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BIOLOGICAL MONITORING OF EXPOSURE TO INORGANIC LEAD

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INTRODUCTION

The literature on the toxicology of lead is enormous. A large number of reviews have been published, some of them recently (Boeckz, 1986; Brunekreef, 1984; Chamberlain, 1983; Department of Health and Social Security, 1980; EPA, 1986; Hernberg, 1983; Medical Research Council, 1985; Smith, 1985; Swedish Criteria Group for Occupational Standards, 1981; Tsuchiya, 1986; WHO, 1977, 1980).

In this review, only data of immediate relevance for the possibilities for biological monitoring of lead exposure and risk of lead poisoning will be surveyed.

EXPOSURE

Main Sources

Lead has had widespread use as a pigment in house paint in some countries, and peeling paint may cause exposure. Organolead compounds are added to petrol. During combustion in the engine, organic lead is transformed to inorganic lead, and is emitted almost entirely as such. This causes exposure to inorganic lead, in particular in subjects living in areas with heavy traffic (Fachetti et al., 1982; Rabinowitz and Needleman, 1982; Rabinowitz et al., 1984; Schutz et al., 1984). Also, industrial emissions may cause exposure in neighborhood populations (Schutz et al., 1984). To some extent these sources may cause exposure directly through inhalation of aerosol. However, some of the exposure is secondary to a general contamination of the environment by dustfall. Street and home dust may thus contain high lead levels. In children, the mouthing behavior thus becomes important. Also, a secondary contamination of food items results in more widespread increases of lead exposure.

The lead exposure varies in different areas of the world. In industrialized countries (Friberg and Vahter, 1983; Quinn, 1985; Rabinowitz et al., 1984; Schutz et al., 1984) it is generally higher than in areas remote from industries and traffic (Piomelli et al., 1980; Poole et al., 1980). Within the Western countries, the relative importance of different sources of lead exposure varies: in Scotland, lead exposure through drinking water is

prevalent (Quinn, 1985); in other areas, petrol is a major cause of exposure (Rabinowitz et al., 1984); in some areas of the U.S. and in some states of Australia, lead-based house paint (Price et al., 1984), or industrial emissions (Landrigan and Baker, 1981; Popovac et al., 1982).

Ingestion

The intake of lead through diet is low in certain areas of the world; in Sweden it averages 30 µg/day (Schutz, 1979), but is higher in other areas, amounting to a few hundred µg/day (cf. Tsuchiya, 1986). The intake through drinking water is low in many areas, about 1 µg/day or less, but it may be very high in other regions, sometimes as high as 3 mg/day (cf. Tsuchiya, 1986). In addition, very high oral intake of lead (several mg/day) may originate from lead-glazed pottery and lead-soldered cans. Also, wine may contain very high lead levels.

Inhalation

The exposure through air is also low in most areas, the average levels being 0.1 µg/m^3 or less, corresponding to an inhaled amount of less than 2 µg/day. In some areas it may be much higher, up to about 10 µg/m^3, corresponding to a daily inhalation of about 200 µg (cf. Tsuchiya, 1986). The particle size distribution may vary considerably among different areas. For example, in London, U.K., 60 percent of the particles were less than 0.3 µm and only 1 percent above 10 µm. In Los Angeles, U.S.A., only 30 percent of the particles were less than 0.3 µm, and a considerable fraction more than 10 µm (cf. Chamberlain, 1985). The size distribution is of great importance for the deposition in the airways (see below).

In addition, inhalation exposure occurs through tobacco (Quinn, 1985). The lead content in a cigarette is 3-12 µg. About 2 percent of this is inhaled by the smoker (cf. Tsuchiya, 1986).

Occupational

In addition to the exposure from the general environment, exposure to lead may occur in many occupational settings, e.g., lead mines, primary and secondary lead smelters, storage-battery factories, brass foundries, and glass works. Other occupations include handling of lead-stabilizers in the polyvinylchloride industry, and painting with red lead oxide paint, as well as scraping of painted devices (Hernberg, 1983; Christoffersson et al., 1984). In the occupational setting, exposure occurs both through inhalation (air and smoking of contaminated tobacco) and through ingestion (contaminated food, drink, and snuff).

Time Trend

In several industrialized countries, the lead exposure in the general population seems to have decreased rather rapidly (Annest et al., 1983; Billick et al., 1979; Elinder et al., 1985; Elwood, 1983; Fachetti et al., 1982; Rabinowitz and Needleman, 1982; Schutz et al., 1984; Skerfving et al., 1986), probably as a result of actions taken against such sources as lead in petrol, lead in canned food, lead contamination of drinking water, industrial lead emissions, and/or occupational lead exposure.

METABOLIC MODEL

Absorption

Ingestion. Lead is absorbed from the gastrointestinal tract. In various radiotracer studies, 4-21 percent (average about 8 percent) of soluble lead

salts taken with meals was absorbed (Blake et al., 1983; Chamberlain et al., 1978; Harrison et al., 1969; Moore et al., 1980; Rabinowitz et al., 1980). In fasting subjects, absorption was considerably larger, 37-70 percent (average about 60 percent) according to different investigations (Blake and Mann, 1983; Flanagan et al., 1982; Heard and Chamberlain, 1983; Rabinowitz et al., 1980). From studies of the uptake of stable lead, an average absorption of 15-20 percent absorption may be estimated (Chamberlain, 1985; Gross, 1981; Kehoe, 1961).

There are indications of a higher gastrointestinal absorption in children than in adults (Alexander et al., 1974; Ziegler et al., 1978). In adults, there seems to be considerable interindividual variation in lead uptake from the gut (Blake, 1976; Hursh and Suomela, 1968;). In humans, simultaneous intake of calcium and phosphate may reduce absorption of lead (Chamberlain, 1985; Heard and Chamberlain, 1984). In animal experiments, the intake of milk, vitamin D, and iron affected absorption (cf. Tsuchiya, 1986). In rats, very large lead doses were absorbed less efficiently than small ones (Aungst et al., 1981). In humans, there was no effect of moderate lead doses on the fractional uptake of lead (Chamberlain, 1985; Heard and Chamberlain, 1983).

Inhalation. The pattern of deposition of inhaled lead in the respiratory tract is affected by the particle size of the inhaled aerosol and the ventilation rate. Particles with an aerodynamic diameter greater than 5 μm are mainly deposited in the upper airways, cleared by the mucociliary mechanism, and swallowed. A fraction of this lead is then absorbed from the gastrointestinal tract. Particles with a diameter below 1 μm are, to a greater extent, deposited in the alveolar region of the lung. It is possible that subjects breathing mainly through the nose have a deposition of lead in the nose, thus reducing exposure compared with subjects breathing mainly through the mouth.

At a particle size of 0.05 μm and a respiratory rate of 15/min, about 40 percent of the inhaled lead is deposited in the airways (Chamberlain, 1985; Chamberlain et al., 1975, 1978; Gross, 1981; Kehoe, 1961; Wells et al., 1977). At a particle size of 0.5 μm, the deposition is lower, about 20 percent (Chamberlain, 1985).

The rate of absorption of lead from the particles deposited in the lung depends on the solubility of the chemical species of lead. In human radiotracer experiments, the absorption usually is completed within 24 hours (Booker, 1969; Chamberlain, 1985; Hursh and Mercer, 1970; Hursh and Suomela, 1968; Morrow et al., 1980). Such a rapid absorption is in accordance with the lack of accumulation of pulmonary lead content in deceased lead workers compared with subjects without occupational exposure (Barry, 1975). On the other hand, increased levels of lead have been found in dead lead workers who had been exposed to a lead compound with low solubility (lead sulfide) (Brune et al., 1980).

Distribution

Blood. Lead is absorbed into the blood plasma (and the lymph, which is later emptied into the blood plasma). Little is known about the binding of lead in plasma. It is assumed, though, that plasma lead consists of a major protein-bound fraction and a diffusible fraction. Some of the plasma lead may represent very recent absorption. Lead rapidly equilibrates between plasma and extracellular fluid. More slowly, but still within minutes, lead is transferred from plasma into blood cells. Within the blood, 99 percent of the lead content is in the red cells, and only about 1 percent in the plasma (Chamberlain et al., 1975; De Silva, 1981; Hursh and Suomela, 1968; Manton and Cook, 1984). In the red blood cells, the lead is bound to hemoglobin, and other components (Raghavan et al., 1980). The relative distribution within blood cells depends on individual factors and the intensity of the exposure.

The ratio of lead content in red cells and plasma is not constant over blood-lead levels. Thus, the fraction in plasma rises with increasing blood lead concentration (De Silva, 1981; Manton and Cook, 1984). This is probably of importance for the distribution to different organs. Thus, it is not certain that lead levels in whole blood, over a wide range of concentrations, have a constant relation to levels in other organs (see below).

Soft tissues. From the blood plasma, absorbed lead is distributed to different organs. Among the soft tissues, the liver and the kidney attain the highest concentrations (Barry, 1975; Brune et al., 1980; Skerfving et al., 1983). Lead does, to some extent, pass the blood-brain barrier (Barry, 1975; Skerfving et al., 1983). Judging from animal experiments (cf. Mahaffey, 1983), the degree of passage of lead into the nervous system is probably higher in children than in adults.

In animal experiments (Aungst et al., 1981; Hietanen et al., 1980), there is no constant relationship between lead levels in blood and in soft tissues. Thus, accumulation in liver and kidney is higher than in blood, while it is lower in the central nervous system (CNS). The peripheral nervous system (PNS) may accumulate considerably more lead than the CNS.

Skeleton. A large proportion of the absorbed lead is incorporated into the skeleton (Barry, 1975; Grandjean and Holma, 1973; Gross et al., 1975; Gusserow, 1861). The skeleton contains more than 90 percent of the body burden of lead (Barry, 1975). In lead workers, that fraction may be even higher (Barry, 1975; Skerfving et al., 1983).

The lead content in the skeleton is not a homogeneous pool. By analogy with calcium, there is probably a small but rapidly exchangeable skeletal lead pool. In addition, there are at least two other pools: One is contained in trabecular bone (Barry, 1975; Rabinowitz et al., 1977; Skerfving et al., 1983; Schutz et al., in press a). In addition, there is a lead pool in cortical bone (Ahlgren et al., 1980; Barry, 1975; Christoffersson et al., 1984, 1987; Lindh et al., 1980; Rabinowitz et al., 1977; Skerfving et al., 1983; Somervaille et al., 1983). The skeleton contains about 20 percent trabecular and about 80 percent cortical bone, but the surface area on the two types of bone is similar. Thus, the turnover of the trabecular bone lead pool is much faster than that of the cortical bone lead pool (Schutz et al., in press a).

The lead content in the skeleton in subjects without occupational exposure varies in different areas of the world. It was a few milligrams in prehistoric subjects living in a world without traffic and industries (Ericson et al., 1969), about 10 mg in contemporary Scandinavians (Grandjean and Holma, 1973; Grandjean, 1975; Schutz et al., in press a), and it is about 100 mg in subjects from the U.K. (Barry, 1975; Crawford and Crawford, 1969) and the U.S. (Ericson et al., 1979; Gross et al 1975; ICRP, 1980; Kehoe, 1961).

In lead workers (Ahlgren et al., 1980; Campbell et al., 1970; Christoffersson et al., 1984, 1987; Gossman and Heilenz, 1967; Kijewski and Lowitz, 1982; Skerfving et al., 1983; Somervaille et al., 1983; Schutz et al., in press a; Westerman et al., 1965), and in subjects with high lead exposure from other sources (Eastwell et al., 1983; Price et al., 1984), including persons who died with lead poisoning (Gossman and Heilenz, 1967; Kehoe, 1961; Schwerd, 1960), the skeletal lead content may be on the order of one gram.

Excretion

Lead is excreted from the body mainly through the urine and the feces. The excretion into urine is mainly through glomerular filtration and tubular secretion, as indicated by experimental animal studies (Vander et al., 1977). The urinary excretion rises with increasing blood lead levels; the increase is

nonlinear, probably exponential (Manton and Cook, 1984; Schutz and Skerfving, 1976; Schutz et al., 1987; Skerfving et al., 1985; Tola et al., 1973). This may be due to a rising fraction of lead in plasma with increasing blood lead level (Manton and Cook, 1984), although this possibility needs confirmation. There seems to be considerable interindividual variation in urinary lead excretion at similar blood lead levels (Skerfving et al., 1985).

Lead is also eliminated by endogenous fecal excretion (Chamberlain et al., 1975, 1978; Rabinowitz et al., 1977). At low exposures, excretion in the feces is about half that in urine and at higher levels probably relatively smaller, although this needs confirmation.

Lead is also, to some extent, excreted in sweat (Rabinowitz et al., 1977). Amounts without practical importance are excreted in nails and hair (Rabinowitz et al., 1976). In addition, there is some excretion in milk (Lamm and Rosen, 1974).

Lead crosses the placenta and causes exposure of the fetus. The relative distribution in the fetus is the same as in the adult organism (Barltrop, 1969). The blood-lead level in the child at birth is approximately the same as in the mother (Hubermont et al., 1978).

Kinetics

Compartments and Mathematics. From a theoretical point of view, it may safely be assumed that the metabolism of lead involves a large number of different compartments with varying levels of lead and different kinetics. From a practical point of view, it is important to find a sufficiently simple model, without disregarding completely the possibility of reasonably accurate predictions. Different authors have argued for one (Fisher, 1969), two (Ahlgren et al., 1980; Black et al., 1968; Schutz et al., in press b; Steenhout, 1982; Sterling et al., 1964), three (Batschelet et al., 1979; ICRP, 1980; Marcus, 1979; Rabinowitz et al., 1977), four (Chamberlain, 1985; Fisher, 1969; Marcus, 1985a,b; Skerfving, et al., 1985), and even five (Bernard, 1977) compartments, in models of human lead metabolism.

Based upon the above-mentioned information, at least five compartments must be assumed: Plasma and extracellular fluid, blood cells, soft tissues (probably including a small, rapidly exchangeable fraction of the skeleton), trabecular bone, and cortical bone (Fig. 1).

The next problem is to choose suitable mathematical expressions for the transfer of lead to and from the different compartments. Sometimes power

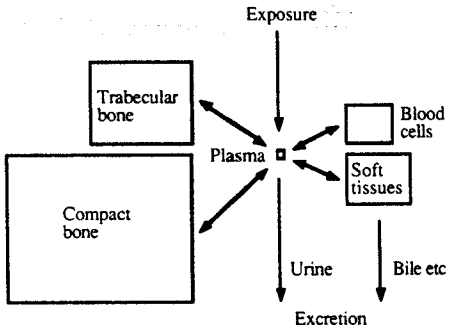

Fig. 1. Metabolic model for inorganic lead in man. Plasma denotes blood plasma and extracellular fluid.

functions have been employed. However attractive to obtain a good fit to empirical data, power functions have limited value from a conceptual point of view. In that sense, linear exponential models are more useful.

Is a linear model applicable to lead metabolism There are data indicating nonlinearity, e.g., the relationship between lead levels in air and lead levels in blood (see below), as well as between lead levels in blood and urine (Manton and Cook 1984; Schutz and Skerfving, 1975, 1976; Skerfving et al., 1985; Tola et al., 1973). On the other hand, data on blood lead do not indicate concentration-dependent kinetics, as similar elimination rates have been noted both at very low and very high levels (Campbell et al., 1984; Chamberlain and Massey, 1972; Chamberlain et al., 1978; McRoberts, 1973; Rabinowitz et al., 1977; Schutz et al., in press b; Skerfving et al., 1983).

Rabinowitz et al. (1977) analyzed data from experiments in humans exposed to relatively low dietary doses of labeled lead. They found a better fit of a three-compartment linear model, as compared to a two-compartment model. Another group (Schutz et al., in press b; Skerfving et al., 1983) tested one, two and three compartments on sets of curves for blood lead decrease in former lead workers. They found a good fit for a two-compartment linear model, while three compartments gave an only marginally better fit. It thus seems that, at least from a practical point of view, a two-compartment linear model is useful, especially for evaluation of blood lead data.

Turnover rates. The turnover rates in a linear exponential model may be expressed as transfer constants, mean residence times, or half-times . The half-time in the soft tissue compartments(s) of man is 3-4 weeks (Rabinowitz et al., 1977; Schutz et al., in press b; Skerfving et al., 1983). Data on the elimination of lead from blood after cessation of exposure indicate interindividual variation (Schutz et al., in press b; Skerfving et al., 1983), that exceeds that of the uncertainty in the estimates of the true slopes.

The half-time of lead in finger-bone (mainly cortical bone) is half a decade (Christoffersson et al., 1987); in vertebra (mainly trabecular) it is shorter, probably a couple of years (Schutz et al., in press a). A few months after end of lead exposure, the lead levels in blood mainly indicate the level in the skeleton (Grandjean and Kon, 1981; Schutz et al., in press b). The time trend of such data also are in favor of an average half-time for the skeleton of half a decade (Schutz et al., in press b; Skerfving et al., 1983).

This suggested turnover of at least an important fraction of the skeletal lead pool fits with a series of other estimates from a metabolic model (Tsuchiya and Sugita, 1971), data on decrease of radiolead in the skull (Wrenn et al., 1972; Cohen et al., 1973), data on decline of lead of trabecular bone (Grossman and Heilenz, 1967; Westerman et al., 1965), and data on decay of blood lead (Araki et al., 1983).

Considerably longer half-times (8-71 years) have been estimated on basis of bone remodeling rate (Jaworowski, 1965), various metabolic models (Fisher, 1969; Bernard, 1977; Smith and Hursh, 1977; Holtzman, 1978; Steenhout, 1982; Sugita, 1978), and in vivo measurements of radiolead in the skull (Cohen and Spitz, 1975).

The data on the elimination of lead from blood during a long period after cessation of exposure indicate an interindividual variation in skeletal lead kinetics (Schutz et al., in press b). Indications of such a difference have also been reported in dogs (Fisher, 1969). These interindividual variations in kinetics of lead metabolism, both in soft tissues and in bone, probably reflect large differences between individuals in soft tissue and skeletal lead levels at a certain rate of absorption, and an accordingly different risk of adverse effects. Subjects who have a high elimination in the urine are

probably favored. However, it is not possible to define, at this stage, whether a rapid turnover of the blood lead is an advantage. It could mean a rapid elimination from the body which of course is an advantage; it may also mean a high degree of incorporation of lead into the skeleton, which might mean a detoxification on a short-term perspective, but will cause a higher endogenous lead release in the future.

HEALTH EFFECTS IN HUMANS

Inorganic lead can affect the body in several ways. It may disturb heme synthesis, erythrocyte survival, the nervous system, the kidneys, the gastrointestinal tract, reproduction, and possibly also cause cardiovascular effects, mutagenic effects, and cancer (WHO, 1980).

Heme Synthesis

Inorganic lead inhibits reactions in the formation of heme, a constituent of hemoglobin, and a number of enzymes in all cells of the body (WHO, 1977, 1980). Lead thus inhibits the enzymes delta-aminolevulinic acid dehydratase (ALAD), ferrochelatase (heme synthetase), and probably also coproporhyrinogen decarboxylase. This leads to a metabolic block, with an accumulation of delta-aminolevulinic acid (ALA) and coproporphyrin (CP) in blood plasma, followed by excretion of those metabolites in the urine. Also, there is an accumulation of protoporphyrins (protoporphyrin IX, PP; zinc protoporphyrin, ZPP; "total free erythrocyte protoporphyrin", FEP) in erythrocytes (E-PP). Lead also inhibits the enzyme pyrimidine-5'-nucleotidase (Py-5-N) in red cells (Angle et al., 1982). These changes have not in themselves been shown to be detrimental to health, but they may be used for biological monitoring of lead exposure (see below).

The effect on red cell formation may result in reticulocytosis and occurrence of stippled erythrocytes in peripheral blood (EPA, 1986; WHO, 1977, 1980; Zielhuis, 1975). The life-span of circulating erythrocytes also becomes shortened, probably because an inhibition of the Na-K-ATPase. The combined effects of lead on heme synthesis and on life-span of the blood cells may result in anemia.

Nervous System

Exposure to inorganic lead can damage the PNS and in rare cases cause peripheral motor neuropathy (EPA, 1986; WHO, 1977, 1980). This is due to demyelination, axonal degeneration, and possibly also presynaptic block. In lead-exposed subjects without clinical signs of peripheral neuropathy, neurophysiological examinations may reveal motor nerve conduction velocity disturbances and electromyographic abnormalities.

Lead exposure may also cause encephalopathy, especially in children (EPA, 1986; WHO, 1977, 1980). The classical signs are ataxia, coma, and convulsions. After recovery from acute encephalopathia, residual clinical signs may remain. In subjects without obvious clinical signs of encephalopathia, impaired performance in psychometric tests and mild, subjective, and non-specific symptoms (e.g., fatigue, anxiety, and loss of memory) may occur (Hanninen et al., 1979). It seems that the effects on the CNS are, at least in some cases, and at least partially, reversible (Baker et al., 1985). However, not enough is known about the prognosis.

Kidneys

Lead exposure may also cause kidney damage (EPA, 1986; Weeden, 1982; WHO, 1977, 1980). Morphologically, there is interstitial nephritis, tubular

damage, and, at a late stage of the disease, also glomerular involvement. An early morphological finding is tubular nuclear inclusion bodies. Functionally, the kidney effects may cause leakage of tubular enzymes into urine (Meyer et al., 1984), defective tubular reabsorption of low weight proteins filtered through the glomerulus, leading to urinary excretion of such proteins, defective tubular secretion of uric acid, resulting in hyperuricemia (sometimes with clinical gout), and decrease of glomerular filtration rate, resulting in azotemia.

Reproduction

Experimental oral exposure of male animals to high levels of lead has resulted in decreased fertility, and increased perinatal death (cf. Rom, 1976). Sperm abnormalities have been noted in lead workers (Lancranjan et al., 1975); however, this needs confirmation.

As mentioned above, lead passes through the placenta to the fetus. Exposure of pregnant rodents to a high dose of lead caused resorption of embryos, and offspring showed low weight, birth defects, increased perinatal mortality, as well as disturbances of development (cf. Rom, 1976). Indications of an increased risk of abortions and other damage to the human fetus can be found in older literature, but the information is incomplete. Even though the data are not conclusive, inorganic lead must be regarded as potentially embryotoxic/fetotoxic in man.

Other Nongenetic Effects

Lead affects the gastrointestinal tract, causing constipation or diarrhea, epigastric pain, nausea, indigestion, loss of appetite, and colic (WHO, 1977).

There are some indications of a toxic effect of lead on the heart (WHO, 1980). Also, lead may cause cerebrovascular damage (WHO, 1980). There are several recent studies which indicate an association between blood-lead levels and high blood pressure (cf. Pirkle et al., 1985). It is not clear whether this is a causal relationship or due to confounding factors or due to decreased lead excretion reflecting a lowered glomerular filtration rate caused by the blood pressure.

Genotoxicity

Genotoxic effects in the form of chromosome damage in peripheral lymphocytes have been noted in some studies of people exposed to lead (e.g., Forni et al., 1976). The significance of this is unclear. Also, other studies (e.g., Hoffman et al., 1984) have not shown such an effect. Even though some animal experiments provide indication that inorganic lead can be carcinogenic, epidemiological studies of workers exposed to lead do not support the existence of such an effect in man (Gerhardsson et al., 1986; IARC, 1980).

MEDIA FOR BIOLOGICAL MONITORING

Blood-lead levels

Sampling and analysis. Blood lead levels (B-Pb) are usually determined from analysis of venous blood; sometimes capillary blood has been employed. The level in capillary blood may be higher than in venous blood (Mahaffey et al., 1982), due to higher packed cell fraction and contamination from the skin, the difference being dependent upon the sampling technique.

As lead in blood is mainly present in the blood cells, levels in blood cells would be a suitable measure. But for practical reasons, levels in whole blood are usually employed. Levels in plasma may contain information of the most recent lead absorption (see above). However, the very low levels in plasma cause serious problems, mainly through contamination. Thus, plasma-lead levels have no practical use.

The packed cell volume may vary, as a result of lead exposure, or for other reasons. To be able to make a fully accurate evaluation of a whole-blood load level, it is thus advisable to determine the packed cell volume (hematocrit) in connection with the blood-lead analysis. However, in practice, this is seldom done routinely.

Nowadays, B-Pb levels are usually analyzed by atomic absorption spectrometry, either flame or flameless (electrothermal). Also, anodic stripping voltametry is employed widely. The analysis may cause considerable errors. It is thus important to employ a rigid quality control program, both internal and external (Friberg, 1983).

Traditionally, B-Pb levels are given as µg/100 ml. In this paper, mol/l will be used, and as a complement, µg/l (1 µmol/l=207 µg/l, 200 µg/l=0.96 µmol/l).

Kinetics. In subjects without occupational exposure, the whole B-Pb levels may be remarkably stable over time (Delves et al., 1984). After a rise of the exposure intensity, the lead level in blood usually increases gradually, to reach a steady state after weeks to months (Benson et al., 1976; Christoffersson et al., 1984; Forni et al., 1976; Griffin et al., 1982; Gross, 1981; Kehoe, 1961; Lerner et al., 1982; Neri et al., 1983; Stuik, 1974; Tola et al., 1973). However, after heavy exposure, the levels may rise by ten-fold within a few hours (De Silva, 1981; Schutz and Skerfving, 1976).

As mentioned above, after cessation of exposure, the B-Pb level decreases. There is an initial rapid decrease, while later the decrease is slower (Fig. 2). The average decline rate is compatible with an initial phase with a half-life of about one month, if a second, slow phase is taken into consideration (Ahlgren et al., 1980; Campbell et al., 1984; Chamberlain and Massey, 1972; Chamberlain et al., 1978; De Silva, 1981; Griffin et al., 1975; Gross, 1981; Hesley et al., 1976; Kang et al., 1983; Kehoe, 1961; Lynam and Nelson, 1982; McRoberts, 1973; O'Flaherty et al., 1982; Rabinowitz et al., 1977; Schlegel and Kufner, 1979; Schutz et al., in press b; Skerfving et al., 1983; Stuik, 1974). There is considerable interindividual variation (Schutz et al., in press b; Skerfving et al., 1983).

The decay rate of the slow phase has a half-time of about five years, again with interimdividual variation (Schutz et al., in press a). Analysis by one-compartment kinetics may thus give an entirely misleading picture of the blood lead kinetics.

The slow phase is dependent upon release of lead from the skeleton into the blood stream (Blanchard et al., 1969; Christoffersson et al., 1984; Eisenbud et al., 1969; Gotchy and Schiager, 1969; Schutz et al., in press a,b; Skerfving et al., 1983). This causes an endogenous lead exposure, which is dependent on the skeletal lead pool (Christoffersson et al., 1984, 1987; Schutz et al., in press a,b), and may be both considerable and long-lasting (Christoffersson et al., 1984, 1987; Corsi et al., 1984; Grandjean and Kon, 1981; Hesley and Wimbish, 1981; Neri et al., 1983; Prerovska and Teisinger, 1970; Schutz et al., in press a,b; Skerfving et al., 1983).

In a group of lead workers, the impact of the slow compartment corresponded to an average of 1.8 µmol/l (37 µg/l), about 64 percent of the total B-Pb level, and ranged as far as up to 2.7 µmol/l (Schutz et al., in press b: Skerfving et al., 1983). The relative importance of the skeletal

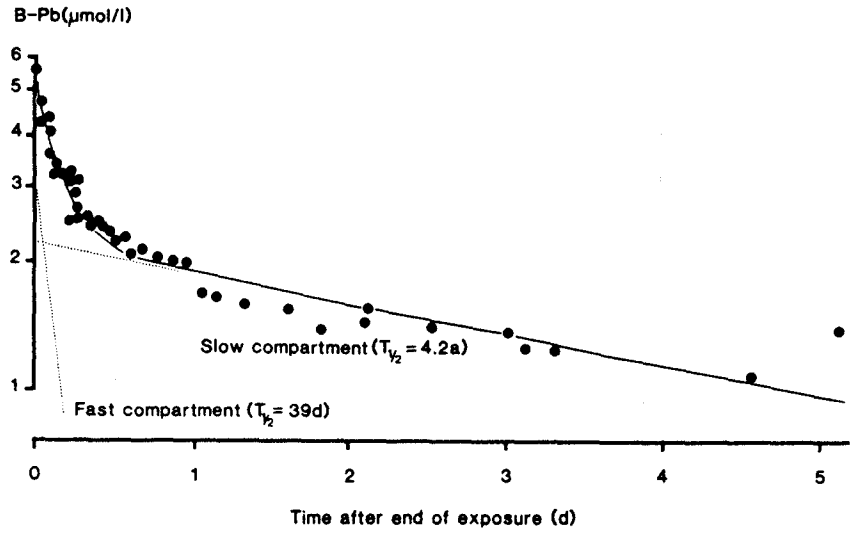

Fig. 2. Decay of blood lead level (logarithmic) after end of exposure in an ex-lead worker. A linear two-compartment model was fitted to the data. A "background" of 0.3 μmol/l has been subtracted. Biological half-times ($T_{1/2}$) for the compartments are given.

lead pools is, of course, also dependent upon the rate of recent absorption. Thus, the fraction is usually higher in retired workers than in active ones (Ahlgren et al., 1980; Schutz et al., in press b). In subjects without occupational lead exposure, fractions of 10-70 percent have been estimated (Chamberlain, 1985; Holtzman, 1978; Manton, 1977, 1985). One possibility, in epidemiological studies of long-term effect of lead exposure, is to use the time-integrated B-Pb level as an exposure index (Christoffersson et al., 1984; Hanninen et al., 1979; Schutz et al., in press b).

Reference values. B-Pb levels in subjects without occupational exposure vary with age (children, especially 1-3 year olds, have higher levels than adults (cf. Chamberlain, 1983), sex (males have higher levels than females), drinking and smoking habits (e.g., Elinder et al., 1985), and with area of residence. In areas without industry and traffic, the average level is about 0.15-0.25 μmol/l (30-50 μg/l) (Piomelli et al., 1980; Poole et al., 1980). In Sweden, the average level is about 0.3 μmol/l (50 μg/l) (Elinder et al., 1985; Friberg and Vahter, 1983; Schutz et al., 1984; Skerfving et al., 1987). In other areas, the levels may be considerably higher, up to an average 1 μmol/l (200 μg/l) (Friberg and Vahter, 1983). In some population strata, almost one fifth have had levels above 1.5 mol/l (300 μg/l) (Mahaffey et al., 1982).

The B-Pb levels are decreasing over time in many countries (Annest et al., 1983; Billick et al., 1979; Elinder et al., 1985; Elwood, 1983; Fachetti et al., 1982; Rabinowitz and Needleman, 1982; Schutz et al., 1984; Skerfving et al., 1987).

Relationship between lead exposure and blood lead levels. A long series of studies, both experimental and epidemiological, have been devoted to the relationship between lead exposure and lead levels in blood. Several detailed reviews have been published (Brunekreef, 1984; Chamberlain, 1983, 1985; Hammond et al., 1981). The matter is far from simple. As mentioned above, exposure may occur from various sources: air, food, and drinking water. Especially in children, exposure from lead in dustfall, house dust, and soil may be important.

Simultaneous estimates of all these factors have never been performed in one study. Moreover, in studies where exposure via inhalation has been assessed, outdoor measurements at sampling stations have usually been used instead of personal sampling in the breathing zone. This may cause problems, e.g., because of the difference in air lead levels outside and inside houses. Also, the particle size and solubility of the aerosol, and pulmonary ventilation affects the absorption. Similarly, relevant sampling of food and drinking water is not easy.

Generally, the studies have shown a relationship between absorption of lead, both through inhalation intake (Brunekreef, 1984; Chamberlain, 1983; Hammond et al., 1981) and through gastrointestinal intake (Bruaux et al., 1985; Department of the Environment, 1982; Nutrition Foundation Expert Advisory Committee, 1982; Thomas et al., 1979) and B-Pb concentration. In both cases the relationship is nonlinear, with a slower increased rate of B-Pb as the absorption increases.

At ambient exposure in children, Brunekreef (1984), after a careful review of available data (Fig. 3), concluded that, in the air lead level range of 0.5-1.5 $\mu g/m^3$ the B-Pb level increased about 0.14 $\mu mol/l$ (30 $\mu g/l$) per $\mu g/m^3$. In adults, the increase within the same air lead range was smaller, 0.05-0.1 $\mu mol/l$ (10-20 $\mu g/l$) per $\mu g/m^3$ (Chamberlain, 1983; Hammond et al., 1981).

In the industrial setting, several studies of the relationship between air and blood lead concentrations have shown only poor if any correlations, which may be due to lack of relevance of the air measurements (time, site of sampling, particle size). However, it has been estimated (WHO, 1980), that at air lead levels up to 50 $\mu g/m^3$ (particle size unspecified) and exposure for 40 hours per week, an increase of 10 $\mu g/m^3$ would cause an increase in the B-Pb level by about 0.25 $\mu mol/l$ (50 $\mu g/l$). However, there are wide variations, due to differences in the exposure pattern and variations in the metabolism of lead. According to one estimate by use of a theoretical model

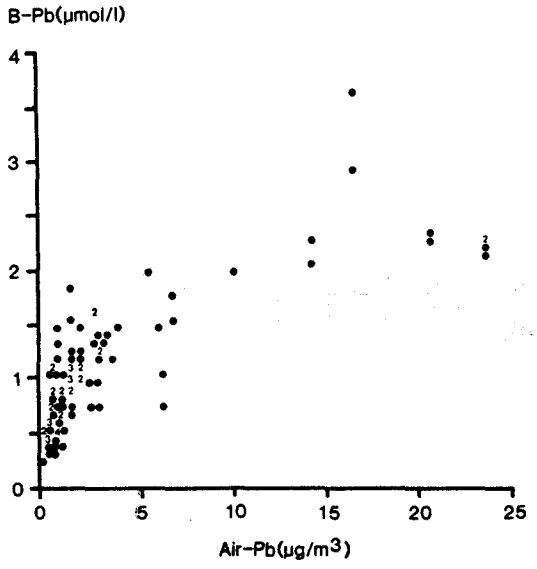

Fig. 3. Relationship between air lead (Air-Pb) at nearby sampling stations and blood lead (B-Pb) levels in 96 different child populations from various parts of the world. Data from Brunekreef (1984).

(Occupational Safety and Health Administration, 1978) at a time-weighted average level of 25 μg/m^3 (5 percent of the time above 50 μg/m^3), 0.5 percent of the workers would have B-Pb levels above 3 μmol/l (about 600 μg/l and two thirds below 2 μmol/l (about 200 μg/l). This does, however, vary in different work environments, depending upon particle size distribution and solubility (Fronies et al., 1986).

Other authors have focused upon the gastrointestinal intake of lead. In adults, at dietary lead intakes below 500 μg/day, an increase of dietary lead intake by 100 μg/day, causes an average increase of B-Pb level by approximately 0.15-0.20 μmol/l (30-40 μg/l) (Bruaux et al., 1985; Nutrition Foundation Expert Advisory Committee, 1982). In infants, the corresponding blood lead increase seems to be steeper, about 0.25 μmol/l (50 μg/l) (Department of the Environment, 1982).

Relationship Between Blood Lead Levels and Effect/response

Heme synthesis. Even a very small increase of the blood lead level inhibits the enzyme ALAD in erythrocytes (E-ALAD; Schutz and Skerfving, 1976; Zielhuis, 1975). Also, lead inhibits Py-5-N in red cells. Such an effect may occur event at very low blood-lead levels (0.5 μmol/l; 100 μg/l) (Angle et al., 1982). These effects cannot, in themselves, be considered detrimental to health, because no associated pathology has been described.

Somewhat higher blood lead levels are associated with an increase in E-PP. This increase is exponential (e.g., Corsi et al., 1984). It is steeper in women than in adult males. At a B-Pb level of 1.5 μmol/l (about 300 μg/l), about 50 percent of the females and about 15 percent of the males display an elevation (Schutz and Haeger-Aronsen, 1978; Zielhuis, 1975: WHO, 1980). This effect cannot, in itself, be considered detrimental to health. Even in severe lead poisoning, the amount of PP corresponds to less than 1 percent of the hemoglobin. But the PP level in blood may be used as an index of exposure (see below).

At higher B-Pb levels, there is an increase of the excretion of ALA and CP in urine (U-ALA, U-CP). The increase of U-ALA compared with blood-lead level is exponential (Chisolm et al., 1976; Schutz and Skerfving, 1976). The effect in children and women is more pronounced than in adult males. In the range 1.5-2.0 μmol/l (300-400 μg/l) about 40 percent of the women and 15 percent of the adult males display an increase of U-ALA (WHO, 1980). Again, these effects may not be detrimental to health, although the fact that ALA accumulation may have neurotoxic effects suggests that future studies in this area are important. However, U-ALA and U-CP levels may be used for monitoring of exposure (see below).

A slight increase in U-ALA or U-CP is usually not associated with any measurable effect in the form of reduced hemoglobin level in blood. At higher B-Pb levels (3-4 μmol/l, 600-800 μg/l) (Baker et al., 1979; Tola et al., 1973), disturbance of heme synthesis, in combination with - and probably more important - shortened life span of the erythrocytes, causes a reduction of the hemoglobin level in blood, resulting in anemia. This is, of course, a definite adverse effect.

Nervous system. The PNS is a target organ for inorganic lead. As stated above, there are indications from animal experiments that there is no close relationship between B-Pb and lead levels in the PNS, the latter having a greater tendency to accumulate lead. However, there is a general association between B-Pb and effects on the PNS. Several studies have shown that chronic lead exposure reduced conduction velocity in peripheral motor nerves in subjects without clinical symptoms or signs of disease (Ashby, 1980; Buchthal and Behse, 1979). In adults, discrete effects of this nature probably occur

at B-Pb levels, as low as about 2.5 μmol/l (500 μg/l) (Jeyaratnam et al., 1985; Seppalainen et al., 1979; WHO, 1980), even though, in some studies (Persson et al., 1979; Spirey et al., 1980) levels as high, or even higher, have not been associated with detectable functional disturbances. These discrepancies may be due to differences in exposure patterns and/or methodology. In a small prospective study, there were statistically significant effects at even lower B-Pb levels, about 1.5 μmol/l (300 μg/l) (Seppalainen et al., 1983). The significance of such neurophysiological disturbancies is not clear. There are conflicting results as to their reversibility (Araki et al., 1980; Corsi et al., 1984). However, in light of the fact that more excessive lead exposure may cause severe nervous tissue damage, early effects should also be regarded as adverse.

Lead also affects the CNS. The insidious effects on the CNS are difficult to measure. In psychometric tests, it has been possible to demonstrate minor effects in groups of lead workers with B-Pb levels of 2.5-3.0 μmol/l (500-600 μg/l), or higher (Baker et al., 1985; Hanninen et al., 1978; Hogstedt et al., 1983). In a small prospective study, there were indications of an effect even at a B-Pb level of about 1.5 mol/l (300 μg/l) (Mantere et al., 1984).

Several reports indicate that infants may suffer CNS damage at much lower lead absorption, perhaps even at or below B-Pb levels of about 1 μmol/l (200 μg/l) (cf. Rutter, 1983). However, this is controversial. It has been claimed (Medical Research Council, 1985; Smith, 1985) that the methodological difficulties are so great that definite conclusions on this issue cannot be drawn from the available data.

Kidneys. The kidney is a target organ for effects of inorganic lead. As stated above, there are indications from animal experiments that there is no close relationship between B-Pb and levels in the kidney, the latter having a greater tendency to accumulate lead. Effects on kidney function occur at B-Pb levels of about 3.0-3.5 mol/l (600-700 μg/l) or higher (Lilis et al., 1979; Ramirez-Cervantes et al., 1978). One problem in the interpretation of data on kidney damage is the lack of clear dose-response relationship. This may be due to the fact that disturbances of renal function may remain for a long time, the effect thus possibly being associated with earlier, higher exposures.

An increase of the urinary excretion of the tubular enzyme N-acetyl-beta-glucosaminidase (NAG) has been noted among workers having median B-Pb levels of about 2.5 mol/l (500 μg/l) (Meyer et al., 1984). Further, an effect on the kidney is possibly the cause of the reduction of serum levels of 1,25-dihydroxycholecalciferol (the major active form of vitamin D), that occurs in children at much lower B-Pb levels (Mahaffey et al., 1982). The relevance to health of these findings is not clear.

Urinary Lead Levels

As mentioned above, lead is excreted in the urine. Thus, urinary lead (U-Pb) levels have sometimes been used for biological monitoring of lead exposure and risk, particularly in occupational exposure. After an increase of lead exposure, the U-Pb level increases gradually, reaching an apparent steady state after weeks (Griffin et al., 1975; Gross, 1981; Kehoe, 1961; Tola et al., 1973). The increase is faster than that of B-Pb (Gross, 1981; Kehoe, 1961). There is a correlation between lead levels in urine and whole blood (Manton and Cook, 1984; Schutz and Skerfving, 1976; Skerfving et al., 1985; Tola et al., 1973). However, the association is not linear, the U-Pb level increases relatively more than the B-Pb concentration. A possible explanation of these observations is a dependence of urinary lead primarily upon plasma lead, which seems to increase relatively more than the whole-blood lead-level. There may be a considerable interindividual variation in the urinary lead excretion at a certain whole B-Pb level (Skerfving et al., 1985).

After a decrease of lead exposure, the U-Pb level decays rather rapidly (Gross, 1981; Kehoe, 1961; Skerfving et al., 1985).

The U-Pb concentration is dependent upon urine flow, which may vary considerably. One way of correcting for this is to relate the excretion to time; often, 24 hour urinary samples have been employed. However, this is impractical, as all urine is often not sampled, and as the need to sample during working hours causes risk of contamination. Thus, spot samples voided outside the work site are usually employed. Then, the lead content should be corrected for the degree of dilution of the urine. This can be made by relating the content to the urinary content of creatinine or by recalculating the lead content to a certain urinary density, usually 1.020.

Fecal Lead Excretion

Excretion of lead in feces may be used as an index of dietary lead intake (Bruaux et al., 1985). However, due to obvious practical difficulties, it is seldom useful.

Hair-Lead Levels

Lead is incorporated in hair (Rabinowitz et al., 1976). Several studies have shown a correlation between lead levels in blood and hair (Medical Research Council, 1985). Analysis of hair strands (Grandjean, 1984) may give a time-integrated index of the exposure for several months back. Thus, scalp hair has been used for biological monitoring of lead content in the body at the time of formation of the part of the hair analyzed.

However, there are problems. Lead levels in hair in an individual can vary, even between hairs obtained from the same region of the scalp. Further, the levels in subjects with similar exposure may vary with sex and hair color. In addition, the level in hair is a result not only from endogenous incorporation, but also from external contamination which of course may be substantial, especially in subjects living near or working in lead works (Grandjean, 1984). Accordingly, many authors have tried to wash the hair prior to analysis to get rid of the contamination. However, the washing may cause loss of endogenous lead. Also, washing of the hair while still on the scalp of the exposed subject may cause a loss of endogenous lead, which then is more pronounced in long hair, which has been washed many times, thus causing a spuriously low index of the body burden at the time of hair formation.

Because of these difficulties, lead level in hair have, in spite of its obvious advantages in terms of easiness at sampling, and its character of a time-integrated index, have attained only rather limited use (cf. Tatcher et al., 1982).

Teeth Lead Levels

Lead is incorporated in teeth. The lead level in teeth has been used as an index of lead exposure, especially the shedded deciduous teeth in children (e.g., Møller et al, 1982; Needleman et al., 1979; Smith et al., 1983). But methods have also been developed for determination of lead in teeth in situ (Bloch et al., 1976). The tooth lead level may perhaps be a cumulative index of the lead exposure from the prenatal period, when the teeth are formed, up to the time of shedding (Medical Research Council, 1985).

There is a poor correlation between lead levels in blood and teeth, probably because of their different time perspectives. Within one tooth, there is a considerable variation of lead level between enamel and primary and secondary dentine.

Incorporation in enamel and primary dentine is highest in connection with the prenatal formation of the tooth and much lower later. Circumpulpal secondary dentine may accumulate lead continuously and may thus be a time-integrated index of exposure up to shedding (Grandjean et al., 1984). Further, considerable variation in tooth-lead concentration has been noted in the same child, especially when the teeth are of different types, or from different jaws. Moreover, it is difficult to make a homogenate from a tooth, and to do that without loosing materials, resulting in interlaboratory variation reported at analyses of lead in teeth.

Lead levels in teeth have some practical limitations when used for biological monitoring. However, it may be used, especially as an index of integrated exposure during the prenatal and early extrauterine life in groups of individuals, provided the sampling and analyses are well controlled.

Skeletal Lead Levels

It is possible to use the skeletal lead level as an index of exposure. It reflects earlier exposure. Samples may be obtained by biopsy (e.g., Schutz et al., in press a; Westerman et al., 1965), which is usually not practical. Also, it may be determined by in vivo X-ray fluorescence (XRF), discussed below.

Lead Mobilization Test

Lead is chelated by calcium-disodium-ethylenediamine-tetraacetate (calcium disodium edetate; $CaNa_2EDTA$) and d-penicillamine. When these substances are administered, the lead excretion in urine increases, and may be used for biological monitoring of lead exposure and risk of poisoning. $CaNa_2EDTA$ (e.g., Prerovska and Teisinger, 1970) is a more potent chelating agent than penicillamine, and has thus been used more frequently; on the other hand, it has to be given parenterally, while penicillamine may be given orally (Schutz et al., 1987). Both compounds have side effects with prolonged administration, but none have been reported with single dose administration.

$CaNa_2EDTA$ is given either as an intravenous infusion (e.g., Corsi et al., 1984; Hansen et al., 1981) or as a single or twice-repeated intramuscular injection (e.g., Chisolm et al., 1976; Markowitz and Rosen, 1984), in the latter case mixed with procain to reduce the pain. The dose administered has varied considerably, but is usually about 25 mg/kg body weight. The chelating agent is almost completely eliminated during the 24 hours following injection, and urine is accordingly usually collected during that period. However, the long period of urine collection causes considerable problems in nonhospitalized individuals. It has been shown that a period of 6-8 hours is sufficient (Markowitz and Rosen, 1984; Schutz et al., 1987). The result (chelatable lead) is either expressed as the total amount of lead excreted during the defined time period or as the amount of lead excreted in relation to the amount of chelating agent administered.

After an increase in lead exposure, there is a gradual increase of chelatable lead, which reaches a steady state after approximately a year (Bruegstrup Hansen et al., 1981). The shape of the accumulation curve is similar to that of blood lead, but seems to level off later. There is a correlation between B-Pb and chelatable lead; the increase of chelatable lead on B-Pb is exponential (Chisolm et al., 1976; Schutz et al., 1987). After the end of lead exposure, the chelatable lead remains increased for several years (Corsi et al., 1984; Prerovska and Teisinger, 1970; Schutz et al., 1987).

The mobilized lead originates probably mainly from the soft tissue pool, although the small, rapidly exchangeable skeletal pool also contributes (Schutz et al., 1987; Wielopolski et al., 1985), probably indirectly, by its

effect on the soft tissue pool. However, at least in adults, bone-lead pool does not significantly affect the chelatable lead (Schutz et al., 1987). It has been claimed that the chelatable lead is a better index of the metabolically active lead pool than is B-Pb. The reason for this is mainly the linear relationship to urinary excretion of ALA (see below).

Lead mobilization tests may be too complicated for use in routine biological monitoring. The tests provide little information in addition to that obtained by determination of the blood lead level. It may be of some use, though, in subjects with previous exposure to lead, but who have only low recent exposure. In these persons, the B-Pb may be only slightly increased, but the mobilization test may be significantly elevated. Its main use has been in children with suspected or threatening lead poisoning, mainly to determine whether prolonged chelation therapy should be initiated. In subjects with decreased glomerular filtration, the test is not useful, as the excretion of the chelate in those cases is very prolonged (Weeden et al., 1979).

Monitoring of Effects

As discussed above, inorganic lead inhibits several steps in heme formation. These abnormalities may be used for biological monitoring.

Delta-amino levulinic acid dehydratase. An inhibition of E-ALAD has been demonstrated at exposures associated with very low blood levels (about 0.5 μmol/l, 100 μg/l), and is directly parallel in time to changes in B-Pb (Skerfving and Schutz, 1976). A disadvantage is that total inhibition occurs at B-Pb levels of about 3.0 μmol/l (600 μg/l). Also, the activity may be inhibited by other metals, e.g., methylmercury (Schutz and Skerfving, 1975), and by ethanol intoxication (Moore et al., 1971). ALAD contains zinc and, theoretically, simultaneous zinc exposure might affect the dose-response relationship between lead and ALAD. However, occupational zinc exposure causes only minor effects (Meredith and Moore, 1980).

Delta-amino levulinic acid and coproporphyrin. Levels of ALA and CP in urine has been used extensively for biological monitoring of lead exposure. There is a time-lag of only a few hours after changes in the lead absorption (Schutz and Skerfving, 1976). There seems to be a considerable interindividual variation of excretion of the metabolites at the same lead absorption. If used, the urinary levels should be corrected for the flow rate of urine, by relation to creatinine, or to a defined density. Alternatively, it may be related to a defined time period. There are other kinds of interference. Thus, U-ALA and U-CP is increased in hepatic porphyrias and U-CP in certain cases of hepatocellular injury (cf. Chisolm, 1978).

Protoporphyrin. E-PP has been used extensively for biological monitoring of lead exposure (cf. Schutz and Haeger-Aronsen, 1978; Zielhuis, 1976). A main advantage is the simplicity of the analyses; they may even be determined at the work place by a simple and rapid fluorometric technique.

Further, an additional advantage is the time pattern of the effect; it integrates the exposure over several months. The level is affected by the life-span of the red blood cells, i.e., about 120 days. After an increase of exposure, the level increases more slowly than does the blood lead level, and after cessation of exposure, the level decreases more slowly than the B-Pb (Schlegel and Kufner, 1979).

Moreover, there are indications that the E-PP level correlates better with certain effects on the kidney (Lilis et al., 1979) and nervous system (Grandjean et al., 1978), than does the B-Pb level. Whether this is due to the kinetics discussed above, or to the fact that the E-PP level reflects a metabolic effect, and not only an accumulation of lead, is not known.

But there are definite problems in connection with E-PP for biological monitoring, both in the analysis and in the interpretation of results. Iron deficiency causes an increase of erythrocyte protoporphyrin (cf. Chisolm, 1978), which may be a problem, especially in women and children though rarely seen in healthy males. Also, the interindividual variation in response at a certain lead absorption seems to be considerable. Thus, a pre-exposure determination is of value. A rare inborn error of metabolism, erythropoietic protoporpyria, also produces markedly elevated levels.

The effect on heme synthesis may result in reticulocytosis and stippled erythrocytes in peripheral blood. The life-span of circulating erythrocytes also becomes shortened. The combined effects of lead on heme synthesis and on life-span of the blood cells results may result in anemia. Neither is adequate for biological monitoring, as they represent adverse effects, as do determinations of function of the nervous system and the kidneys.

CURRENT PRACTICE OF BIOLOGICAL MONITORING

The current practices for biological monitoring of lead exposure vary widely among countries. In general, the monitoring is focused mainly on the the B-Pbs and the frequency of sampling is governed by the intensity of the lead exposure. Sometimes E-PP, U-Pb, U-ALA and/or U-CP are employed. Also, mobilization tests are used, but mainly in the clinical diagnosis of lead poisoning.

Occupational Exposure

The following are examples of strategies for biological monitoring of occupational lead exposure.

In Sweden, any subject to be employed in work involving lead exposure should be examined by a physician (Swedish National Workers Protection Agency, 1984). The examination includes a medical and occupational history (including information on relevant exposures). Blood pressure, hemoglobin level, protein concentration in urine, and B-Pb level are determined. If the examination reveals that the presumptive lead worker will run an increased risk by the lead exposure, he shall not be exposed. A full medical examination should be repeated in lead workers every third year.

Further, after onset of exposure, the B-Pb level shall be determined after one month. Thereafter, the B-Pb level is analyzed each third month. If the level at three successive samplings is below 2 μmol/l (about 400 μg/l), the subsequent sampling may be performed each six months. If the levels are below 1.0 μmol/l (200 μg/l) further examination is not needed.

If the B-Pb level is above 2.0 μmol/l (about 400 μg/l) the employer shall investigate the cause of the uptake, and measures to decrease the exposure shall be taken. A worker who displays a blood lead level of more than 3.0 μmol/l) may not be employed in lead-exposing work until he has been examined medically and the B-Pb level has decreased under 2.0 μmol/l (about 400 μg/l). Temporary exemption from this rule has been made for workers with a particularly long and heavy exposure history whose skeletal lead burden are such, that they will only reach the required B-Pb level after a very long exposure-free period. The same applies to a worker who has displayed levels in the range 2.5-3.0 μmol/l (500-600 μg/l) at three consecutive samplings.

Female workers under the age of 50 shall be informed of the risks to the fetus during pregnancy and shall inform the employer immediately if she becomes pregnant. She may not then be employed in work causing lead exposure during pregnancy and lactation.

In Finland (Hernberg, 1983 and personal communication), a population of workers in which B-Pb levels exceed 2.0 µmol/l (about 400 µg/l) need not be monitored regularly. If any worker has a level above 2.0 µmol/l (400 µg/l), all workers should be monitored at least once; at 3.0 µmol/l (600 µg/l) or more monitoring is repeated at least two times, and at 3.5 µmol/l (700 µg/l) or more (or if a case of clinical lead poisoning has occurred) at least six times a year. Individuals with a B-Pb level exceeding 2.5 µmol/l (500 µg/l) must be removed from the exposed job.

In the U.S., an action limit at B-Pb levels of 400 µg/l (1.9 µmol/l) has been proposed (Occupational Safety and Health Administration, 1978). The European Community (1979) has recommended a maximum permissible level of 600 µg/l (about 300 µmol/l) in individual workers and 550 µg/l (about 2.7 µmol/l) as the 50th percentile in groups of workers. The corresponding values for U-ALA are 12 and 6 mg/l. This is a minimum requirement. Different member countries have issued various standards, sometimes in accordance with the minimum, sometimes lower.

WHO (1980) recommended a health-based maximum B-Pb level of 400 µg/l (1.9 µmol/l) in adult male workers and for female workers in the nonfertile age. Further it was recommended, that in female workers in the fertile age, the B-Pb level should not be significantly higher than in the general population. U-ALA should not increase above the laboratory's upper "normal" level (e.g., mean plus 2 standard deviations) for a general adult population with B-Pb level not exceeding 200 µg/l (1.0 µmol/l). For E-PP level, a 50 percent increase could be accepted.

Environmental Exposure

In the U.S., the Center for Disease Control (1985) has recommended that children, who have B-Pb levels of 700 µg/l (about 3.5 µmol/l) or more (500 µg/l if the E-PP level exceeds 250 µg/l whole blood or more), be treated with chelating agents. Children who have B-Pb levels above 500 µg/l (2.5 µmol/l) (or 250 µg/l if the E-PP level exceeds 110 µg/l whole blood) shall be evaluated further with a mobilization test. In children having B-Pb levels exceeding 250 µg/l (1.2 µmol/l), and E-PP levels exceeding 35 µg/l whole blood, effort shall be made to remove sources of lead exposure from the child's environment. All children with B-Pb levels exceeding 250 µg/l shall be followed.

FUTURE POSSIBILITIES

Today, B-Pb level determination is the main tool for biological monitoring of lead exposure. As said above, it is affected both by recent and by "historical" lead absorption, in the latter case due to continuous mobilization of the skeletal lead pool. This dual origin of the blood lead may cause problems in the interpretation of what a high B-Pb level really means, and whether it should result in action to find and eliminate lead exposure. In this case, determination of bone lead may be of value, as it allows evaluation of the contribution of recent exposure to the B-Pb level.

Further, some of the effects of lead exposure may be induced by long-time lead absorption, or may be irreversible; clinical signs remaining for a long time, sometimes perhaps even after a reduction of exposure having caused a decrease of B-Pb levels. This may cause problems with interpretation of the results in cross-sectional studies, in which present B-Pb levels are correlated with measures of effect. Then, the skeletal lead level may give information, that allows conclusions regarding the earlier history of lead absorption in the individual.

In particular cases, the skeletal lead level has been estimated in bone ɔsies (Gossman and Heilesz, 1967; Manton, 1985; Rabinowitz et al., 1977; ıtz et al., in press a; Kesterman et al., 1965). But this is, of course, a practical possibility for biological monitoring.

Lead levels in bone may also be measured in vivo by X-ray fluorescence hnique. These measurements have been performed in finger-bone (Ahlgren et , 1980; Christoffersson et al., 1984, 1987; Eastwell et al., 1983; Price et , 1984) and tibia (Somervaille et al., 1983; Wielopolski et al., 1986) The ısurements take about half an hour and cause exposure to only a low radiation e. The detection limit in finger-bone is about 20 µg/g wet weight, which much higher than the levels found in subjects without particular exposure chutz et al., in press a), but sufficient for use in the occupational setting ılgren, 1980; Christoffersson et al., 1984, 1987) and in other particular ɔosure (Eastwell et al., 1983; Price et al., 1984). For measurements in ɔia, the detection limit is similar (Somervaille et al., 1983). The method ror at analysis in finger-bone is about 15 percent, which is sufficient for ny purposes.

In lead workers, there is an increase in skeletal lead levels with creasing time of exposure (Christoffersson et al., 1984; Schutz et al., in ess a; Skerfving et al., in press), although the interindividual variation ı bone-lead concentration at a certain exposure time is considerable. That ıriation, at least to a great extent, depends on variations in intensity of posure, and accordingly in lead absorption, in different individuals cupied in different working environments. The skeletal lead level is thus ɔnsiderably better associated with blood lead level integrated over time of cupational lead exposure.

The rate of turnover of lead differs between different parts of the keleton. It is considerably faster in trabecular bone than in cortical Schutz et al., in press a). The rate of turnover of lead in the finger-bone, hich contains both trabecular and cortical bone, corresponds to a half-life f about half a decade (Christoffersson et al., 1987). This means that, in his type of bone, a steady state is reached after decades of exposure Skerfving et al., in press). The finger-bone lead level can thus be expected o give a picture of the time-integrated lead absorption over a long time. It s possible that use of a more typical cortical bone, such as the tibia Somervaille et al., 1983), may give a picture of the lead exposure even farther back in time. But that possibility remains to be investigated.

Other possibilities, which should be investigated, is whether urinary lead level is a better measure of high exposure, absorption, and effects of lead than is B-Pb, and whether E-PP levels correlate better with different kinds of effects than do B-Pb.

SUMMARY

The metabolism and effects of inorganic lead have been summarized, with special reference to biological monitoring of exposure and risk of poisoning. From a practical point of view, a two-compartment model describes the metabolism sufficiently well. The whole-blood lead reflects both compartments; a rapid one (reflecting soft tissues) with a half-time of about one month, and a slower one (reflecting the bone-lead pool) with a half-time of half a decade. There are considerable interindividual variations in lead metabolism, which will probably result in significant differences in risk at a certain intensity of lead uptake.

The whole-blood lead level is the most valuable tool for biological monitoring as the blood lead level is affected by recent absorption. The