5.   Summary of Data Reported and Evaluation

5.1   Exposure data

Lead is found at low concentrations in the earth's crust predominantly as lead sulfide (*galena*), but the widespread occurrence of lead in the environment is largely the result of anthropogenic activity. The utility of lead and lead compounds was discovered in pre-historic times. Lead has been used in plumbing and tableware since the time of the Roman Empire. Lead usage increased progressively with industrialization and rose dramatically with the widespread use of the automobile in the twentieth century. Lead has found major uses in pipes and plumbing, pigments and paints, gasoline additives, construction materials and lead–acid batteries. The uses of lead in pipes, paints and gasoline additives have resulted in substantial introductions of lead into the environment and human exposure, and are being phased out in many countries. The predominant use of lead is now in lead–acid batteries and, to a lesser extent, in construction materials and lead-based chemicals.

As a result of anthropogenic activity, lead can enter the environment at any stage from its mining to its final use, including during recycling, and it contaminates crops, soil, water, food, air and dust. Once lead is introduced, it persists. The important routes of human exposure from these sources are inhalation or ingestion. The dispersion of lead throughout the global environment and consequent human exposure has arisen predominantly from the widespread use of leaded gasoline. Some geographic areas, for instance near lead mines and smelters, have high environmental concentrations of lead. The past and present use of lead-based paints can result in substantial risk for localized exposure to lead-contaminated dust. Small industries (e.g. jewellery-making, ceramics, soldering, leaded glass) and individual activities (smoking, home renovations, use of herbal remedies and cosmetics, certain crafts and hobbies, and unregulated recycling) can lead to high exposure. Occupations in which the highest potential exposure exists include mining, primary and secondary smelting, production of lead–acid batteries, pigment production, construction and demolition.

Efforts to reduce environmental concentrations of lead, predominantly through the decreased use of leaded gasoline, have resulted in substantial decreases in the introduction of lead into the environment. In contaminated environments, dust control and hygienic measures can considerably decrease exposure. In spite of the persistence of lead in the environment, human exposure has decreased substantially in countries where control measures have been implemented over the past 10–30 years.

5.2   Human carcinogenicity data

Occupational studies

For lung cancer, six occupational cohort studies of highly exposed workers are particularly informative (battery workers in the USA, battery workers in the United Kingdom, primary smelter workers in Italy, Sweden and the USA (two studies)). Potentially confounding exposures to other known occupational lung carcinogens were largely absent in the battery workers. Several of the cohorts of smelter workers had low documented exposures to arsenic, the principal occupational potential confounder of interest; the smelter workers in Sweden had potentially high exposures to arsenic. Overall, with the exception of the smelter workers in Sweden, these studies were consistent in showing no or a slight excess of lung cancer compared with external reference populations. Observed excesses were quite small and well within the range that might be explained by chance or confounding by smoking. Few or no data for dose–response analyses and no smoking data were available for these cohorts. The Swedish study of smelter workers showed a statistically significant twofold excess of lung cancer but this excess may well have been caused by exposure to arsenic. A Finnish study of workers across many industries, whose blood lead concentrations were sampled as part of a surveillance programme, was judged to be moderately informative. Exposure to lead in this study was lower than in the six cohorts of highly exposed workers but higher than in the general population. There was a modest trend of increasing lung cancer with increasing levels of exposure in the Finnish cohort; this trend was not statistically significant.

For stomach cancer, five (battery workers in the UK and the USA, primary smelter workers in Italy and the USA (two studies)) of the six occupational cohort studies used for the evaluation of lung cancer were judged to be particularly informative. In four of these five studies, there was a fairly consistent excess of 30–50% of stomach cancer compared with external reference populations. Exposure to arsenic is not considered to be a cause of stomach cancer and any potential confounding by smoking is likely to be small. Some analyses of limited exposure surrogates were carried out, but these did not implicate lead exposure as the cause of the stomach cancer excess. However, little or no data for quantitative dose–response analysis were available in these cohorts. It is possible that ethnicity, dietary habits, prevalence of *Helicobacter pylori* infections or socioeconomic status played a role in the stomach cancer excesses.

Five of the six cohort studies of highly exposed workers reported findings for kidney cancer. In one study, there was a twofold statistically significant excess of kidney cancer, based on comparison with an external reference population. In the remaining four studies, mortality was either close to, or below, expected values. All five studies were based on small numbers of deaths.

Four of the six cohort studies of highly exposed workers reported findings for tumours of the brain and nervous system. On the basis of comparisons with external reference populations, mortality showed no consistent pattern. In addition, in a nested case–control study, the cohort of workers from Finland showed a statistically significant posi-

tive dose–response relationship between blood lead concentrations and the risk for glioma. The cohort in the Finnish study had lower exposures to lead than the other occupational cohorts; all studies were based on small numbers of deaths.

Environmental studies

Among the general population studies, the most informative are the two follow-up studies on the US NHANES II population. A limitation of these two studies is the reliance on one blood lead measurement per subject to define exposure. Both studies, analysing essentially the same population, found a positive dose–response relationship between blood lead concentrations and lung cancer, which approached or attained statistical significance. However, these results within a low-dose population are not consistent with those for lung cancer in more highly exposed occupational populations, for whom no consistent lung cancer excess is apparent. At least some of the reported dose–response relationships for lung cancer in these two studies may be due to residual confounding from smoking, which was correlated with blood lead concentrations. Higher concentrations of blood lead were apparent in those with lower income, so it is also possible that residual confounding from occupational exposure to lung carcinogens may have contributed to positive dose–response trends.

5.3   Animal carcinogenicity data

Lead acetate

Oral exposure to lead acetate has been shown to be carcinogenic in the rat kidney in seven separate studies, producing adenomas and adenocarcinomas after chronic exposure in males and/or females. Both of the studies that allowed assessment of a dose–response relationship showed that such a relationship existed. In another experiment the offspring of female mice exposed to oral lead acetate during pregnancy and lactation showed dose-related increases in renal tumours as adults in the absence of chronic lead-induced nephropathy.

Brain gliomas were observed after oral exposure to lead acetate in rats in two separate studies.

One study in rats indicated that oral exposure to lead acetate was associated with tumours of the adrenal gland, testes and prostate in males and adrenal gland in females. In a study of a mixed population of male and female rats, oral exposure to lead acetate was associated with tumours of the lung, pituitary, prostate, mammary gland and adrenal gland.

Lead subacetate

One experiment in male and female mice and six experiments in male and/or female rats showed that oral exposure to lead subacetate induced renal cancer. One of these studies showed a dose–response relationship. Brain gliomas were observed in rats after

oral administration of lead subacetate in one study. Three studies show that repeated intraperitoneal injections of lead subacetate increased lung tumour multiplicity in strain A mice. One study of oral exposure to lead subacetate in strain A mice was negative for lung tumours. In one study, hamsters exposed orally to lead subacetate did not develop tumours.

Lead powder

Two studies in rats exposed to lead powder orally or by intramuscular injection and one study on intrarenal injection of lead powder in rats did not produce tumours.

Lead oxide

In one experiment, inhalation of lead oxide did not produce tumours in male rats.

Lead chromate

One study showed that injection-site sarcomas were induced by a single subcutaneous injection of lead chromate in rats. One study of intramuscular injection of lead chromate in rats produced renal tumours. One study of intramuscular injection of lead chromate in mice and one study of intrabronchiolar implantation of different lead chromates in rats were negative. The role of chromium in the carcinogenic response of lead chromate in these studies cannot be excluded.

Lead phosphate

In four separate studies, injection of lead phosphate subcutaneously, or combined subcutaneously and intraperitoneally, was shown to produce renal cancers in rats.

Lead arsenate

One study of oral administration of lead arsenate in male and female rats was negative.

Tetraethyl lead

One experiment with repeated subcutaneous injections of tetraethyl lead was found to be inadequate for evaluation.

Administration of lead compounds with known carcinogens or modifiers

Three experiments showed that oral exposure to lead subacetate enhanced N-ethyl-N-hydroxyethylnitrosamine-induced renal carcinogenesis in male rats. One study showed that oral lead subacetate-induced renal tumours in rats were increased by concomitant oral administration of calcium acetate. One study in strain A mice showed that calcium acetate and magnesium acetate inhibited lung adenomas induced by intraperitoneal injection of lead subacetate. Intratracheal instillations of combinations of lead oxide and benzo[a]-pyrene in hamsters produced lung tumours not observed with either agent alone. Oral exposure to lead nitrate increased the incidence of N-nitrosodimethylamine-induced renal

tumours in male rats while intraperitoneal injections of lead subacetate enhanced *N*-nitrosodimethylamine-induced lung tumour multiplicity in mice.

Overall, extensive experimental evidence shows that various water-soluble and -insoluble lead compounds can induce kidney tumours in rodents. In addition, one study showed that renal tumours can occur in the absence of lead-induced nephropathy. It is also noteworthy that the induction of brain gliomas, which are rarely spontaneous, occurred after oral exposure to lead in rats. Lead proved to be an effective renal tumour carcinogen/promoter in rats and mice exposed to various organic renal carcinogens.

5.4   Other relevant data

Toxicokinetics and metabolism of lead

Inorganic lead

Lead absorption from the gastrointestinal tract in both humans and experimental animals is strongly influenced by age (neonates and the young absorb a larger fraction than adults), fasting/fed status (fasting humans and experimental animals absorb much larger fractions than their fed counterparts), nutrition (fat and caloric intakes; phosphorus, copper, zinc and especially iron and calcium status, all affect lead absorption), solubility (soluble lead compounds are better absorbed) and particle size (in controlled studies in rats, lead absorption from ingested mining wastes was shown to be inversely proportional to particle size). There are no data indicating that the fraction of lead absorbed from an inhalation exposure is dependent on the amount of lead in the lung. Patterns and rates of particle deposition are highly dependent on particle size and ventilation rate, but all lead deposited deep in the lung is eventually absorbed. Limited studies indicate that dermal absorption of inorganic lead is negligible, although slightly increased by high perspiration rates in humans.

In both humans and experimental animals, absorbed lead is rapidly distributed from blood plasma simultaneously into erythrocytes, soft tissues, and bone. The half-life of lead in blood and soft tissues is 20–30 days in adult humans and 3–5 days in adult rats. In both humans and rats, the soft-tissue concentrations of lead are highest in liver and kidney and much lower in brain. Plasma, rather than whole blood, is generally accepted as the source of lead available for distribution and excretion, although plasma lead comprises only 0.2–0.3% of whole blood lead concentrations when these are < 6 µg/dL. The fraction of whole blood lead in plasma is substantially larger at high blood lead concentrations than at low blood lead concentrations.

The majority of lead is stored in bone (in adults > 90%) and is partitioned mainly into trabecular and cortical bone. The higher rate of remodelling in trabecular bone is reflected in a shorter half-life of lead in trabecular bone (2–8 years) compared with that in cortical bone (> 20 years). Bone can be a significant source of endogenous lead, in particular when the bone resorption rate is increased, such as during pregnancy, lactation, the period just after menopause, and during weightlessness.

After oral ingestion, inorganic lead that has not been absorbed in the gastrointestinal tract is excreted in the faeces. Absorbed lead is excreted in the urine and, via the bile, in the faeces. Excretion of lead through sweat is of minor importance.

Organic lead

Organic lead compounds, such as tetraethyl lead and tetramethyl lead, behave as gases in the respiratory tract and are absorbed to a greater extent than are inorganic lead particles. Organic lead compounds are also absorbed through the skin of both humans and experimental animals.

Tetraethyl lead and tetramethyl lead are oxidatively dealkylated in the body. Any inorganic lead produced from these reactions is distributed in the same way as administered inorganic lead. In humans and rats exposed to alkyl lead, concentrations of lead are highest in the liver and kidneys followed by the brain and heart. The rates of metabolite production are not known in detail for either humans or experimental animals.

In humans, tetraethyl lead is excreted in the urine as diethyl lead, ethyl lead, and inorganic lead. In rats and rabbits, dialkyl lead is the major metabolite found in urine. One of the end-products of metabolism of tetraalkyl leads is inorganic lead, which is also excreted in the faeces.

In humans, exhalation of unmetabolized tetraethyl lead and tetramethyl lead from the lung is a major route of excretion.

Toxic effects of inorganic lead

Typical clinical manifestations of lead poisoning include weakness, irritability, asthenia, nausea, abdominal pain with constipation, and anaemia.

Lead interferes with numerous physiological processes. In the haeme biosynthetic pathway, it inhibits δ-aminolevulinic acid dehydratase (also known as porphobilinogen synthase), probably through its high affinity for the zinc-binding site in the enzyme. Although lead displaces zinc more readily in one of the alloenzymes of the protein, the relationship between δ-aminolevulinic acid dehydratase genotype and sensitivity to lead at different blood lead concentrations is at present unclear. Lead also causes an increase in zinc protoporphyrin, by a mechanism which is not fully established. Lead inhibits pyrimidine-5′-nucleotidase, resulting in accumulation of nucleotides, and subsequent haemolysis and anaemia.

Renal manifestations of acute lead poisoning include glycosuria, aminoaciduria and phosphaturia. Chronic exposure to low concentrations of lead is associated with increased urinary excretion of low-molecular-weight proteins and lysosomal enzymes. Chronic exposure to high concentrations of lead results in interstitial fibrosis, glomerular sclerosis, tubular dysfunction and, ultimately, in chronic renal failure. Lead has also been implicated in the development of hypertension secondary to nephropathy.

A considerable body of evidence suggests that children are more sensitive than adults to the neurotoxic properties of lead. Although clinical symptoms of toxicity generally become apparent at blood lead concentrations of 70 µg/dL, many important disturbances

occur at much lower concentrations. These include electrophysiological anomalies of evoked brain potential in response to auditory stimuli and reduced peripheral nerve conduction. Both cross-sectional and prospective studies of children have found impairments in cognition, attention, and language function at concentrations of lead previously thought to be harmless. In studies with larger samples, better measures of lead burden and neuro-behavioural function, and more advanced statistical techniques, effects are detectable at blood lead concentrations below 10 µg/dL. The relative effect is greater below 10 µg/dL than above this level. Recently, attention has shifted from the impact of lead on cognition to its effects on behaviour. Exposure to lead has been found to be associated with attentional dysfunction, aggression and delinquency.

Exposure to lead is associated with cardiovascular effects and with changes in endocrine and immune functions.

Many of the effects of lead exposure in humans have been confirmed in experimental systems. At the cellular level, lead has mitogenic properties; it affects various regulatory proteins, including those that depend on the presence of zinc.

Studies on the reproductive and developmental toxicity of lead did not show consistent effects, morphologically or quantitatively, on markers of male fertility. It is not clear whether the effects are caused by a direct interaction of lead with the reproductive organs, or by modulation of the endocrine control of reproduction, or both.

There is consistent evidence in humans, in the form of case series and epidemiological studies, that the risk for spontaneous abortion (pregnancy loss before the 20th week of gestation, but after the stage of unrecognized, sub-clinical loss) is increased by maternal exposure to high concentrations of lead.

In humans, prenatal lead exposure is associated with an increased risk for minor malformations, low birth weight and reduced postnatal growth rate. The effect on postnatal growth rate is apparent only in those children with continuing postnatal lead exposure.

Differences in reproductive end-points between species make it unlikely that useful conclusions can be extrapolated from animals to humans.

Genotoxicity of inorganic lead compounds

Human studies

Humans occupationally exposed to lead show evidence of genotoxicity as measured in a variety of assays. In some studies, these effects were correlated with blood lead concentrations. However, all the human genotoxicity studies involved co-exposure to lead and other compounds, making it difficult to attribute genetic and other effects to lead alone.

In a limited number of studies on non-occupationally exposed individuals, no genotoxic effects were found that were correlated with blood lead concentrations.

Studies in experimental systems

Mutations were not induced in bacteria by either lead acetate or lead chloride, but were induced by both lead chromate and lead bromide. In these last two cases, however, the activity appeared to be due to the anions. In cultures of various mammalian cells, lead

acetate, lead chromate and lead nitrate induced DNA strand breaks. Furthermore, most studies revealed positive mutagenic responses even though the extent of mutagenicity and the lead concentrations at which the responses were observed varied considerably, depending on cell type and experimental conditions. Tests for sister chromatid exchange and chromosomal aberrations showed variable responses. Micronucleus formation has been shown to occur at low concentrations of lead. In a single study, lead sulfide induced micronuclei, gene mutations and sister chromatid exchanges. Organo-lead compounds do not appear to have been tested *in vitro*.

Studies of genetic toxicity in animals have been conducted by the oral, inhalation, subcutaneous, intraperitoneal and intravenous routes. It should be noted that blood lead concentrations were not available in these studies, except in a single study in cynomolgus monkeys, and that the exposure concentrations were generally far higher than those reported in human occupational studies. DNA strand breakage has been demonstrated in lead-exposed animals, and variable results have been found in tests for induction of sister chromatid exchange. Micronucleus induction in bone-marrow cells of lead-exposed animals has been demonstrated in some studies. Most studies of chromosomal aberrations have demonstrated increased frequencies in mice, rats and in the one study in cynomolgus monkeys reported. Aneuploidy has been demonstrated in lead-exposed rats and mice. Increases in the proportion of morphologically abnormal sperm have also been found in mice and cynomolgus monkeys, but not in rabbits. Dominant lethal effects were not observed in male mice exposed to lead in a single study.

In conclusion, lead is a toxic metal and one expression of this property is genetic toxicity. There is, however, little evidence that it interacts directly with DNA at normally encountered blood lead concentrations. The genetic toxicity of lead appears to be mediated in part by increases in, and modulation of, reactive oxygen species. In addition, lead interacts with proteins, including those involved in DNA repair. This latter mechanism might be responsible for enhancing the genotoxicity of other agents. These properties could result in mutation, changes in gene expression and cell proliferation, all of which would contribute to a carcinogenic response if exposure is sustained.

5.5   Evaluation

There is *limited evidence* in humans for the carcinogenicity of inorganic lead compounds.

There is *inadequate evidence* in humans for the carcinogenicity of organic lead compounds.

There is *sufficient evidence* in experimental animals for the carcinogenicity of inorganic lead compounds.

There is *sufficient evidence* in experimental animals for the carcinogenicity of lead acetate, lead subacetate, lead chromate, and lead phosphate.

There is *inadequate evidence* in experimental animals for the carcinogenicity of lead oxide and lead arsenate.

There is *inadequate evidence* in experimental animals for the carcinogenicity of organic lead compounds.

There is *inadequate evidence* in experimental animals for the carcinogenicity of tetraethyl lead.

There is *inadequate evidence* in experimental animals for the carcinogenicity of lead powder.

Overall evaluation

Inorganic lead compounds are *probably carcinogenic to humans (Group 2A)*.

Organic lead compounds are *not classifiable as to their carcinogenicity to humans (Group 3)*.

The Working Group noted that organic lead compounds are metabolized, at least in part, to ionic lead both in humans and animals. To the extent that ionic lead, generated from organic lead, is present in the body, it will be expected to exert the toxicities associated with inorganic lead.