

APPENDIX A:

LEAD

FIRING RANGES

Abudhaise et al (1996) studied lead exposure in users of military indoor firing ranges in Amman, Jordan.¹ Study subjects comprised 54 military trainees, 31 firearm instructors and 50 controls (administrative employees of the firing range). Airborne lead concentration was measured during shooting sessions of conventional lead ammunition during a three-week training course. Each cadet shot 1200 lead bullets on average. The airborne concentration of lead rose substantially at the end of the training exercise from pre-training level and this level exceeded the permissible exposure level of 50 ug per cubic metre; range A 43 to 378 and range B 30 to 867 ug per cubic metre. After three weeks of training, the blood lead level (ug/dL) was significantly higher in instructors (19) and trainees (22.9) compared to controls (2.1) ($p < 0.001$). Although the blood lead level did not exceed recommended levels. In the trainees, blood lead levels rose from a pre-training mean of 2.2 to a post-training mean of 22.9 ug/dL ($p < 0.001$). Subjects had no symptoms of lead poisoning. Amino levulinic acid dehydrogenase (ALAD) activity was measured as a sensitive test for assessing the biological effects of lead at low concentration. ALAD activity was significantly lower in firing instructors and trainees compared to controls and significantly decreased at the end of the training exercise compared to pre-training levels. The authors considered that this indicated a subcritical lead effect. The authors concluded that users of indoor firing ranges were at risk of lead intoxication and periodic biological monitoring of frequent users of firing ranges was recommended. The authors noted other studies of firing ranges where the airborne lead concentration was also raised (Fischbein et al 1980, Muskett and Caswell 1980, Valway et al 1989). Studies had also reported cases of clinical lead poisoning in users of firing ranges but these were associated with blood lead levels that exceeded the recommended safety level of 40 ug/dL (Fischbein et al 1979, Landrigan et al 1975, Novotny et al 1987).

White and Narula (1996) described a case of lead poisoning in a 37-year old car mechanic who was a recreational user of an UK indoor firing range.² The patient had used an unventilated indoor firing range for six years but in the preceding four months had increased his shooting from 150 to 600 rounds of cast ammunition three times a week. He complained of bilateral hip pain, abdominal cramps and poor concentration in the preceding four months and rhinitis for two months. A CT scan showed osteomeatal complex disease and thickened ethmoidal cells. Use of a facial respirator while shooting improved his symptoms. A blood lead level was elevated at 2.1 umol/L (normal < 1.5 umol/L; 40 ug/dL = 1.93 umol/L).

Shannon (1999) reported a case series of four adolescent females who were competitive "marksmen" at the same US indoor firing range with elevated blood lead levels.³ Levels were 18, 19, 20 and 28 ug/dL respectively. One subject had an initial finger-stick lead level > 100 ug/dL. The subject with the highest lead level had a

¹ Abudhaise B, Alzoubi M, Rabi A (1996). Lead exposure in indoor firing ranges: environmental impact and health risk to the range users. *International Journal of Occupational Medicine and Environmental Health* 9: 323-329. ID 27730

² White S, Narula A (1996). A complication of indoor pistol shooting. *Journal of Laryngology and Otolaryngology* 110: 663-4. ID 27518.

³ Shannon M (1999). Lead poisoning in adolescents who are competitive marksmen. *NEJM* 341: 852. ID 27387

value of 20 ug/dL after one month. All subjects were asymptomatic. The author mentioned another report of chronic lead intoxication among firing range instructors at an indoor firing range in Taiwan (Chau et al 1995).

Tumpowsky et al (2000) reported data collected by the Massachusetts Occupational Lead Registry on adults with elevated blood lead levels between 1991 and 1995.⁴ Lead poisoning was defined as a blood lead level of at least 25 ug/dL in a person for whom there were no reports of blood lead levels exceeding this value during the previous calendar year. There were 2,584 cases of lead poisoning in 2,457 separate individuals. There were 664 cases involving a blood lead level of at least 40 ug/dL [a level where increased medical surveillance is necessary]. Information about the source of exposure was obtained from affected individuals or their physicians in 646 of the 664 cases. 99 of the 646 cases were attributed to non-occupational lead exposure and recreational shooting range use accounted for 36% of these 99 cases. The authors noted that there had been numerous reports of lead absorption from recreational use of firing ranges in Massachusetts and elsewhere. Airborne lead concentrations at firing ranges have been reported as high, often 500 to 1000 ug per cubic metre.

ADVERSE HEALTH EFFECTS FROM LEAD

The US Agency for Toxic Substances and Disease Registry (1999) produced a thorough review of the toxicological profile for lead.⁵ Using this profile as a basis, adverse health effects from lead exposure appear to be several including:

- Death from severe lead encephalopathy
- Gastrointestinal; abdominal pain, constipation, nausea, vomiting, anorexia, weight loss are early symptoms of lead poisoning in occupationally exposed subjects or with acute exposures to high levels.
- Haematological; profound effects on heme synthesis, decreased haemoglobin levels in adults seen at blood lead levels (PbB) of 50 ug/dL.
- Musculoskeletal; case reports of high occupational exposure to lead and occurrence of muscle weakness, cramps, joint pain, and bluish-tinged line in the gums.
- Renal; nephropathy in some studies of lead-exposed workers at blood lead levels of approximately 60 to > 100 ug/dL. Acute nephropathy was seen in lead-intoxicated children, with primarily oral exposure and sometimes in lead workers. Chronic nephropathy was reported mainly in lead workers, with primarily inhalational exposure. Lead induced nephropathy can be a cause of gout.
- Neurological; encephalopathy can occur at blood lead levels of 100-120 ug/dL. This can lead to death or in permanent cognitive impairment. Neurobehavioural change at low blood lead levels in adults is still unresolved. Neurobehavioural dysfunction has not been demonstrated in lead-exposed workers at blood lead levels below 40 ug/dL. Peripheral neuropathy has been seen at blood lead levels as low as 30 ug/dL.

⁴ Tumpowsky C, Davis L, Rabin R (2000). Elevated blood lead levels among adults in Massachusetts, 1991-1995. Public Health Reports 115: 364. ID 27386

⁵ Agency for Toxic Substances and Disease Registry (1999). US Department of Health and Human Services. Toxicological Profile For Lead. ID 26502

- Reproductive; lowered sperm counts and increases in the number of abnormal sperm may be associated with blood lead concentration below 40 ug/dL.
- Carcinogenic in animals at extremely high doses [renal tumours in rats and mice] but evidence for carcinogenicity in humans considered inadequate.

There is no evidence of birth defects in humans resulting from paternal exposure to lead. An association between blood lead and hypertension is still controversial.

Sections of this report are reproduced as follows⁶:

INTRODUCTION

Lead is a naturally occurring bluish-gray metal found in small amounts in the earth's crust. It has no characteristic taste or smell. Metallic lead does not dissolve in water and does not burn. Lead can combine with other chemicals to form what are usually known as lead compounds or lead salts. Some lead salts dissolve in water better than others. Some natural and manufactured substances contain lead but do not look like lead in its metallic form. Some of these substances can burn — for example, organic lead compounds in some gasolines.

Lead has many different uses. Its most important use is in the production of some types of batteries. It is also used in the production of ammunition, in some kinds of metal products (such as sheet lead, solder, some brass and bronze products, and pipes), and in ceramic glazes. Some chemicals containing lead, such as tetraethyl lead and tetramethyl lead, were once used as gasoline additives to increase octane rating. However, their use was phased out in the 1980s, and lead was banned for use in gasoline for transportation beginning January 1, 1996. Other chemicals containing lead are used in paint. The amount of lead added to paints and ceramic products, caulking, gasoline, and solder has also been reduced in recent years to minimize lead's harmful effects on people and animals. Lead used in ammunition, which is the largest non-battery end-use, has remained fairly constant in recent years. Lead is used in a large variety of medical equipment (radiation shields for protection against X-rays, electronic ceramic parts of ultrasound machines, intravenous pumps, fetal monitors, and surgical equipment). Lead is also used in scientific equipment (circuit boards for computers and other electronic circuitry) and military equipment (jet turbine engine blades, military tracking systems).

Most lead used by industry comes from mined ores ("primary") or from recycled scrap metal or batteries ("secondary"). Human activities (such as the former use of "leaded" gasoline) have spread lead and substances that contain lead to all parts of the environment. For example, lead is in air, drinking water, rivers, lakes, oceans, dust, and soil. Lead is also in plants and animals that people may eat.

⁶ Agency for Toxic Substances and Disease Registry (1999). US Department of Health and Human Services. Toxicological Profile For Lead. ID 26502

TOXICOKINETICS

The absorption, distribution, metabolism, and elimination of lead has been extensively studied in both animals and humans. While some of the precise pharmacokinetic mechanisms that control these physiological processes are unknown, available data can be used to quantify the uptake and disposition of lead in the human body for various populations of children and adults. Lead absorption is influenced by the route of exposure, chemical speciation, the physicochemical characteristics of the lead and exposure medium, and the age and physiological states of the exposed individual (e.g., fasting, nutritional calcium and iron status). The primary sites for inorganic lead absorption are the gastrointestinal and respiratory tracts. The bioavailability of ingested soluble lead in adults may vary from less than 10% when ingested with a meal to 60–80% when ingested after a fast.

The rate of deposition of particulate airborne lead in adult humans is approximately 30–50% and is modified by factors such as particle size and ventilation rate (EPA 1986a). Once deposited in the lower respiratory tract, particulate lead is almost completely absorbed, and all chemical forms of lead also seem to be absorbed (EPA 1986a; Morrow et al. 1980).

Nonlinear relationships observed between uptake and blood lead concentrations may be explained by both capacity-limited absorption in the gastrointestinal tract, and capacity-limited binding of lead with red blood cells. Immediately following absorption, lead is widely distributed to blood plasma and soft tissues, then it redistributes and accumulates in bone. Bone lead accounts for approximately 73% of the total body burden in children, increasing to 94% in adults due to changes in bone turnover rates with age.

Lead in blood is primarily in the red blood cells (99%) rather than the plasma (DeSilva 1981; EPA 1986a; Everson and Patterson 1980; Hursh and Suomela 1968). Most of the lead found in red blood cells is found bound within the cell rather than the erythrocyte membrane.

Inorganic lead ions are not known to be metabolized in the body but they are complexed by macromolecules. Lead that is not retained in the body is excreted principally by the kidney as salts or through biliary clearance into the gastrointestinal tract in the form of organometallic conjugates. Excretion rates measured in infants, children, and adults are highly variable, although available data suggest that the fraction of absorbed lead that is retained in humans decreases with age. In addition, acute and chronic lead exposure studies in mice, rats, and non-human primates show that, in general, there is greater excretion of lead in feces than in urine due to the high molecular weights of lead conjugates. Exhalation is a major route of excretion following inhalation exposure of organic lead in humans.

MEASUREMENT OF LEAD

Lead in Soft Tissues (ie Blood)

Biomarkers of exposure for inorganic and organic forms of lead are usually the measurement of total lead levels in tissues or fluids. Total lead measurements of biological media includes all metabolites and endogenous lead sources as well as any original lead-containing exposure agent. Tetra alkyl lead compounds may also be measured in the breath.

Measurement of PbB concentration is the most widely used biomarker of lead exposure. A PbB level greater than 10 µg/dL indicates that excessive lead exposure may be occurring (CDC 1991). The half-life of lead in human blood is 28–36 days (Griffin et al. 1975b; Rabinowitz et al. 1976); thus, levels in blood reflect relatively recent exposure (Graziano 1994; Lyngbye et al. 1990b). Nevertheless, because lead cycles between the blood and bone, a single blood lead determination cannot distinguish between low-level intermediate or chronic exposure and high-level acute exposure. Both types of exposure could result in the same blood level because of recycling from bone. Therefore, PbB levels cannot serve as exact measures of lead exposure or the total body lead burden because of the intervening processes of transfer, mobilization, and storage among the different body compartments. Furthermore, the relationship between blood lead and lead exposure and uptake for both inhalation and gastrointestinal exposure is nonlinear, such that the increase in PbB concentration is less at high exposure levels than at low exposure levels (EPA 1986a; Manton and Cook 1984). This behavior may be attributed to changes in tissue lead kinetics, reduced lead absorption, or increased excretion, such that blood lead may be an imperfect measure of tissue lead burdens and of changes in tissue levels in relation to changes in external exposure (EPA 1986a). In addition, there are nonlinear relationships between different metabolic and toxic effects on one hand, and PbB on the other; this is most likely due to saturation of the erythrocytes. Despite the limitations of PbB levels in indexing tissue burden and exposure changes (Skerfving et al. 1993), this parameter still remains the one readily accessible measure that can demonstrate in a relative way the relationship of various effects to increases in exposure. The biological exposure index (BEI) for lead in blood of exposed workers is 30 µg/dL (ACGIH 1996). This PbB level represents the threshold for effects seen in at least some adults; therefore, because of individual variations in sensitivity, many people may not experience the stated effect until much higher PbB levels are reached and conversely, effects can be seen below the stated blood levels. Furthermore, instability of PbB levels have been reported to occur in infants in which the average increase in blood lead from birth to 2 years of age was 5 µg/dL while levels for older children were found to be more stable (Rabinowitz et al. 1984). The influence of age, sex, and smoking may also be potential confounders for the interpretation of PbB measurements (Rabinowitz et al. 1976; Somashekaraiah et al. 1990; Watanabe et al. 1987).

Lead in Bones and Teeth

The development of noninvasive X-ray fluorescence (XRF) techniques for measuring lead concentrations in bone has enabled the exploration of bone lead as

a biomarker of lead exposure in children and in adults (Batuman et al. 1989; Hu et al. 1989, 1990, 1991, 1995; Rosen et al. 1993; Wedeen 1988, 1990, 1992). Lead in bone is considered as a biomarker of cumulative exposure to lead because lead accumulates in bone over the lifetime and most of the lead body burden resides in bone. Lead is not distributed uniformly in bone. Lead will accumulate in those regions of bone undergoing the most active calcification at the time of exposure. During infancy and childhood, bone calcification is most active in trabecular bone, whereas in adulthood, calcification occurs at sites of remodeling in cortical and trabecular bone. This would suggest that lead accumulation will occur predominantly in trabecular bone during childhood, and in both cortical and trabecular bone in adulthood (Auferheide and Wittmets 1992). Patella, calcaneus and sternum XRF measurements primarily reflect lead in trabecular bone, whereas XRF measurements of mid-tibia, phalanx, or ulna reflect primarily lead in cortical bone. Lead levels in cortical bone may be a better indicator of long term cumulative exposure than lead in trabecular bone, possibly because lead in trabecular bone may exchange more actively with lead in blood than does cortical bone. This is consistent with estimates of a longer elimination half-time of lead in cortical bone, compared to trabecular bone (Borjesson et al. 1997; Nilsson et al. 1991; Schutz et al. 1987). Evidence that cortical bone lead measurements may provide a better reflection of long-term exposure than do measurements of trabecular bone comes from studies in which cortical and trabecular bone lead measurements have been compared to concentrations of lead in blood. Lead levels in trabecular bone (in adults) correlate more highly with contemporary PbB concentrations than do levels of lead in cortical bone (Erkkila et al. 1992; Hernandez-Avila et al. 1996; Hu et al. 1996b, 1998; Watanabe et al. 1994). Cortical bone lead measurements correlate well with time-integrated PbB measurements, which would be expected to be a better reflection of cumulative exposure than contemporary blood lead measurements (Borjesson et al. 1997; Roels et al. 1994). Bone lead levels tend to increase with age (Hu et al. 1996b; Kosnett et al. 1994; Roy et al. 1997), although the relationship between age and bone lead may be stronger after adolescence (Hoppin et al. 1997). These observations are consistent with cortical bone reflecting cumulative exposures over the lifetime.

The association of lead uptake and release from bone with the normal physiological processes of bone formation and resorption renders lead biokinetics sensitive to these processes. Physiological states (eg pregnancy, menopause, advanced age) or disease states (eg osteoporosis, prolonged immobilization) that are associated with increased bone resorption will tend to promote the release of lead from bone which, in turn, may contribute to an increase in the concentration of lead in blood (Bonithon-Kopp et al 1986c; Markowitz and Weinburger 1990; Silbergeld et al 1988; Thompson et al 1985).

Relationships between bone lead levels and health outcomes have been studied in several cross-sectional epidemiology studies, however, not as extensively as have other biomarkers of exposure such as PbB concentration (Hu 1998a, 1998b). These studies suggest that bone lead levels may be better predictors of certain health outcomes in adults than are contemporary PbB concentrations; these include declines in hematocrit and blood hemoglobin, hypertension and decreased birthweight (Gonzalez-Cossio et al. 1997; Hu et al. 1994, 1996b).

ELEVATED LEAD LEVEL

Blood lead levels measured as a part of the National Health and Nutrition Examination Surveys (NHANES) revealed that between 1976 and 1991, the mean PbB levels of the U.S. population aged from 1 to 74 years dropped 78%, from 12.8 to 2.8 µg/dL. The prevalence of PbB levels > 10 µg/dL also decreased sharply from 77.8% to 4.3%. The major cause of the observed decline in PbB levels is most likely the removal of 99.8% of lead from gasoline and the removal of lead from soldered cans (Pirkle et al. 1994). PbB levels were consistently higher for younger children than for older children, for older adults than for younger adults, for males than for females, for blacks than for whites, and for central-city residents than for non-central-city residents. PbB levels also correlated with low income, low educational attainment, and residence in the Northeast region of the United States.

A PbB level of 50 µg/dL has been determined to be an approximate threshold for the expression of lead toxicity in exposed workers. OSHA (US Occupational Safety and Health Administration) regulations limit the concentration of lead in workroom air to 50 µg/m³ for an 8-hour workday.

When employee exposures to lead can not be maintained at or below 50 µg/m³ through engineering and work practice controls, the employer is required to provide the employees with respirators as a means of supplemental control. OSHA specifies 30 µg/m³ of air as the action level for employee exposure to airborne concentrations of lead (OSHA 1995). Under the requirements for medical surveillance and biological monitoring, the blood lead level of employees exposed to lead above the action level for more than 30 days per year must be determined at least every 6 months. The frequency for sampling an employee's blood for lead levels increases to every 2 months if the results of his previous blood analysis indicated a blood lead level at or above 40 µg/dL (OSHA 1995). OSHA requires continuing the 2-month sampling scenario until the employee's blood lead level measures below 40 µg/dL for 2 consecutive samplings. If an employee is working in an area where exposure to lead is at or above the action level, and the employee's periodic blood test or a follow-up test indicates a blood lead level at or above 50 µg/dL, the employer is required to remove the employee from that work area (OSHA 1995).

The ACGIH (American Conference of Governmental Industrial Hygienists) has adopted BEIs (Biological Exposure Index) for various substances. The BEI for a substance is an industrial hygiene reference value to be used in evaluating potential health hazards. It is important to note that BEIs are guideline values, and that they are not intended for use as measures of adverse effects or for diagnosis of occupational illness (ACGIH 1998). They represent the level of substance most likely to be observed in specimens (e.g., blood or urine) collected from a healthy worker who has been exposed to a chemical at its threshold limit value (TLV). The TLV refers to the airborne concentration of a substance at which nearly all workers may be repeatedly exposed, day after day, without adverse health effects. BEIs apply to 8-hour exposures occurring 5 days per week. The BEI for lead is 30 µg/dL (ACGIH 1998).

The recommended exposure level (REL) for lead in the air adopted by the National Institute of Occupational Safety and Health (NIOSH) is 0.1 mg/m³ (NIOSH 1997a). NIOSH also recommends maintaining air concentrations so that worker blood lead remains at less than 60 µg/dL (NIOSH 1997a).

OCCUPATIONAL EXPOSURE

Potentially high levels of lead may occur in the following industries: lead smelting and refining industries, battery manufacturing plants, steel welding or cutting operations, construction, rubber products and plastics industries, printing industries, firing ranges, radiator repair shops and other industries requiring flame soldering of lead solder, and gas stations (EPA 1986a; Feldman 1978; Goldman et al. 1987; NIOSH 1978a). In these work areas, the major routes of lead exposure are inhalation and ingestion of lead-bearing dusts and fumes. In the smelting and refining of lead, mean concentrations of lead in air can reach 4,470 µg/m³; in the manufacture of storage batteries, mean airborne concentrations of lead from 50 to 5,400 µg/m³ have been recorded; and in the breathing zone of welders of structural steel, an average lead concentration of 1,200 µg/m³ has been found (Fu and Boffeta 1995). Evaluations by NIOSH from 1979 to 1990 in radiator repair shops found that 68% of the workers sampled had airborne lead exposures exceeding the OSHA standard of 0.05 mg/m³ (Tharr 1993). Also, past studies of PbB levels of 56 radiator shop mechanics in the Boston area revealed that 80% had PbB levels greater than 30 µg/dL and 16 had PbB levels exceeding 50 µg/dL (Tharr 1993).

Studies have been conducted to determine exposure of firearm instructors to lead at outdoor firing ranges when either nonjacketed (pure lead) or jacketed (copper-coated) bullets were used. Instructors are likely to have higher exposure than shooters because they spend more time at the range. In studies at an outdoor range in Virginia, the mean breathing zone lead level when nonjacketed bullets were fired was 67.1 µg/m³ for one instructor and 211.1 µg/m³ for another (Tripathi et al. 1991). When jacketed bullets were used, breathing zone levels decreased to 8.7 µg/m³ or less. PbB levels of the instructors did not exceed the OSHA return standard of 1.93 µmol/L (40 µg/dL) or removal standard of 2.4 µmol/L (50 µg/dL) in either case.

When shooters fired conventional lead bullets, their mean exposures to airborne lead were 128 µg/m³ in the personal breathing zone and 68 µg/m³ in the general area. When totally copper-jacketed lead bullets were fired, the mean breathing zone and general area air sample concentrations were 9.53 and 5.80 µg/m³, respectively (Tripathi et al. 1990). At an outdoor uncovered range in Los Angeles, instructors who spent an average of 15 to 20 hours per week behind the firing line were found to be exposed to breathing zone lead concentrations of 460 and 510 µg/m³ measured as 3-hour, time-weighted averages. The PbB of one instructor reached 3.38 µmol/L (70 µg/dL). After reassignment to other duties, repeat testing indicated his PbB had dropped to 1.35 µmol/L (28 µg/dL) (Goldberg et al. 1991).

In 1991, NIOSH conducted a survey of the Federal Bureau of Investigations (FBI) Firearms Training Unit firing ranges and related facilities to determine occupational lead exposures among FBI and Drug Enforcement Agency (DEA)

firing range personnel (NIOSH 1996). Sixty-one personal breathing-zone and 30 area samples for airborne lead were collected. Exposures ranged up to 51.7 µg/m³ (mean 12.4 µg/m³), 2.7 µg/m³ (mean 0.6 µg/m³), and 4.5 µg/m³ (mean 0.6 µg/m³) for range instructors, technicians, and gunsmiths, respectively. Exposure of custodians ranged from non-detectable to 220 µg/m³ during short-term cleaning of a large indoor range. Carpet dust sampling of dormitory rooms of students who practiced at the firing ranges revealed statistically significant ($p < 0.0005$) higher dust-lead concentrations when compared to non-student dormitories (dust-lead concentration range of 116 to 546 µg/g with a geometric mean of 214 µg/g in the student's rooms versus a dust-lead concentration range of 50 to 188 µg/g with a geometric mean of 65 µg/g for the non-student rooms). This suggested that the students were contaminating their living quarters with lead.

Those who use recreational shooting ranges may be exposed to lead and soluble lead compounds, such as carbonates and sulfates, in soil. Surface lead concentrations at a range in Michigan were 10 to 100 times greater than background level of 25 mg/kg; mobilization of lead appeared to be occurring and may present a threat to ground and surface waters (Murray et al. 1997).

Field surveys of three radiator repair shops in the Cincinnati area revealed that local exhaust ventilation (LEV) systems are effective in controlling airborne lead levels. The highest concentration of airborne lead measured during a brief period of continuous soldering in a shop equipped with an LEV was only 7.1 µg/m³. In a shop where no LEV was used, the 13 personal samples averaged 209 µg/m³ with a maximum of 810 µg/m³ measured for a 56-minute sample worn while tearing down and resoldering a single radiator (Tharr 1993).

Workers occupationally exposed to lead apparently carry lead home on clothing, bodies, or tools. PbB levels of children in households of occupationally exposed workers were almost twice those of children in neighboring homes whose parents were not occupationally exposed to lead (median ranges were 10–14 and 5–8 µg/dL, respectively) (Grandjean and Bach 1986). Young children (<6 years old) of workers exposed to high levels of lead in workplace air at an electronic components plant (61–1,700 µg lead/m³ ambient concentrations) had significantly elevated PbB levels (13.4 µg/dL) compared with children from the same locale whose parents did not work in the electronics plant (7.1 µg/dL) (Kaye et al. 1987). Exposures of lead workers' families have been identified in nearly 30 different industries and occupations. Industries in which exposure of family members has been reported most often include lead smelting, battery manufacturing and recycling, radiator repair, electrical components manufacturing, pottery and ceramics, and stained glass making (NIOSH 1995). Children of lead-exposed construction workers may also be at increased risk (Whelan et al. 1997).

ADVERSE HEALTH EFFECTS

People living near hazardous waste sites may be exposed to lead via ingestion of contaminated water or soils or by inhalation of lead particles in the air. For people not living in the vicinity of hazardous waste sites, the major route of exposure to lead is ingestion, particularly of lead-contaminated water, food, soil, lead-based paint chips, or dusts (the latter two are particularly relevant to children

in lower-income urbanized populations). For occupationally exposed individuals, the predominant route of exposure is the inhalation of lead particles with oral ingestion also important in many cases.

Lead has been shown to affect virtually every organ and/or system in the body in both humans and animals. The most sensitive target organs of lead appear to be the nervous system (particularly in children), the hematopoietic system, and the cardiovascular system. There is evidence in both humans and animals to suggest that the kidneys and the immune and reproductive systems are also adversely affected by lead. Lead has also been shown to be carcinogenic in animals. The adverse health effects noted in humans are generally supported by observations in laboratory animals. No MRLs have been developed for lead.

The lack of a clear threshold for health effects and the need to consider multi-media routes of exposure makes evaluating the risks from exposure to lead in the environment difficult. In addition, factors such as absorption potential of the lead compound of interest, and age and nutritional status of the population complicate the development of generic guidance.

Death

Death can be the end result in cases of severe lead encephalopathy in both adults and children. The National Academy of Sciences (NAS 1972) analyzed unpublished data obtained from the patient populations reported in Chisolm (1962, 1965) and Chisolm and Harrison (1956) and concluded that the range of blood lead levels associated with death from lead encephalopathy in children was approximately 125–750 µg/dL (mean, 327 µg/dL). A case report described a 70-year-old female nursing home resident who drank lead ceramic glaze (Roberge et al. 1994). During the next 10 days her mental status progressively deteriorated, and her abdomen became distended. On admission to the hospital her PbB level was 259 µg/dL. After several days of chelation therapy, her PbB decreased to 21 µg/dL. In spite of the reduction in PbB, the patient's lethargy and confusion persisted and she developed renal failure and associated anasarca, as well as brief apneic periods. She expired on the 16th day and the cause of death was listed as lead intoxication; an autopsy was not performed.

The results of mortality studies conducted on occupationally exposed workers are discrepant, and all the studies have design flaws that limit the validity of the conclusions that can be drawn from their results. One study found a statistically significant increase in mortality due to malignant neoplasms, chronic renal disease, and "ill-defined" causes in lead-exposed workers (Cooper 1988; Cooper et al. 1985). Another study found a statistically significant increase in mortality due to cardiovascular disease in lead-exposed workers (Fanning 1988), and another found a statistically significant increase in the incidence of deaths from cerebrovascular disease in lead-exposed newspaper printers (Michaels et al. 1991). Two additional studies found no statistically significant increase in mortality due to lead exposure (Gerhardsson et al. 1986b, 1995a). Slightly lower blood lead levels were recorded in the study by Gerhardsson et al. (1986b) than in the study by Cooper et al. (1985). A follow-up evaluation of the cohort studied by Gerhardsson et al. (1986b) provided evidence suggesting an increased mortality

due to lung cancer among lead workers (Lundstrom et al. 1997). Suggestive evidence of excess death from cardiovascular disease among adults diagnosed with lead poisoning as children was presented by McDonald and Potter (1996). Weak evidence of an association between increase mortality due to renal cancer and long-term lead exposure was presented by Cocco et al. (1997).

Mortality data from longer-term studies in animals are often inconclusive. However, based on the information available in humans, it is apparent that high body burdens of lead can result in death, which is most often secondary to lead-induced encephalopathy.

Systemic Effects

Respiratory Effects

There are no conclusive data available to indicate that lead adversely affects the respiratory system in humans. However, one inhalation study in animals indicates that continuous prolonged (28-day) exposure to lead nitrate particles may be irritating to the lungs, as evidenced by the pulmonary edema and hemorrhage seen in the lungs of the lead-exposed mice at necropsy (Hillam and Ozkan 1986). These effects were not seen in animals continuously exposed for 14 days, suggesting that the apparent adverse respiratory effects were dependent on the duration of exposure and are cumulative.

However, the irritative properties of inhaled lead depend partially on the solubility and pH of the species. In this study, the animals were exposed to lead nitrate, which is acidic and, therefore, irritating. These results are not sufficient to determine whether prolonged inhalation exposure of humans to high levels of lead particles other than lead nitrate (such as may occur near hazardous waste sites) may result in pulmonary irritation.

Cardiovascular Effects

The evidence from occupational, clinical, and general population studies suggests that lead affects the cardiovascular system in humans, producing cardiac lesions and electrocardiographic abnormalities at high levels of exposure. However, the association between PbB and blood pressure is still a matter of controversy. The contribution of lead, compared with many other factors that affect blood pressure, appears to be relatively small, usually not accounting for more than 1–2% of the variation when compared with other significant factors (EPA 1986a). The evidence in humans, at this time, does not support a conclusive positive association between increased PbB levels and blood pressure.

The animal data demonstrate that lead increases blood pressure, despite confounding experimental design factors such as species tested, age of animals, route of administration, dose used (doses that are high enough to induce nephrotoxicity may produce hypertension as a secondary effect), method of measuring blood pressure, and use of anesthesia. In reviewing the database on the mechanism of lead's hypertensive action in animals, EPA (1986a) concluded that although lead, even at very low levels, produces effects on the renin-angiotensin

system in animals, these changes are not established as the cause of hypertension. Rather, hypertension is more likely to be due to changes in vascular reactivity and level of sympathetic tone, both of which may be dependent on lead-related changes in intracellular calcium ion concentration (EPA 1986a).

Interpretation of the blood lead-blood pressure data in epidemiological studies of the general population remains an area of controversy. Factors that contribute to the controversy include the methodology used to monitor blood lead and blood pressure, and statistical issues. The association between blood lead and blood pressure was the subject of a 1987 Symposium on Lead-Blood Pressure Relationships (Environmental Health Perspectives, Volume 78, June 1988) and of several population studies (Elwood et al. 1988; Grandjean et al. 1989; Neri et al. 1988; Pocock et al. 1988; Staessen et al. 1990, 1991). In addition, data from the NHANES II study were re-analyzed by Coate and Fowles (1989) and Gartside (1988). As summarized by Victery et al. (1988), both S. J. Pocock and J. Schwartz, considered the evidence from general population epidemiological studies and concluded that a doubling of PbB levels is associated with an increase of approximately 1–2 mm Hg in systolic blood pressure. Pocock concluded that the overall evidence from the human studies did not support a causal relationship between PbB and blood pressure. Schwartz concluded that, although a causal inference could not readily be drawn from the epidemiological data alone, such an inference was consistent with the animal data. Based on the data for both humans and animals, Schwartz concluded that a causal relationship is likely. Staessen et al. (1994a) reviewed 21 animal studies published since 1977 and concluded that most found a positive association between blood pressure and lead exposure. However, in the articles in which all the lead doses had been higher than 1 ppm, the association between blood pressure and exposure was found to be positive in 7, inconsistent in 3, absent in 4, and negative in one. Five out of 6 studies that employed doses not exceeding 1 ppm reported a small pressor effect, and one of these 5 failed to show a dose-response relationship when exposure was increased from 0.1 to 1 ppm. Staessen et al. (1994a) noted that publication bias may have inflated the number of positive studies appearing in the literature. They suggested that the significance to human health of lead doses between 0.1 pm and 1 ppm given to genetically heterogeneous rats, dogs, or pigeons still needs to be elucidated.

The results from more recent studies have not clarified the issue. In a study of the general population in Belgium in which 2 sets of data were collected at a 6-year interval, Staessen et al. (1996) found that blood pressure was not correlated with PbB or ZPP concentrations in men or women. The study further found that the risk of becoming hypertensive was not associated with PbB or ZPP concentrations measured at the first data collection. Results from the evaluation of participants in the Normative Aging Study showed that an increase in tibia bone lead of about 29 µg/g was associated with an increased odds ratio of hypertension of 1.5 (Hu et al. 1996a). However, the authors acknowledged that the procedures used to estimate long-term ethanol ingestion and smoking habits were rather crude. Hu et al. (1996a) further stated that given the cross-sectional nature of the investigation and the fact that tibia lead is an indicator of long-term absorption and stores in cortical bone, they could not specifically evaluate the temporality of the relationship, making premature any inference on causality.

Schwartz (1995) used meta-analysis to examine the evidence for an association between PbB concentrations and systolic blood pressure in males. The results of the analysis showed a highly significant and moderately consistent association — a decrease in PbB from 10 µg/dL to 5 µg/dL was associated with a decrease of 1.25 mm Hg (95% CI=0.87–1.63 mm Hg). Hertz-Picciotto and Croft (1993) reviewed all the major studies conducted since 1980 and concluded that an increase in blood pressure was associated with increases in blood lead in most, but not all, of the population-based studies. Regarding occupational cohorts, the reviewer's opinion was that the results are mixed, but that overall the studies suggested a small positive association between PbB and blood pressure. Staessen et al. (1994b) conducted a meta-analysis of 23 studies that included 33,141 subjects from either the general population (13 surveys) or from occupational groups (10 studies). Separate analyses (whenever possible) of data from men and women and white and black subjects showed that the association between blood pressure and PbB was similar in both genders and in each race. In all 23 studies combined, a doubling in the PbB concentration was associated with a 1 mm Hg rise in systolic pressure and with a 0.6 mm Hg increase in diastolic pressure. Staessen et al. (1994b) noted that the association with systolic pressure strongly relied on the inclusion of one study in which women had their blood pressure measured at the end of pregnancy (Rabinowitz et al. 1987). The association with diastolic blood pressure was, to a large extent, due to the results of the NHANES II survey (Harlan et al. 1985; Pirkle et al. 1985). IPCS (1995) also reviewed the literature and concluded that no causal relationship has been demonstrated between body burden of lead and blood pressure.

Limited data on occupationally exposed men indicate that the effect of lead on blood pressure may be mediated in part through the renin-angiotensin system, as evidenced by lead-related increases in plasma renin and angiotensin I levels (Campbell et al. 1985) and the kallikrein-kinin system, as indicated by a correlation between renin and kallikrein (Boscolo et al. 1981). Evidence from patients with essential hypertension and renal impairment suggests that excessive lead absorption may be involved in the development of both conditions (Batuman et al. 1983).

Gastrointestinal Effects

Colic, which is characterized by a combination of abdominal pain, constipation, cramps, nausea, vomiting, anorexia, and weight loss, is a consistent early symptom of lead poisoning in occupationally exposed cases or in individuals acutely exposed to high levels of lead. Colic is also seen in children with lead poisoning.

Although gastrointestinal symptoms typically occur at PbB levels of 100–200 µg/dL, they have sometimes been noted in workers whose PbB levels were as low as 40–60 µg/dL (Awad et al. 1986; Baker et al. 1979; Haenninen et al. 1979; Holness and Nethercott 1988; Kumar et al. 1987; Marino et al. 1989; Matte et al. 1989; Muijser et al. 1987; Pagliuca et al. 1990; Pollock and Ibels 1986; Schweitzer et al. 1990).

Histopathological evidence of lead-induced gastrointestinal damage has not been reported. Adverse gastrointestinal effects have not been noted in animal studies,

but it is difficult to study the symptoms of colic that are noted in humans in the laboratory situation.

Hematological Effects

Lead has long been known to have profound effects on heme synthesis.

Numerous studies of both occupationally-exposed subjects and the general population have tried to correlate PbB levels with changes in hematological parameters. Of all the parameters examined, ALAD activity appears to be the most sensitive indicator of lead exposure. For example, in studies of the general population, ALAD activity was inversely correlated with PbB levels over the entire range of 3–34 µg/dL. In contrast, the threshold for increase in urinary ALA in adults is a PbB concentration of approximately 40 µg/dL; for increases in blood EP or ZPP the threshold in adults is around 30 µg/dL; and the threshold for increased ZPP in children is about 15 µg/dL in children. Threshold PbB levels for decreased hemoglobin levels in adults and children have been estimated at 50 µg/dL and 40 µg/dL, respectively. Although the measurement of ALAD activity seems to be a very sensitive hematological marker of lead exposure, the inhibition of the enzyme is so extensive at PbB levels 30 µg/dL that the assay cannot distinguish between moderate and severe exposure.

Musculoskeletal Effects

Several case reports of individuals who experienced high exposures to lead either occupationally or through the consumption of illicit lead contaminated whiskey described the occurrence of a bluish-tinged line in the gums (Eskew et al. 1961; Pagliuca et al. 1990). The etiology of this "lead line" has not been elucidated. This effect has also been observed in workers exposed to high lead levels who had exposures via dust or fume. Individuals having high exposures to lead have also been reported to complain of muscle weakness, cramps, and joint pain (Holness and Nethercott 1988; Marino et al. 1989; Matte et al. 1989; Pagliuca et al. 1990).

Hepatic Effects

Limited evidence exists to suggest that lead affects hepatic mixed function oxygenases by inhibiting the formation of the heme-containing protein, cytochrome P-450 (Alvares et al. 1975; Saenger et al. 1984). Abnormal liver function in individuals exposed to high levels of lead could not be conclusively linked to lead because prior medical histories were not known. Studies in animals provide limited evidence that lead may affect the liver. Reported in the literature include effects on hepatic glycogen and DNA content and the ability to incorporate amino acids into proteins (Barratt et al. 1989). This evidence is not conclusive because these end points are relatively non-specific, and no histopathological evaluation or organ function tests (i.e., serum enzymes) were performed. Based on the information available in humans and animals, it is difficult to conclude that lead adversely affects the liver.

Renal Effects

Exposure to lead that results in PbB ranging from approximately 60 to >100 µg/dL has been associated with nephropathy in some studies of lead-exposed workers (e.g., Chia et al. 1995a). The characteristics of early or acute lead-induced nephropathy in humans include nuclear inclusion bodies, mitochondrial changes, and cytomegaly of the proximal tubular epithelial cells; dysfunction of the proximal tubules (Fanconi's syndrome) manifested as aminoaciduria, glucosuria, and phosphaturia with hypophosphatemia; and increased sodium and decreased uric acid excretion. These effects appear to be reversible.

Characteristics of chronic lead nephropathy include progressive interstitial fibrosis, dilation of tubules and atrophy or hyperplasia of the tubular epithelial cells, few or no nuclear inclusion bodies, reduction in glomerular filtration rate, and azotemia. These effects are irreversible. The acute form is reported in lead-intoxicated children, whose primary exposure is via the oral route, and sometimes in lead workers. The chronic form is reported mainly in lead workers, whose primary exposure is via inhalation. Animal studies provide evidence of nephropathy similar to that in humans, and particularly to the acute form.

In human studies where no renal biopsies have been performed to prove conclusively the occurrence of nephropathy, the results have not been consistent. This could partially be explained by the choice of the renal function parameter studied. The only parameter of renal function shown to be affected in some studies is an increase in the levels of N-acetyl-D-glucosaminidase (NAG). NAG is a lysosomal enzyme present in renal tubular cells that has been shown to be a sensitive indicator of early subclinical renal tubular disease. Increases in NAG in lead-exposed individuals have been seen at PbB levels of around 62 µg/dL, which suggests that lead may affect renal tubular function to a greater extent than glomerular function. The marker is not specific and is also increased by exposure to cadmium. IPCS (1995) reviewed the epidemiological data and concluded that renal function impairment was not associated with PbB levels below 62 µg/dL when measured by BUN and serum creatinine levels in workers exposed to lead. It should be mentioned, however, that Kim et al. (1996a) found an association between PbB and serum creatinine in a group of older men with PbB concentration lower than 62 µg/dL. IPCS (1995) stated that urinary NAG is a more sensitive indicator since altered levels were found at PbB levels <62 µg/dL. This is consistent with the results of a recent study that found a significant increase in urinary NAG in children with a mean PbB concentration of 34.2 µg/dL (Verberk et al. 1996). In that study, NAG activity increased 14% per 10 µg/dL PbB and was the only one out of 5 renal parameters evaluated that exhibited an association with PbB. Some investigators have suggested that the elevation of urinary NAG activity may be a response to a sharp increase in the renal lead burden rather than a response to the cumulative dose (Chia et al. 1994) and that a preferable early indicator of renal toxicity is an increase in urinary α1µ-globulin, which correlated well with a time-integrated blood level index in lead exposed workers (Chia et al. 1995a, 1995b). The results from Verberk et al. (1996) suggest that tubular function may be a more sensitive target for lead toxicity in children than in adults, but the results need to be confirmed. A study of adults from the general population provided suggestive evidence of impaired renal function in subjects with PbB 70 µg/dL (Staessen et al. 1992).

Kidney function has been evaluated not only in relation to PbB levels, but also in relation to bone lead concentrations, which provide a better assessment of cumulative dose of lead to the kidneys than blood lead. In a study of lead-exposed workers whose mean tibia lead was three times that of controls (66 versus 21 µg/g bone mineral) bone lead showed a modest but positive statistical association with both baseline and peak creatinine clearance after a protein challenge (Roels et al. 1994). No association existed with PbB (mean 43 µg/dL), urinary lead, or blood ZPP.

Excessive lead exposure has also been implicated as a causative agent in kidney disease associated with gout and essential hypertension (Batuman et al. 1981, 1983). Gout patients with renal impairment, and hypertensive patients with renal impairment, had significantly higher lead stores (as determined by the 3-day EDTA lead mobilization test) than gout patients or hypertensive patients without renal impairment, respectively. Therefore, excessive lead absorption may be involved in the renal impairment seen in patients with gout or essential hypertension.

Endocrine Effects

Controversial data exist regarding thyroid function in workers occupationally exposed to lead. A weak but statistically significant negative correlation was found between duration of exposure to lead and thyroxin and free thyroxin levels in workers with PbB levels that were 56 µg/dL and had over 10 years of exposure (Tuppurainen et al. 1988). According to the author, this finding could be explained by a direct effect of lead on the thyroid gland; an effect on the hypothalamopituitary level; and an effect on the peripheral turnover of thyroid hormones. A different study found no indication of altered thyroid function in workers from a lead acid battery factory (Gennart et al. 1992a). However, in the latter study the PbB levels were generally lower than in the workers examined by Tuppurainen et al. (1988), which would indicate that thyroid changes are not good indicators of moderate lead exposure.

Ocular Effects

Visual problems have been noted in some human studies. These are mostly anecdotal in nature and not well documented.

Immunological Effects

The effects on the immune system of young rats at PbB levels of 29 µg/dL (Faith et al. 1979; Luster et al. 1978), of mice at PbB levels of 15–45 µg/dL (Hillam and Ozkan 1986), and of rabbits at PbB of 1–2 µg/dL (Zelikoff et al. 1993) raise the concern that low-level exposure of humans to lead may also have adverse effects on the immune system. The best available human data, while not fully adequate to address this issue, gave no indication of immune system effects in children with blood lead levels of 40 µg/dL (Reigart and Graher 1976) and very inconsistent responses of both the cell and humoral components of the immune system in lead workers with mean blood lead levels ranging from 19 to 80 µg/dL (Alomran and Shleamoon 1988; Ewers et al. 1982; Fischbein et al. 1993;

Pinkerton et al. 1998; Sata et al. 1998; Ündeger et al. 1996). The inconsistent results may reflect differences in measures of exposure (i.e., current PbB versus cumulative indices of exposure) and/or methodological differences in the evaluation of specific immunological endpoints. Overall, there has been no evidence of marked immunotoxic effects of lead at the exposure levels studied.

Neurological Effects

The data on neurobehavioral toxicity of exposure to lead suggest that children are more sensitive, as indicated by responses at lower PbB levels, than are adult humans, and that animals are affected at roughly the same PbB levels as are humans.

In humans, encephalopathy can occur at PbB levels as low as 100–120 µg/dL in some adults (Kehoe 1961a, 1961b, 1961c; Smith et al. 1938) and at PbB levels as low as 80–100 µg/dL in some children (EPA 1986a; NAS 1972). This condition can result in death or in permanent cognitive impairment, particularly in children. Furthermore, children with high PbB levels (>80–100 µg/dL) and symptoms of lead poisoning, but no symptoms of acute encephalopathy, also have an increased incidence of lasting neurological and behavioral impairment (EPA 1986a).

Adults may have overt neurological signs and symptoms and impairment on neurobehavioral tests at blood lead levels as low as 40–60 µg/dL (Baker et al. 1979, 1983; Campara et al. 1984; Haenninen et al. 1979; Maizlish et al. 1995; Williamson and Teo 1986; Zimmerman-Tanselia et al. 1983). These blood lead levels are comparable to those at which other symptoms of lead poisoning, such as gastrointestinal symptoms, occur. Common limitations of studies examining neurobehavioral effects of lead in adults include inadequate estimation of cumulative exposure and inadequate control for age and intellectual ability before exposure. The importance of evaluating several measures of exposure (present, past, and cumulative) is illustrated, for example, by Lindgren et al. (1996), who found no association between current, and relatively low (27.5 µg/dL) PbB levels and neuropsychological variables in lead workers. The lack of association at these PbB levels was not inconsistent with what others had found, but a significant association became apparent when performance was measured against a cumulative dose estimate. Ehle and McKee (1990) reviewed several studies published between 1978 and 1986 and concluded that “the issue of psychological and neuropsychological effects of low-level lead in adults remains to be resolved in the studies reviewed. The methodologies were so varied and the cultures in which the studies were conducted so diverse that it is impossible to generalize across findings.” Similar conclusions were drawn by Balbus-Kornfeld et al. (1995) after evaluation of 21 studies, mostly cross-sectional studies. Two recent studies presented evidence of an association between decreased neurobehavioral performance and PbB in aging subjects with mean PbB concentrations around 5 µg/dL (Muldoon et al. 1996; Payton et al. 1998).

Children appear to be much more sensitive to lead-related neurobehavioral alterations than adults. Neurobehavioral dysfunction has not been demonstrated in lead-exposed workers at PbB concentrations below 40 µg/dL, whereas cognitive

and sensorimotor deficits have been shown in children to be associated with PbB concentrations as low as 10 to 15 µg/dL.

The overall results from evaluations of peripheral nerve function, specifically conduction velocity, suggest that an inverse relationship exists between blood lead and speed of conduction. The role of lead was apparent in a study by Araki et al. (1980) who found significant improvement in motor nerve conduction velocity in workers following reduction of PbB by chelation therapy. The inconsistencies among studies may reflect differences in the nerves evaluated, methodologies, characterization of lead exposure, and control for confounding. Davis and Svendsgaard (1990) conducted a meta-analysis of 32 studies and found that the median motor nerve shows more reliable effects of lead than other nerves. The LOAEL for decreased nerve conduction velocity observed in adults appeared to be a PbB concentration of 30 µg/dL (Seppalainen et al. 1983). It is possible that decreased peripheral conduction velocity may have affected performance on some of the behavioral tests such as reaction time, grip strength, and eye-hand coordination.

Reproductive Effects

There is sufficient qualitative evidence to support the conclusion that at high occupational exposure levels lead has significant adverse effects on human reproduction, including increased incidences of spontaneous abortion, miscarriages, and stillbirths. The mechanisms responsible for these effects are unknown at this time, but many factors may contribute to these results. These factors include indirect effects of lead on maternal nutrition or hormonal status before and during pregnancy to more direct gametogenic effects that could affect parental fertility in either sex. The available data do not permit any estimate of effect levels in women, although two studies found no effect on the rate of spontaneous abortions at PbB levels of 10 µg/dL. Regarding male reproductive function, evidence is accumulating from the more recent studies (Alexander et al. 1996; Gennart et al. 1992b; Lerda 1992; Lin et al. 1996) that adverse effects such as lowered sperm counts, and increases in the numbers of abnormal sperm may be associated with PbB concentrations below the currently accepted worker protection criteria of 40 µg/dL. Studies that did not find decreased fertility among lead-exposed male workers are not necessarily in contradiction with those that did find such an effect. As discussed for example by Bonde and Kolstad (1997) in their study of Danish workers, reduced fecundity does not necessarily translate into reduced fertility in populations such as the Danish one where most couples plan the size of their family and have easy access to contraception. Impairment of fecundity may go on unnoticed because couples continue to try until they become pregnant.

Studies in males indicated that effects on sperm may start to appear at PbB levels around 40 µg/dL.

Lead-induced effects on male reproductive functions have been reported in humans (Assennato et al. 1987; Chowdhury et al. 1986; Lancranjan et al. 1975; Lerda 1992; Wildt et al. 1983). A group of 150 workmen with long-term lead exposure were categorized by clinical and toxicological data into four groups: lead-

poisoned (mean PbB level, 74.5 µg/dL), and moderately (mean, 52.8 µg/dL), slightly (mean, 41 µg/dL), or physiologically (mean, 23 µg/dL) exposed to lead (Lancranjan et al. 1975). The lead-poisoned group and the moderately exposed group had decreases in fertility, as measured by asthenospermia, hypospermia, and teratospermia. The effect of lead was thought to be directly on the testes because tests for changes in gonadotropin secretion were negative. Secretion of androgens by the testes was not affected.

Another study compared two groups of men in a Swedish battery factory (Wildt et al. 1983). The men exposed to high levels of lead had PbB levels of 50 µg/dL at least once prior to the study and had mean PbB levels of 46.1 and 44.6 µg/dL (range, 25–75 µg/dL) during fall and spring test periods. The controls (exposed only to low environmental levels of lead) had PbB levels that seldom exceeded 30 µg/dL, and had mean PbB levels of 21.1 and 21.5 µg/dL (range, 8–39 µg/dL) during fall and spring test periods. The high-lead group tended to exhibit decreased prostate/seminal vesicle function as measured by seminal plasma constituents, low semen volumes, and lower functional maturity of sperm (as measured by swelling of the sperm heads in detergent [sodium dodecyl sulfonate] solution).

Chowdhury et al. (1986) reported that occupational exposure of 10 men to lead caused a significant decrease in sperm count and motility and an increased percentage of abnormal spermatozoa. The average PbB concentration in the lead-exposed group was higher (42.5 µg/dL) compared to controls (14.8 µg/dL). Assennato et al. (1987) reported decreased sperm production in 39 battery factory workers with high PbB levels ranging from 50 to 61 µg/dL, compared to 39 nonexposed workers. Lerda (1992) reported significant decreases in sperm count and motility, as well as increases in the percent of dead sperm and in sperm with anomalies in a group of 30 workers in a battery factory compared to 30 controls. PbB levels in the exposed workers ranged from 40 to 98 µg/dL, whereas the range in controls was 18–26 µg/dL. Although some parameters were within the normal range for the general population, they were significantly different than those from the referent group. These studies, however, were limited by the small sample size. Alexander et al. (1996) published the results of the evaluation of a much bigger cohort (n=2,469) of males employed at a lead smelter; 152 workers provided blood samples and 119 also provided semen samples. The workers were divided into four groups according to their current PbB concentration: <15, 15–24, 25–39, and >40 µg/dL; the geometric mean sperm concentrations were, respectively, 79.1, 56.5, 62.7, and 44.4 million cells/mL and the geometric mean total sperm counts were 186, 153, 137, and 89 million cells. The p value for the trend was 0.04. Workers with current PbB concentration of > 40 µg/dL had an increased risk of below normal sperm and total sperm count relative to those with PbB concentrations of <15 µg/dL. Independent of current lead exposure, sperm concentration, total sperm count, and total motile sperm count were inversely related to measures of long-term lead exposure. The authors also found no association between lead exposure and measures of lead motility, sperm morphology, or serum concentrations of reproductive hormones.

The effect of lead exposure on male fertility was examined in a group of 74 workers in a lead factory (Gennart et al. 1992b). Fertility was assessed by

examining the birth experiences of their wives through a logistic regression model. Workers had a mean age of 39 years, had been exposed for a mean of 10.7 years, and had a current mean PbB level of 46.3 µg/dL. They were compared with a group of 138 unexposed individuals whose mean PbB concentration was 10.4 µg/dL. In the exposed workers there was a tendency before exposure to an increased birthrate. However, a significant decrease in fertility was observed during the period of exposure relative to the unexposed group; duration of exposure was also associated with decreased fertility. As indicated by the authors, the main limitation of the study was the fact that the worker's wives could not be interviewed, and therefore, the medical and occupational factors that might also have affected their reproductive system could not be assessed. The results of an assessment of male fertility in a much bigger cohort evaluated 4,256 lead-exposed workers and 5,148 matched comparison subjects (Lin et al. 1996). Exposed workers were defined as having a PbB level 40 µg/dL before 1986 or 25 µg/dL for the study period (1981–1992). The results showed that the lead-exposed workers had fewer births than expected relative to the comparison group, and this was observed among all age categories with the exception of the 51- to 55-year-old group. Those with the highest cumulative exposure (mean PbB level x duration) had the most obvious reduction in fertility. However, Lin et al. (1996) stated that the study conclusion may be limited by the inability to control for some confounders such as marital status or contraceptive use.

In contrast with the results summarized above, two studies found no significant effects of lead exposure on fertility. Coste et al. (1991) conducted a person-year analysis and reported no effects on fertility (defined as the number of live births to a couple) among men exposed to lead in a French battery factory. Exposed workers (229) were categorized into groups with PbB levels of <40 µg/dL, 40–60 µg/dL, and >60 µg/dL. Nonexposed workers (125) did not have their PbB levels recorded. In agreement with these results are the findings of a study that examined fertility among 1,349 male battery plant employees and 9,596 reference workers at 3 Danish plants (Bonde and Kolstad 1997). The mean PbB concentration in a subset of 400 workers who provided 4,639 blood samples was 39.2 µg/dL. This study found no association between employment at the plants and changes in fertility in terms of birth rate, either during years of employment or during subsequent years. The authors point out, however, that their findings do rule out that the time taken to achieve a pregnancy is increased among battery workers because most pregnancies in Denmark are planned.

The relation between concentration of circulating pituitary and testicular hormones was evaluated in a group of 122 workers in three lead battery factories (Ng et al. 1991). A group of 49 nonexposed subjects was used for comparison. The mean PbB level in workers was 35.2 µg/dL (mean in controls was 8.3 µg/dL) and the mean duration of exposure was 6 years. The results showed that increasing age was significantly associated with increases in luteinizing hormone (LH) and follicle stimulating hormone (FSH) concentrations, but not with testosterone or prolactin concentrations. Smoking was significantly associated with decreased prolactin concentrations. Compared with control subjects, workers exposed for less than 10 years had normal testosterone but significantly higher levels of FSH and LH; those exposed for 10 or more years had lower testosterone, but normal FSH and LH. As a group, the exposed workers had testosterone levels comparable

to controls; however, older (40 years) workers had significantly lower testosterone levels than older control subjects. LH and FSH concentrations showed a moderate increase with PbB in the 10–40 µg/dL range; no clear association was observed for prolactin and testosterone. These results are in general agreement with those of earlier studies of lead workers with higher PbB levels (66 µg/dL), which indicates that lead acts directly on the testes to cause severe depression of sperm count and peritubular testicular fibrosis, and also produces reduced testosterone synthesis or disrupts regulation of LH secretion at the hypothalamic-pituitary level (Braunstein et al. 1978; Cullen et al. 1984; Rodamilans et al. 1988). Although some of these studies had limitations such as concomitant exposure of workers to other chemicals, lack of matched control group, small sample size, and in some cases a possibility of observed effects being precipitated by the EDTA chelation (as in Braunstein et al. 1978), taken together they provide evidence for lead-induced endocrine disturbances and reproductive dysfunction in male workers.

Studies in animals have, in general, been supportive of the reproductive findings of studies in humans. Studies in male monkeys exposed for lifetime and using exposure protocols to evaluate different developmental ages have reported structural alterations in the testis at PbB levels relevant to the human population (Foster et al. 1996, 1998). Moreover, exposure only during infancy resulted in noticeable alterations at the age of 10 years (Foster et al. 1998). Studies in a rat “lifetime” model showed that continuous lead exposure produces a developmental delay in sexual maturity (Ronis et al. 1998b, 1998c) by suppressing the normal sex steroid surges observed at birth and during puberty.

Genotoxic Effects

Evaluation of the genotoxicity of lead in humans has focused on evaluations of lymphocytes from occupationally or environmentally exposed persons (Table 2-10) and in vitro studies of structural chromosomal aberrations and sister chromatid exchange in cultures of lymphocytes taken from healthy individuals (Table 2-11).

Results of studies with human lymphocyte cultures exposed in vitro to lead acetate were nearly equally divided between positive (Beek and Obe 1974; Niebuhr and Wulf 1984) and negative (Beek and Obe 1975; Deknudt and Deminatti 1978; Gasiorek and Bauchinger 1981; Schmid et al. 1972).

Eleven male volunteers aged 20–30 years ingested lead acetate for 49 days. PbB levels were kept at approximately 40 µg/dL. The frequency of chromosome aberrations was assayed after lymphocyte culture for 72 hours and found to be no different from that of 10 controls. The lymphocytes from lead-exposed subjects did show a higher mitotic activity (Bulsma and DeFrance 1976).

Results of assays made following in vivo exposure from occupational sources are contradictory, but do suggest that lead may have an effect on chromosomes. Increased frequency of sister chromatid exchange was not observed in one study of occupationally exposed adults with blood lead levels of 48.7 µg/dL (Maki-Paakkanen et al. 1981) or in environmentally exposed children with PbB levels of 30–63 µg/dL (Dalpra et al. 1983). A slight positive correlation between sister chromatid exchanges and increasing duration of exposure has been reported in

lead-exposed workers (Grandjean et al. 1983). This observation was independent of PbB level. Similar slight increases of sister chromatid exchanges in lead-exposed workers that may have been confounded by age effects were reported in a study that used too few controls to show conclusive results (Leal-Garza et al. 1986). Increased frequencies of chromosomal aberrations (primarily chromatid-type) were seen in 21 battery factory workers; these elevations were positively correlated with PbB levels, and showed a marked increase when PbB levels reached 50 µg/dL. Sister chromatid exchanges were also significantly elevated in these workers when PbB levels reached 80 µg/dL (Huang et al. 1988b). This study examined a fairly small number of workers, but appropriate selection criteria were used in order to minimize the effects of other potential genotoxic factors, such as smoking, drinking, viral diseases, exposure to medical X-rays, chelation agents, or use of medications with known clastogenic effects. A common problem in these occupational studies is possible concurrent exposures to many other agents in the occupational environment.

Occupational exposure to lead is associated with increased mitotic activity in peripheral lymphocytes, increased rate of abnormal mitosis (Forni et al. 1976; Sarto et al. 1978; Schwanitz et al. 1970), and increased incidence of chromosomal aberrations (Al-Hakkak et al. 1986; Forni et al. 1976, 1980; Nordensön et al. 1978; Schwanitz et al. 1970) at PbB levels ranging from 22 to 89 µg/dL. While a positive correlation between PbB levels and the frequency of chromosomal aberrations has been reported (Nordensön et al. 1978), most of the available data on occupationally exposed workers show no increase in the frequency of chromosomal aberrations when PbB levels ranged from 38 to 120 µg/dL (Bauchinger et al. 1977; Maki-Paakkanen et al. 1981; O'Riordan and Evans 1974; Schmid et al. 1972; Schwanitz et al. 1975) or in environmentally exposed children with PbB levels of 12–33 µg/dL (Bauchinger et al. 1977).

Maternal and fetal chromosomal aberrations were observed in mice following prenatal exposure to subembryotoxic doses of lead nitrate (Nayak et al. 1989a). Pregnant Swiss Webster mice were given intravenous doses of lead nitrate at levels of 12.5, 25, 50, and 75 mg/kg body weight on the 9th day of gestation. On day 18, the animals were killed, and maternal bone marrow cells and fetal liver cells were examined for chromosomal aberrations. Low levels of constitutive changes mostly in the form of deletions were seen at all doses administered in both maternal and fetal cells indicating that prenatal exposure to lead may induce genotoxic changes in the fetus.

A single intracardiac dose of 40 µg/g body weight lead acetate induced a 25-fold increase in mitosis of mouse liver cells 5 hours after injection (Choie and Richter 1978). Results were mixed for various manifestations of genotoxicity or cell cycle disruptions in several experiments with lead acetate in mammals (Bruce and Heddle 1979; Deknudt and Gerber 1979; Deknudt et al. 1977; Jacquet and Tachon 1981; Jacquet et al. 1977; Muro and Goyer 1969; Tachi et al. 1985; Willems et al. 1982).

Acute intraperitoneal exposure to 25 mg lead/kg as acetate resulted in no increase in the number of micronuclei in bone marrow polychromatic erythrocytes in mice examined 6 hours after dosing (Jacquet et al. 1977). In contrast, a significant

increase in the frequency of micronuclei was observed in bone marrow from mice treated intraperitoneally with single doses of 0.4 to 50 mg lead/kg as lead nitrate; increases were observed 12 to 36 hours after dosing (Jagetia and Aruna 1998). The response was not dose-related. With few exceptions, the frequency of micronuclei was significantly higher in male mice than in females at all doses and at all post-treatment periods. Lead acetate administered intraperitoneally to Sprague-Dawley rats caused an increase in the percentage of aberrant bone marrow cells in female, but not male rats. The aberrations were primarily chromatid gaps, although there was no dose dependency across the four dose points used (Tachi et al. 1985).

Several genotoxic end points were assayed in male rabbits after subcutaneous injection of doses of 0, 0.25, and 0.50 mg lead acetate/kg body weight 3 times a week for 14 weeks. No treatment-related effects were seen in sperm count, morphologic abnormalities of sperm, histopathology of the testes, or on the number of sister chromatid exchanges in lymphocytes or the relative number of micronuclei in bone marrow erythrocytes (Willems et al. 1982). Tests for gene mutations, DNA modification, and recombinations in various microorganisms (See Table 2-11) using lead acetate (Bruce and Heddle 1979; Dunkel et al. 1984; Nishioka 1975; Rosenkranz and Poirier 1979; Simmon 1979a, 1979b; Simmon et al. 1979), lead nitrate (Kharab and Singh 1985), and lead chloride (Fukunaga et al. 1982; Nishioka 1975) were consistently negative with or without metabolic activation. Lead chloride was shown to be mutagenic in *Salmonella typhimurium* strain TA102 without S9 activation; it was nonmutagenic in three other strains with and without activation (Wong 1988). A positive response was observed by Nestmann et al. (1979) for lead chromate, but further testing clarified that the positive response was associated with the chromate rather than the lead moiety. Lead chloride has been shown to inhibit both RNA (Hoffman and Niyogi 1977) and DNA (Sirover and Loeb 1976) synthesis.

In mammalian test systems *in vitro* (Syrian or Chinese hamster cells), lead acetate gave conflicting results for structural chromosomal aberrations (Bauchinger and Schmid 1972; Robison et al. 1984). Lead acetate increased the frequency of DNA repair (Robison et al. 1984), and the frequency of achromatic lesions and gaps (Bauchinger and Schmid 1972); both lead acetate (Bauchinger and Schmid 1972) and lead sulfate (Costa et al. 1982) interfered with normal mitotic division. Both lead sulfide and lead nitrate were mutagenic at the hypoxanthine guanine phosphoribosyl transferase (HPRT) locus in Chinese hamster V79 cells (Zelikoff et al. 1988). Because these investigators failed to demonstrate either sister chromatid exchange induction or DNA single-strand breaks following treatment with either lead compound, they propose an indirect mechanism of genotoxicity probably involving DNA repair enzymes. A series of experiments with lead acetate alone and lead acetate in conjunction with ultraviolet radiation indicate that the mechanism of genotoxicity of lead ions may indeed be an indirect one (Hartwig et al. 1990). Lead acetate alone did not induce DNA-strand breaks in HeLa cells or mutations at the HPRT locus, nor did it increase sister chromatid exchange frequency in V79 Chinese hamster cells. However, for all end points tested, lead ions interfered with the processing of UV-induced DNA damage, thus increasing the frequency of the end points measured. These authors suggested the possibility of interference with repair enzymes such as polymerase or ligase, or else interaction with calcium-

regulated processes. An interaction with calcium-regulated processes, such as those modified by calmodulin, would be consistent with other observed interactions with calcium levels (Deknudt et al. 1977). Lead is also known to form complexes with amine and carboxyl groups of proteins, which in turn can lead to enzyme inactivation (Bota et al. 1982). A recent study using Chinese hamster ovary cells suggested that the mutagenicity of lead may be due to lead-induced formation of reactive oxygen intermediates such as hydrogen peroxide (Ariza et al. 1998).

Cancer

The information available regarding the association of occupational exposure to lead with increased cancer risk is generally limited in its usefulness because the actual compound(s) of lead, the route(s) of exposure, and level(s) of lead to which the workers were exposed were often not reported. Furthermore, potential for exposure to other chemicals including arsenic, cadmium, and antimony occurred, particularly in lead smelters, and smoking was a possible confounder (Cooper 1976; IARC 1987). These studies, therefore, are not sufficient to determine the carcinogenicity of lead in humans, and the following discussion is restricted to the most comprehensive of these studies.

The most extensive was a series of reports of a large number of workers at 6 domestic lead production plants (smelters and recycling plants) and 10 battery plants (Cooper 1976; Cooper and Gaffey 1975). A total of 7,032 individuals were studied. PbB lead levels were available for 1,850 individuals, and the distribution was as follows: 1,433 had a PbB concentration 40 µg/dL, 488 had 70 µg/dL, 188 had 80 µg/dL, and 77 had 100 µg/dL. Increased incidences of total malignant neoplasms were observed for both categories of lead workers, but the increase was statistically significant only for lead production workers. The increase in total malignancies appeared to be due to small, statistically nonsignificant increases in digestive and respiratory tract tumors (evident in both the lead production and battery workers) and urinary tract tumors (in production workers). In a statistical reanalysis of the Cooper and Gaffey (1975) data, Kang et al. (1980) determined that the incidence of total malignant neoplasms, cancers of the digestive tract, and cancers of the respiratory tract were statistically elevated in both lead production workers and battery workers.

In a follow-up to the original study, Cooper (1981) reported that lead had no cancer-inducing properties, although standard mortality ratios (SMRs) of 125–149% for total malignant neoplasms, 172% for respiratory cancer, and 229% for cancers of other sites were reported in battery workers. In a subsequent evaluation of a more select subset from the original study, Cooper et al. (1985) reported increased SMRs for total malignancies in both groups of workers (statistically significant only in the battery workers) attributed to digestive and respiratory cancers. These small excesses of cancer deaths could not be correlated with onset, duration, or level of exposure. In addition, no adjustments could be made for other concomitant industrial exposures or for smoking. The attributable risk of smoking could easily explain the small increase in respiratory cancer in an industrial cohort that contained an excess of heavy smokers. Also, a marginally significant increase in digestive tract cancer in acid-lead battery workers was observed

during the early years of lead exposure (when lead levels were presumably higher than in later years) (Fanning 1988; Malcolm and Barnett 1982).

In a historical cohort mortality study of 1,990 primary lead smelter workers, an SMR of 2.04 for mortality from renal cancer was calculated (Selevan et al. 1985). The cohort consisted of workers who had worked at least 1 year, with at least 1 day of employment at the smelter between 1940 and 1965. The cohort had been heavily exposed to lead and in 1976 the PbB levels averaged 56.3 µg/dL. Exposures to cadmium and arsenic were generally minor. A follow-up study of this cohort was conducted from 1977 through 1988 (Steenland et al. 1992). Analysis of the follow-up study revealed an excess of kidney cancer, particularly in the high-lead group (SMR 2.39). Although, as the authors indicate, the study is limited by lack of detailed data on lead exposures, potential confounding exposures to cadmium and arsenic, lack of smoking data, and small cohort size, the results are of interest because animal studies associate lead exposure with kidney cancer (see Section 2.2.2.8). In addition, two cases of renal cancer have been reported in occupationally exposed men who had symptoms of lead poisoning and high blood lead levels (Baker et al. 1980; Lilis 1981). In one case, the tumor was reported to contain a high level of lead and to have histopathological characteristics similar to those of kidney tumors induced by lead in animals (Baker et al. 1980).

In a study of cancer incidence in workers exposed to tetraethyl lead, a statistically significant association was found between exposure to this compound and rectal cancer (odds ratio = 3.7; 90% confidence limits of 1.3–10.2) (Fayerweather et al. 1997). The odds ratio increased four times at the high-to-very high cumulative exposure level, demonstrating a dose-response relationship. When a 10-year latency was assumed, the association became even more pronounced. No increases in the incidence of cancer at other sites (i.e., brain, kidney, lung, spleen, and bone) were observed in the exposed workers. A study that comprised 20,700 Finnish workers exposed to lead during 1973–1983 found a 1.4-fold increase in the overall cancer incidence and a 1.8-fold increase in the incidence of lung cancer among workers who had ever had a blood lead level 21 µg/dL (Anttila et al. 1995). The overall mortality for the whole cohort, however, was less than expected, and there was no clear excess mortality for specific causes of death. In order to examine the association of lung cancer with indices of lifetime exposure to lead and to obtain information on potential confounders, the authors conducted a case-referent study on lung cancer within the study base. Analysis of the results showed an increased odds ratio for lung cancer for concomitant exposure to lead and engine exhaust. In a subsequent study of this same cohort, an excess risk of nervous system cancer, specifically gliomas, was found in workers with a PbB concentration 29 µg/dL compared with those whose PbB concentration had not exceeded 14.4 µg/dL (Anttila et al. 1996). However, the authors stated that no firm conclusions could be drawn because of the small number of cases, the rather short follow-up time, and the low response rate.

Fu and Boffetta (1995) conducted a meta-analysis of case-control and cohort epidemiology studies focusing on overall cancer, stomach cancer, lung cancer, kidney cancer, and bladder cancer. They found a significant excess risk of overall cancer, lung cancer, and bladder cancer. The corresponding relative risk ratios (RR) and 95% CI were 1.11 (1.05–1.17), 1.29 (1.10–1.50), and 1.41 (1.16–1.71).

The RR for kidney cancer was also high, but did not achieve statistical significance. When meta-analysis was restricted to studies that were conducted in battery or smelter industries where exposure to lead was heavy, slightly higher RRs for cancers of the stomach (1.50) and lung (1.42) were found. A serious limitation of this analysis is that no corrections for confounders could be made because there were no data available in most reports. Some of these confounders included cumulative exposure to lead, smoking and dietary habits, and exposure to other chemicals.

According to EPA (IRIS 1999), the available human epidemiological studies lack quantitative exposure data for lead and for possible confounding exposures (e.g., arsenic, smoking). Cancer excesses in the lung and stomach of lead-exposed workers that are reported are relatively small, dose-response relationships are not demonstrated neither is there consistency in the site of cancers reported. EPA (IRIS 1999) concluded that the human data are inadequate to refute or demonstrate the potential carcinogenicity of lead exposure.

The available data on the carcinogenicity of lead following ingestion by laboratory animals indicate that lead is carcinogenic, and that the most common tumors to develop are renal tumors (Azar et al. 1973; Koller et al. 1985; Van Esch and Kroes 1969). Administration of lead compounds by the parenteral route produced similar results. Lead subacetate was positive at high dosages in the strain A mouse lung adenoma bioassay (Poirier et al. 1984; Stoner et al. 1976), but the positive response was blocked by simultaneous administration of calcium or magnesium acetate (Poirier et al. 1984). Subcutaneous administration of lead phosphate to rats was associated with high incidence of renal tumors (Balo et al. 1965; Zollinger 1953). Lead acetate was positive in Syrian hamster embryo cell transformation tests (Dunkel et al. 1981; Pienta et al. 1977), in MLV-infected rat embryo cell transformation test (Dunkel et al. 1981), and in enhanced simian adenovirus (SA-7) transformation of Syrian hamster embryo cells (Casto et al. 1979). Lead oxide also enhanced SA-7 transformation of Syrian hamster embryo cells (Casto et al. 1979).

The extremely high cumulative doses of lead used in these studies are difficult to extrapolate to low-level exposure in humans, and thus do not provide a sufficient basis for quantitative risk assessment (see discussion below). In addition, it is possible that the high doses required to induce renal tumors may have produced a carcinogenic effect that resulted from nonspecific tissue damage and was independent of any direct effect of lead. Furthermore, the relevance of chemically-induced male rat kidney tumors to potential carcinogenicity in humans has been questioned (EPA 1991c). IPCS (1995) reviewed the literature on cancer and lead and concluded that “renal tumors can occur in rats and mice administered high doses of lead. However, the evidence for the carcinogenicity of lead and inorganic lead compounds in humans is inadequate.”

Nonetheless, EPA (1988b) concludes that the animal data are sufficient to demonstrate that lead and (inorganic lead) compounds, particularly soluble lead salts, are carcinogenic to animals. Although dose-response data are available from animal studies, EPA (1988b) recommends that a numerical estimate of cancer potency or risk based on such data should not be used because of the

uncertainties involved in such an extrapolation, some of which may be unique to lead. Current knowledge of the pharmacokinetics of lead indicates that an estimate derived by standard methods would not adequately delineate the potential risk (IRIS 1999). EPA (IRIS 1999) has assigned lead and (inorganic) lead compounds a classification of B2, probable human carcinogen.

The International Agency for Research on Cancer (IARC 1987) concluded that the evidence for carcinogenicity of lead and inorganic lead compounds was inadequate in humans and sufficient in animals. IARC (1987) classified lead and inorganic lead compounds in IARC Group 2B, possible human carcinogen. The Department of Health and Human Services (DHHS) has determined that lead acetate and phosphate may reasonably be anticipated to be carcinogens based on sufficient evidence from animal studies, but inadequate evidence from human studies (NTP 1994).

Developmental Effects

Evidence from human studies on congenital anomalies as an end point (Ernhart et al. 1985, 1986; McMichael et al. 1986; Needleman et al. 1984) indicate no association between prenatal exposure to low levels of lead and the occurrence of major congenital anomalies.

No reports were found indicating low levels of lead as a cause of major congenital anomalies. Needleman et al. (1984), however, demonstrated an association between blood lead levels and minor congenital anomalies. Using logistic regression modeling techniques and controlling for a number of possible confounders, the authors reported a significant association between cord blood lead levels and the collective occurrence of minor anomalies in 4,354 infants born in Boston. Data were obtained from hospital records. The most common of these anomalies were hemangiomas, lymphangiomas, minor skin anomalies (tags and papillae), and undescended testicles. No individual anomaly was significantly associated with blood lead levels. Major malformations, birth weight, and gestational age were not associated with PbB lead levels.

This conclusion is further supported by developmental toxicity studies conducted in rats and mice; these studies provide no evidence that lead compounds (acetate or nitrate) are teratogenic when exposure is by natural routes (i.e., inhalation, oral, dermal). Intravenous or intraperitoneal injection of lead compounds (acetate, chloride, or nitrate) into pregnant rats, mice, or hamsters, however, has produced malformations in several studies reviewed by EPA (1986a).

The effects of low levels of lead on birth weight and gestational age are controversial.

The association between low birth weight and parental occupational lead exposure variables was studied by Min et al. (1996). The study comprised 220 cases (birth weight <2,500 g) and 522 controls (birth weight > 2,500 g) selected among 3,572 participants in the Baltimore-Washington Infant Study. Parental occupational exposure was inferred from jobs held during the period 6 months before pregnancy to the end of pregnancy. Only a few mothers were potentially exposed to lead

either directly or indirectly during the exposure period of interest; therefore, the analysis included fathers only. Twenty-one percent of the fathers were potentially exposed to lead either directly or indirectly. Univariate analyses of low birth weight in relation to various measures of lead exposure showed that the risk of low birth weight was significantly increased only among infants of fathers with direct and high levels of lead exposure. This association persisted after adjusting for relevant confounders. Although reports of sperm abnormalities and reduced fertility among lead-exposed men (Section 2.2.1.5) would support a direct male-mediated effect, Min et al. (1996) suggested that a direct paternal preconceptional effect on birth weight, which is gained after 24 weeks of gestation, is unlikely. A more likely explanation discussed is that prenatal exposure occurs by indirect maternal contact with contaminated work clothing or tools brought home. Limitations of the study include lack of actual measures of exposure in the workplace, possible additional non-occupational exposure to lead, and simultaneous occupational exposure to other chemicals.

EFFECT OF DOSE AND DURATION OF EXPOSURE ON TOXICITY

The principal adverse health effects of lead can be related to concentrations of lead in blood (see Section 2.2.1). Correlation and regression analyses of data on blood lead concentrations and various health effects define a spectrum of effects that become apparent in human populations having a range of PbB levels approaching 10–15 µg/dL. These include effects on heme metabolism, erythrocyte pyrimidine nucleotide metabolism, serum vitamin D levels, mental and physical development, and blood pressure. As PbB concentrations increase above the range of 10–15 µg/dL, more pronounced effects on all of the above end points occur. At levels exceeding 30 µg/dL, anemia, nephrotoxicity and more overt neurological impairment can occur.

MECHANISMS OF TOXICITY

Because lead affects virtually every organ or system in the body, it is not surprising that the proposed mechanisms of lead toxicity involve fundamental biochemical processes. These proposed mechanisms include lead's ability to inhibit or mimic the action of calcium and to interact with proteins (Bressler and Goldstein 1991; Fowler 1992; Goering 1993; Goldstein 1993; Goyer 1993). In its interaction with proteins, lead binds primarily with sulfhydryl, amine, phosphate and carboxyl groups, with sulfhydryl having the highest affinity. The stability of lead complexes increases with increasing numbers of binding sites, and with optimal spacing, such as with vicinal sulfhydryls. Lead's ability to mimic calcium in the activation of calmodulin (discussed below under cardiovascular and neurological effects) involves binding to carboxyl groups; lead's ability to mimic calcium in the activation of protein kinase C (discussed under cardiovascular, neurological and carcinogenic effects) probably involves binding to sulfhydryl groups. Hence, the calcium agonist and protein-binding mechanisms sometimes overlap (Goering 1993).

Suggested mechanisms for the renal carcinogenesis of lead in rodents include: (1) an alteration of genetic function by lead in association with the high-affinity lead-binding protein following translocation to the nucleus (see previous discussion on

mechanism of renal effects); (2) tumor promotion by activation of protein kinase C, which, in addition to the functions noted above, phosphorylates growth factor receptors and oncogenes; and (3) stimulation of cellular proliferation or cystic hyperplasia (which may be secondary to other mechanisms) (Fowler 1992; Goyer 1992, 1993).

SYNERGY

Alcoholics and Smokers

Alcoholics, and people who consume excess amounts of alcohol, may be at increased risk of hematological, neurological, and hepatotoxic effects. In animal studies, lead and alcohol synergistically inhibited blood ALAD activity and hepatic glutamic oxaloacetic transaminase (GOT, AST) and glutamic pyruvic transaminase (GPT, ALT) activity, depressed dopamine and 5-hydroxytryptamine levels in rat brain, increased lead burdens in tissue organs, and elevated blood ZPP (Dhawan et al. 1989; Flora and Tandon 1987). Smokers are also at elevated risks of lead intoxication since cigarette smoke contains lead and other heavy metals such as cadmium and mercury (Calabrese 1978), which have been shown to be synergistic in experimental animals (Congiu et al. 1979; Exon et al. 1979; Fahim and Khare 1980).

The US National Toxicology Program's 10th Report on Carcinogens considered that lead acetate and lead phosphate were reasonably anticipated to be human carcinogens based on sufficient evidence of carcinogenicity in experimental animals (IARC 1972, 1980, 1982, 1987).⁷ Renal adenomas and carcinomas and cerebral gliomas were induced in rats of both genders after dietary lead acetate. Subcutaneous injections of lead phosphate induced renal cortical tumors including carcinomas in rats. There was inadequate evidence for the carcinogenicity of lead acetate and phosphate in humans (IARC 1987).

The International Agency for Research on Cancer (1987) concluded that lead and inorganic lead compounds were possibly carcinogenic to humans (Group 2B), while organolead compounds were not classifiable as to their carcinogenicity to humans (Group 3).⁸ The summary evaluation is reproduced below.

Evidence for carcinogenicity to humans (inadequate)

Three epidemiological studies of workers exposed to lead and lead compounds were reviewed previously [ref: 1]: one on smelters and battery workers in the USA, one on workers exposed to tetraethyllead in the USA, and one on copper smelters in the USA; data on the first of these populations have been updated [ref: 2]. A study on battery workers in the UK [ref: 3] is now available, and studies of a

⁷ National Toxicology Program. US Department of Health and Human Services. 10th Report on Carcinogens. Accessed at <http://ehp.niehs.nih.gov/roc/toc10.html> on 16th July 2003

⁸ International Agency for Research on Cancer (1987). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. Supplement 7. Lyon, France. D21.1

US lead smelter [ref: 4] and of a Swedish copper smelter [ref: 5] have also been reported. A statistically significant excess of cancers of the digestive system (21 observed, 12.6 expected) was found in the study of battery workers in the UK, spanning 1925-1976, although the excess was confined to the years 1963-1966 [ref: 3]. Significant excesses of stomach cancer (34 observed, 20.2 expected) and of respiratory cancers (116 observed, 93.5 expected) were seen in the study of US battery plant workers [ref: 2], although there was a downward trend in standardized mortality ratio by number of years of employment; in the lead production facilities, the excesses noted for stomach and respiratory cancers were not significant [ref: 2]. A nonsignificant excess of respiratory cancer (41 observed, 36.9 expected) was reported in one of the studies of smelters [ref: 4], with 28 observed and 25.7 expected in the group with high exposure to lead. Excesses were also noted in this study for kidney cancer (6 observed, 2.9 expected) and bladder cancer (6 observed, 4.2 expected) [ref: 4]. A small study of workers at a Swedish smelter [ref: 5] with long-term exposure to lead demonstrated a nonsignificant excess of lung cancers (8 observed, 5 expected). Two cases of kidney cancer in lead smelter workers have also been reported [ref: 6,7]. The excesses of respiratory cancer in these studies were relatively small, showed no clear-cut trend with length or degree of exposure, and could have been confounded by factors such as smoking or exposure to arsenic. A study of workers manufacturing tetraethyllead revealed excesses of respiratory cancer (15 observed, 11.2 expected) and brain cancer (3 observed, 1.6 expected) [ref: 8].

Evidence for carcinogenicity to animals (sufficient for inorganic lead compounds; inadequate for organolead compounds)

Lead acetate and lead subacetate were tested for carcinogenicity by oral, subcutaneous and intraperitoneal administration in rats, lead phosphate was tested by subcutaneous and intraperitoneal administration in rats, and lead subacetate was tested by oral administration in mice. Renal tumours were produced in animals of each species by each route of administration. Rats given lead acetate or lead subacetate orally developed gliomas. Lead subacetate also produced an increased incidence of lung adenomas in mice after intraperitoneal administration [ref: 1]. Oral administration of lead dimethyldithiocarbamate (ledate) increased the incidence of reticulum-cell sarcomas in male mice of one strain [ref: 9] but was not carcinogenic to mice or rats in another experiment [ref: 10].

Synergistic effects were reported [ref: 1,11-14] in the kidneys of rats given lead acetate and N-nitroso-N-(hydroxyethyl)ethylamine, N-(4'-fluoro-4-biphenyl)acetamide or 2-(nitrosoethylamine)ethanol orally and in the lungs of hamsters given lead oxide with benzo[a]pyrene intratracheally. Lead subacetate given in the diet increased the incidences of liver and kidney tumours induced in rats by 2-acetylaminofluorene given in the diet [ref: 1].

The lead compounds tested for carcinogenicity in animals are almost all soluble salts that were selected on the basis of ease of administration. Metallic lead, lead oxide and lead tetraalkyls have not been tested adequately.

Other relevant data

Studies of chromosomal aberrations in people exposed to lead have given conflicting results: positive reports have been published concerning workers in lead-battery industries and lead smelters, but other studies of workers under comparable conditions have given negative results. Increased incidences of sister chromatid exchanges have been reported in the peripheral blood lymphocytes of workers exposed to lead but not in those of children exposed to high levels of lead in the environment. An increased incidence of sperm abnormalities was seen in men exposed occupationally to lead [ref: 15].

*Although a few studies in rodents treated with lead salts in vivo have shown small (but significant) increases in the frequency of chromosomal aberrations and micronuclei in bone-marrow cells, most studies showed no increase. Lead salts caused morphological sperm abnormalities in mice but not in rabbits. Sister chromatid exchanges and unscheduled DNA synthesis were not induced in cells of animals treated with lead salts in vivo. Lead salts did not induce chromosomal aberrations in human lymphocytes in vitro. Conflicting results have been obtained in assays for transformation in cultured rodent cells. Lead salts did not cause aneuploidy in *Drosophila*, mutation or gene conversion in yeast or mutation or DNA damage in bacteria [ref: 15].*

Tetraethyl- and tetramethyllead did not induce mutation in bacteria [ref: 15].

Overall evaluation

Lead and inorganic lead compounds are possibly carcinogenic to humans (Group 2B).

Organolead compounds are not classifiable as to their carcinogenicity to humans (Group 3).