240 g/dscm, combined emissions, corrected to 7% oxygen.
40 CFR 80 - PART 80, SUBPART A - DEFINITION. Promulgated 38 FR 1255, 1/10/73, as amended at 38 FR 33741, 12/6/73; 42 FR 25732, 5/19/77. U.S. Codes: 42 U.S.C. 7414, 7545, and 7601(a).	Definition of unleaded gasoline is < 0.05 g of lead per gallon and < 0.005 g phosphorus/gallon.
40 CFR 80 - PART 80, SUBPART B - CONTROLS AND PROHIBITIONS. Promulgated 38 FR 1255, 1/10/73, as amended at 6/26/96. U.S. Codes: 42 U.S.C. 7414, 7545, and 7601(a).	No person shall sell gasoline with > 0.05 g of lead per gallon.
40 CFR 80 - PART 80, SUBPART D - REFORMULATED GASOLINE. Promulgated 59 FR 7813, 2/16/94. U.S. Codes: 42 U.S.C. 7414, 7545, and 7601(a).	Reformulated gasoline may not contain lead.
40 CFR 80 - PART 80, SUBPART G - DETERGENT GASOLINE. Promulgated 59 FR 54706, 11/1/94. U.S. Codes: 42 U.S.C. 7414, 7545, and 7601(a).	Detergent gasoline must meet the requirements outlined, including the definition of unleaded gasoline.
40 CFR 80 - PART 80, APPENDIX B - TEST METHODS FOR LEAD IN GASOLINE. Promulgated 38 FR 1255, 1/10/73. U.S. Codes: 42 U.S.C. 7414, 7545, and 7601(a).	Test methods have been established for lead in gasoline.
40 CFR 86 - PART 86, SUBPART F - EMISSION REGULATIONS FOR 1978 AND LATER NEW MOTORCYCLES; TEST PROCEDURES. Promulgated 42 FR 1137, 1/5/77. U.S. codes: 42 U.S.C. 7401 - 7671q.	For leaded fuel, the lead content shall not exceed 0.1 g of lead per gallon.

Regulatory citation	Regulatory action
40 CFR 116 - PART 116 - DESIGNATION OF HAZARDOUS SUBSTANCES. Promulgated: 43 FR 10474, 03/13/78. U.S. Codes: 33 U.S.C. 1251 et seq.	Lead acetate, lead arsenate, lead chloride, lead fluoroborate, lead fluoride, lead iodide, lead nitrate, lead stearate, lead salt, lead sulfate, lead sulfide, and lead thiocyanate are classified as hazardous substances.
40 CFR 117 – PART 117 – DETERMINATION OF REPORTABLE QUANTITIES FOR HAZARDOUS SUBSTANCES. Promulgated: 44 FR 50776, 08/29/79. U.S. Codes: 33 U.S.C. 1251 et seq., as amended by the Clean Water Act of 1977.	Discharges to water of amounts equal to or greater than the Reportable Quantity (RQ) must be reported to EPA. RQs for environmental releases of lead acetate, lead chloride, lead fluoborate, lead fluoride, lead iodide, lead nitrate, lead stearate, lead sulfate, lead sulfide, and lead thiocyanate are 10 lb (4.54 kg). The RQ for lead arsenate is 1 lb (0.454 kg).
40 CFR 136 - GUIDELINES ESTABLISHING TEST PROCEDURES FOR THE ANALYSIS OF POLLUTANTS. Promulgated: 55 FR 33442, 8/15/90. U.S. Codes: 33 U.S.C. 1251, et seq., as amended by the Clean Water Act of 1977.	Established test methods for the identification of lead.
40 CFR 141 - PART 141, SUBPART E - SPECIAL REGULATIONS, INCLUDING MONITORING REGULATIONS AND PROHIBITION ON LEAD USE. Promulgated: 52 FR 20674 6/2/87, as amended at 65 FR 2002, 1/12/00. U.S. Codes: 42 U.S.C. 300 g-6(e).	All plumbing shall be lead-free. The definition of lead-free is: solder and flux must contain $\leq 0.2\%$ lead; pipes and pipe fittings must contain $\leq 8.0\%$ lead.
40 CFR 141 - PART 141, SUBPART I - NATIONAL PRIMARY DRINKING WATER REGULATIONS, CONTROL OF LEAD AND COPPER. Promulgated: 56 FR 26548, 6/7/91. U.S. Codes: 42 U.S.C. 300f, g, and j.	To protect a safe drinking water supply, a treatment technique that includes corrosion control, source water treatment, lead service line replacement, and public education has been set for lead. An action level of 0.015 mg/l has been established for lead; this action level is exceeded if the concentration of lead in > 10% of the tap water samples is > 0.015 mg/L.
40 CFR 141 - PART 141, SUBPART Q - PUBLIC NOTIFICATION OF DRINKING WATER VIOLATIONS. Promulgated: 65 FR 26035, 5/4/00. U.S. Codes: 42 U.S.C. 300f, g, and j.	Public water systems must notify the public for violations of maximum contaminant levels or treatment techniques for all regulated contaminants, including lead.
40 CFR 258 - PART 258 - CRITERIA FOR MUNICIPAL SOLID WASTE LANDFILLS. Promulgated 56 FR 51016, 10/9/91. U.S. Codes: 33 U.S.C. 1345(d)(e); 42 U.S.C. 6902(a), 6907, 6912(a), 6944, 6945(c), 6949a(c).	Lead is considered a hazardous inorganic compound in municipal solid waste landfills. A maximum contaminant level (MCL) of 0.05 mg/L has been set for lead.
40 CFR 261 - PART 261 - IDENTIFICATION AND LISTING OF HAZARDOUS WASTES. Promulgated: 46 FR 4619, 1981 with numerous amendments. U.S. Codes: 42 U.S.C. 6905, 6912(a), 6921, 6922, and 6938.	Solid wastes containing lead are subject to notification requirements and the constituent maximum concentration of lead in any composite wastewater sample is 0.15 mg/L.
40 CFR - PART 264, SUBPART CC - AIR EMISSION STANDARDS FOR TANKS, SURFACE IMPOUNDMENTS AND CONTAINERS. Promulgated 56 FR 62927, 12/6/94. U.S. Codes 42 U.S.C. 6906, 6912, 6922-6925, 6937, 6938.	The Sisterville Plant in West Virginia shall monitor for lead.

Regulatory citation	Regulatory action
40 CFR - PART 264, SUBPART EE - HAZARDOUS WASTE MUNITIONS AND EXPLOSIVES STORAGE. Promulgated 62 FR 6652, 2/12/97. U.S. Codes 42 U.S.C. 6906, 6912, 6922-6925, 6937, 6938.	Lead must be monitored for in groundwater.
40 CFR 266 - PART 266, SUBPART H - HAZARDOUS WASTE BURNED IN BOILERS AND INDUSTRIAL FURNACES. Promulgated 56 FR 7208, 2/21/91 and 64 FR 53075, 9/30/99. 42 U.S.C. 1006, 2002(a), 3004, 3014, 6905, 6906, 6912, 6922, 6924, 6925, 6937.	Reference air concentrations have been set for release of lead from hazardous waste burned in boilers and industrial furnaces as follows: lead = 0.00009 mg/L, tetraethyl lead = 0.0000001 mg/L.
40 CFR 266 - PART 266, SUBPART M - MILITARY MUNITIONS. Promulgated 62 FR 6654, 2/12/97. 42 U.S.C. 1006, 2002(a), 3004, 3014, 6905, 6906, 6912, 6922, 6924, 6925, 6937.	Military munitions wastes containing lead must be stored as hazardous wastes.
40 CFR 268 - PART 268 - LAND DISPOSAL RESTRICTIONS. Promulgated 51 FR 40638. 42 U.S.C. 6905, 6912(a), 6921, 6924.	Lead is listed as a hazardous waste restricted from land disposal.
40 CFR 300 - PART 300, SUBPART L - NATIONAL OIL AND HAZARDOUS SUBSTANCES POLLUTION CONTINGENCY PLAN; INVOLUNTARY ACQUISITION OF PROPERTY BY THE GOVERNMENT. Promulgated 62 FR 34602, 6/26/97. U.S. Codes: 42 U.S.C. 9605 and 33.U.S.C.1321(d).	Provides procedures for responding to discharges of oil and hazardous substances. In the hazard ranking system, lead has a human toxicity factor value of 10,000.
40 CFR 302 – PART 302 – DESIGNATION, REPORTABLE QUANTITIES, AND NOTIFICATION. Promulgated: 50 FR 13474, 04/04/85. U.S. Codes: 42 U.S.C. 9602, 9603, and 9604; 33 U.S.C. 1321 and 1361.	This part designates RQs for lead acetate, lead subacetate, lead chloride, lead fluoborate, lead fluoride, lead iodide, lead nitrate, lead phosphate, lead stearate, lead sulfate, lead sulfide, lead thiocyanate, and tetraethyl lead are 10 lbs (4.54 kg). The RQ for lead arsenate is 1 lb (0.454 kg).
40 CFR 372 – PART 372 – TOXIC CHEMICAL RELEASE REPORTING: COMMUNITY RIGHT-TO-KNOW. Promulgated: 53 FR 4525, 02/16/88; 1/16/01. U.S. Codes: 42 U.S.C. 11023 and 11048.	Toxic release information is collected for lead to inform the general public and the communities surrounding covered facilities about releases of toxic chemicals, to assist research, and to aid in the development of regulations, guidelines, and standards. The reporting threshold for lead and lead compounds was lowered to 100 lbs (1/16/01).
40 CFR 401 – PART 401 – GENERAL PROVISIONS. Promulgated: 39 FR 4532, 02/01/74. U.S. Codes: 33 U.S.C. 1251, 1311, 1314 (b) and (c), 1316 (b) and (c), 1317 (b) and (c) and 1326(c); 86 Stat. 816 et seq.; Pub. L. 92-500.	Lead and lead compounds are classified as toxic pollutants under the Clean Water Act.
40 CFR 414 - PART 414 - ORGANIC CHEMICALS, PLASTICS, AND SYNTHETIC FIBERS. Promulgated 52 FR 42568, 11/5/87, as amended at 57 FR 41844, 9/11/92. U.S. codes: 33 U.S.C. 1311, 1314(b)(c)(e), 1316(b)(c), 1317(b)(c), 1318, and 1361.	Effluent limitation guidelines have been set for tetraethyl lead and tetramethyl lead for organic chemicals, plastics, and synthetic fiber manufacturers.

Regulatory citation	Regulatory action
40 CFR 415 - PART 415, SUBPART AR - INORGANIC CHEMICALS MANUFACTURING POINT SOURCE CATEGORY, LEAD MONOXIDE PRODUCTION SUBCATEGORY. Promulgated 47 FR 28278, 6/29/82. U.S. codes: 33 U.S.C. 1311, 1314(b)(c)(e), 1316(b)(c), 1317(b)(c), 1318, and 1361.	Effluent limitation guidelines have been set for lead for inorganic chemicals manufacturers.
40 CFR 420 - PART 420 - IRON AND STEEL MANUFACTURING POINT SOURCE CATEGORY. Promulgated 47 FR 23284, 5/27/82. U.S. codes: 33 U.S.C. 1311, 1314(b)(c)(e), 1316(b)(c), 1317(b)(c), 1318, and 1361.	Effluent limitation guidelines have been set for lead for iron and steel manufacturers.
40 CFR 421 - PART 421 - NONFERROUS METALS MANUFACTURING POINT SOURCE CATEGORY, SUBPART G - PRIMARY LEAD SUBCATEGORY. Promulgated 49 FR 8790, 3/8/84. U.S. codes: 33 U.S.C. 1311, 1314(b)(c)(e), 1316(b)(c), 1317(b)(c), 1318, and 1361.	Effluent limitation guidelines have been set for lead for nonferrous metals manufacturers.
40 CFR 423 - PART 423 - STEAM ELECTRIC POWER GENERATING POINT SOURCE CATEGORY. Promulgated 47 FR 52304, 11/19/82. U.S. codes: 33 U.S.C. 1311, 1314(b)(c)(e), 1316(b)(c), 1317(b)(c), 1318, and 1361.	Effluent limitation guidelines have been set for lead for steam electric power generating manufacturers.
40 CFR 455 - PART 455 - PESTICIDE CHEMICALS, SUBPART A - ORGANIC PESTICIDE CHEMICALS MANUFACTURING SUBCATEGORY. Promulgated 43 FR 17776, 4/25/78. U.S. codes: 33 U.S.C. 1311, 1314(b)(c)(e), 1316(b)(c), 1317(b)(c), 1318, and 1361.	Effluent limitation guidelines have been set for lead for organic pesticide manufacturers.
40 CFR 461 - PART 461 - BATTERY MANUFACTURING, POINT SOURCE CATEGORY, SUBPART C - LEAD SUBCATEGORY. Promulgated 49 FR 9134, 3/9/84. U.S. codes: 33 U.S.C. 1311, 1314(b)(c)(e), 1316(b)(c), 1317(b)(c), 1318, and 1361.	Effluent limitation guidelines have been set for lead for battery manufacturers.
40 CFR 464 - PART 464 - METAL MOLDING AND CASTING POINT SOURCE CATEGORY. Promulgated 50 FR 45247, 10/30/85. U.S. codes: 33 U.S.C. 1311, 1314(b)(c)(e), 1316(b)(c), 1317(b)(c), 1318, and 1361.	Effluent limitation guidelines have been set for lead for metal molding and casting manufacturers.
40 CFR 468 - PART 468 - COPPER FORMING POINT SOURCE CATEGORY. Promulgated 48 FR 36957, 8/15/83. U.S. codes: 33 U.S.C. 1311, 1314(b)(c)(e), 1316(b)(c), 1317(b)(c), 1318, and 1361.	Effluent limitation guidelines have been set for lead for copper forming manufacturers.

Regulatory citation	Regulatory action
40 CFR 471 - PART 471 - NONFERROUS METALS FORMING POINT SOURCE CATEGORY, SUBPART A - LEAD-TIN-BISMUTH FORMING SUBCATEGORY, SUBPART F - TITANIUM FORMING SUBCATEGORY, SUBPART G - URANIUM FORMING SUBCATEGORY, SUBPART J - METALS POWDERS SUBCATEGORY. Promulgated 48 FR 36957, 8/15/83. U.S. codes: 33 U.S.C. 1311, 1314(b)(c)(e), 1316(b)(c), 1317(b)(c), 1318, and 1361.	Effluent limitation guidelines have been set for lead for metals powders, titanium forming, uranium, and lead-tin-bismuth forming manufacturers.
40 CFR 503 - PART 503 - STANDARDS FOR THE USE AND DISPOSAL OF SEWAGE SLUDGE. Promulgated 58 FR 9387, 2/19/93. U.S. Codes: 33 U.S.C. 1345 (d) and (e) and 33 U.S.C. 1251 et seq.	The following standards have been set for lead in sewage sludge applied to the land, placed on a surface disposal site, or fired in a sewage sludge incinerator: ceiling concentration = 840 mg/kg; cumulative pollutant loading rate = 300 kg/hectare; annual loading rate = 15 kg/hectare/365 days.
40 CFR 745 - PART 745 - LEAD-BASED PAINT PREVENTION IN CERTAIN RESIDENTIAL STRUCTURES. Promulgated 61 FR 9085, 3/6/96. U.S. Codes: 15 U.S.C. 2605, 2607, 2681-2692 and 42 U.S.C. 4852(d).	A seller must disclose to the purchaser any lead-based paint in a home for sale; paint used in home renovations must not contain lead ≥ 1.0 mg/cm^2 or $\geq$ 0.5% by weight; a pamphlet on the health hazards of lead must be provided to the homeowner. Amended 3/6/01: Dust-lead hazard consists of lead ≥ 40 μg/ft^2 on floors or 250 μg/ft^2 on interior window sills. Soil-lead hazard consists of lead ≥ 400 ppm (μg/g) in play area, or average of 1,200 ppm in bare soil.

The regulations in this table have been updated through the 2001 Code of Federal Regulations 40 CFR, July 1, 2001

Table A-3. FDA regulations

Regulatory citation	Regulatory action
21 CFR 73 - PART 73 -LISTING OF COLOR ADDITIVES EXEMPT FROM CERTIFICATION. Promulgated: 42 FR 15643, 03/22/77. U.S. Codes: 21 U.S.C. 321, 341, 342, 343, 348, 351, 352, 355, 361, 362, 371, 379e.	Concentration limits for lead in various color additives used in foods, drugs, cosmetics, and medical devices may not exceed 5–70 ppm. The concentration of lead acetate may not exceed 0.6% (weight to volume) in hair coloring for scalp use only.
21 CFR 74 - PART 74 - LISTING OF COLOR ADDITIVES SUBJECT TO CERTIFICATION. Promulgated: 42 FR 15654, 03/22/77. U.S. Codes: 21 U.S.C. 321, 341, 342, 343, 348, 351, 352, 355, 361, 362, 371, 379e.	Concentration limits for lead in various color additives used in foods, drugs, cosmetics, and medical devices may not exceed 10–40 ppm.

Regulatory citation	Regulatory action
21 CFR 109 - PART 109 - UNAVOIDABLE CONTAMINANTS IN FOOD FOR HUMAN CONSUMPTION AND FOOD-PACKAGING MATERIAL. Promulgated: 42 FR 52819, 09/30/77. U.S. Codes: 21 U.S.C. 321, 336, 342, 346, 346a, 348, 371.	A conspicuous stick-on label shall be on the surface of ornamental or decorative ceramics clearly visible to consumers that states one of the following messages: "Not for Food Use. May Poison Food," "Not for Food Use. Glaze contains lead. Food Use May Result in Lead Poisoning," and "Not for Food Use-Food Consumed from this Vessel May be Harmful,"
21 CFR 109 and 509 - PARTS 109 and 509 - ACTION LEVELS FOR POSIONOUS OR DELETERIOUS SUBSTANCES IN HUMAN FOOD AND ANIMAL FEED. Compliance Policy Guide 545.450	Action levels for lead in ceramicware are: flatware = 3.0 μg/mL leaching solution, small hollowware (other than cups and mugs) = 2.0 μg/mL leaching solution, large hollowware (other than pitchers) = 1.0 μg/mL leaching solution, cups and mugs = 0.5 μg/mL leaching solution, pitchers = 0.5 μg/mL leaching solution.
21 CFR 109 and 509 - PARTS 109 and 509 - ACTION LEVELS FOR POSIONOUS OR DELETERIOUS SUBSTANCES IN HUMAN FOOD AND ANIMAL FEED. Compliance Policy Guide 545.500	Action levels for silver-plated hollowware are: product intended for use by adults = 7 μg/mL leaching solution, product intended for use by infants and children = 0.5 μg/mL leaching solution.
21 CFR 189 - PART 189 - SUBSTANCES PROHIBITED FROM INDIRECT ADDITION TO HUMAN FOOD THROUGH FOOD-CONTACT SURFACES. Promulgated: 60 FR 33109, 06/27/95. U.S. Codes: 21 U.S.C. 321, 342, 348, 371.	Food packaging must not contain lead solder.
21 CFR 584 - PART 584 - FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE IN FEED AND DRINKING WATER OF ANIMALS. Promulgated: 61 FR 43453, 08/23/96. U.S. Codes: 21 U.S.C. 321, 342, 348, 371.	Amorphous fumed hydrophobic silica or precipitated hydrophobic silica may be used as an anticaking/free-flow agent in vitamin preparations for animal feed provided that lead concentration do not exceed 10 ppm.

The regulations in this table have been updated through the 2001 Code of Federal Regulations 21 CFR, April 1, 2001.

Table A-4. OSHA regulations

Regulatory citation	Regulatory action
29 CFR 1910 - PART 1910.1025, SUBPART Z - TOXIC AND HAZARDOUS SUBSTANCES. Promulgated 60 FR 52856, 10/11/95, as amended numerous times. U.S. codes: 29 U.S.C. 653, 655, 657.	Establishes permissible exposure limit (PEL) for lead of 50 μg/m^3 as an 8-hour time-weighted average (TWA). Action level of 30 μg/m^3 TWA, 8-hour workday. Initiates exposure monitoring, medical surveillance, and training and education.
29 CFR 1910 - PART 1910.1200, SUBPART Z - HAZARD COMMUNICATION. Promulgated 59 FR 17479, 4/13/94; 59 FR 65947, 12/22/94; and 61 FR 5507, 2/13/96. U.S. codes: 29 U.S.C. 653, 655, 657.	Requires that the hazards of all chemicals produced or imported are evaluated, and that information concerning their hazards is transmitted to employers and employees. Hazard communication programs are to include container labeling and other forms of warning, material safety data sheets and employee training.

Regulatory citation	Regulatory action
29 CFR 1910 - PART 1910.1450, SUBPARAT Z - OCCUPATIONAL EXPOSURE TO HAZARDOUS CHEMICALS IN LABORATORIES. Promulgated 61 FR 5507, 2/13/96. U.S. codes: 29 U.S.C. 653, 655, 657.	Establishes requirements for laboratory use of hazardous chemicals, including initial exposure determination, development of a chemical hygiene plan, employee information and training, and other requirements.
29 CFR 1926 - PART 1926, SUBPART D - OCCUPATIONAL HEALTH AND ENVIRONMENTAL CONTROLS. Promulgated 57 FR 26627, 5/4/93, as amended numerous times. U.S. codes: 40 U.S.C. 333, 29 U.S.C. 653, 655, 657.	Establishes PEL for lead of 50 μg/m^3 as an 8-hour TWA in construction. Action level of 30 μg/m^3 TWA, 8-hour workday. Initiates exposure monitoring, medical surveillance, and training and education.

The regulations in this table have been updated through the 2001 Code of Federal Regulations 29 CFR, July 1, 2001.