Environmental Health Criteria 4

OXIDES OF NITROGEN

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While every effort has been made to present information in the criteria documents as accurately as possible without unduly delaying their publication, mistakes might have occurred and are likely to occur in the future. In the interest of all users of the environmental health criteria documents, readers are kindly requested to communicate any errors found to the Division of Environmental Health, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda which will appear in subsequent volumes.

In addition, experts in any particular field dealt with in the criteria documents are kindly requested to make available to the WHO Secretariat any important published information that may have inadvertently been omitted and which may change the evaluation of health risks from exposure to the environmental agent under examination, so that information may be considered in the event of updating and re-evaluating the conclusions contained in the criteria documents.

WHO TASK GROUP ON ENVIRONMENTAL HEALTH CRITERIA FOR OXIDES OF NITROGEN

Tokyo, 23–27 August 1976

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ENVIRONMENTAL HEALTH CRITERIA FOR OXIDES OF NITROGEN

A WHO Task Group on Environmental Health Criteria for Oxides of Nitrogen met in Tokyo from 23 to 27 August 1976. Dr Y. Hasegawa, Medical Officer, Control of Environmental Pollution and Hazards, Division of Environmental Health, WHO, opened the meeting on behalf of the Director-General and expressed the appreciation of the Organization to the Government of Japan for kindly acting as host to the meeting. In reply the group was welcomed by Dr M. Hashimoto, Director-General of the Air Quality Bureau, Environment Agency, Japan. The Task Group reviewed and revised the second draft criteria document and made an evaluation of the health risks from exposure to oxides of nitrogen.

The first and second drafts of the criteria document were prepared by Dr G. Freeman, Director, Department of Medical Sciences, Stanford Research Institute, Menlo Park, CA, USA. The comments on which the second draft was based were received from the national focal points for the WHO Environmental Health Criteria Programme in Bulgaria, Canada, Czechoslovakia, Federal Republic of Germany, India, Japan, New Zealand, Poland, Sweden, the USA and the USSR; and from the Food and Agriculture Organization of the United Nations (FAO), Rome, and the World Meteorological Organization (WMO), Geneva. The collaboration of these national institutions and international organizations is gratefully acknowledged.

The Secretariat also wishes to acknowledge the most valuable collaboration in the final phase of the preparation of this document, of Professor C. M. Shy, School of Public Health, University of North Carolina, NC, USA, Dr D. E. Gardner, Chief, Biomedical Research Branch, Health Effects Research Laboratory, Environmental Protection Agency, Research Triangle Park, NC, USA, and Dr R. G. Derwent, Environmental and Medical Sciences Division, Atomic Energy Research Establishment, Harwell, England.

This document is based primarily on original publications listed in the reference section. Much valuable information may also be found in other published criteria documents (North Atlantic Treaty Organization, 1973; US Department of Health, Education, and Welfare, 1976; US Environmental Protection Agency, 1971a) and in the reviews on oxides of nitrogen by Cooper & Tabershaw (1966), Morrow (1975), and Stern, ed. (1968). Details of the WHO Environmental Health Criteria Pro-

gramme including some terms frequently used in the documents may be found in the general introduction to the Environmental Health Criteria Programme published together with the environmental health criteria document on mercury (Environmental Health Criteria 1, Geneva, World Health Organization, 1976).

The following conversion factors have been used in this document. [a]

nitric oxide	1 ppm = 1230 $\mu g/m^3$	carbon monoxide	1 ppm = 1150 $\mu g/m^3$
nitrogen dioxide	1 ppm = 1880 $\mu g/m^3$	ozone	1 ppm = 2000 $\mu g/m^3$
nitrous oxide	1 ppm = 1800 $\mu g/m^3$	sulfur dioxide	1 ppm = 2600 $\mu g/m^3$

1. SUMMARY AND RECOMMENDATIONS FOR FURTHER RESEARCH

1.1 Summary

1.1.1 Chemistry and analytical methods

In the context of this criteria document, the term oxides of nitrogen is understood to include nitric oxide (NO) and nitrogen dioxide (NO_2). Other oxides of nitrogen which exist in the atmosphere are not known to have any biological significance and have not been referred to in this document. At the point of discharge from man-made sources, the predominant oxide of nitrogen is nitric oxide which is readily converted to nitrogen dioxide by chemical reactions in the atmosphere.

Nitric oxide and nitrogen dioxide can be measured separately or collectively by manual or automated techniques. However, whereas a certain analytical method can be quite reliable for one compound ("chemiluminescence" for nitric oxide; "Saltzman method" for nitrogen dioxide), difficulties may arise in the simultaneous monitoring of both oxides. Gas-phase titration, permeation tubes, and gravimetric standards have been used for the accurate calibration of these analytical procedures.

1.1.2 Sources of oxides of nitrogen

On a global scale, quantities of nitric oxide and nitrogen dioxide produced naturally by bacterial and volcanic action and by lightning by

[a] When converting values expressed in ppm to $\mu g/m^3$, the numbers have been rounded up to 2 or, exceptionally 3 significant figures and, in most cases, concentrations higher than 10,000 $\mu g/m^3$ have been expressed in mg/m^3.

far outweigh those generated by man's activities. However, as they are distributed over the entire earth's surface, the resulting background atmospheric concentrations are very small.

The major source of man-made emissions of oxides of nitrogen into the atmosphere is the combustion of fossil fuels in stationary sources (heating, power generation) and in motor vehicles (internal combustion engines). Other contributions to the atmosphere come from specific non-combustion industrial processes, such as the manufacture of nitric acid and explosives. Indoor sources include smoking, gas-fired appliances, and oil stoves. Differences in the nitrogen dioxide emission of various countries are mainly due to differences in fossil fuel consumption.

Worldwide emissions of oxides of nitrogen in 1970 were estimated at approximately 53 million tonnes.

1.1.3 Environmental levels and exposures

The natural background concentration of nitrogen dioxide over land areas is usually in the range of 0.4–9.4 $\mu g/m^3$ (0.0002–0.005 ppm). This concentration is 1–2 orders of magnitude lower than the concentrations normally found in urban areas. Annual mean nitrogen dioxide concentrations in urban areas throughout the world are typically in the range of 20–90 $\mu g/m^3$ (0.01–0.05 ppm), although it is exceedingly difficult to generalize.

Data for shorter averaging periods show considerable variations depending on meteorological and seasonal conditions and on the proximity and nature of local sources of pollution. Generally, the highest monthly means of nitrogen dioxide levels in large urban areas are about 60–110 $\mu g/m^3$ (0.03–0.06 ppm), the highest daily means 130–400 $\mu g/m^3$ (0.07–0.22 ppm), and the highest hourly values 240–850 $\mu g/m^3$ (0.13–0.45 ppm).

In contrast with typical primary air pollutants, nitrogen dioxide concentrations do not show consistent seasonal behaviour throughout all urban areas of the world and are not necessarily highest during the months of maximum photochemical activity.

Exposure from indoor sources such as home appliances and smoking should not be underestimated. In the immediate proximity of domestic gas-fired appliances, nitrogen dioxide concentrations of up to 2000 $\mu g/m^3$ (1.1 ppm) have been measured. Tobacco smoke has been reported to contain nitric oxide levels of about 98–135 mg/m^3 (80–110 ppm) and nitrogen dioxide levels of about 150–226 mg/m^3 (80–120 ppm), but these levels may fluctuate considerably with the conditions of combustion.

1.1.4 Effects on experimental animals

Reversible and irreversible adverse effects may be caused by exposure to nitrogen dioxide, depending upon the concentration, length, and mode of exposure, the species of animal tested, and the presence of infectious agents.

Morphological changes reported in a number of animal species including the mouse, rat, rabbit, guineapig, and monkey, appeared to be most prominent in the terminal bronchiolar and alveolar duct epithelia. Exposure to about 470–1900 $\mu g/m^3$ (0.25–1.0 ppm) resulted in numerous pathophysiological changes including bronchitis, bronchopneumonia, atelectasis, protein leakage into the alveolar space, changes in collagen, elastin, and mast cells of the lungs, reduction or loss of cilia and adenomatous changes.

At concentrations of 3800–47 000 $\mu g/m^3$ (2.0–25 ppm) these effects became more pronounced. The more sensitive ciliated bronchiolar and type 1 alveolar lining cells were injured first and were replaced by the proliferation of more resistant nonciliated cells, and type 2 cells, respectively. Prolonged exposure resulted in a reduction in diameter of small airways by exudate, hypertrophy of the respiratory epithelium, and swelling of the basement membrane.

In studies on the effect of nitrogen dioxide on lung function, increased respiratory rates were reported in rats exposed to concentrations as low as 1500 $\mu g/m^3$ (0.8 ppm). Reductions in both diffusion capacity and peak expiratory flow rates were demonstrated in beagles exposed to a combination of nitrogen dioxide at 1210 $\mu g/m^3$ (0.64 ppm) and nitric oxide at 310 $\mu g/m^3$ (0.25 ppm). Biochemical changes included alterations in the action of several pulmonary enzymes, in the lipid content of the lungs, in the stability of pulmonary surfactant, and a decrease in the lung glutathione levels. As the nitrogen dioxide concentration increased to 11 75 mg/m^3 (6–40 ppm), the effects became more pronounced.

A number of extrapulmonary effects have been reported at nitrogen dioxide concentrations of 560–3700 $\mu g/m^3$ (0.3 to 2.0 ppm). Examination of blood from exposed animals showed changes in the number of circulating erythrocytes, in enzyme activity, and in antibody titres. Within the range of these concentrations, effects were also noted on the conditioned reflexes of the central nervous system (600 $\mu g/m^3$, 0.32 ppm) and on the endocrine and reproductive systems (2400 $\mu g/m^3$, 1.3 ppm) of rats.

With increasing levels of exposure, a variety of other effects were demonstrated. These included decrease in growth rate (5000 $\mu g/m^3$, 2.7 ppm) and loss in physical performance (9400 $\mu g/m^3$, 5.0 ppm).

The most successful analytical method in recent years has been atomic absorption spectroscopy. It has proved to be versatile and sufficiently sensitive for most purposes, but reliable results, particularly for biological specimens such as blood, can be obtained only after considerable experience has been acquired.

Determinations of haem intermediates and of porphobilinogen synthase (EC 4.2.1.24) (ALAD)[a,b] activity in blood are important methods for estimating the biological consequences of overexposure to lead. There is a great need for standardization of both these methods and of ways of expressing the results.

1.1.2 Sources and pathways of exposure

The major sources of lead in the environment that are of significance for the health of man, arise from the industrial and other technological uses of lead. The major dispersive non-recoverable use of lead is in the manufacture and application of alkyllead fuel additives. Because of current legislative actions with respect to the maximum permissible concentration of lead in gasoline, the consumption of lead for the production of alkyllead additives decreased from 1973 to 1975 and a further decline for the latter half of the 1970s may occur as more cars equipped with catalysts which require lead-free gasoline will come into use.

From a mass balance point of view, the transport and distribution of lead from stationary or mobile sources is mainly *via* air. Although large amounts are probably also discharged into soil and water, lead tends to localize near the points of such discharge. Lead that is discharged into the air over areas of high traffic density falls out mainly within the immediate metropolitan zone. The fraction that remains airborne (about 20 %, based on very limited data) is widely dispersed. Residence time for these small particles is of the order of days and is influenced by rainfall. In spite of widespread dispersion, with consequent dilution, there is evidence of lead accumulation at points extremely remote from human activity, e.g. in glacial strata in Greenland.

The biota acquires lead both by surface deposition and by secondary transfer from soil to plants and from plants to animals. However, the impact of man-made lead pollution on the lead content of plants and

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[a] In the first instance, enzymes are named according to the 1972 recommendations of the Commission on Enzyme Nomenclature but throughout the rest of the document the more familiar names or abbreviations are used.

[b] Formerly known as δ-aminolevulinate dehydratase or δ-aminolevulinic acid dehydratase.

animals is not perceptible except in localized areas of intense air pollution, e.g. around smelters and in the immediate vicinity of roads with heavy traffic.

The concentration of lead in air varies from 2–4 $\mu g/m^3$ in large cities with dense automobile traffic to less than 0.2 $\mu g/m^3$ in most suburban areas and still less in rural areas. The concentration of lead in drinking water is generally less than 10 µg/litre, but in some areas where the water is soft (low in calcium and magnesium) and where, at the same time, lead pipes and lead-lined water storage tanks are used, the concentration may reach 2000–3000 µg/litre. At this concentration (and even at concentrations of several hundred µg/litre) a perceptible rise in the body burden of lead occurs, which is reflected in elevated values of lead in the blood (Pb-B).

The contribution of food to man's exposure to lead is highly variable. Some recent studies in the USA have estimated the daily oral intake in food and beverages to be about 100 µg whereas earlier studies and some recent European studies indicated the intake to be in the range of 200–500 µg/day. However, a recent Swedish study reported volumes of the order of 20 µg/day. No specific category of food has been identified as being especially high in lead content other than wine and foods that are stored in lead-soldered cans or lead-glazed pottery. Processed milk contains considerably more lead than fresh cow's milk which has a similar concentration to human milk. The reported lead concentrations range from less than 5 µg/litre to 12 µg/litre. If this information is correct, milk could be a significant source of lead for infants.

Various miscellaneous sources of lead have been identified as being highly hazardous. These include lead-glazed ceramics used for beverage storage, illicitly-distilled whisky, and discarded automobile battery casings when used for fuel.

In certain countries, gross overexposure of some infants and young children has been recorded. The major sources are lead-based paint in old houses and in the soil surrounding these homes, and the soil surrounding lead smelters. Lead in street dust due to atmospheric fallout, and miscellaneous lead-containing objects chewed or eaten by children are other possible sources of exposure, but their relative importance is not clear.

The highest exposure occurs in workers who come into contact with lead during mining, smelting, and various manufacturing processes where lead is used. The major pathway of exposure is inhalation. The concentration of air lead in the working environment of smelters and storage battery factories often exceeds 1000 $\mu g/m^3$. For other industries, data are either not available or indicate a lower level of exposure.

Extensive surveys have been made on blood concentrations in both

adults and young children. Such data are useful indicators of overall exposure to lead.

1.1.3 Metabolism

A number of studies have been made which indicate that 35 % of the lead inhaled by man is deposited in the lungs. The relative importance of the mucociliary escalator mechanism and of direct absorption from pulmonary deposition is poorly understood and the contribution of airborne lead to total daily intake cannot be estimated from metabolic data. But when sustained Pb-B is used as a measure of lead absorption, it can be assumed from human data that continuous exposure to 1 μg of lead per m^3 of air would contribute lead levels of about 1.0–2.0 μg/100 ml of blood.

About 10 % of lead taken in from food and beverages is absorbed. However, using data from several sources, the dietary contribution to Pb-B can only be roughly estimated as 6–18 μg of lead per 100 ml of blood per 100 μg of dietary lead intake.

From both animal and human studies, the general features of lead distribution and excretion are fairly clearly defined. The body burden of lead can be subdivided into a large, slow-turnover compartment and a smaller more rapidly-exchanging compartment. Anatomically, the larger compartment is mainly located in bones. The amount of lead in this compartment increases throughout life. The smaller compartment consists of the soft tissues and includes the blood. Lead levels in soft tissues and in blood continue to increase up to early adulthood and then change little. Elimination of lead from the body is mainly by way of the urine (about 76 %) and the gastrointestinal tract (about 16 %). The other 8 % is excreted by miscellaneous routes (sweat, exfoliation of the skin, loss of hair) about which little is known.

Alkyllead compounds (tetraethyllead and tetramethyllead) are dealkylated both to trialkyl derivatives and to inorganic lead. Details of alkyllead metabolism have been learned from animal studies and have not been defined in man.

1.1.4 Experimental studies on the effects of lead

The extensive animal studies that have been conducted concerning the biological effects of lead indicate that, with rare exceptions, the toxic phenomena that have been observed in man have also been successfully reproduced in animals. Although animal studies have provided a more profound understanding of the effects of lead than could be learned from

studies of man himself, they have not been of much use in the elucidation of dose–effect and dose–response relationships in man.

Major differences that have been noted are as follows: (1) benign and malignant tumour induction has occurred in rats and mice exposed to lead acetate and in rats exposed to lead subacetate and lead phosphate but carcinogenic effects have not been seen in man; (2) clear-cut reductions in fertility have been observed in experimental animals but not in man, although data have been reported which suggest that this might be so; (3) hyperactivity and other behavioural disturbances have been observed in rats, mice, and sheep without prior encephalopathy. This is especially important because of current suspicions that widespread, slight brain damage occurs in young children with relatively low exposure not preceded by encephalopathy. Evidence also exists for compensatory increases in ALAD in animals with continuing exposure to lead whereas all human studies to date have been negative in this respect.

1.1.5 Clinical and epidemiological studies on the effects of lead: Evaluation of health risk to man from exposure to lead

Studies of the effects of lead on man may be divided into two general types. The first type is the retrospective study of the causes of mortality in lead-exposed populations in contrast with those in matched control groups. Several studies showed that at high exposure levels ($Pb-B > 80$ µg/100 ml[a]), a slightly higher number of deaths occurred due to cerebrovascular disease and chronic nephritis. In one study, where the mortality rate due to cancer was observed, no statistically significant differences were found between the industrially exposed workers and the control group.

The second type of study concerns morbidity rates due to the effects of lead on specific organs and systems. In some cases, it has been possible to estimate the level of the exchangeable body burden (expressed as Pb-B) at which a given intensity of effect (dose-response relationship) has been observed in certain sections of a selected group. For other effects it has only been possible to specify the Pb-B level at which no effect was observed in reasonably large groups of people (no-detected-effect level).

The haematopoietic system shows effects at lower Pb-B levels than any other system. The effects are, in order of sensitivity: inhibition of erythrocyte ALAD, elevation of erythrocyte protoporphyrin IX (FEP), rise in urinary δ-aminolevulinic acid (ALA) and coproporphyrin (CP) ex-

[a] In this document, the concentrations of lead in blood are expressed in µg/100 ml although in some original papers the values are given in µg/100 g. For practical purposes, the difference of about 5 % can be neglected.

cretion, inhibition of erythrocyte sodium-potassium adenosine triphosphatase (EC 3.6.1.3) (Na-K-ATP'ase), and fall in haemoglobin level. A fall in haemoglobin level is clearly an indication of adverse effects. The no-detected-effect level for this effect is a Pb-B concentration equivalent to 50 μg/100 ml in adults and 40 μg/100 ml in children.

The effects of inorganic lead on the central nervous system have been under intensive investigation in recent years, particularly with regard to subtle effects on behaviour, mainly in children, but also to some extent in adults. Substantial doubts remain as to the validity of some of the studies because the relationship between the exposure to lead at the time the damage occurs and at the time the effects are first observed is not known. Nevertheless, a no-detected-effect level has been specified that is lower than for classical lead encephalopathy. The no-detected-effect level is estimated to be at Pb-B values of about 60–70 μg/100 ml for adults and of about 50–60 μg/100 ml for children.

The renal effects of lead are of two general types. The first is tubular, characterized by the Fanconi triad of aminoaciduria, hyperphosphaturia, and glycosuria. It occurs with relatively short-term exposure and is reversible. The second type of renal effect is characterized anatomically by sclerotic changes and interstitial fibrosis. Functionally, filtration capacity is reduced. These changes are of a progressive nature and may lead to renal failure. It is probable that exposures leading to this type of nephropathy are rarely encountered even in industry today. A no-detected-effect level cannot be specified.

The problem of the toxic effects of alkyllead is almost entirely restricted to workers who are occupationally exposed. There is very little information concerning dose–effect and dose-response relationships and even the frequency of occurrence of toxic effects and their relation to specific work activities is not well documented.

1.2 Recommendations for Further Research

1.2.1 Analytical methods

One of the major needs is for the standardization of analytical methods, particularly with regard to the haem intermediates, ALAD, and erythrocyte Na-K-ATP'ase. At the present time, it is often impossible to compare studies conducted in one laboratory with those of another. This is particularly true for enzymatic methods that give different results depending on pH, oxygen tension, and the presence or absence of other factors, e.g. other metals that can influence the action of lead. It is of equal importance that a standard mode of expressing results be introduced in order to achieve

valid interlaboratory comparisons. Thus, measurements involving urine should be expressed per unit of creatinine excreted per unit time; this would probably take body mass into consideration.

In view of the highly variable results that have been obtained in the interlaboratory comparisons conducted to date, more cooperative efforts should be undertaken and maintained on a continuous basis. It is recommended that all published data include interlaboratory comparison results for the methods used. International standard specimens of the commonly investigated biological media with reliably determined concentrations of lead should be developed and made available to investigators.

Finally, standardized methods of statistical treatment of analytical data should be adopted and adhered to.

1.2.2 Sources of lead intake

It is apparent that the estimations of lead in the diet of man vary greatly. Future studies should include specifications concerning the characteristics of the individuals for whom lead consumption data are being reported, including sex, age, weight, and physical activity. Since the ultimate purpose of food studies is to evaluate the contribution made to the total dose, it is important that future reports also include the observed Pb-B levels and, preferably, other indices, such as δ-aminolevulinic acid in urine (ALA-U), PP and ALAD in erythrocytes. Food studies should also include estimates of the lead concentration of various components of the total diet. Only with such studies will it be possible to arrive at decisions regarding the control of lead in foods.

More precise information is available concerning the contribution of airborne lead to Pb-B and although this seems to be a minor contributor to Pb-B for the general population compared with diet, additional studies are needed both in occupational situations, and for the general population. The studies should be of a relatively long-term nature and should be done, as far as possible, with personal air samplers maintained in operation continuously throughout the day during the period of study.

There is a great need to study the sources of lead affecting infants and young children including the contributions of food, milk and other beverages, and air, and also miscellaneous sources, e.g. paint, soil, and dust.

1.2.3 Epidemiological studies

Prospective studies are needed of the health effects of both inorganic and organolead compounds, with particular reference to a more thorough

estimation of the nature of the lead exposure, Pb-B levels, and measurable effects. It would seem particularly useful to make further studies on occupational groups, beginning at the time of their entry into the high lead environment.

1.2.4 Interactions of lead with other environmental factors

In both epidemiological studies and in experimental studies on animals, not enough emphasis has been placed on the environmental variables that can affect man's response to lead. The list of such variables is long and is documented in this report. Particular attention should be paid to the influence of other metals, air pollutants, and the nutritional status of the subjects, since these factors have been identified as interacting with lead either in regard to its deposition in the body or in regard to its biological effects in target organs.

1.2.5 Significance of biological effects

Numerous abnormalities have been identified, the toxic significance of which is obscure, e.g. elevated free erythrocyte PP and marginal erythrocyte ALAD inhibition. There is an urgent need to study the significance of these findings in relation to human health.

2. PROPERTIES AND ANALYTICAL METHODS

2.1 Physical and Chemical Properties of Lead and its Compounds

Lead (atomic number, 82; atomic weight, 207.19; specific gravity, 11.34) is a bluish or silvery grey soft metal. The melting point is 327.5°C and the boiling point at atmospheric pressure 1740°C. It has four naturally occurring isotopes (208, 206, 207, and 204 in order of abundance), but the isotopic ratios for various mineral sources are sometimes substantially different. This property has been used to carry out non-radioactive-tracer environmental and metabolic studies.

Although lead has four electrons in its valence shell, only two ionize readily. The usual oxidation state of lead in inorganic compounds is therefore +2 rather than +4. The inorganic salts of lead (II), lead sulfide, and the oxides of lead are generally poorly soluble. Exceptions are the nitrate, the chlorate and, to a much lesser degree, the chloride (Table 1). Some of the salts formed with organic acids, e.g. lead oxalate, are also insoluble.

Table 1. Some physical and chemical data on lead and selected lead compounds[a]

Name	Synonym and formula	Molecular weight	Melting point (°C)	Boiling point (°C)	Solubility in cold water (g/litre)	Soluble in
lead	Pb	207.19	327.502	1740	insoluble	HNO_3; hot concentrated H_2SO_4
acetate	$Pb(C_2H_3O_2)_2$	325.28	280	—	443	hot water; glycerine; alcohol (slightly)
azide	$Pb(N_3)_2$	291.23		explodes 350	0.23	acetic acid; hot water (0.9 g/litre)
carbonate	cerrusite $PbCO_3$	267.20	315 (decomposes)		0.0011	acid; alkali; decomposes in hot water
chlorate	$Pb(ClO_3)_2$	374.09	230 (decomposes)		very soluble	alcohol
chloride	cotunite $PbCl_2$	278.10	501	950	9.9	NH_4 salts; slightly in dilute HCl and in NH_3; hot water (33.4 g/litre)
chromate	crocoite, chrome yellow $PbCrO_4$	328.18	844	decomposes	0.000058	alcohol; alkali
nitrate	$Pb(NO_3)_2$	331.20	470 (decomposes)		376.5	alcohol; alkali; NH_3; hot water (1270 g/litre)
orthophosphate	$Pb_3(PO_4)_2$	811.51	1014		0.00014	alkali; HNO_3
oxalate	PbC_2O_4	295.21	300 (decomposes)		0.0016	HNO_3
oxide: di-	plattnerite PbO_2	239.19	290 (decomposes)		insoluble	dilute HCl; acetic acid (slightly)
mono-	litharge PbO	223.19	888		0.017	HNO_3; alkali; NH_4Cl
red	minium Pb_3O_4	685.57	500 (decomposes)		insoluble	HCl; acetic acid
sesqui-	Pb_2O_3	462.38	370 (decomposes)		insoluble	decomposes in acid and hot water
stearate	$Pb(C_{18}H_{35}O_2)_2$	774.15	115.7		0.5	hot water (0.6 g/litre); ether (0.05 g/litre)
sulfate	anglesite $PbSO_4$	303.25	1170		0.0425	NH_4 salts; concentrated H_2SO_4 (slightly)
sulfide	galena PbS	239.25	1114		0.00086	acid
tetraethyllead	$Pb(C_2H_5)_4$	323.44	−136.80	200 decomposes, 91	insoluble	benzene; petroleum; alcohol; ether
tetramethyllead	$Pb(CH_3)_4$	267.3	−27.5	110	insoluble	benzene; petroleum; alcohol; ether

[a] Adapted from Weast, R. C., ed. Handbook of Chemistry and Physics, 55th edition, Cleveland, Ohio, Chemical Rubber Company, 1974.

Under appropriate conditions of synthesis, stable compounds are formed in which lead is directly bound to a carbon atom. Tetraethyllead and tetramethyllead are well-known organolead compounds. They are of great importance owing to their extensive use as fuel additives. Both are colourless liquids. Their volatility is lower than for most gasoline components. The boiling point of tetramethyllead is 110°C and that of tetraethyllead is 200°C. By contrast, the boiling point range for gasoline hydrocarbons is 20–200°C. Thus evaporation of gasoline tends to concentrate tetraethyllead and tetramethyllead in the liquid residue.

Both tetramethyllead and tetraethyllead decompose at, or somewhat below, the boiling point. Analysis of automobile exhaust gases shows that the ratio of tetramethyllead to tetraethyllead increases as the engine warms up, indicating that tetramethyllead is more thermostable than tetraethyllead (Laveskog, 1971). These compounds are also decomposed by ultraviolet light and trace chemicals in air such as halogens, acids, or oxidizing agents (Snyder, 1967).

2.2 Analytical Procedures

2.2.1 Sampling

Particular attention should be paid to the cleanliness of the instruments and the purity of chemicals to prevent the appearance of artifacts due to the secondary contamination by lead, especially in the sampling of foods and biological media.

In air sampling, high-volume samplers are preferable for accuracy (when it is necessary), but the low-volume technique is also useful for obtaining extensive data. As in all sampling for suspended particulate matter, the accuracy of volume meters should be checked periodically. The size of the pores of filters for collecting lead-containing particles should be small, possibly less than 0.2 μm for glass-fibre filters (Lee & Goransen, 1972). Liquid scrubbers containing iodine monochloride and solid scrubbers with activated carbon, cristobalite, or iodine crystals have been used for sampling organic lead compounds in air, in the range of about 1 $\mu g/m^3$ or less (Snyder, 1967; ASTM, 1970; Laveskog, 1971; Coleville & Hickman, 1973; Purdue et al., 1973) up to 10 $\mu g/m^3$ (Harrison et al., 1974).

Depending on the purpose of sampling, care should be taken to select the appropriate site for sampling devices and to achieve the best possible sampling conditions by:

— estimating the required amount of particulates before deciding on the sample volume and the sampling procedure;

— placing the sampling devices in the appropriate position (e.g. breathing air level, level of inlet tubes of house ventilators, window level in the case of a traffic-laden town street, at a reasonable distance from the highway in uninhabited zones, etc),

— taking the samples at appropriate rates and volumes (e.g. daily breathing volumes, daily ventilating capacities of installations) and for a sufficient time to make possible the estimation of the average concentration (e.g. during a work shift, or a 24-hour or longer period for general population exposure);

— taking into account the use of appropriate areas (cattle grazing, recreational zones, children's playgrounds etc.)

In addition, whenever possible, a procedure should be used that makes it possible to evaluate particle-size distribution and the physico-chemical properties of the lead compounds involved, including the shape of the particles and the state of their aggregation.

Stationary samplers can provide general indices of the exposure of individuals within a certain area. For estimating exposure through inhalation, personal samplers are highly desirable (Azar et al., 1973).

Techniques for sampling water are less complex than for air. The major question is whether or not the water should be filtered before analysis since it is known that lead occurs in water both in the particulate fraction and in solution. For most purposes at least, it is reasonable to sample water without any fractionation of the material collected.

However, in some cases it may be necessary to determine the biological availability for absorption of the various forms of lead that occur in water, and in soil. The latter is a dust source and may be a food contamination source as well.

The preparation of soil and soil dust samples for lead analysis usually involves drying (at 100°C), homogenization by grinding, and sieving (Thornton & Webb, 1975; Bolter et al., 1975).

For the study of lead in foods, two general methods have been used. These are the duplicate portions technique and the equivalent composite technique (theoretical diet). These two general techniques and others have been reviewed recently with reference to their advantages and disadvantages (Pekkarinen, 1970). The duplicate portions technique involves the collection for analysis of duplicates of the meals actually consumed by the individual. When carried out over a long enough period, the technique has the advantage of defining variability in consumption. Kehoe (1961) used this method for the daily determination of lead consumption over long periods. Considerable variation in lead consumption was found in individuals even when consumption was averaged for four- or eight-week

collection periods. The disadvantages of the method are the expense and the exacting nature of the method of collecting samples; these factors tend to limit the numbers of individuals included in such studies.

The equivalent composite technique consists of formulating the ingredients of meals typical for subpopulations and analysing them. The advantages are economy and ease of collection. This approach may or may not include the cooking process. The disadvantage is uncertainty as to how typical or representative the formulation is. Even when the cooking process is included, there may be significant differences in the manner of preparation for the study in comparison with that carried out under actual home conditions.

The main problem in the sampling of body fluids and tissues for lead analysis is potential secondary contamination with lead. Special precautions must be taken to ensure that all blood-collecting and blood-storage materials are as free from lead as possible. All glass equipment involved in blood collection and storage should be made of lead-free silicate glass, rinsed first in mineral acid, then with copious amounts of glass-distilled or deionized water. Polypropylene syringes have been recommended (NAS-NRC, 1972). Needles should be of stainless steel with polypropylene hubs. Blood is often drawn directly from the needle into vacuum tubes. It is wise to confirm periodically the absence of significant amounts of lead in the anticoagulant used in the blood container, although this has not been reported as a problem.

New analytical techniques make it possible to determine lead concentrations in microlitre quantities of blood. The trend towards the procurement of micro-samples of blood by skin prick increases the hazard of secondary contamination of the blood. Only one systematic investigation on the significance of this problem has been reported. Mitchell et al. (1974) describe a procedure whereby sample contamination appears to be avoided. This is achieved by spraying collodion over the cleansed skin before lancing. The correlation between the concentration of lead in micro-samples and in macro-samples obtained by venipuncture was fairly good ($r = 0.92$). The same general precautions must be taken in the collection of urine samples as in the collection of blood samples.

Ceramic surfaces are analysed to determine the quantity of lead likely to be leached by different foods and beverages. In all cases acetic acid solutions are used but the concentrations vary from 1 to 4%. The temperature of the tests ranges from 20 to 100°C and the duration from 30 minutes to more than 24 hours (Laurs, 1976; Merwin, 1976).

2.2.2 Analytical methods for lead

The analytical methods currently in use for the estimation of lead content are of two general types, destructive and non-destructive. In the former, the sample is first oxidized to destroy all organic matter. The ash is then usually dissolved in an aqueous medium, either for further preparative steps or for direct instrumental analysis. Non-destructive methods are of more recent origin and are still too complicated for routine studies. They include X-ray fluorescence analysis and fast neutron activation. In selecting methods, consideration must be given to the cost of the equipment and the time involved in performing the analyses.

The oldest and best known of the general methods currently in wide use are those based on the formation of the red complex that lead forms with dithizone (diphenylthiocarbazone). Numerous specific procedures have been developed based on the spectrophotometric determination of lead dithizonate. A typical example is the "US Public Health Service" method commonly used for the determination of lead in biological materials (NAS-NRC, 1972). The method has evolved over many years. A study of its reliability was reported by Keenan et al. (1963). An interlaboratory comparison was made of analyses of blood and urine with and without the addition of lead. Ten laboratories participated in the study. For blood, the concentration of lead calculated in the principal laboratory was 20 μg/100 ml. The average reported by the participating laboratories was 26 μg/100 ml with a standard deviation of ±0.82 μg/100 ml. For samples of blood to which lead was added, the average result was right on the mark, 70 μg/100 ml ± 0.78. For "spiked" urine, determined by the primary laboratory to contain 750 μg/litre, the average reported result was 679 ± 5.5 μg/litre.

Perhaps no method of instrumental analysis for lead has enjoyed such a rapid acceptance in recent years as atomic absorption spectroscopy. In conventional atomic absorption spectroscopy, the source of heat is a flame into which the sample solution is aspirated. More recently, various procedures have been developed whereby the receptacle containing the sample is heated electrically. This type of modified procedure is termed flameless atomic absorption spectroscopy. The main advantage of this approach is that sample size is reduced from the millilitre to the microlitre range with no commensurate loss of sensitivity. Another advantage is that the heated receptacle can be used for ashing the sample immediately prior to the spectrophotometric analysis. Numerous reports have appeared describing various kinds of flameless instrumentation and their application in the analysis of the lead content of blood and other materials (Cernik, 1974; Delves, 1970; Ediger & Coleman, 1973; Matousek & Stevens, 1971; Kubasik et al., 1972; Hwang et al., 1971; Sansoni et al., 1973; Schramel,

1973; Schramel, 1974). It has been reported that the analytical capabilities of this method for determining lead in whole blood are comparable with that of the conventional flame atomic absorption method (Kubasik et al., 1972; Hicks et al., 1973).

Electroanalytical methods have also been found useful for lead determinations. These include polarography and, more recently, anodic stripping voltametry. The polarographic method was developed specifically for lead by Teisinger (1935). The low sensitivity of the method as applied to lead in blood and urine required working close to the detection limits. This is obviously a disadvantage when determining the normal levels of lead in blood and urine. Various modifications of the original method have been used for the evaluation of industrial exposures (Weber, 1947; Baker, 1950; Brezina & Zuman, 1958). This method found wide application until more effective masking procedures were developed to increase the specificity of the dithizone method. Anodic stripping voltametry is gaining in popularity for lead analysis. Results have been compared using a dithizone method, an atomic absorption method, and anodic stripping voltametry (Matson, 1971). Generally, there was good agreement between all three methods in the estimation of the lead contents of blood and urine. In another study, anodic stripping voltametry was compared with atomic absorption spectroscopy and polarography for the analysis of lead in blood and urine (Horiuchi et al., 1968). The authors concluded that there were no significant differences between the results obtained by the various methods. Anodic stripping voltametry has also been compared with conventional and flameless atomic absorption spectroscopy and with potentiometric determination using ion-specific electrodes to estimate the lead content of water (Kempf & Sonnenborn, 1973).

Two non-destructive methods for lead analysis have been under investigation in recent years. These are neutron activation and X-ray fluorescence. The first of these is not likely to find wide application for lead analysis in the near future because of the cost and the need for access to a fast neutron source. Its advantage is that the concentration of many elements can be determined simultaneously.

X-ray fluorescence is also theoretically capable of detecting, non-destructively, all elements in a substance. A major obstacle to the wide application of this method is the profound matrix effect of the substances being analysed. Another problem is the backscatter from the exciting source. These design problems and approaches to their solution have been discussed recently by Kneip & Laurer (1972). Lead analysis by means of X-ray fluorescence with proton excitation has been successfully used with biological samples (Möller et al., 1974). It has also been used as the

standard method for the determination of lead on filters from air sampling equipment by the Warren Springs Laboratory in the United Kingdom. In the USA, the most extensive application of X-ray fluorescence for lead analysis has been for estimating the concentration and amount of lead on the walls of houses. For this purpose, several portable units have been designed and are being used in surveys of dwellings for hazardous concentrations of lead. Since the instruments in question scan surfaces, instrument response is in terms of lead detected per unit area and not per unit weight or volume of paint film. This creates difficulties, since the thickness of the total paint film varies depending on how many times a surface has been painted. Ordinances should perhaps be revised to specify tolerances based on surface area. The accuracy of these instruments is severely limited. These factors have been studied using one of the commercially available instruments (Spurgeon, 1973). In another report from the US National Bureau of Standards (Rasberry, 1973), four commercial instruments were tested as received from the manufacturer. It was found that all the instruments had a detection limit below 1 mg/cm^2, but that between 1 and 6.6 mg/cm^2, errors as large as 30–50 % occurred. It is difficult to evaluate the adequacy of such instruments since it is not at all clear where the cut-off is between hazardous and non-hazardous amounts of lead per unit area of paint film. Thus, if the cut-off were known to be at or above 1 mg/cm^2, the instruments would clearly be useful.

The accuracy and precision of various methods for the lead analysis of biological materials have been appraised in a number of interlaboratory comparison programmes both at the national (Keppler et al., 1970; Donovan et al., 1971) and international levels (Berlin et al., 1973). In general, these published studies have indicated that the accuracy of the measurements is unsatisfactory, with less than half of the laboratories performing adequately. More recently, in a programme involving sixty-six European laboratories, it was observed that even when only the laboratories that measured lead in blood and urine with a precision of greater than 10 % were selected, the interlaboratory variability still remained high. It is possible that the performance could be improved by rapid distribution of the sample and by improved sample preparation techniques, e.g. by subjecting blood samples to ultrasonic irradiation prior to despatch to participating laboratories.

The paper punch disc microtechnique (Cernik & Sayers, 1971; Cernik, 1974) was used in a population survey of blood lead content performed in Western Ireland (Grimes et al., 1975). Over 400 duplicate samples were analysed double-blind by one laboratory. The assay showed a satisfactory agreement with the results obtained by other laboratories using various techniques.

Comparisons have also been reported of the agreement between results obtained by the same investigator using different analytical methods. Yeager et al. (1971) compared the results obtained using a standard dithizone procedure and flame atomic absorption spectroscopy. The results from common digests of the same material were compared. The materials included blood, urine, tissue, faeces, food, and bone. Since the two methods are based on entirely different analytical principles, a straight line with a slope equal to 1 and an intercept equal to 0, obtained when the results of atomic absorption spectroscopy analyses were plotted against the results of the dithizone method, suggested that the two methods were equally accurate.

These studies show that blood sample preparation is important to ensure sufficient homogeneity for microanalytical techniques.

2.2.3 Methods for the measurement of some biochemical effects of lead

The classic method for the urinary δ-aminolevulinic acid (ALA) determination was developed by Mauzerall & Granick (1956). The major procedural difficulty was separation from interfering substances. A number of modifications and simplifications have been made by several authors (Davis & Andelman, 1967; Grabecki et al., 1967; Williams & Few, 1967; Sun et al., 1969; Tomokumi & Ogata, 1972).

The original Mauzerall & Granick method does not discriminate between ALA and aminoacetone, a fact that these authors were careful to point out. This is probably not very important when ALA excretion is greatly increased due to lead exposure, but for marginal elevations, it may be a serious problem. In healthy humans on a normal diet, the urinary excretion of ALA and that of aminoacetone are nearly equal (Marver et al., 1966). These authors and also Urata & Granick (1963) separated ALA from aminoacetone by chromatography.

One interlaboratory comparison study of ALA methods has been reported (Berlin et al., 1973). The methods used by the laboratories were those of Mauzerall & Granick (1956), Davis & Andelman (1967) and of Grabecki et al. (1967). The results using the Grabecki method were significantly higher than those using the Mauzerall & Granick method. Results with the Davis & Andelman method gave a mean value intermediate between the other two. The coefficients of variation were quite high: 33%, Grabecki; 28%, Mauzerall & Granick; and 49%, Davis & Andelman. It should also be noted that in the case of the Grabecki method, the colorimetric reaction was influenced by various interfering substances in the individual urine samples. This source of error was not considered in the interlaboratory comparison (Mappes, 1972).

Comparisons have also been reported between these different techniques by Roels et al. (1974) who evaluated the critical factors in the urine preparation which affected the different methods. The ionic strength and pH of the urine can affect the results of some of the methods.

In the methods used for the determination of ALAD activity, the amount of porphobilinogen (PBG) formed per unit time by a standard amount of enzyme source is measured. Limited data indicate that ALAD in blood is stable for several hours, even at room temperature (Hernberg et al., 1970); however, storage at lower temperatures improves the stability. The major variables reported to influence the activity of the enzyme are pH (Nikkanen et al., 1972), oxygen tension (Gibson et al., 1955), the nature of the anticoagulant (Collier, 1971), and the presence or absence of activators (Bonsignore et al., 1965; Collier, 1971; Granick et al., 1973; Hapke & Prigge, 1973). Measurement of ALAD activity in erythrocytes is a relatively simple procedure that can be conducted without sophisticated equipment. This makes it attractive as a measure of the haematological effects of exposure to lead. A number of investigators have shown it to be fairly specific for lead.

In its simplest and most frequently used form, the method of Bonsignore et al. (1965) requires the incubation of a mixture of blood, ALA, and water under aerobic conditions at 38°C. However, many investigators have modified the procedure and results from different laboratories are not necessarily comparable. In a recent interlaboratory comparison (Berlin et al., 1973), nine participants used various modifications of the Bonsignore method. Thus, it was only possible to compare the activity ratios between different blood samples. For two blood samples this ratio showed a coefficient of variation of only 13%.

Recently a "European standardized method" has been developed, tested in a collaborative study, and agreed upon by nineteen laboratories. The results of these tests compare very favourably with blood lead determinations. The interlaboratory coefficient of variation for ALAD was 10% (Berlin et al., 1974).

Porphyrins exhibit intense fluorescence when excited by light at approximately 400 nm (Soret band). They may be quantitatively determined either by measurement of light absorption in the Soret band region or by the measurement of fluorescence (Sassa et al., 1973; Chisolm, 1974).

A number of methods have been reported for the measurement of protoporphyrin IX. Some of these methods discriminate between different porphyrins, measuring specifically the concentration of protoporphyrin IX in erythrocytes (Schwartz & Wikoff, 1952; Wranne, 1960; Schlegel et al., 1972; Granick et al., 1972; Sassa et al., 1973). Other methods measure the

total concentration of free erythrocyte porphyrins including copro- and uro-porphyrins (Kammholtz et al., 1972; Piomelli, 1973; Schiele et al., 1974b). It is, however, scarcely necessary to make a distinction between the two kinds of procedure as over 90% of the free erythrocyte porphyrins are made up of protoporphyrin IX (Baloh, 1974). A particular advantage of the more recently developed procedures for the measurement of FEP is that they can be performed on microcapillary samples of blood (Kammholz, 1972; Granick et al., 1972; Sassa et al., 1973; Piomelli, 1973; Schiele et al., 1974a). The Piomelli procedure utilizes two successive extractions into ethylacetate–acetic acid with subsequent transfer of porphyrins into hydrochloric acid. The procedure of Granick et al. (1972) is simpler. Ethylacetate–acetic acid and hydrochloric acid are successively added to the sample of blood. In both procedures the ethylacetate serves to remove and retain interfering impurities in the blood. The data obtained by these two methods are not strictly comparable.

All the methods described measure protoporphyrin in the free base form. Lamola & Yamane (1974) have recently demonstrated that the protoporphyrin IX associated with iron deficiency and lead intoxication is present as a zinc chelate. This is not so in the case of erythropoietic porphyria. On the basis of these observations they developed a fluorimetric method for zinc chelate (Lamola et al., 1975). The major advantage of this method is its simplicity and rapidity. Microlitre samples are analysed fluorimetrically, after dilution, without any extraction steps.

The measurement of coproporphyrins in urine is generally done by extraction of the porphyrins into either ethylacetate–acetic acid (Sano & Rimington, 1963) or diethyl ether (Askevold, 1951) followed by transfer into hydrochloric acid. Absorbance is then measured at 401 nm with the corrections recommended by Rimington & Sveinsson (1950). The method is apparently specific, since uroporphyrins, the most likely source of interference, are not extracted into the organic phase under these conditions (Rimington & Sveinsson, 1950). An alternative method has been reported whereby the fluorescence of the hydrochloric acid extract is measured after adsorption on to magnesium hydroxide (Djurić, 1964). Certain precautions are necessary if urine is to be analysed for coproporphyrins. Coproporphyrins are unstable in acid urine and, furthermore they are light-sensitive (Schwartz et al., 1951). They may be stored safely in the dark at 4°C if the pH is maintained between 6.5 and 8.5.

3. SOURCES OF LEAD IN THE ENVIRONMENT

3.1 Natural Occurrence

3.1.1 Rocks

Lead occurs naturally in the earth's crust in the concentration of about 13 mg/kg. As with all elements, there are some areas with much higher concentrations including the lead ore deposits scattered throughout the world.

The most important sources of lead are igneous and metamorphic rocks, with lead concentrations in the range of 10–20 mg/kg (Wedepohl, 1956, Vinogradov, 1956, 1962; Turekian & Wedepohl, 1961). The concentration of lead in sedimentary rocks is of the same order of magnitude. The lead content of carbonaceous shales from the United States of America and Europe ranges from 10 mg/kg to 70 mg/kg (Wedepohl, 1971; Davidson & Lakin, 1962). The lead contents of shale and sandstone are similar but that of phosphate rocks is higher, and may exceed 100 mg/kg (Sheldon et al., 1953). Unconsolidated sediments in bodies of freshwater and in shallow marine areas have a similar lead content to shales. Deep marine sediments have quite a high lead content by comparison, commonly containing 100–200 mg/kg (Riley & Skirrow, 1965).

The lead content of coal is relatively low. However, when expressed on an ash-weight basis, the concentration is generally higher than that of igneous, metamorphic, and sedimentary rocks, but not more than ten-fold (Abernethy et al., 1969).

3.1.2 Soils

Surface soils are in direct contact with the contemporary environment; thus, special care must be taken to distinguish between soils that acquire lead only from natural sources and soils that are polluted by man. Acidic soils generally have a lower lead content than alkaline soils. The nature of the organic matter in soil also has a considerable influence on its lead content. Some organic matter is rich in chelating components, and it binds lead, either promoting its movement out of the soil or fixing the metal, depending on the solubility properties of the complex. Although all of these factors no doubt play a role in determining the lead content of specific soils, the concentrations usually encountered in areas, remote from human activity, are similar to concentrations found in rocks, with an average range of 5–25 mg/kg (Swaine, 1955). More recent data from various parts of the world have confirmed this estimate.

3.1.3 Water

Analyses of groundwater have revealed lead concentrations varying from 1 to 60 μg/litre (Kehoe et al., 1933, 1944; Bagchi et al., 1940). Most data refer to water that has been filtered to remove particulate matter. Colloidal lead is only partially removed by filtration and to different degrees. Water that is pumped from the ground is usually not filtered prior to analysis. The content of colloidal material is probably insignificant in such samples owing to natural filtration which removes colloidal particles fairly effectively.

There have been a large number of investigations concerning the concentration of lead in natural surface waters. From the data available, Livingstone (1963) estimated that the global mean lead content in lakes and rivers is 1–10 μg/litre. Although this estimate includes man-made pollution, it probably still represents a fair approximation of natural conditions since water flowing through the ecosystems has a considerable self-cleaning capacity.

The concentration of lead in sea water has been found to be lower than in freshwaters. Tatsumoto & Patterson (1963) report 0.08–0.4 μg/litre in seawaters off the coast of California. In deep waters the concentration was even lower. According to Chow (1968) surface waters off Bermuda, which are free from continental influences, have lead concentrations averaging 0.07 μg/litre, while central Atlantic waters contain an average of 0.05 μg/litre. Although there seem to be somewhat higher lead concentrations in the surface waters of the Pacific and the Mediterranean, compared with the central Atlantic, the concentrations at depths below the 1000-m level are very similar, i.e. around 0.03–0.04 μg/litre (Chow, 1968).

3.1.4 Air

The atmospheric concentration of lead measured at points most remote from civilization is of the order of 0.0001–0.001 $\mu g/m^3$ (Jernigan et al., 1971; Chow et al., 1969; Egorov et al., 1970; Murozumi et al., 1969). The sampling sites in these studies were mainly over remote areas of oceans and over Greenland. Patterson (1965) estimated from geochemical data that the concentration of lead in air of natural origin is about 0.0006 $\mu g/m^3$. If that is a correct estimate, even the air over uninhabited, remote, continental areas may be contaminated by human activities. For example, Chow et al. (1972) reported that the concentration of lead in the air over remote, uninhabited mountains of southern California had a concentration of 0.008 $\mu g/m^3$.

3.1.5 Plants

Lead occurs naturally in all plants, as well as in soil, air, and water. Extremely variable concentrations of lead in plants have been reported but nevertheless, certain generalizations have been made. Warren & Delavault (1962) have concluded that the normal concentration of lead in leaves and twigs of woody plants is 2.5 mg/kg on a dry weight basis. For vegetables and cereals they estimated normal concentrations to be 0.1–1.0 mg/kg dry weight. Mitchell (1963) found that the usual concentration of lead in pasture grasses was 1.0 mg/kg dry weight. These figures should be multiplied by a factor of 20 to convert concentration on a dry weight basis to an ash weight basis.

3.1.6 Environmental contamination from natural sources

The contribution of natural sources of lead to lead concentrations in the environment is small. As regards exposure of man, these sources are negligible. Through various breakdown processes, rocks yield lead which is transferred to the biosphere and the atmosphere and ultimately back to the earth's crust in the form of sedimentary rocks. Soluble lead has for thousands of years entered the oceans with river discharges, and the amount has been estimated by Patterson (1965) at some 17 000 tonnes per year. Sources contributing to airborne lead are silicate dusts, volcanic halogen aerosols, forest fires, sea salts aerosol, meteoric and meteoritic smoke, and lead derived from the decay of radon. The last mentioned source generates the lead isotope ^{210}Pb in trace amounts, the mean air residence time of which has been calculated to be about four weeks; the radioactive half-life is 22 years (Hill, 1960).

3.2 Production of Lead

3.2.1 Lead mining

Lead is produced from ores and recycled lead products. Lead occurs in a variety of minerals the most important of which are galena (PbS), cerrusite ($PbCO_3$) and anglesite ($PbSO_4$). Galena is by far the most important source of primary lead. It occurs mostly in deposits associated with other minerals, particularly those containing zinc. Mixed lead and zinc ores account for about 70% of total primary lead supplies. Ores containing mainly lead account for about 20% and the remaining 10% is obtained as a by-product from other deposits, mainly zinc and copper-zinc deposits (Federal Institute for Minerals Research and German Institute for

Economic Research, 1972). The proportions of various metals may differ in the ores of different countries. Silver is the most important of the other metals frequently present in lead deposits but copper may also be present in concentrations high enough to be commercially important. Other minor constituents of lead ores are gold, bismuth, antimony, arsenic, cadmium, tin, gallium, thallium, indium, germanium, and tellurium. The lead content of ores is comparatively low, i.e. 3–8 %, but even ores with lower lead contents may be commercially valuable.

The level of world mine production of lead concentrates from ores has increased in recent years. According to the International Lead and Zinc Study Group and the World Bureau of Metal Statistics, the world mine production of lead (lead content) was about 3.6 million tonnes in 1975, as compared with about 2.6 million tonnes in 1965. These figures include production estimates for socialist countries with a planned economy made by the World Bureau of Metal Statistics. The most important lead mining countries, producing over 100 000 tonnes each in 1975, were Australia (10 % of the total world output), Bulgaria (3 %), Canada (9.6 %), China (3.8 %), Mexico (4.5 %), Peru (5.5 %), United States of America (16 %), USSR (14.5 %), and Yugoslavia (3.5 %). In addition, some other countries had a production of over 2 % of the world total, e.g. Ireland, Japan, Democratic People's Republic of Korea, Morocco, Poland, Spain, and Sweden. There are about 40 countries producing only small amounts each, making together only some 12 % of the world production. One estimate of proven lead reserves of the world is 93 million tonnes of lead metal content. (Federal Institute for Minerals Research and German Institute for Economic Research, 1972.)

3.2.2 Smelting and refining

Smelting and refining is classified as primary or secondary, the former producing refined lead from concentrates (primary lead); the latter recovering lead from scrap (secondary lead). The raw materials for secondary lead are process (new) scrap arising during manufacturing processes, and recycled (old) scrap which arises when lead-containing manufactured goods are discarded. Old material makes up the bulk of the scrap, the most important source being storage batteries, which account for 70–80 % of the total supply of scrap.

Secondary lead accounts for about half the consumption in the United States of America and it has been estimated that about 35 % of the total world lead supply comes from secondary sources (Federal Institute for Minerals Research and German Institute for Economic Research, 1972).

Table 2. Lead production and consumption in some industrialized countries (kilotonnes)[a]

Country	Lead ore production (metal content)			Metal production			Consumption (refined metal)		
	1973	1974	1975[b]	1973	1974	1975[b]	1973	1974	1975[b]
EUROPE	1134	1134	1069	2054	2115	1871	2118	2125	1831
Belgium	·	·	·	98	95	103	52	64	54
Bulgaria	105	110	108	100	105	108	80	85	91
Denmark	–	·	·	13	15	13	19	23	20
France	25	24	22	186	178	150	214	199	188
Germany, Federal Republic of	40	35	37	300	319	260	290	260	210
Ireland	53	34	55	·	·	·	1	3	2
Italy	27	24	27	100	112	70	234	242	200
Netherlands	·	·	·	25	26	20	38	41	38
Poland	70	70	72	68	70	66	87	90	40
Spain	64	65	58	120	102	85	121	116	90
Sweden	74	73	69	42	41	37	34	36	32
UK	–	·	·	265	277	229	282	266	238
USSR	570	590	504	640	660	600	600	620	544
Yugoslavia	106	109	117	97	115	130	66	80	84
AFRICA	223	183	178	116	117	93	65	66	75
Morocco	90	86	·	1	1	·	–	–	·
South Africa	63	55	53	64	64	49	27	31	39
AMERICA	1430	1412	1379	1666	1677	1565	1718	1706	1339
Canada	388	314	348	187	127	172	69	63	55
Mexico	168	169	163	177	204	179	88	83	74
Peru	199	201	185	83	80	72	10	9	10
USA	570	616	575	1100	1128	1008	1423	1374	1027
ASIA	273	284	291	413	423	395	457	412	386
Democratic Republic of Korea	90	100	100	60	65	60	20	20	20
Japan	53	44	51	228	228	195	267	217	186
People's Republic of China	130	140	140	125	130	140	170	175	180
OCEANIA	396	360	384	221	225	191	82	79	75
Australia	396	360	384	221	225	191	74	72	68
Other countries	55	53	48	102	108	88	189	203	233
TOTALS	3617	3569	3497	4642	4723	4260	4883	4882	4154

[a] Sources: International Lead, Zinc Study Group, and World Bureau of Metal Statistics.
[b] Estimated.

Table 2 gives the production of lead ore, the total metal production, and the consumption of some industrialized countries.

3.2.3 Environmental pollution from production

Mining, smelting, and refining, as well as the manufacture of lead-containing compounds and goods, can give rise to lead emissions. According to a study of the industrial sources of air pollution by lead in the USA, Davis (1973) reported that 9 % of the total of 18 000 tonnes generated from such sources was attributable to the production of primary lead.

Smelters of lead ores are well known to create pollution problems in local areas. Their influence on the surrounding air and soil depends to a large extent on the height of the stack, the trapping devices in the stacks, the topography, and other local features. The emissions can cover a considerable area. The zone of air pollution for one large smelter in the USA extended to approximately 5 km from the smelter while soil contamination extended as far as 10 km (Landrigan et al., 1975b). The larger area of the zone of soil pollution compared to the zone of air pollution probably was due to the fact that current emission control devices are more effective than earlier ones used to be. The opposite situation was found around the Mežica mine and smelter in Yugoslavia (Djurić et al., 1971; Kerin, 1972, 1973). In this case, the zone of air pollution extended as far as 10 km from the smelter stack. Soil was grossly contaminated (>200 mg/kg) as far away as 7 km. There was also heavy pollution of water courses through effluents.

Secondary smelters producing lead from scrap are comparatively small, numerous, and frequently situated close to human settlements. Several studies showed that pollution in the surroundings of such smelters had been severe enough to produce an increase in the intake of lead by people living nearby (section 5.1.1).

3.3 Consumption and Uses of Lead and its Compounds

Figures for the consumption of lead are available for most industrialized countries. The estimated total world consumption of lead in 1975 was about 4.1 million tonnes (Table 2). The use of lead is greatly influenced by the growth of the automobile industry which in 1974 took about 56 % of total consumption. Table 3 is compiled from statistics of lead consumption for the Federal Republic of Germany, France, Italy, Japan, the United Kingdom, and the United States of America. There has been a notable increase in the consumption for batteries over the period 1969–1974.

3.3.1 Storage battery industry

The manufacture of electric storage batteries is responsible for the largest consumption of lead (Table 3). This industry uses both metallic lead in the form of a lead–antimony alloy, and lead oxides in about equal proportions. The metallic lead is in the grids and lugs, while the oxides, litharge (PbO), red lead (Pb_3O_4), and grey oxide (PbO_2), are used in the active material that is pasted on the plates. The demand for lead batteries

decreased in 1974 and 1975 concommitantly with the decline in total consumption (Table 2) as a result of the economic recession in several of the major lead-producing countries. However, the fall in the demand for batteries has also been attributed to the longer life-time of batteries, (Stubbs, 1975) which in 1967 was considered to be about 29 months (US Bureau of Mines, 1969) but according to Stubbs is, at present, close to 4 years. The battery industry also constitutes the major source of lead for secondary lead production. It has been estimated that up to 80% of the lead in storage batteries is recovered at secondary smelters (Ziegfeld, 1964).

Table 3. Percentage of total lead consumption by different industries in six major industrial countries

Industry	1969[a]	1974[b]
Batteries	35.9	44
Alkyllead	12.0	12.0
Cable sheathing	10.9	9.2
Chemical pigments	10.9	12.0
Alloys	8.1	10.8
Semi-manufacturers	16.5	12.0

[a] Federal Institute for Minerals Research and German Institute for Economic Research, 1972.

[b] Based on data provided by Stubbs, R. L., Lead Development Association, London.

The lead battery is likely to retain its position as a convenient source of electricity in the forseeable future. The nickel–cadmium battery does offer some advantages but is about three times more expensive. Better battery design, improvements in the electrical systems in cars and lower mileages because of higher gasoline costs are factors that may retard the growth rate for lead consumption by the battery industry. New applications for batteries may, on the other hand, increase demand.

3.3.2 Alkyllead fuel additives

Alkyllead compounds have been in use as anti-knock additives in gasoline for almost 50 years. Use of these compounds (almost exclusively tetraethyllead and tetramethyllead) increased steadily up to 1973 (Table 4). In 1973, the world consumption of refined lead for the manufacture of lead additives was about 380 000 tonnes (International Lead and Zinc Study Group, 1976). The moderate decrease in consumption in 1974 was almost entirely attributable to a decrease of 22 000 tonnes in the use of lead for gasoline additives in the USA. A further decline in the consumption was estimated in the USA in 1975, amounting to some 50 000 tonnes (Table 4); thus, the consumption in 1975 declined by 30% in comparison with the 1973 consumption (Stubbs, 1975). In the USA, the manufacture of alkylleads is, after batteries, the largest lead consuming industry. By

Table 4. Consumption of refined lead for the manufacture of alkylleads (kilotonnes)[a]

Country	1972	1973	1974	1975[b]
USA	253	249	227	175
Europe (total)	(87)	(89)	(89)	(91)
France	13	14	14	14
Germany, Federal Republic of	9	9	10	9
Italy	15	12	10	10
United Kingdom	50	54	56	58
Others	n.a.[b]	40[b]	40[b]	35[b]
Total	340	378	357	301

[a] From: International Lead and Zinc Study Group, 1976.

[b] Estimated data; n.a. – not available.

comparison, lead additives make up only 6% of the European market for lead (International Lead and Zinc Study Group, 1973). The decrease in the use of lead for fuel additives is likely to continue in the latter half of the 1970s as more cars fitted with catalysts requiring lead-free gasoline will come into use. The regulations on the maximum permissible concentrations of lead in gasoline will further affect the consumption of lead in fuels. The US Environmental Protection Agency's reduction programme aiming at 0.13 g of lead per litre of gasoline by 1 January 1979 was ratified in March 1976 by the US Court of Appeals. The maximum permissible level in the Federal Republic of Germany has been 0.15 g of lead per litre since 1 January 1976, and in Japan has been, 0.31 g of lead per litre since July 1971. Some European countries introduced limits of 0.4 g of lead per litre (e.g. Austria, Norway, Sweden, Switzerland) but most European governments have deferred their decision because of the economic implications of lowering the lead content (International Lead and Zinc Study Group, 1976).

3.3.3 Cable industry

The relative importance of the cable industry as a lead consumer has declined considerably (Table 3), mainly owing to the introduction of plastic sheathing/insulation. However, the total amount of lead used is still notable (Table 5). The use of lead in cable production is comparatively greater in Europe and several developing countries than in the United States of America. Alloys used for cable sheathing contain small amounts of many other elements including cadmium, tellurium, copper, antimony, and arsenic.

3.3.4 Chemical industry

Although a wide range of lead pigments are still produced they are increasingly being substituted by other, less toxic, pigments. Red lead

(minium) is used extensively in the painting of structural steel work and lead chromate is often used as a yellow pigment. The use of lead for pigment manufacture in 1974 is given in Table 5.

Lead arsenate was, at one time, an important insecticide but is now little used and current consumption figures are not available.

Table 5. Consumption of lead in cables and pigments in five industrial countries in 1974 (kilotonnes)[a]

Country	Cable	Pigments
France	40	32
Germany, Federal Republic of	52	80
Italy	50	47
Japan	21	50
United Kingdom	44	35
Total	205	244

[a] Data from International Lead Zinc Study Group statistics.

The use of lead for the manufacture of alkyllead additives was discussed in section 3.3.2. The petroleum industry also uses a small amount of litharge dissolved in sodium hydroxide solution to remove sulfur compounds in the refining of petroleum.

3.3.5 Miscellaneous

Industries producing semi-manufactured components account for an important proportion of the total consumption. The surface of lead oxidises readily and is then very resistant to corrosion. The building and construction industries use lead sheet for roofing and other flashings, wall cladding, and sound insulation. Lead also forms alloys readily and is used in solder, bearing metals, brasses, type metal, collapsible tubes, and for radiation shielding. The ammunition industry is another major consumer of lead. There are many minor uses of lead compounds but these account for only a very small proportion of total lead consumption.

3.3.6 Environmental pollution from consumption and uses of lead

The combustion of alkyllead additives in motor fuels accounts for the major part of all inorganic lead emissions. The consumption of lead for the manufacture of alkylleads was estimated at 380 000 tonnes in 1973 and 300 000 tonnes in 1975 (section 3.3.2). Of this amount, over 70 % is like to enter the environment immediately after combustion, the rest being trapped in the crank case oil and in the exhaust system of the vehicles (Davis, 1973; Huntzicker et al., 1975). Moreover, part of the lead retained in the lubricating oil will enter the environment through different pathways

(section 3.4). The degree of pollution from the combustion of alkyllead naturally differs from country to country, depending on the car density. The importance of alkyllead combustion is exceptionally high in the USA, where 20 % of the total lead consumed is for the manufacture of alkyllead compounds, the corresponding values in 1969 being only 5 % for France and 11 % for Italy and the United Kingdom. The estimated total world emissions from this source were, according to the figures mentioned above, at least 266 000 tonnes in 1973 and 210 000 tonnes in 1975.

In the study by Davis (1973) on lead emissions into the air from industrial sources in the USA, 11 % (1900 tonnes) was attributed to the processing of alkyllead additives. The manufacture of storage batteries emitted smaller amounts (480 tonnes) and emissions were still smaller in the production of lead oxide, lead pigments, type metal, solder, etc. The amounts of effluent from these industries were not studied. The dispersion of lead through the exhausts of workrooms should also be considered. These emissions although not very large may still contribute significantly to the pollution of the surrounding areas. The possibility of contamination of the home environment through working clothes should be borne in mind.

The magnitude of the pollution arising from the vast number of lead containing items that are subjected to weathering or are decomposed in the course of time is difficult to appraise. According to one estimate, about 50 % of paint is removed from surfaces protected by lead pigments in a period of about seven years before re-painting (Patterson, 1965). Heavy contamination of the dust and soil around houses painted with lead paints has been consistently reported (Ter Haar & Aranow, 1974).

Only an unknown, but probably small fraction of the lead used in metallic form for the production of sheeting, cable, printing metal, etc. is ever released into the environment. Contamination of domestic water supplies, foods, and beverages resulting from the use of lead pipes, PVC pipes, glazed ceramics, and from cans with lead containing solders may under certain conditions be hazardous to man's health (sections 5.1.2 and 5.1.4).

The lead content in tobacco has been attributed to lead residues present in the soils of tobacco fields as a result of the former use of lead arsenate as an insecticide (section 5.1.4).

3.4 Waste Disposal

A substantial part of lead wastes are remelted in secondary smelters (see section 3.2.2).

Municipal incinerators have recently been investigated for lead emissions. An unknown proportion of the non-recycled, lead containing, consumer products, e.g. collapsible tubes, bottle caps, cable scrap, battery casings, and products painted with lead pigments, are incinerated. Depending on the type of furnace and on purification devices, these emissions may be considerable (Davies, 1973; Mattsson & Jaakkola, 1974).

Waste lubricating oil has been contaminated through the combustion of lead alkyls. Over 50 % of the oil is dumped or used as road oil. In 1970, the total amount of waste oil generated in the USA was about 2400 million litres. Waste crankcase oil contains about 1 % lead. Thus, the estimated amount of lead discharged into the environment from this source in the USA was nearly twice the amount originating from, for instance, the production of primary lead (Davis, 1973).

The extent of environmental pollution by lead arising from the incineration of sewage and sludge is not known.

3.5 Miscellaneous Sources of Environmental Pollution

When studying all industrial sources emitting lead into air, Davis (1973) reported that out of a total of 18 000 tonnes, copper smelting accounted for 8 % and the production of steel and iron another 8 %. Smaller amounts were generated in the production of primary zinc and also in the production of cement.

Coal contains small amounts of lead with a wide range of concentrations in different coals. Concentrations found by Abernethy et al. (1969) in coal from various districts in the USA ranged from 0.6 to 33.1 mg/kg. According to Patterson (1965) about 5 % of the ash leaving boilers as stable fly-ash aerosols is made up of small particles of a few micrometres. This silicate matter contains about 100 mg of lead per kg. Large quantities of coal are burnt to produce steam in power stations, steel works, and in manufacturing industries.

Small amounts of lead are generated from burning oil, which also has a very broad range of lead concentrations. The average concentrations in oil appear to be below 0.5 mg/kg (Davis, 1973). The possible future use of sewage sludge as fertilizer is discussed in section 4.

4. ENVIRONMENTAL TRANSPORT AND DISTRIBUTION

From a mass-balance point of view, the transport and distribution of lead from stationary or mobile sources into other environmental media is

mainly through the atmosphere. Large discharges may also occur directly into natural waters and on to the land but, in such cases, lead tends to localize near the points of discharge owing to the very low solubility of the compounds that are formed upon contact with soil and water. The mass transfer of lead from air to other media is as yet poorly defined and the various mechanisms involved in the removal of lead from air are not fully understood. Although some data indicate that an important proportion of the lead may be removed through sedimentation (Atkins, 1969) the most efficient clearing mechanism is probably rain (Ter Haar et al., 1967). In a study of the concentration of lead in rainfall at 32 stations in the United States of America the average was 34 µg/litre (Lazrus et al., 1970). Most of these data were collected in areas with a high population density. Over rural areas of the USA the concentration was found to be approximately 18 µg/litre (Ter Haar et al., 1967).

Lead is rapidly removed from water when it passes through soil and bottom sediments. This is due to the high capacity of organic matters to bind the lead firmly. Because of this clearing mechanism, lead concentrations in both natural waters and water supplies are generally low (section 5.1.2).

Table 6 Distribution of lead from motor vehicles in the Los Angeles basin[a]

Environmental area	Fractional fallout
Retained in car	0.25
Near fallout	0.40
Far fallout	0.08
Airborne	0.24
Unaccounted for	0.03

[a] Adapted from Huntzicker et al., 1975.

An attempt was made to account for the lead emitted by automobiles in the Los Angeles Basin (Huntzicker et al., 1975) which is an area of exceptionally dense motor traffic. Limited environmental monitoring data tended to confirm the approximate correctness of the calculations. The transport pattern was classified as "near fallout", "far fallout" and "airborne". "Near fallout" was defined as the deposition in the immediate vicinity of roadways. "Far fallout" was defined as the fallout away from roadways, but within the basin, and "airborne" designated small particles carried away from the basin and ultimately deposited elsewhere. The data are shown in Table 6 and indicate that most of the emission was deposited within the basin. The fallout figures are calculated from the estimated behaviour of the airborne particles based on particle size distribution. If

these results are approximately valid for other metropolitan areas, soil and water pollution from automobile emission fallout is predominantly limited to the immediate metropolitan area. The particles carried away from the area by air transport are probably widely dispersed and diluted since the atmospheric retention time of small particles is probably fairly long. It has been estimated that the residence time of airborne particles ranges from 6 days to 2 weeks in the lower troposphere and from 2 to 4 weeks in the upper troposphere (SCEP, 1970). Residence time will vary with a number of factors such as wind currents and rainfall. Yamamoto et al. (1968) demonstrated that atmospheric turbidity varied inversely with rainfall, owing to the washout effect of rain.

In spite of the great dilution of airborne lead that occurs during transport from centres of human activity, there is evidence indicating that a long-term global accumulation of lead has occurred. This long-term accumulation has been studied in glacial ice and snow deposits. Studies in Greenland showed that ice formed in about 1750 had lead concentrations 25 times greater than ice estimated to have been formed in about 800 B.C. From 1750, the concentration increased steadily to about 1940. From 1940 to the present day, the rate of increase has risen even more sharply. The most recent ice layers examined (about 1968) had a concentration 400 times greater than the natural background. Similar studies in the region of the Antarctic have also shown a rise, but it has not been so dramatic (Murozumi et al., 1969). Jaworowski (1968) conducted studies of Polish glaciers similar to those conducted in Greenland. He observed an approximate 16-fold increase in the lead concentration over the past 100 years. Chronological increases in the lead content of Swedish mosses have also been reported from 1860 to 1968 (Rühling & Tyler, 1968). These increases, about 4-fold in the past hundred years, were thought to reflect first the increase in coal combustion and later the introduction of leaded gasoline.

The transfer of air lead to the biota may be direct or indirect. For plants, the fallout contribution may be direct via the above ground parts, or it may be indirect by way of the soil. The pattern and degree of lead accumulation appears to be substantially influenced by the state of growth. Mitchell & Reith (1966) found that the lead content of certain plants increased 10-fold or more from the period of active growth to the time when growth ceased in the late fall. Some trees apparently have the capacity to accumulate high concentrations of lead. Kennedy (1960) reported that the tips of larches, firs, and white pines contained 100 mg of lead per kg dry weight, when grown in the lead mining areas of Idaho where the soil lead concentration was 20 000 mg/kg. The total concentration of lead in soil does not correlate well with the concentration in the plant but a correlation

does exist when adjustment is made for the degree to which the soil lead can be brought into an aqueous solution of ammonium lactate and acetic acid (Kerin et al., 1972).

Thus, there is no doubt that plants acquire lead from the soil and air, but interspecies differences are prominent (Dedolph et al., 1970). It does not seem likely, however, that lead deposited on the leaves of plants transfers readily to other parts. Thus, Ter Haar (1970) showed in greenhouse studies that atmospheric lead at 1.45 $\mu g/m^3$ did not influence the lead content of tomatoes, beans, carrots, potatoes, wheat, and cabbage heads, but did have an effect on the lead content of lettuce and bean leaves.

Transfer of lead from plants to animals is not well-defined. However, the concentration of lead in meat and eggs is quite similar, on a wet weight basis, to the concentration found in vegetables and grains (Schroeder et al., 1961). There is no evidence of biological accumulation proceeding from plants to animals.

Much remains to be learned about the environmental transport and distribution of lead. The potential pathways of lead from air to man are indicated in Fig. 1. Special attention should be given to the potential

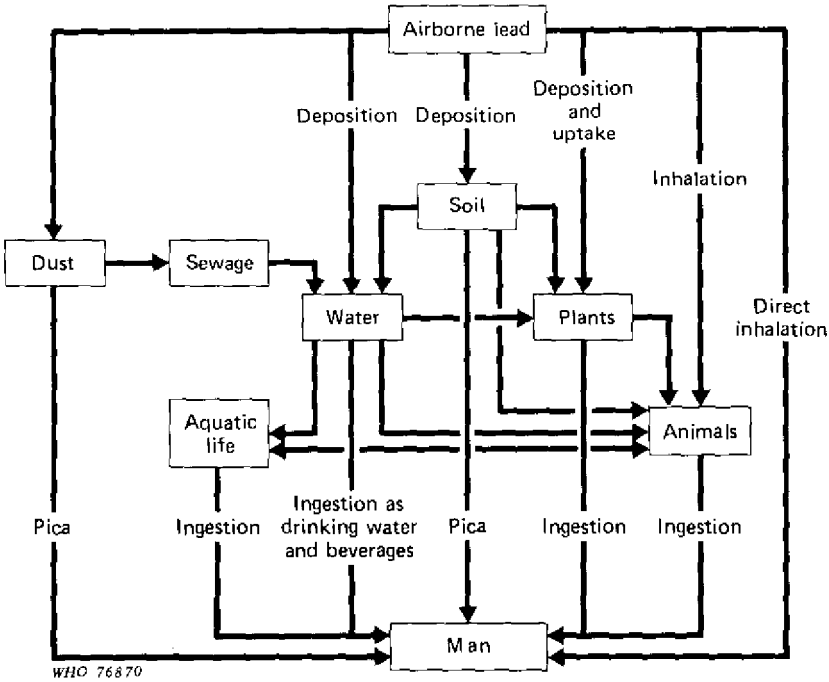

Fig. 1 Contribution of airborne lead to total lead intake.

transfer of the fallout lead in cities that is washed into the sewage systems. Sewage sludge is currently being considered for use as fertilizer. Most cities have dual sewage system, i.e., storm and sanitary sewers, and it was shown in the report of the US Environmental Protection Agency Office of Research and Monitoring (1972) that storm runoff is far from being clean and probably warrants being treated in many instances. However, lead is not currently viewed as a hazard in this case because sludges have a high phosphate content which tends to minimize the bio-availability of the lead for plants (Chaney, 1973).

Little information exists with regard to the biotransformation of lead by microorganisms in the environment. However, Wong and his collaborators (1975) have reported that microorganisms in lake sediments can transform certain inorganic and organic lead compounds into volatile tetramethyllead. The authors were not able to explain completely the pathways of this transformation. A possible mechanism for the conversion of trimethyllead acetate into tetramethyllead in anaerobic systems was presented by Jarvie et al. (1975), who proposed that this takes place through the formation of an intermediate sulfide which decomposes into tetramethyllead. There is need for further research along these lines.

5. ENVIRONMENTAL LEVELS AND EXPOSURES

In the preceding chapter the general pattern of the environmental transport and distribution of lead was described. This chapter is more specifically concerned with the different circumstances under which people are exposed to lead to a degree that may be hazardous to their health.

5.1 Exposure of the General Population

The general population is exposed to lead by ingestion of food, and water, and by inhalation. In addition, children are exposed by eating non-food items, and those working in the lead industries suffer exposure over and above their exposure as members of the general population. These categories of exposure will be considered separately.

5.1.1 Air

The highest concentrations of lead in ambient air are found in dense population centres. The larger the city, the higher the ambient air lead concentration. As one moves away from the centre of the city, the

concentration falls progressively. For urban stations, an average concentration of 1.1 $\mu g/m^3$ has been reported; for non-urban stations (near the city) the average was 0.21 $\mu g/m^3$; for stations somewhat farther removed it was 0.10 $\mu g/m^3$, and for remote areas, 0.02 $\mu g/m^3$ (McMullen et al., 1970). Air over streets with heavy traffic contained more lead than air over streets with light traffic, and considerably more than the ambient air over rural areas.

There is a clear pattern in this picture, the non-urban sites showing less than 0.5 $\mu g/m^3$, while the urban sites have values ranging from 1 to 5–10 $\mu g/m^3$. The highest levels have been recorded on highways during rush hours, 14–25 $\mu g/m^3$ (WHO Expert Committee, 1969).

The results of continuous monitoring for 1971–72, in 27 European cities, by 43 uniform sampling stations are summarized in Table 7 (Commission of European Communities, 1973).

Table 7 Air lead concentrations in some cities of the European Community (1971–72)[a]

Location	Continuous measurements		Traffic-hour measurements	
Non-urban	monthly averages	< 0.5 $\mu g/m^3$	–	
	daily maxima	< 1 $\mu g/m^3$		
Small cities				
residential areas	monthly averages	< 1 $\mu g/m^3$	–	
	daily maxima	< 2 $\mu g/m^3$		
traffic areas			monthly averages	< 3 $\mu g/m^3$
			individual measurements	< 8 $\mu g/m^3$
Metropolitan areas				
residential areas	monthly averages	< 2 $\mu g/m^3$	individual measurements	< 4 $\mu g/m^3$
	daily averages up to	8 $\mu g/m^3$		
traffic areas	monthly averages up to	6.5 $\mu g/m^3$	monthly averages	< 10 $\mu g/m^3$
	daily values up to	10 $\mu g/m^3$	single measurements up to	20 $\mu g/m^3$

[a] Data from the Commission of the European Communities (1973).

The ambient air lead levels at 15 national sampling stations in Japan in 1973 were 0.30 $\mu g/m^3$ for the average 24-hour value, 2.72 $\mu g/m^3$ for the maximum 24-hour value, and 0.01 $\mu g/m^3$ for the minimum (Environment Agency, Japan, 1975).

People who live in close proximity to dense automobile traffic are exposed to appreciably higher concentrations than others. In Los Angeles, California, where general ambient air levels are unusually high, the monthly mean concentration near traffic was as high as 6.4 $\mu g/m^3$ (US Department of Health, Education and Welfare, 1965). This is in contrast to the general ambient air level of 2–4 $\mu g/m^3$ reported for that city (Tepper & Levin, 1972). There is also a diurnal pattern whereby the concentration rises and falls in approximate proportion to the vehicular traffic activity

(US Department of Health, Education and Welfare, 1965; Lahmann, 1969; Heller & Kettner, 1969; Chovin et al., 1973). Most studies report that a seasonal variation also occurs (Tepper & Levin, 1972; Georgii & Jost, 1971).

Nearly all air lead measurements in communities have been made outdoors. Only a small number of indoor concentration studies are available (e.g. Fugaš et al., 1973; Yocom et al., 1971; Daines et al., 1972). Indoor levels vary from slightly lower than, to about $\frac{1}{3}$ of, comparable outdoor levels. Higher indoor levels are found only in lead industry environments. In the absence of specific data, reference should be made to the much more voluminous literature available on the penetration of undifferentiated particulate pollution into buildings. This was reviewed by Benson (1972). In general, very small particles enter buildings readily, and exist there at levels similar to those outside. Larger particles, near stationary sources and very close to roadways, penetrate buildings less readily.

Studies of air lead concentrations over a number of years or even a decade, at the same or similar locations, have produced quite variable results. Occasionally air lead levels have declined as in Cincinnati, Ohio (US Department of Health, Education and Welfare, 1965). This was attributed to greatly decreased coal consumption. The US National Air Surveillance Network, which has most of its stations in city centres, has shown little change in large cities and variable behaviour in smaller cities (NAS-NRC, 1972). Tepper & Levin (1972) and Chow & Earl (1970) have shown considerable increases in air lead levels at a number of stations in large cities. In 1967, Ott et al. (1970) developed a predictive model of increasing automotive pollution based on carbon monoxide emission patterns. Since air lead comes largely from vehicular sources, this report should be considered when changes in air lead with time are evaluated.

The respiratory uptake of lead from air depends on total lead concentration, particle size distribution, particle shape, chemical composition, physicochemical properties, and respiratory volume (section 6.1.1).

The particle size distribution of lead in ambient air has been studied by a number of investigators. As regards pulmonary deposition and absorption, the mass median equivalent diameter[a] rather than the microscopic particle size is considered appropriate. Robinson & Ludwig (1967) reported a mass median equivalent diameter of 0.25 μm, with 25% of the particles smaller than 0.16 μm and 25% larger than 0.43 μm. These data

[a] Mass median equivalent diameter = equivalent diameter above and below which the weights of all larger and smaller particles are equal.

were representative of a variety of areas in Los Angeles, the San Francisco Bay area, Cincinnati, Chicago, and Philadelphia. There was little variation from one city to another. Other studies conducted in the United States of America gave similar results (Mueller, 1970; Robinson et al., 1963). More recently Lee et al. (1972) have reported mass median equivalent diameters of 0.42–0.69 μm for six United States cities. Jost et al. (1973) reported that 50 % of particles had mass median equivalent diameters of less than 0.4 μm and 20 % of more than 0.5 μm.

Not much is known about the chemical form in which general ambient air lead occurs. Ter Haar & Bayard (1971) studied the composition of airborne lead particulates with an electron microprobe analyser. They studied particulates collected directly from the exhaust pipe of a car and also from air at various distances from a busy highway. Their results (Table 8) indicate that car exhaust lead is initially composed of halides that are converted to oxides, sulfates, and carbonates with aging.

Alkyllead vapours occur in ambient air because some of the alkyllead in gasoline escapes combustion. Purdue et al. (1973) have recently reported on the organic lead concentration in an underground parking garage and in the general ambient air of six major cities in the USA. In the parking garage, the total air lead level was 11.7 $\mu g/m^3$, of which 16.7 % was organic lead. In the six major cities, the organic lead concentration was about 10 % of total lead. There is some uncertainty as to the accuracy of the organic lead data since the concentrations found approached the detection limit of the method. In another study in Los Angeles, using a different method for trapping organic lead, approximately 2 % of the lead was found to be organic (Snyder, 1967). Differences found in the concentration of organic lead relative to particulate lead can perhaps be explained in part by differences in proximity to the emitting source. Laveskog (1971) made repeated studies over several months on the presence of organic lead in the air at a number of locations in Stockholm. The levels were uniformly low (under 10 % of the total lead) except for 2 brief periods. These occurred near a gasoline station, and were attributed to the evaporation of spilled fuel. Colwill & Hickman (1973) verified this concept in similar studies near gasoline handling installations.

The air in the vicinity of lead smelters may be appreciably polluted and thus can affect the general population. A detailed study has recently been made of the environmental impact of a large ore smelter near El Paso, Texas (Landrigan et al., 1975b). The annual mean concentration in 1971 was approximately 80 $\mu g/m^3$ in the immediate vicinity of the smelter and fell off rapidly, attaining a near-background level of 1 $\mu g/m^3$ about 5 km away. Approximately 42 % of the particle mass had an aerodynamic diameter of less than 2 μm. In a similar study conducted near a smelter and a mine in

Table 8. Composition of airborne lead particles by electron microprobe analyser.[a]

Sample	Percentage of total particles counted						
	$PbCl_2$	$PbBr_2$	PbBrCl	Pb(OH)Cl	Pb(OH)Br	$(PbO)_2PbCl_2$	$(PbO)_2PbBr_2$
Exhaust pipe							
Zero time	10.4	5.5	32.0	7.7	2.2	5.2	1.1
18 h	8.3	0.5	12.0	7.2	0.1	5.6	0.1
Eight Mile Road							
Near road	11.2	4.0	4.4	4.0	2.0	2.8	0.7
400 yards	10.5	0.7	0.6	8.8	1.1	5.6	0.3
Rural site	5.4	0.1	1.6	4.0		1.5	-

Sample	Percentage of total particles counted						
	$(PbO)_2PbBrCl$	$PbCO_3$	$Pb_3(PO_4)_2$	PbO_2	$(PbO)_2PbCO_3$	$PbO\,PbSO_4$	$PbSO_4$
Exhaust pipe							
Zero time	31.4	1.2	-	2.2	1.0	-	0.1
18 h	1.6	13.8	-	21.2	29.6	0.1	-
Eight Mile Road							
Near road	2.0	15.6	0.2	12.0	37.9	1.0	2.2
400 yards	0.6	14.6	0.3	25.0	21.3	4.6	6.0
Rural site	1.0	30.2	-	20.5	27.5	5.0	3.2

[a] From: Ter Haar & Bayard (1971).

the Meža Valley, Yugoslavia, the air lead concentration, 10 km away, ranged from 1.3 to 24.0 μg/m^3 (Djurić et al., 1971). Five air sampling stations were located at various distances within 10 km of the smelter stack. About 45 % of the particles had a diameter equal to or less than 0.3 μm and an additional 25 % were in the range of 0.31–0.8 μm. Although not specified, it is probable that these particle sizes were expressed as aerodynamic diameters, since the authors refer to this range as being of optimum size for absorption. The extensive pollution in some directions was probably due to the topography. The Meža Valley is only a few hundred metres wide and depending on wind direction, the lead particles can be conveyed long distances.

Roberts et al. (1974) reported the lead levels in air, dust, soil, and in the blood of children living near two secondary smelters in Toronto. Monthly mean air lead levels (1.0–5.3 μg/m^3) were about twice those encountered in other parts of the city, but were subject to greater daily variation. Lead levels in dustfall of 200–1500 mg/m^2/month, and soil levels of 16 000–40 000 mg/kg of soil near the smelter declined to background levels within 300–400 m of the stacks. From 13 to 30 % of the children living within 300 m of the stacks had blood lead levels of over 40 μg/100 ml.

Pollution of the surrounding country by a secondary lead smelter has been reported to have affected the lead absorption of adults living 1–4 km from the main emitter (Nordman et al., 1973). Air lead concentrations were not reported. The dustfall lead concentrations ranged from

10 mg/m²/month (4 km from the chimney) to 200 mg/m²/month (200 m from the chimney). There was a correlation between blood lead concentration and degree of erythrocyte ALAD inhibition on the one hand and the proximity of habitation to the smelter on the other. A correlation between Pb-B values and monthly dustfall lead was also demonstrated.

5.1.2 Water

Man's exposure to lead through water is generally low in comparison with exposure through air and food (WHO Working Group, 1973). The lead concentration in the water supplies of most of the 100 largest American cities, as determined in 1962, ranged from a trace to 62 µg/litre (Durfor & Becker, 1964). Since 1962, continuous monitoring of American water supplies has indicated that the US Public Health Service prescribed limit of 50 µg/litre has not been exceeded (NAS-NRC, 1972). In another study, only 41 out of 2595 samples of tap water contained more than 50 µg/litre, and 25% contained no measurable amount of lead (McCabe, 1970).

Under some circumstances, the concentration of lead in drinking water can become extremely high. Gajdos & Gajdos-Török (1973) described two cases of severe clinical lead poisoning attributable to a municipal water supply that contained lead levels of 2.6 mg/litre. In another case, in rural Scotland, four people developed clinical lead poisoning and others showed biochemical evidence of grossly elevated lead exposure (Goldberg, 1974). The concentration of lead in the domestic water supply was 2–3 mg/litre. In this case, the reason for the extreme contamination was that the water was stored in lead tanks. In another study, conducted in Glasgow, Scotland, it was shown that lead pipes in the plumbing of homes can also result in high concentrations of lead in soft water (water low in calcium and magnesium) (Beattie et al., 1972a). Homes with both lead-lined water storage tanks and lead pipes had the highest concentration. The plumbosolvency of water standing in lead pipes is influenced significantly by several factors. The solvency increases about four-fold with increasing acidity over the pH range from 6 to 4. Increases of a somewhat lesser degree were also noted with increasing alkalinity over the range of pH from 8 to 10 (Moore, 1973). The same author also pointed out the increasing plumbosolvency of water with increasing temperature and with decreasing calcium concentration. Quite recently it was shown that lead concentrations in tap water were highly dependent on the volume of water flushed through the system before sampling. The concentrations were also considerably lower when a 95/5 (tin/lead) solder had been used in the copper piping instead of the 50/50 or 60/40 solders (Wong & Berrang, 1976).

When water was left standing overnight in plastic pipes, some degree of leaching of lead into the water was observed (Heusgem & DeGraeve, 1973).

The source of lead in this case was probably lead stearate which is used as a stabilizer in the manufacture of polyvinyl plastics. The problem of plastic pipes has been discussed recently (Schaller et al., 1968; Packham, 1971). Packham did not feel that there was a hazard associated with the use of such material in domestic water supply systems. But more study is needed, particularly of situations in which water stands in the pipes for prolonged periods.

Lead levels in surface and ground waters were recently reviewed by a WHO Working Group (1973). Natural surface waters have been reported to contain usually less than 0.1 mg/litre (Kopp & Kronen, 1965). In unpolluted areas the concentrations are of the order of 1 μg/litre or less (Žukovickaja et al., 1966). Some rivers in France were recently analyzed by Servant (1973) who found that, in the Midi-Pyrenees region, the mean concentration of dissolved lead varied from 6.7 to 10.4 μg/litre.

5.1.3 Food

The contribution of food to man's exposure to lead has been under study for many years, beginning with the study of Kehoe et al. (1933) who found lead in every item of food in both industrial and primitive societies. The concentration of lead in various items of food is best described as highly variable. In fact, there seems to be about as much variation within specific items of food as between different categories of foods. For example, Schroeder et al. (1961) found that the range was 0–1.5 mg/kg for condiments, 0.2–2.5 mg/kg for fish and seafood, 0–0.37 mg/kg for meat and eggs, 0–1.39 mg/kg for grains, and 0–1.3 mg/kg for vegetables.

Estimates of actual consumption of lead in food and beverages have been made using two general approaches. Some investigators have used the duplicate portions sampling method. Others have derived theoretical intakes based on nutritional tables and known concentrations of lead in the dietary components (composites technique, see section 2.2.1). The results of studies using the two methods are given in Table 9. In general, the composites technique appears to yield somewhat higher mean values for adults than the duplicate portion technique. There are considerable differences in the daily intakes reported from different countries. Whether these differences are real or due to factors associated with the methods used remains to be assessed. Inadequacies in sampling and in the analytical methods used may account for a considerable part of the differences; few of the studies cited present any evidence of interlaboratory quality control of the analytical assays. Most estimates do not specify the age, sex, or level of physical activity assumed in arriving at the estimates. These are very important determinants of dietary intake. Thus, the calorie requirement

for a 25-year-old male in the United States of America is approximately 2900 calories, whereas it is only 1900 calories for women, age 35–55 (Altman & Dittmer, 1968). Horiuchi et al. (1956) were quite aware of the vast differences in food intake among different categories of adults and between adults and children. They made an effort to take these factors into account in developing their estimates of lead intake from dietary sources.

Daily faecal lead excretion can also be used as a means of estimating daily lead ingestion, since only approximately 10% of dietary lead is absorbed (Kehoe, 1961). This approach, which was used by Tepper & Levin (1972) (section 6.1.2.2), presents some uncertainty regarding actual absorption and neglects contributions to faecal lead from gastrointestinal secretion, which cannot be estimated.

A factor that is usually ignored is the occurrence of lead in various foods at concentrations below the practical detection limits. Thus, Kolbye et al. (1974) arrived at different estimates based on the assumptions they made regarding whether or not lead was present in all items eaten. There was uncertainty as to how to cope with the problem of lead concentrations reported as "zero" or "trace" in certain samples. When "zeros" and "traces" were accepted as meaning absolutely no lead, the estimated daily lead intake was 57.4 µg for an 18-year-old man. This seemed unduly low, particularly in the light of the fact that the faecal lead excretion of normal American women is 90–150 µg/day (Tepper & Levin, 1972). Certain assumptions were therefore made regarding the "zeros" and "traces". If it was assumed only that "traces" really represented 0.09 mg/kg, the

Table 9. Dietary lead intake.

Method	Age	Sex	Activity	Lead/day (µg)		No. of subjects	References
				range	average		
Duplicate portions	adult	male	sedentary	120–350	218	9	Kehoe, 1961
	adult	male	sedentary	74–216	113	17	Coulston et al., 1972[a]
	21–30 years	4 male 1 female	—	237–306	274	5	Thompson, 1971
	adult	—	—	4.8–83.0	17.8	—	Schutz et al., 1971
	adult	male	medium–heavy	119–360	231	35	Nordman, 1975
	adult	female	medium	89–305	178	36	Nordman, 1975
	3 months–8.5 years			—	40–210[b]	8	Alexander et al., 1973
Composites technique	adult	male	heavy work	—	455	-	Horiuchi et al., 1956
	adult	male	medium	—	299	—	Horiuchi et al., 1956
	10 years	male		—	254	—	Horiuchi et al., 1956
	10 months	male		—	126	—	Horiuchi et al., 1956
	18 years	male	medium	—	57–233[a]	—	Kolbye et al., 1974
	adult	male	medium	—	139	-	NRC (Canada), 1973
	adult	male	medium	—	518	—	Lehnert et al., 1969
	adult	male	medium	—	505	-	Zurlo et al., 1970

[a] See page 52
[b] Ranging from 40 µg in a breast-fed infant to 210 µg in an 8½-year-old child, as calculated using ICRP.

calculated intake became 159 μg/day. When the additional assumption was made that "zero" had a finite value of 0.05 mg/kg, the calculated daily intake of an 18-year-old male became 233 μg. Another source of error in establishing how much is consumed relates to food preparation. Lead may be either added to the diet or removed in the course of preparation. Both Horiuchi et al. (1956) and the report from the British Ministry of Agriculture, Fisheries and Foods (1972) took special pains to explain how this problem was handled.

Published reports on lead levels in wine (Truhaut et al., 1964; Zurlo & Griffini, 1973) show that important variations occur from sample to sample. Considering ordinary wines there does not seem to be any significant difference between white, red, and rosé (Truhaut et al., 1964). Average lead concentrations of 130–190 μg/litre could be calculated (range 60–255 μg/litre), but even higher mean values (299 μg/litre) have recently been reported (Boudene et al., 1975). Wine therefore is likely to be a substantial source of lead for some people, and may account for part of the differences in Pb-B levels (section 5.4) and in daily dietary lead intake between various countries.

The concentration of lead in milk is a matter of special concern because milk is a major dietary constituent for infants. Human breast milk has been reported to contain 12 μg/litre (Murthy & Rhea, 1971) and < 5 μg/litre (Lamm & Rosen, 1974). Cow's milk has been reported to have a similar concentration, when taken directly from cows for analysis; 9 μg/litre (Hammond & Aronson, 1964). The concentration of lead in processed cow's milk is higher than in human milk or in milk obtained directly from cows. The types of processing vary considerably as does the degree of apparent lead contamination. Thus whole milk concentrations are only moderately elevated. Mitchell & Aldous (1974) reported an average of 40 μg/litre in whole bulk milk and Kehoe (1961) reported 20–40 μg/litre for local USA market milk. By contrast, evaporated milk and formulas have still higher concentrations. Mitchell & Aldous (1974) reported an average of 202 μg/litre for evaporated milk. Somewhat higher values were reported by Murthy & Rhea (1971) (330–870 μg/litre) and somewhat lower by Lamm & Rosen (1974) (110 ± 11 μg/litre).

A major contribution to the lead content of processed milk as well as of other food products appears to be lead solder used in the seams and caps of cans. It has been shown that foods preserved in such cans frequently have much higher concentrations of lead than do the same items packed in glass containers (Mitchell & Aldous, 1974).

Although plants do not take lead up from the soil readily, fruits and vegetables grown in areas exposed to smelter emissions may be appreciably contaminated. Kerin (1972) determined lead in the total diet of peasants

near a smelter and found that the daily ingestion of lead with food was 670 - 2640 µg.

5.1.4 Miscellaneous

The intake of lead in food, air, and water is a major concern as regards the general population because of the pervasive nature of these exposures. Another frequent exposure source, smoking, probably makes a small contribution to the lead burden (section 5.4.1). However, surprisingly little information is available concerning the concentration of lead in smoking tobacco. Cogbill & Hobbs (1957) reported the concentration of lead in two separate brands of cigarettes and in a composite sample of five brands. Concentrations were 19, 80, and 39 mg/kg at 58 % relative humidity or 21, 84, and 41 µg per cigarette. The amount of lead transferred to mainstream smoke was 1.0, 3.3, and 1.9 µg per cigarette which represented 4.8, 3.9, and 6 % transfer. Arsenic/lead ratios found in the tobacco indicated that the source of lead was probably lead arsenate. At one time lead arsenate was used extensively as an insecticide in American tobacco fields but other pesticides rapidly replaced it shortly after World War II. Residues of lead arsenate have probably persisted in the fields and could contaminate plants externally. More recently, Szadkowski et al. (1969) reported 0.483 ±0.267 µg of lead per cigarette in the total smoke for eight brands of cigarette. This represented 19 % of the total lead in the tobacco or 2.6 µg per cigarette. No distinction was made between mainstream and sidestream smoke[a]. Untabulated data from a study by Menden et al. (1972) indicated that only about 2 % of lead in non-filter types of cigarettes was transferred to the mainstream smoke. The average content of lead in commercial cigarettes was given as 10.40–12.15 µg/cigarette (Petering & Menden, private communication). Most of the lead was found in the ash; the lead content of the sidestream of individual cigarettes varied considerably with a maximum value of 16 %. Assuming an average lead content ranging from 2.5 to 12.2 (Lehnert et al., 1967; Szadkowski et al., 1969; Rabinowitz, 1974; Petering & Menden, private communication) and a 2 % transfer to the mainstream smoke (Menden et al., 1972) are fair estimates, and without taking into account the possible contribution from the sidestream smoke, a crude assessment of the direct inhalation intake of lead from smoking 20 cigarettes a day would be about 1–5 µg.

Certain other sources of exposure are important. These sources do not affect any major segment of the population but collectively they no doubt

[a] i.e. the smoke which drifts off the burning end of cigarette between puffs.

account for the majority of the cases of clinical lead poisoning in the general population.

The presence of high concentrations of lead in illicitly distilled whisky occurs commonly in the USA and causes poisoning in adults. The condensers used in homemade stills are often discarded automobile radiators. These contain substantial amounts of lead in the soldered joints. The concentration of lead in the final product frequently exceeds 10 mg/litre. The problem of lead poisoning from this source exists predominantly in the southeastern parts of the USA where illicit whisky production is most common.

Another source of poisoning is improperly glazed earthenware vessels. Improper glazing results in the leaching of lead into the vessel, particularly when the contents are acidic. Cases of poisoning, both fatal and non-fatal, have been recorded from the use of improperly glazed pottery. Klein et al. (1970) reported two cases (one fatal) in which apple juice stored in the incriminated vessel for 3 days contained 1300 mg/litre. In another case the ceramic mug responsible was used for drinking cola[a], pH 2.7 (Harris & Elsea, 1967). After two hours of standing in the mug, the cola contained lead levels of 6.8 mg/litre. It was estimated that this patient drank 3.2 mg of lead per night in this fashion for two years. Other cases have been reported from Yugoslavia (Beritić & Stahuljak, 1961) and from the United Kingdom (Whitehead & Prior, 1960). The problem involves the storage of acid materials in the vessels. In a test of the leaching of lead from commercial and handcrafted pottery, Klein et al. (1970) found that 4% acetic acid allowed to stand at room temperature in the vessels for 18 hours often acquired concentrations of lead in excess of 100 mg/litre. In fact, in more than half of the cases, the concentration of lead exceeded 7 mg/litre.

Another source of lead poisoning in the general population is the use of discarded storage battery casings for fuel. There is some uncertainty as to whether the cases of poisoning that have been recorded (Williams et al., 1933; Gillet, 1955) were due to inhalation of lead fumes or to hand-to-mouth transfer of fallout material. The prevalence of children in the number of recorded cases supports the argument for hand-to-mouth transfer.

Because of the wide variety of applications of lead, additional potential hazards are still being identified. For example, the use of lead wire core wicks in candles was only recently called to the attention of the USA authorities (Bridbord, unpublished results, 1973).

[a] A popular carbonated non-alcoholic beverage.

5.2 Exposure of Infants and Young Children

5.2.1 Soil, dust, and paint

The young child of pre-school age is exposed to special hazards from environmental sources of lead. This is because such children frequently exhibit the habit of licking, chewing, or actually eating foreign objects. Lead-based paints have long been considered the major source of excessive lead intake in young children. Thus, Sachs (1974) reported that 80% of patients seen because of evidence of excessive lead absorption had a history of eating paint or plaster and in another 10% X-ray examination revealed paint in the abdomen. The author also was of the opinion that if X-ray examinations had been repeated at each visit to the clinic, evidence of paint ingestion would have appeared in all patients. A similar view was expressed by Chisholm & Harrison (1956). In their series of 105 children whose homes were investigated, 102 of the homes contained at least one source of paint containing 5% lead or more. Of even greater significance was the fact that the painted surfaces identified as sources were flaking.

Other investigators have attempted to assess the importance of paint as a source of excessive lead exposure. Griggs et al. (1964) found a positive correlation between the presence of elevated urinary lead or coproporphyrin and the presence of flaking paint in the homes. Nonetheless, in many instances the homes of children with abnormal urine had no flaking paint indoors. Unfortunately data were not given as to the number of children with abnormal urine and no evidence of flaking paint indoors or outdoors. Guinee (1973) reported that in an extensive survey of the homes of children having blood lead concentrations equal to or greater than 60 μg/100 ml, 75% of the homes had at least one surface in which the paint contained more than 1% lead. Furthermore, children with elevated blood lead concentrations were more likely to live in homes where the painted surfaces were cracked than children with low blood lead values.

All of these studies indicate that lead in painted surfaces in houses is almost certainly the major source of lead for infants and young children. Some other studies suggest that the issue is not that clear-cut. Greenfield et al. (1973) reported that, in one study, 18 out of 19 rural children with elevated blood lead concentrations lived in homes having at least one accessible painted surface containing 1% or more of lead, whereas paint containing 1% or more of lead could be found on accessible surfaces in only 60% of the homes of inner city children with excessive lead exposure. The implication is that sources of lead other than paint were often responsible for the exposure of city children. Two equally rational interpretations are that an insufficient number of surfaces were tested in the

children's homes or that children often spend time in several homes, some of which might not have been tested for lead-based paint.

Studies of sources of lead all too often ignore the fact that painted surfaces on the outside of houses are a potential source of lead or, for that matter, that the soil surrounding the houses may have accumulated substantial concentrations of lead from the weathering of outer walls. With regard to the latter, Fairey & Gray (1970) reported that the concentration of lead in the soil near homes where paediatric lead poisoning had occurred was over 1000 mg/kg in 27 out of 30 cases. By contrast, only 30 out of 170 soil samples taken from yards selected at random (and not associated with cases of lead poisoning) had concentrations of lead in excess of 1000 mg/kg. Bertinuson & Clark (1973) have reported extremely high soil lead values close to residences in the older section of Cincinnati. In one case, because the distance across the yard from the base of the house to a road with heavy traffic was sufficient, it was possible to assess the relative contributions of lead from car exhaust and lead from the weathering of the house. The gradient ranged from 12 000 mg/kg adjacent to the house, down to 400 mg/kg, about 10 m from the road. This suggested that weathering of painted surfaces of the house could have been the major source of soil lead in this instance. Although the high concentrations of lead in the soil in the vicinity of houses may be due to weathering of lead-based paint, it is possible that in many cases it is also due to the accumulation of combusted alkyllead from car exhaust. In this connexion, recently-reported data of Ter Haar & Aranow (1974) are particularly informative. They surveyed the profile of lead in soil, extending from the base of 36 urban residences out to the street gutters. Eighteen of the residences were of brick construction and 18 were of frame construction. In summary form, their data were as shown in Table 10. The data reflect the likelihood of the major contribution of

Table 10. Lead in dirt in Detroit (mg/kg dry dirt)[a]

Location	Painted frame houses		Brick houses	
	Mean	Range	Mean	Range
Within 0.6 m of house				
front	2349	(126–17590)	351	(78–1030)
back	1586	(162–4951)	501	(72–2350)
sides	2257	(140–7284)	426	(91–1160)
	1846	(104–7000)	595	(40–2290)
3 m from house				
front	447	(58–1530)	156	(39–316)
back	425	(149–1410)	200	(72–480)
Near sidewalk	627	(152–1958)	324	(86–1130)
curb	572	(320–1957)	612	(147–2420)
gutter	966	(415–1827)	1213	(304–3170)

[a] Adapted from Ter Haar & Aronow (1974).

weathered lead-based paint to soil lead. But they also strongly suggest that vehicular sources make a significant and sometimes very substantial contribution to soil lead near the sidewalks.

Street dust has also been found to contain high concentrations of lead. Using recent data from 77 midwestern cities in the USA, it was calculated that the concentration of lead averaged 1636 mg/kg dust in residential areas, 2413 mg/kg in commercial areas, and 1512 mg/kg in industrial areas (Hunt et al., 1971).

In order for soil or street dust to be a significant source of lead for man, it is, of course, necessary that it be ingested and/or inhaled. Evidence regarding the likelihood that young children would ingest soil or street dust is extremely fragmentary. However, in a recent study of 58 children with increased lead burdens, it was found that 37 had a history of eating dirt and sand, compared with 34 eating plaster, 20 eating paint flakes, 15 chewing on furniture, 14 chewing window sills, and 7 eating wallpaper (Pueschel et al., 1972). Further inferential evidence as to the possible significance of soil and dust as a source of lead is to be found in the recent Smeltertown episode near El Paso, Texas, referred to earlier (Landrigan et al., 1975b). This town is the site of a large smelter which processes lead ores, among others. The young children in the town have high blood lead concentrations. In a sample of 14 children of 1–5 years of age, 78.6–100% were found to have lead concentrations equal to or greater than 40 μg/100 ml blood. The concentration of lead in the surface soil of Smeltertown has a median value of 3700 mg/kg. One is tempted to conclude that the blood lead levels of these young children increased owing to ingestion of this soil. However, the picture is somewhat confounded by the fact that older children also showed a high incidence of elevated blood lead concentrations but to a lesser degree; and older children are not generally considered to exhibit pica. Smeltertown adults had normal blood lead concentrations. Intake of lead by inhalation would probably have affected adults as well as children. Thus, it is likely that lead intake by the children was by direct oral intake. The painted surfaces in the residences were seldom in a flaking condition and were not found to be more than two or three layers thick, in contrast to the multiple layers usually found in city slum areas where lead poisoning is prevalent. The information available therefore suggests that the sources of lead were soil and dust. Indeed, there was a highly significant correlation between the concentration of lead in the blood of the children and the concentration of lead in household dust.

The presence of high concentrations of lead in soil is not necessarily hazardous. Thus, children living on soils containing lead levels of up to 8000 mg/kg showed only minimal elevations in blood lead concentration (Barltrop et al., 1974). This was found to be so even among the children

with pica for soil. Perhaps climatic differences are important. Smeltertown in Texas is extremely dry and dusty whereas the region studied by Barltrop and coworkers was in England, where the soil is presumably not as accessible to children owing to the relatively heavy cover of vegetation. The play behaviour of children also determines to a certain extent their exposure to lead (Einbrodt et al., 1974).

Since dust and dirt occur indoors as well as outdoors, some attention has been directed recently to the significance of indoor dust. Transfer of lead-bearing house dust to the hands of young children has recently been demonstrated (Sayre et al., 1974). The house dust of inner city old houses contained far more lead than the dust of newer, suburban houses. Furthermore, the hands of the children in inner city houses were heavily contaminated with lead, whereas the hands of suburban children were not. It is not at all certain that the source of lead in the house dust was fallout from car exhaust. New housing in the inner city had very little lead in dust. The inference is that the lead was probably from the painted surfaces, since the paint in old houses has high concentrations of lead whereas the paint in new houses in the same area generally has a low lead content. But even the presence of lead-containing dust on children's hands provides little information concerning hazard since the critical question is how much is actually transferred from the hands to the digestive tract.

5.2.2 Miscellaneous

Facial cosmetics have long been a source of lead poisoning in Oriental countries. Kato (1932) discussed the problems encountered in Japan. Face powders, pastes, and liquids were found to contain as much as 67% lead. Exposure of children was considered to be by inhalation of powders, or ingestion of powders and other formulations. More recently, there have been several reports of infant poisoning from a mascara-like cosmetic used by Indian and Pakistani women (Warley et al., 1968; Alexander & Delves, 1972). This substance may contain as much as 88% lead sulfide.

Another source of lead exposure for young children is coloured newsprint (Hankin et al., 1973). It has been found that the coloured inks used in magazine illustrations contain extremely high concentrations of lead. Coloured pages were found to have lead concentrations of 1140–3170 mg/kg.

Children and other family members may be exposed to lead contamination at home by work clothing being worn at home or brought home for cleaning, or by small pieces of metal which may be brought in (Inter-Departmental Working Group on Heavy Metals, 1974).

5.3 Occupational Exposures

It is among the workers who smelt, refine, and use lead in manufacturing items of commerce that the highest and most prolonged exposures are found. Lead poisoning among these people was common at one time. Today, workers, management, and physicians are generally aware of the danger of lead and know how to handle the problem; so, the incidence and severity of poisoning have decreased substantially in recent years. However, much still remains to be done to eliminate lead poisoning completely as an occupational disease. The major hazard today seems to be in small enterprises (Engel et al., 1971) and in some large industries where adequate industrial hygiene programmes do not exist or are difficult to implement, or where awareness of the existence of hazardous circumstances may be lacking.

A recent WHO study of occupational health problems in the Andean countries (El Batawi, unpublished results, 1974) showed that, in Chile for instance, among 580 workers exposed to lead, 21.9 % had an increased level of ALA in the urine. In Colombia, 3370 workers exposed to lead were examined, of whom 4.3 % were considered to be suffering from lead poisoning.

The major route of lead exposure in industry is by inhalation. The generation of lead-bearing dusts and fumes is inevitable. The workers' clothes may also be an important source of exposure. Even the lesser problem of oral intake of lead is really a consequence of the generation of airborne dusts which settle out from the air on to food, water, or other objects that are transferred to the mouth in one fashion or another. Thus, good housekeeping and, above all, good ventilation have a strong impact on exposure. An industrial process may be quite safe in one factory and quite hazardous in another solely because of differences in ventilation engineering or because of differences in housekeeping practices and worker education.

5.3.1 Lead mining, smelting, and refining

The lead mining hazards depend, to some extent, on the solubility of the lead from the ores. The lead sulfide (PbS) in galena is insoluble and absorption through the lung is slight. However, in the stomach, some lead sulfide may be converted to slightly soluble lead chloride which may then be absorbed in moderate quantities.

The process of lead smelting and refining probably has the greatest potential for hazardous exposure of all the lead industries. The most

hazardous operations are those in which molten lead and lead alloys are brought to high temperatures, resulting in the vaporization of lead. This is because condensed lead vapour has, to a substantial degree, a small (< 5 μm), respirable particle size range. Thus, although the total air lead concentration may be greater in the vicinity of ore proportioning bins than it is in the vicinity of a blast furnace in a primary smelter, the amount of particle mass in the respirable size range may be much greater near the latter.

As an example, we can consider the processes involved in the preparation of lead bullion in typical primary lead ore smelters in Salt Lake City, Utah. The various processes are essentially grinding and smelting. The main operations are: (1) ore proportioning; (2) nodulizing and sintering; (3) blast furnace; (4) drossing and reverberation. Air lead concentrations have been determined using personal monitors worn by workers at the various stations. These data are summarized in Table 11.

Table 11. Air lead concentrations in three primary lead smelters (μg/m³)[a]

Smelter	Year	Location[b]	Means[c]	Mean of means	Range (all values)
A	1972–75	(1)	610, 1930, 2860	1800	250–3670
		(2)	970, 470, 450	630	250–1380
		(3)	860, 950, 320	710	200–1700
		(4)	1220, 350, 950	840	260–1640
B	1973–74	(1)	1310, 2330, 4720	2790	370–5160
		(2)	2740, 3460, 770	2320	310–7570
		(3)	860, 140, 530	510	120–1560
		(4)	1270, 540, 5730, 4050	2900	60–7220
C	1973–74	(1)	--	-	-
		(2)	3850, 8740, 830	4470	< 10–31 200
		(3)	1320, 230	780	90–1340
		(4)	80	80	

[a] Data provided by M. Varner, American Smelting and Refining Co., Salt Lake City, Utah, U.S.A.

[b] Locations: (1) Ore proportioning; (2) nodulizing and sintering; (3) blast furnace; (4) drossing and reverberation.

[c] Determined with personal monitors on separate occasions. Each sampling period was 5–7 hours.

Similar data for primary lead smelters elsewhere are not available. However, it is evident that lead exposure in primary smelters may be extremely high. The hazard to the workers in the example cited would be extremely serious were it not for the fact that the use of respirators is mandatory in these particular smelters.

Comparable data are not available for exposures in secondary smelters. Secondary smelters are to be found in or near most large cities. They depend on the local supply of lead scrap in the form of discarded electric storage batteries, cable casings, pipes, and other materials for their supply

of lead. The nature of the operation is similar to the one described for primary smelters, except that no ore-processing is involved. Tola (1974) has recently reported on hazards in secondary lead smelters in Finland. The work practices involved were not described. Thus, it was not indicated whether or not these workers wore respirators on the job. But whatever the work practices may have been, they were not adequate. Out of 20 smelters and founders, 16 had blood lead concentrations equal to or greater than 70 μg/100 ml.

Foundries in which molten lead is alloyed with other metals have also been sources of high atmospheric exposure. In one such operation the concentration of lead was 280–290 μg/m^3 (Berg & Zenz, 1967).

5.3.2 Electric storage battery manufacturing

The electric storage battery industry has been studied fairly carefully with reference to the nature and degree of lead exposure.

Within the manufacturing process, there are numerous specific operations that are hazardous by virtue of the resultant high air lead concentrations. Plate casting is a molten metal operation. The hazard here is from spillage of dross, resulting in dusty floors. Mixing of lead oxide paste runs parallel to grid casting. Here, as in subsequent operations, the major hazard is from lead oxide dust, particularly when loading the mixer with lead oxide powder. Ventilation is needed during loading and frequent clean-up is necessary to prevent the accumulation of dust. Pasting of the plates follows, either by hand or by machine. In either case the hazard is from dust which accumulates as the paste dries. The plates are then cured, oven dried and removed for the forming process. Although the plates must be welded into circuits, the temperature is not high enough to generate

Table 12. Air lead concentrations (μg/m^3) in electric storage battery manufacturing

Operation	Elkins, 1950[a]	Tsuchiya & Harashima, 1965[b]		Williams, et al., 1969[c]		Engels & Kühnen, 1973[d]	
	mean	mean	range	mean	S.E.	mean	range
Oxide mixing	730	2000	250–13 000			5400	180–21 600
Plate casting	260	500	200–620	50	3		
Pasting, hand	750			150	29	710	100–2700
Pasting, machine				220	25	1100	80–13 500
Forming				130	13	220	30–2200
Stacking and breaking	500					880	110–4500

[a] Air sampling time not stated.
[b] Personal air samplers worn for full work shift for 2 weeks
[c] Air sampling time 40–60 minutes.
[d] Approximations derived by collation of various sub-categories from authors' data.

significant concentrations of lead fumes. Once more, the main problem is lead oxide dust, although the amount of handling involved generally does not require ventilation. After another drying process, the plates are stacked to make elements, either by hand or machine. In both cases the process is dusty and ventilation is needed, but particularly with machine stacking. The stacks are then burned to weld together the positive and negative lugs. This is done in a ventilated burning box. Final assembly and finishing are low-hazard operations that do not require ventilation if conducted with care.

Reports have appeared concerning the air lead concentrations associated with the various phases of battery manufacture. The data summarized in Table 12, show that oxide mixing is probably the most hazardous occupation, followed by machine pasting, assuming that the same accumulative time is spent at each activity. This conclusion is borne out by the result of a recent study. The blood lead concentration was found to be most elevated and the erythrocyte ALAD activity was most depressed among men engaged in oxide mixing and pasting (Tola et al., 1971).

The data cited above for air lead concentrations in the lead smelting and refining industry and in the electric storage battery industry may not of course be wholly representative of these industries. But they are sufficiently alarming to suggest that respirators must be worn in most of these operations, as indeed they were in the case of the smelters from which the data were gathered.

5.3.5 Shipbreaking and welding

Any process in which lead-containing metals are heated with torches to high temperatures are potentially hazardous. This is due to the formation of lead fumes with a high fraction of the airborne mass existing in the respirable particle size range. As an example, steel structures are coated with lead-based paint prior to final assembly. Thus, Tabershaw et al. (1943) found the average air lead concentration in the breathing zone of welders of structural steel to be 1200 $\mu g/m^3$. Welding can also be a hazard on occasion, when the coating is so-called zinc silicate, since zinc silicate can contain substantial concentrations of lead. Welding of zinc silicate-coated steel can give rise to breathing zone concentrations of lead far in excess of 150 $\mu g/m^3$, the current threshold limit value in the USA (Pegues, 1960). Even the welding of galvanized steel creates concentrations of 400–500 $\mu g/m^3$. These high values were recorded under conditions of poor ventilation. With good ventilation, welding of zinc silicate-coated steel resulted in lead concentrations of 180 $\mu g/m^3$ near the welder's nose and 70 $\mu g/100$ ml in his blood.

The recovery of scrap metal from the dismantling of ships requires extensive cutting of steel plates with electric torches. These plates are heavily coated with lead-based paint. Consequently, the evolution of lead fumes and their inhalation by the shipbreakers commonly results in lead intoxication. Air samples collected near the breathing zone of shipbreakers show that lead concentrations of as much as 2700 $\mu g/m^3$ are attained, even in the open (Rieke, 1969).

5.3.4 Printing

The hazard in a printing establishment is probably in direct proportion to the dispersion of lead oxide dust, secondary to the remelt operation. An early study was reported by Brandt & Reichenbach (1943) in which melting pots were located in a variety of places where used type was discarded. These pots were maintained at temperatures ranging from 318°C to 477°C. The highest air lead concentration recorded was 570 $\mu g/m^3$, and the highest average concentration for any room was 200 $\mu g/m^3$. Although working methods and industrial hygienic conditions have probably changed considerably since this report was published, a marginal degree of hazard still prevails. Tsuchiya & Harashima (1965) reported a range of lead levels of 30–360 $\mu g/m^3$ at breathing level in several printing shops in Japan.

Biological monitoring of workers in the printing industry has been reported. It was found that four of those engaged in smelting had blood lead concentrations greater than 50 μg/100 ml (Hernberg et al., 1969). There was only one blood lead value greater than 70 μg/100 ml among the 28 workers studied.

5.3.5 Alkyllead manufacture

Tetraethyllead was first distributed as an additive to automobile fuel in 1923. Tetramethyllead was introduced in 1960. Today, the annual production of these two alkyllead compounds accounts for approximately 12% of total lead consumption by industry (see 3.3). Inevitably, workers engaged in the manufacture of these compounds are exposed to both inorganic and alkyllead. Some exposure also occurs at the petroleum refineries where tetraethyllead and tetramethyllead are blended into gasoline.

The process of tetraethyllead manufacture consists of reacting a sodium–lead alloy with ethyl chloride. The alloy is made by combining molten lead with elemental sodium. The alloy is then transported to the autoclaves in hoppers. After the autoclave has been charged, ethyl chloride is added over several hours. The reaction takes place at about 75°C for a further period of 30–60 minutes. Steam distillation is then applied to

remove residual ethyl chloride. The lead sludge is recovered, purified by smelting and re-used. The process generally in use for the manufacture of tetramethyllead is basically the same as for tetraethyllead. The final step is blending with dyes and scavengers. The product is shipped either in drums or tanker lorries.

Although there is a potential hazard from skin absorption of tetraethyl- and tetramethyllead, this is guarded against by the use of protective clothing. In a recent study, a good correlation was found between the organic air lead concentration in a plant and the rate of lead excretion in the urine (Linch et al., 1970). The average concentration of organic lead was 0.179 mg/m^3 for the tetramethyllead operation and 0.120 mg/m^3 for the tetraethyllead operation. The somewhat higher level registered for tetramethyllead was probably because the reaction between the organic reagent and the lead alloy takes place at a somewhat higher temperature and pressure than that employed in tetraethyllead production. Categories of hazard have been established based on the frequency with which workers are removed from exposure because of excessive urinary lead excretion (Table 13).

No exposure data are available for the blenders who mix tetraethyllead and tetramethyllead with gasoline at the refineries, but some exposure is likely to occur. Even at the filling stations where gasoline is pumped into cars, the concentration of organic lead in the vicinity of the pumps is appreciably greater than in the ambient air. Organic lead concentrations of 0.2–1.5 μg/m^3 were found in the vicinity of pumps (Colwill & Hickman, 1973; Harrison et al., 1974), and the concentration of tetraalkyllead emitted from the exhaust pipe of cars varied from 50 to 1000 μg/m^3 when the engine was idling (Laveskog, 1971).

5.3.6 Other industrial exposures

The diversity and extent of the industrial applications of lead makes it impossible to consider all cases. Furthermore, in most instances the actual

Table 13. Degree of hazard from lead exposure in the alkyllead industry[a]

High	Moderate	Low
1. smelting furnaces	1. drumming plant	1. blending
2. charging autoclaves	2. steam distillation	2. pressure vessel inspection
3. unloading and movement of lead pigs	3. alloying	
4. lead recovery	4. autoclave area	
5. maintenance		

[a] Data provided by: M. R. Zavon, Medical Director, Ethyl Corporation, Ferndale, Michigan, USA.

exposure levels have not been assessed. Some technological applications of lead are too recent to have provided much industrial hygiene experience. For example, the use of lead stearate as a stabilizer in the manufacture of poly(vinylchloride) is emerging as a new hazard. In the 1971 Annual Report of the British Chief Inspector of Factories, the number of reported cases of lead poisoning in the plastics industry was second only to that in the lead smelting industry (HM Chief Inspector of Factories, 1973). Other individual cases have been reported in recent years (Scarlato et al., 1969; Maljković, 1971). Lead stearate is milled and mixed with the poly(vinylchloride) and the plasticizer, to the extent of about 1–3%. It seems probable that the source of the problem is the dust that is generated in the mixing process. It appears too, that lead exposure occurs in the rubber tire industry (Sakurai et al., 1974), probably as a result of using lead dithiocarbamate as an accelerator in rubber manufacture.

Table 14. Relative hazard of lead poisoning in some occupations or operations[a]

High hazard	Moderate or slight hazard
Primary and secondary lead smelting	Lead mining
Welding and cutting of lead-painted metal constructions	Plumbing
Welding of galvanized or zinc silicate coated sheets	Cable making
Shipbreaking	Wire patenting
Nonferrous foundries	Lead casting
Storage battery manufacture: pasting, assembling, welding of battery connectors	Type founding in printing shops
Production of lead paints	Stereotype setting
Spray painting	Assembling of cars
Mixing (by hand) of lead stabilizers into poly(vinyl chloride)	Automobile repair
Mixing (by hand) of crystal glass mass	Shot making
Sanding or scraping of lead paint	Welding (occasionally)
Burning of lead in enameling workshops	Lead glass blowing
Repair of automobile radiators	Pottery/glass making

[a] From: Hernberg, 1973.

Drawing from his own experiences and knowledge of the field, Hernberg (1973) has provided a classification of hazard for common industrial activities where lead is used (Table 14).

5.4 Blood Lead Concentrations of Various Populations

Under certain conditions, blood lead levels (Pb-B) are a useful indicator of exposure and are therefore discussed in this section dealing with environmental levels and exposures (see also section 6.1.1.2).

5.4.1 Adult populations

A great deal of data is available on the blood lead levels of adult populations. By far the major proportion of these studies have reported that Pb-B mean values for occupationally unexposed, rural, and urban, populations range from 10 to 25 μg/100 ml (Hofreuter et al., 1961; US Department of Health, Education and Welfare, 1965; Butt et al., 1964; Holmquist, 1966; Lehnert et al., 1970; Horiuchi, 1970; Tepper & Levin, 1972; McLaughlin et al., 1973; Tsuchiya et al., 1975). Studies relating to populations from northern Italy have consistently revealed somewhat higher mean values, ranging from 24 to 35 μg/100 ml (Zurlo et al., 1970; Secchi et al., 1971; Secchi & Alessio, 1974). Similar Pb-B levels were also reported from rural and urban population groups in France (Boudene et al., 1975). In contrast, relatively low values (8.5 μg/100 ml) have been reported for 50 women from southern Sweden (Haeger-Aronsen et al., 1971). These are consistent with recently reported values for the Finnish female general population, ranging from 7.9 (rural), to 9.7 (urban) μg/100 ml (Nordman, 1975).

As a rule, the Pb-B levels of urban populations, and of people heavily exposed to automobile exhausts, have been found to be higher than those of rural populations or of populations living in areas with less traffic (Hofreuter et al., 1961; US Department of Health, Education and Welfare, 1965; Lehnert et al., 1970; Tepper & Levin, 1972) (Table 15). In one recent study, Pb-B levels were determined among adults before and after the opening of a motorway interchange with a high traffic density. Pb-B levels were found to be considerably higher among men and women living in the immediate vicinity of the interchange after it was opened than before (Waldron, 1975). In the evaluation of the results of this study, allowance must be made for the facts that no control group was studied, the procedure of drawing blood samples was changed after opening the interchange, the sampling took place at different times of the year and no data were given pertaining to the control of the analytical method used (atomic absorption spectroscopy). Thus, the possibility of systematic errors cannot be ruled out. On the other hand, Stopps (1969) found that the Pb-B levels of people living in various places remote from civilization had group means of 12–23 μg/100 ml, values not significantly different from group means reported for people living in urban areas of highly industrialized countries. No information was given in the report concerning procedures or quality control of the analytical methods.

A distinct increase in the lead absorption has been recorded in people living in the vicinity of lead smelters (Secchi et al., 1971; Nordman et al., 1973; Martin et al., 1975; Graovac-Leposavić et al., 1973).

Men have higher Pb-B levels than women (NAS-NRC, 1972). This

Table 15. Summary of concentration of lead in blood of selected groups of males, USA[a]

Mean (μg/100 ml)	No. of subjects	Identity of groups
11	9	Suburban nonsmokers, Philadelphia
12	16	Residents of rural California county
13	10	Commuter nonsmokers, Philadelphia
15	14	Suburban smokers, Philadelphia
19	291	Aircraft employees, Los Angeles
19	88	City employees, Pasadena
21	33	Commuter smokers, Philadelphia
21	36	City Health Dept. employees, Cincinnati
21	155	Policemen, Los Angeles
22	11	Live and work downtown, nonsmokers, Philadelphia
23	140	Post Office employees, Cincinnati
24	30	Policemen, nonsmokers, Philadelphia
25	191	Firemen, Cincinnati
25	123	All policemen, Cincinnati
25	55	Live and work downtown, smokers, Philadelphia
26	83	Police, smokers, Philadelphia
27	86	Refinery handlers of gasoline, Cincinnati (1956)
28	130	Service station attendants, Cincinnati (1956)
30	40	Traffic police, Cincinnati
30	60	Tunnel employees, Boston
31	17	Traffic police, Cincinnati (1956)
31	14	Drivers of cars, Cincinnati
33	45	Drivers of cars, Cincinnati (1956)
34	48	Parking lot attendants, Cincinnati (1956)
38	152	Garage mechanics, Cincinnati (1956)

[a] From: US Department of Health, Education and Welfare, 1965.

difference does not appear to be totally attributable to the higher haematocrit values of men (Tepper & Levin, 1972; Nordman, 1975). At least part of the difference is likely to be accounted for by the higher food consumption of men.

No association has been established between Pb-B levels and age in adults (NAS-NRC, 1972; Tepper & Levin, 1972; Nordman, 1975).

The influence of cigarette smoking is not fully evaluated; some researchers have reported higher Pb-B levels for smokers than for non-smokers (Hofreuter et al., 1961; US Department of Health, Education and Welfare, 1965; Tepper & Levin, 1972), while others have been unable to confirm such an association (Lehnert et al., 1967; Jones et al., 1972; McLaughlin & Stopps, 1973; Nordman, 1975; Tsuchiya et al., 1975).

5.4.2 Children

European studies of Pb-B levels in children indicate that, in general, the values are similar to or possibly even lower than those in adults. Pb-B levels of 200 children aged 4–13 years in rural western Ireland have been reported to be below 13 μg/100 ml with 45% of the results below 10 μg/100 ml (Grimes et al., 1975). A group of 363 children aged from 8 days to 8 years was surveyed in the Nüremberg/Erlangen area. The children displayed a mean Pb-B level of 3.3 ± 2.6 μg/100 ml in the first year of life; the Pb-B level

increased year by year and reached a mean of 11.5 ± 4.9 μg/100 ml at the age of 6–8 years (Haas et al., 1972a). However, most of the available data on Pb-B levels in children have been obtained as a result of case-finding programmes conducted in the USA. In one study, the average blood level of 230 children, aged 1–5 years, in two rural counties was found to be 22.8 ± 11.0 μg/100 ml (Cohen et al., 1973). An upward correction was made for all haematocrit values below 40%; more than half of the children lived in older houses (more than 25 years old) one-quarter of which had flaking paint or holes in the plaster.

There has been great concern in the USA that a very large number of inner city children have abnormally elevated Pb-B levels. The concern is for children in the blood lead range of 40–80 μg/100 ml. Thus, Blanksma et al. (1969) reported that in 1967, and 1968, 8%, and 3.8%, respectively, of Chicago slum children had Pb-B concentrations in excess of 49 μg/100 ml. This study involved 68 744 children, the majority of whom were between 1 and 6 years of age. The problem is not limited to large cities. Fine et al. (1972) reported on a survey of 14 Illinois communities with populations ranging from 9641 (Robbins) to 126 963 (Peoria). Of a total of 6151 children, 18.6% had Pb-B levels higher than 39 μg/100 ml and 3.1% had levels higher than 59 μg/100 ml. Some of the communities were in the Chicago urban complex, but a considerable number were not. There did not appear to be any great difference in the percentage of children having an excessive concentration of lead among the Chicago urban communities as compared with the downstate and western Illinois communities. The findings are certainly not unique to Illinois. In a recent survey, 34% of 343 children in an impoverished area of Boston had Pb-B levels in excess of 39 μg/100 ml and 12% were over 49 μg/100 ml (Pueschel et al., 1972). Similar data have been gathered recently in New York City and elsewhere.

6. METABOLISM OF LEAD

6.1 Absorption[a]

The absorption of lead from environmental sources is not solely dependent on the amount of lead presented to the portals of entry per unit time. It is also dependent on the physical and chemical state in which the metal is presented and it is influenced by host factors such as age and physiological status. The amount of food eaten and the amount of air breathed, with the proportionate ingestion or inhalation of lead, are functions of metabolic activity. Men engaged in heavy work breathe more air and eat more food than sedentary individuals of the same weight, and

children eat almost as much food and breathe almost as much air as middle-aged adults.

6.1.1 Absorption by inhalation

A large amount of information has accumulated regarding the factors that determine the degree of deposition and retention of inhaled aerosols in general (Task Group on Lung Dynamics, 1966). With appropriate knowledge of the aerodynamic characteristics of lead aerosols, it would be possible to make reasonable predictions from the lung model developed by the ICRP Task Group on Lung Dynamics, concerning the fractional deposition that would occur in the human airways. It would also be possible to predict the pattern of regional deposition in the airways. Unfortunately, the knowledge necessary for making accurate predictions is not available, particularly in the case of industrial exposure.

The ICRP lung model would predict that approximately 35% of the lead inhaled in general ambient air would be deposited in the airways, since the aerodynamic diameter[b] of the lead particles is approximately 0.1–1.0 μm (see section 5.1.1). The lung model would also predict that regional deposition would be predominantly in the alveolar bed and in the deeper regions of the tracheobronchial system. Furthermore, it would predict that fractional deposition of lead dusts generated in an industrial environment would be greater than it would be for lead in general ambient air; however, the deposition would be mainly in the nasopharynx rather than in the pulmonary bed or tracheobronchial region, owing to the larger particle size. Industrial lead fumes, such as those generated in the process of cutting metals with electric torches, would be of small particle size and would behave accordingly. But even the lead aerosols breathed by the general population are not well enough characterized to predict deposition. This is particularly true for the very small particles (<0.1 μm) which are largely deposited by diffusion (Lawther, 1972).

The adequacy of the ICRP lung deposition model is open to question, at least for small particles. The model predicts a total airway deposition of 40–50% for 0.5-μm particles, whereas a study in human volunteers indicated a deposition of only 6–16% depending on the rate and depth of respiration (Muir & Davies, 1967).

Predictions concerning the characteristics of airway clearance of lead aerosols using the ICRP lung model are even more difficult to make than

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[a] In this document, absorption and uptake are used synonymously.

[b] Aerodynamic diameter = diameter of a unit density sphere with the same settling velocity as the particle in question (Task Group on Lung Dynamics, 1966).

predictions regarding deposition. The lung model would predict that the fate of lead deposited in the airways would vary greatly depending on its solubility characteristics and on the inherent toxicity of the particles to the clearance mechanism (lung macrophages and cilia). The chemical forms of lead in air are both numerous and variable, depending on the source and on residence time in the air (see section 5.1.1). In many types of industrial exposure, lead is probably mainly in the form of lead oxide.

6.1.1.1 *Human studies*

Actual studies on the fractional deposition of particles in the respiratory tract of man have not been extensive, especially in the case of lead. Kehoe (1961) studied the deposition of lead in human volunteers with an air lead level of 150 $\mu g/m^3$. The source of lead was combusted tetraethyllead which produced lead (III) oxide (Pb_2O_3) in the air. Subjects breathed air containing particles with an average diameter of 0.05 μm viewed under the electron microscope, with 90% ranging from 0.02–0.09 μm. A diameter of 0.05 μm for lead (III) oxide as seen under the electron microscope represents a mass median equivalent diameter of approximately 0.26 μm (NAS-NRC, 1972). Subjects also breathed air containing particles having an average diameter of 0.9 μm (mass median equivalent diameter = 2.9 μm); 36% of the smaller particles, and 46% of the larger particles, were deposited.

Nozaki (1966) also reported on lung deposition of inhaled lead in man. Lead fumes were generated in a high-frequency induction furnace and were inhaled at a concentration of 10 000 $\mu g/m^3$. Particle size was closely controlled according to the method of Homma (1966). The results (see Table 16) were similar to those of Kehoe (1961) and were reasonably consistent with the ICRP lung deposition model (Task Group on Lung Dynamics, 1966).

These data suggest that an estimate of $30 \pm 10\%$ deposition is reasonable for the usual general ambient air situation and that lead oxide deposition characteristics will vary considerably, depending on the particle size and on the depth and frequency of respiration.

However, one cannot predict the contribution of airborne lead to the body burden of lead on the basis of deposition studies alone. Regional deposition probably varies greatly from one exposure situation to another, that is, the industrial setting *versus* the ambient environment. Also, the nature of lung clearance is unknown and is difficult to study. Nevertheless, it is possible to determine short-term lung clearance by carrying out gamma ray lung scans following inhalation of ^{212}Pb. Such a study in man has been reported (Hursh & Mercer, 1970) but its relevance to the rate of clearance of the chemical and physical forms of lead usually inhaled by man is highly

questionable. Such radioactive lead studies involve the adsorption of ^{212}Pb atoms on carrier aerosol particles. The desorption of lead atoms from aerosol nuclei under these artificial circumstances may be quite significant, and the estimated rate may be totally unlike the clearance rate for ambient air lead particles.

Kehoe (1961) has reported that when a subject breathed large-particle aerosols of lead (III) oxide (approximately 2.9 μm mass median equivalent diameter) for many weeks at 150 μg/m^3 a very substantial increase in faecal excretion occurred, probably reflecting the fact that the particles were largely trapped in the nasopharynx and swallowed. When the same subject inhaled air with a lead concentration of 150 μg/m^3, with the lead in small particles (approximately 0.26 μm mass median equivalent diameter), only a small rise in faecal lead excretion was observed.

During inhalation of particulate air pollutants, the lead dust comes into contact with lung cells, which are primarily responsible for phagocytosis. It must be remembered that alveolar macrophages are damaged *in vitro* by inorganic lead compounds (Beck et al., 1973), and that similar effects have been demonstrated *in vivo* in rats and guinea-pigs (section 6.1.1.4). It

Table 16. Deposition of lead fumes in the airways of human subjects[a]

10 respirations/min; 1350 cm^3 tidal air		30 respirations/min; 450 cm^3 tidal air	
Particle diameter[b] (μm)	% Deposition	Particle diameter[b] (μm)	% Deposition
1.0	63.2	1.0	35.5
0.6	59.0	0.6	33.5
0.4	50.9	0.4	33.0
0.2	48.1	0.2	29.9
0.1	39.3	0.1	27.9
0.08	40.0	0.08	26.5
0.05	42.5	0.05	21.0

[a] Adapted from Nozaki, 1966.
[b] Mass median equivalent diameter.

seems possible, therefore, that the lung defence mechanisms are, to some extent, impaired in an environment with a high air lead concentration, and that the rate of absorption of inhaled particles under such circumstances is affected.

In summary, studies of airway deposition and clearance of lead in man have not, as yet, provided any clear indication of the daily absorption to be expected under realistic conditions. They have only emphasized the necessity to consider other kinds of data to obtain this information.

Since the concentration of lead in the blood is thought to reflect current and recent lead exposure, the degree of lead intake from air should be reflected in this factor.

6.1.1.2 *The relationship of air lead to blood lead in the general population*

The risk to man from lead in air has become a matter of considerable concern in recent years. Studies of lead deposition and retention in the airways of man have not been very enlightening. A more indirect but nonetheless useful approach to the problem starts from the assumption that the concentration of lead in the blood is proportional to the concurrent level of total uptake by way of the several portals of entry. It follows that each environmental source (mainly air, food and water) would contribute to the blood lead concentration in direct proportion to its contribution to the total daily lead uptake. Up to the present time, such a relationship has never been rigorously demonstrated. Goldsmith & Hexter (1967) developed a linear regression plot of log Pb-B *versus* log lead concentration in air. The air lead samples were not necessarily taken at the same time and place as the blood samples. Thus, the regression line was calculated on the basis of rather imprecise information. However, data from experimental human subjects breathing known high concentrations of lead oxide were found to fit the regression line rather well. A cogent criticism is the fact that the validity of the air lead data as applied to the specific blood lead data is very uncertain. The contribution of air lead to blood lead, as inferred from the Goldsmith-Hexter curve, is about 1.3 μg of lead per 100 ml of blood per 1 μg of lead per m^3 of air. Other epidemiological studies have been made of the relationship between air lead and blood lead. Azar et al. (1973) monitored the inhaled air of 150 individuals using personal air samplers continuously, 24 hours per day. The air lead exposure ranged from 2 $\mu g/m^3$ to 9 $\mu g/m^3$. There was a significant correlation between log air lead level and log blood lead level, when data from all the cities involved were pooled. The contribution of air lead to blood lead was found to be somewhat less (approximately 1.0 μg of lead per 100 ml of blood per 1 μg of lead per m^3 of air over the range of air lead concentrations studied), than was estimated from the Goldsmith-Hexter curve.

Another recent epidemiological investigation which examined the relationship between air lead and blood lead levels was the Seven Cities Study (Tepper & Levin, 1972). No significant correlation was found between air lead and blood lead levels over an air lead range of 0.17–3.39 $\mu g/m^3$. A major deficiency was the fact that the air data were obtained from fixed outdoor sampling stations in the 11 cities involved.

Two studies have been reported recently in which the relationship between blood lead and air lead levels was investigated in human volunteers. In one study, 14 male volunteers were exposed to a lead oxide aerosol for 23 hours per day at an average concentration of 10.9 $\mu g/m^3$ for up to 17 weeks. Blood lead concentrations and other parameters were measured before, during, and following the exposure period. A plateau of

blood lead concentration was attained during the exposure, and a return to pre- or near pre-exposure levels was observed during the post-exposure period. The air contribution to the Pb-B levels was approximately 1.4 μg of lead per 100 ml blood per 1 μg of lead per m^3 of air (Coulston et al., 1972b). In another study, male volunteers inhaled an air lead concentration of 3.2 μg/m^3. The blood lead level increased from 18 μg to 25 μg/100 ml,

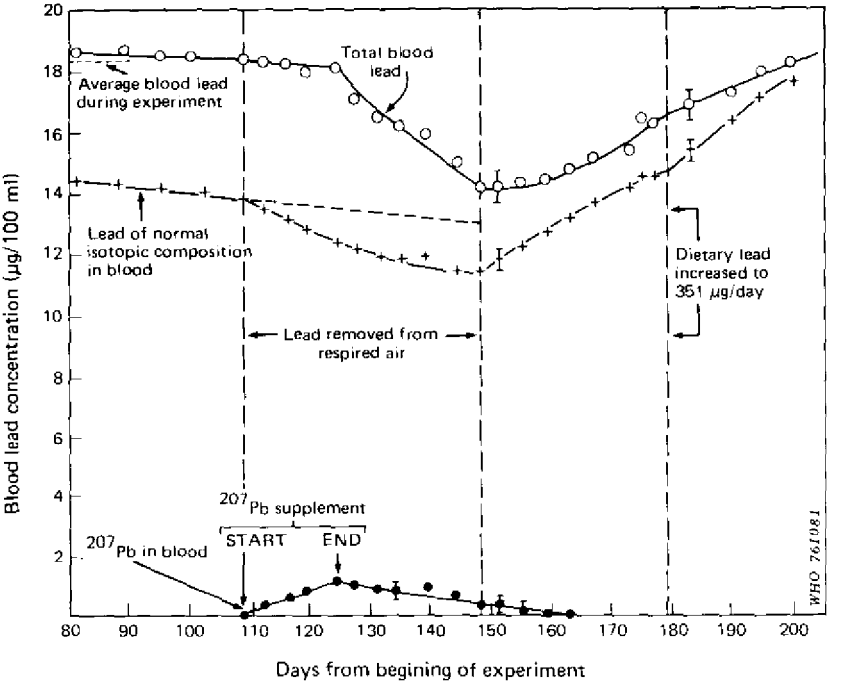

Fig. 2 Effect on blood lead of removal of lead from room air. Adapted from Rabinowitz (1974) with the addition of the dashed line

that is approximately 2 μg of lead per 100 ml blood per 1 μg of lead per m^3 (Coulston et al., 1972c). Rabinowitz (1974) reported a study of a single volunteer using stable lead isotope tracers in which the sudden removal of the normal lead in air by filtration resulted in a reduction of the blood lead concentration from approximately 14.5 μg/100 ml to approximately 11.3 μg/100 ml over a period of 40 days (Fig. 2). The average air lead levels were estimated taking into account measurements made indoors and outdoors, and the time spent in both locations. Prior to the experiment

(day 109), the average air lead concentration was 1.6 μg/m^3 and during the experiment (day 109–148) it was 0.2 μg/m^3. In calculating the contribution of air lead to blood lead at day 148, allowance should be made for the fact that the concentration of lead of normal isotopic composition was decreasing prior to the removal of lead from the air. If this is taken into account the contribution of air lead to blood lead at day 148 would be about 1.7 μg of lead per 100 ml of blood per 1.4 μg of lead per m^3 of air, or 1.2 μg of lead per 100 ml of blood per 1 μg of lead per m^3 of air. It is unfortunate that it was not possible to follow the blood lead concentrations for a longer period of time after removal of lead from room air, since a new steady state had not been fully achieved. The study is also of limited value for application to the general population because only one individual was studied.

On the other hand, the Coulston study was deficient in that the form of air lead breathed (lead (III) oxide) may be deposited in, and cleared from, the airways in a significantly different manner from lead, as it actually occurs in general ambient air.

In conclusion it seems, that there is probably a perceptible effect of air lead on blood lead in the range of air lead concentrations applicable to the general population. The data available suggest that with blood lead levels in the range found in the general population, air lead levels may contribute from 1.0 to 2.0 μg of lead per 100 ml of blood per 1 μg/m^3 of air.

6.1.1.3 *The relationship of air lead to blood lead in occupational exposure*

There is very little precise information concerning the relationship between the concentration of lead in air (Pb-A) and Pb-B levels in subjects who are occupationally exposed. The air sampling technique used in the study of this relationship is of great importance. Personal monitors should be used since in most industrial situations the air lead concentrations to which individuals are exposed may be highly variable, depending on the particular tasks being performed and on the individual's work habits.

Only one study has been reported in which the subjects wore personal monitors and in which the estimated individual Pb-A could be related to Pb-B and some biochemical tests (Williams et al., 1969). In this study, workers in various departments of an electric storage battery factory wore personal samplers for the full work shift for two weeks. There were considerable variations in the measured concentrations of air lead both among departments and among individual personal samples. Relevant data are presented in Table 17.

Using the data reported by Williams et al. (1969) an attempt was made to estimate very crudely the potential contribution of Pb-A to Pb-B in

Table 17. Means and standard errors of measured lead in air and Pb-B levels in different departments of an electric storage battery factory[a]

Department	No.	Pb in air (μg/m³)		Pb-B (μg/100 ml)	
		mean	S.E.	mean	S.E.
Machine pasting	6	218	25	74.2	4.7
Hand pasting	8	150	29	63.2	9.2
Forming	9	134	13	63.0	2.7
Casting	6	52	3	—	—
Plastics dept. A	5	12	0.8	27.2	1.4
Plastics dept. B	5	9	0.8	29.1	1.6

[a] Adapted from Williams et al., 1969.

subjects who were occupationally exposed to lead. Several arbitrary assumptions were made in this estimation:

(1) that the weekly time-weighted average concentration of lead in air (c) is a good measure of the effective inhalation exposure, irrespective of the probable differences in breathing rates during work hours. For a 40-hour working week $c = 0.24\,(\text{Pb-A})_o + 0.76\,(\text{Pb-A})_a$, subscripts o and a referring to the occupational and ambient concentration of lead in air.

(2) that $(\text{Pb-A})_a$ was 1 μg/m³ and that it had contributed 1.4 μg/100 ml to the measured Pb-B values (see 6.1.1.2), and that for each further increase of Pb-A = 1 μg/m³, the increase in Pb-B would be 1.4 μg/100 ml in the range of Pb-A values up to about 10 μg/m³.

(3) that the contributions of the occupational inhalation exposure, non-occupational inhalation exposure, and exposures from other sources (such as food) to the Pb-B levels are additive.

A further oversimplification was that the probable differences in the chemical composition and physical characteristics of air-borne lead in occupational and non-occupational environments were completely neglected.

The contribution, $(\text{Pb-B})_F$, of non-inhalation exposures such as food intake to the measured levels of lead in blood was assumed to be the same for all workers and constant over the two week period of observation. It was calculated from the data of Table 17 for the workers in plastics departments A and B used as control groups, by subtracting the estimated contribution of c to blood lead from the measured Pb-B values, and taking the mean, i.e. $(\text{Pb-B})_F = \frac{1}{2}[27.2 - (3.6 \times 1.4) + 29.1 - (2.9 \times 1.4)]$ $= 23.6$ μg/100 ml. $(\text{Pb-B})_o$ was then obtained by subtracting 23.6 from measured Pb-B values for all other departments.

The results are shown in Table 18.

Table 18. Estimation of blood lead levels potentially derived from effective inhalation exposure c

Department	Measured Pb-B µg/100 ml	$(Pb\text{-}B)_o$ µg/100 ml	c µg/m³	$(Pb\text{-}B)_o/c$
Machine pasting	74.2	50.6	53.1	0.96
Hand pasting	63.2	39.6	36.8	1.1
Forming	63.0	39.4	32.9	1.2
Casting	—	- -	13.2	—
Plastics A	27.2	3.6	3.6	1.0
Plastics B	29.1	5.5	2.9	1.5

From these calculations it would appear that an increase of 1 µg/m³ in the weekly time-weighted average concentration of lead in air would correspond to an increase of approximately 1 µg/100 ml in Pb-B.

A similar but somewhat lower figure for the air lead contribution to Pb-B levels can be arrived at using data from a study, parts of which are reported in two different publications (Prpić-Majić et al., 1973; Fugaš et al., 1973). From their data, they calculated that the time-weighted average concentration of respirable lead particles for 52 workers in unspecified lead trades was 35 µg/m³. Their average Pb-B level was 44.3 µg/100 ml, while the Pb-B level of a control population living in an air environment of 0.2 µg/m³ was 22.4 µg/100 ml. Assuming the Pb-B levels due to non-air sources to be the same for the two groups, i.e. 22.1 µg/100 ml (total (22.4) minus the ambient air contribution to Pb-B $(0.2 \times 1.4 = 0.3)$), the air contribution to the Pb-B level for the industrially exposed group would be 44.3–22.1 or 22.2 µg/100 ml. Since the air lead concentration was 35 µg/m³, 1 µg of lead per m³ contributes 0.6 µg of lead per 100 ml of blood.

Another possible method of estimating the contribution of Pb-A to Pb-B in the occupationally exposed subjects is to find first a functional relationship that fits the Pb-B data from Table 17 and c. A power function $\ln y = \ln 18.9 + 0.34 \ln c$ gives a good fit in the range of $c = 10$ to $c = 50$ (correlation coefficient $r = 0.994$), and enables the estimation of the increase in Pb-B per unit increase in c. The results of these calculations are shown in Table 19. Although still a gross oversimplification, this method seems to give more realistic results because it reflects the fact that, at the higher Pb-A level, Pb-B does not increase linearly with Pb-A, and that therefore, the expected increase in Pb-B per unit increase in c (dy/dc, Table 19) gets smaller and smaller as Pb-A levels grow.

6.1.1.4 *Animal studies*

Animal studies have been useful in the development of the ICRP lung deposition and clearance models, but they have not contributed much to resolution of the specific questions concerning the fate of inhaled lead in man. However, observations made on the effects of inhaled lead on lung

Table 19. Power curve fit[a] to the plot of Pb-B against the time-weighted average concentration of lead in air (c)

Department	c µg/m³	Measured Pb-B µg/100 ml	y µg/100 ml	dy/dc
Machine pasting	53.1	74.2	73.2	0.47
Hand pasting	36.8	63.2	64.6	0.60
Forming	32.9	63.0	62.2	0.64
Casting	13.2	–	45.6	1.09
– –	(10)	– –	41.3	1.41
Plastics A	3.6	27.2	29.3	–
Plastics B	2.9	29.1	27.2	–

[a] $y = 18.9c^{0.34}$ = Pb-B calculated.

macrophages are of special interest. A pronounced reduction in the number of lung macrophages has been demonstrated in rats and guinea-pigs owing to inhalation of lead (III) oxide at both 10 and 150 µg/m³ (Bingham et al., 1968). Maximum reduction occurred within approximately one week. This phenomenon has also been reported by others (Beck et al., 1973; Bruch et al., 1973, 1975). These observations suggest that, with high air lead concentrations at least, the lung clearance mechanism may not be functioning as effectively in diverting lead deposited in the lower airways to the gastrointestinal tract as the ICRP lung clearance model predicts. Thus, Pott & Brockhaus (1971) reported that large doses of lead bromide solution and of lead oxide suspension administered intratracheally to rats (1.5 mg of lead oxide per dose on 8 successive days) were retained by the body as completely as intravenous doses. However, at $\frac{1}{3}$ of this dose, retention was significantly less.

6.1.2 Absorption of lead from the gastrointestinal tract

6.1.2.1 Human studies

The uptake of lead from the gastrointestinal tract has been studied fairly extensively, but as with the uptake of lead from air, the evidence concerning a number of important points is somewhat uncertain. Long-term balance studies conducted by Kehoe (1961) showed that the daily excretion of lead into the urine was a little less than 10% of the intake from food and beverages. He surmised that this fraction represented the amount absorbed from the gastrointestinal tract. In estimates made on this basis, the amount of urinary lead that could have originated from the air is disregarded, as well as the fact that some of the lead absorbed from the gastrointestinal tract is re-excreted into the bowel.

Recent studies by Rabinowitz et al. (1974), using orally administered ^{204}Pb, indicate that the absorption of lead incorporated into the diet is a

Table 20. Comparison of daily oral lead intake with Pb-B levels

Study design	Oral intake (μg/day)	Pb-B[a] (μg/100 ml)	Pb-B per 100 μg oral Pb	Reference
Duplicate portion	113 (men)	20.7	18.3	Coulston et al., 1972b
Faecal excretion	119[b] (women)	15.3	13.0	Tepper & Levin, 1972
Duplicate portion	230 (men)	12.3	5.4	Nordman, 1975
Duplicate portion	180 (women)	7.9	4.4	Nordman, 1975
Composites technique	505 (men)	34.6	6.8	Zurlo & Griffini, 1973[c]

[a] Contributions of air to Pb-B levels are not reported in most of these studies and could not be subtracted from total Pb-B levels.

[b] Calculated from daily faecal excretion of 108 μg of lead assuming gastrointestinal absorption of 10%.

[c] Pb-B levels from Secchi et al. (1971).

little less than 10%, which is consistent with Kehoe's conclusions based on a different experimental approach.

Attention has been directed recently towards the absorption of lead from the gastrointestinal tract in infants and young children. In a study of eight normal children, from 3 months to 8.5 years of age, Alexander et al. (1973) found a high degree of lead absorption (53%). There did not appear to be any significant reduction in fractional retention within the age range studied. This work is subject to criticism because of the large scatter of values and because the conclusions were based on 3-day balances, a period that is probably insufficient for reaching any reliable conclusions.

6.1.2.2 *The relationship of oral intake of lead to blood lead levels in man*

It would be of great interest to be able to relate oral intake of lead to blood lead levels. It is obvious that, as the intake of lead increases, blood lead levels will rise, but a quantitative expression of this relationship at any particular level of lead intake has not been determined. Table 20 compares daily oral lead intake (μg/day) and Pb-B levels (μg/100 ml) found in adult populations without known excessive exposure to lead, from several parts of the world.

From the data in Table 20 it is not possible to draw any reliable conclusions regarding the contribution of foods and beverages to Pb-B levels. The contribution is calculated to be greater in the two American studies than in the European ones. One of these two American studies (Tepper & Levin, 1972) was actually of faecal lead excretion, not of dietary lead. But even if this study were discounted, there remains a considerable discrepancy between the other American study (Coulston et al., 1972b) and the European studies, which cannot be explained.

Each of these studies involved a different number of subjects and involved different analytical techniques. It is also probable that there was also exposure from other environmental sources.

At levels of lead intake above 1000 μg per day, the rise in blood lead

level does not appear to increase linearly with dose, but, in fact, may fit a logarithmic function.

From data published by Kehoe (1961) concerning balance studies on human volunteers, a single individual with a total daily lead intake of 600 μg had blood lead levels in the range of 30–35 μg/100 ml registered over several months, which is consistent with the relationships suggested in Table 20. However, individuals with larger daily additions of lead did not have proportionately higher blood lead levels. A single individual with oral lead intake of 3300 μg per day had a blood lead level in the 50–60 μg/100 ml range, again followed up for several months.

For children, the dietary contribution to blood lead is more difficult to estimate than for adults. Because of the higher absorption of lead, particularly in infants, the contribution of dietary lead to blood lead levels may be higher than for adults.

6.1.2.3 *Animal studies*

The effect of age on gastrointestinal absorption of lead has been studied in experimental animals. The absorption of lead from food has been investigated in many animal studies. Values between 5 and 10% are usual (Pott & Brockhaus, 1971; Schlipköter & Pott, 1973; Horiuchi, 1970).

Kostial et al. (1971) demonstrated that 5–7 day old rats absorb at least 55% of single oral tracer doses of ^{203}Pb. In an extension of these studies, Forbes & Reina (1972) observed that the gastrointestinal absorption of tracer doses of ^{212}Pb, ^{85}Sr and ^{59}Fe was high prior to weaning and decreased rapidly thereafter. In the case of lead, absorption which was 83% at 16 days, decreased gradually to 74% on the day of weaning (22 days) and rapidly thereafter to about 16% at 89 days. The addition of tracer doses of metals to the diet is, however, an artificial situation. Results might have been quite different had appreciable amounts of carrier lead been included. Nevertheless, these observations are consistent with those reported in young children.

Certain dietary factors have also been shown to influence the gastrointestinal absorption of lead. Kello & Kostial (1973) have shown that milk enhances lead absorption in 6-week-old-rats. Fasting enhances lead absorption, at least as determined by Garber & Wei (1974) in mice. Low dietary levels of calcium and of vitamin D enhance lead absorption (Sobel et al., 1938b; Six & Goyer, 1970). It has also been demonstrated that rats on an iron-deficient diet accumulate more lead in their bodies than do rats on an iron-sufficient diet (Six & Goyer, 1972). This seems particularly significant in the light of the fact that young children in socially and economically deficient homes have a high incidence of anaemia and excessively high blood lead concentrations.

The absorption of lead ingested in the form of paint has received attention because of the hazard of lead-based paint to young children. Recent data from experiments on rats indicate that lead chromate and lead naphthenate incorporated into dried paint films are substantially available for absorption, although to a somewhat lesser degree than lead naphthenate in oil or lead nitrate in aqueous solution (Gage & Litchfield, 1968, 1969).

6.2 Distribution and Retention

As with all substances entering the body, a single dose of lead distributes initially in accordance with the rate of delivery of blood to the various organs and systems. Redistribution then occurs to organs and systems in proportion to their respective affinities for lead. Under conditions of continuous intake over long periods of time, a near-steady state is achieved with respect to intercompartmental distribution.

Perturbations in the pattern of distribution occur when large, short-term peaks of lead intake are superimposed on this well-defined pattern of long-term distribution.

6.2.1 Human studies

The kinetics of lead distribution and accumulation in man have not been well defined in man directly. However, from autopsy data, the general pattern of lead metabolism is clearly discernible. Above all, it is clear that lead has a strong tendency to localize and accumulate in bone. The accumulation of lead in the human body begins in fetal life (Horiuchi et al., 1959; Barltrop, 1969). Lead is readily transferred across the placenta and the concentration of lead in the blood of newborn children is similar to that of their mothers, indicating mother–fetus equilibration processes (Haas et al., 1972b; Hower et al., 1975). The distribution of lead in fetal tissue is quite similar to the distribution in adults (Barltrop, 1969).

The total lead content of the body may reach more than 200 mg in men aged 60–70 years, but is lower for women. Barry & Mossman (1970) calculated that in non-occupationally exposed adults, 94–95 % of the total body lead (body burden) was in the bones. A similar estimate was made by Schroeder & Tipton (1968), by Horiuchi et al. (1959), and by Horiguchi & Utsunomiya (1973). These recent reports serve to reaffirm the long-recognized affinity of lead for bone. They also provide the additional observation that the concentration of lead in bones increases throughout most of life. This is in contrast to soft tissues. Most soft tissues do not show a significant age-related change in lead concentration after the second decade of life (Barry, 1975). This is also true of the concentration of lead in

whole blood (US Department of Health, Education and Welfare, 1965; Horiuchi & Takada, 1954) and in blood serum (Butt et al., 1964). Thus, it appears that the skeleton is a repository for lead that reflects the long-term accumulative human exposure, whereas the body fluids and soft tissues equilibrate reasonably fast and therefore reflect current and recent exposure. Little is known as to whether the mobilization of lead lying inactive in the bones can occur so rapidly that signs of poisoning appear. There is need for more studies in this field.

The concentration of lead in the blood is of prime importance in the evaluation of lead exposure. It is relied upon as an aid to the diagnosis of poisoning and as an index of exposure to assess hazardous conditions both in occupationally-exposed people and in the general population. It has long been known that lead circulating in the blood is mainly found in the erythrocytes (Cantarow & Trumper, 1944). The concentration of lead in erythrocytes is about 16 times greater than in plasma (Butt et al., 1964). The nature of the association of lead with the erythrocyte is not clearly understood. Numerous studies have been reported concerning the *in vitro* addition of lead to erythrocytes suspended in plasma or saline solutions. But the validity of such studies is open to serious question. Thus, Clarkson & Kench (1958) found that lead added *in vitro* was readily removed by EDTA, whereas residual lead present in the cells prior to the addition of lead could not be removed. This suggests a difference in regard to: (1) the degree of binding, (2) the site of binding in or on the cell, or (3) the type of binding of the lead. Recent studies indicate that lead is mainly bound to human erythrocyte protein, notably to haemaglobin, rather than to stroma (Barltrop & Smith, 1971, 1972).

The rate of equilibration of lead in blood with sources of input and with other body compartments has been studied in man by Rabinowitz et al. (1973, 1974) using a stable lead isotope tracer (^{204}Pb). The data reported indicate that with a constant daily oral input of ^{204}Pb, a virtually constant concentration of the tracer in the blood is achieved after approximately 110 days. Upon withdrawal of the tracer ^{204}Pb from the diet, the ^{204}Pb concentration in the blood disappears with a half-time of approximately 19 days. The kinetics of disappearance and accumulation suggest that first order rate processes of exchange are involved with regard to this relatively mobile compartment. Tola et al. (1973) also provided data which indicate that the concentration of lead in the blood rises fairly rapidly to a new steady state level when men are newly introduced into an occupational lead environment. The time required for the blood lead concentration to achieve a new plateau reflecting the new environment is about 60 days.

The body burden of lead increases from birth to old age (Schroeder & Tipton, 1968; Barry & Mossman, 1970; Barry, 1975). When data for

various specific organs and systems are examined, it becomes evident that there are two general pools of lead within the total organism. The major one, in terms of total lead, consists of bone. This pool is clearly highly accumulative. As a consequence, lead in bone accumulates through most of the life span. Other organs and systems are much less accumulative and, to different degrees, tend to stabilize relatively early in adult life reflecting a greater turnover rate of lead compared with that in bone.

There is good reason to make a distinction between total body burden and exchangeable body burden since the organs and systems comprising the exchangeable body burden are the ones having the greater toxicological significance. It is also extremely important to note that lead in whole blood is a part of the exchangeable fraction of the body burden. Among adults in the general population there is no age-related difference in regard either to the concentration of lead in whole blood or in blood serum. Thus, in a general way, the Pb-B level reflects the concentration of lead in soft tissues, and long-term changes in Pb-B levels with changes in exposure levels are probably accompanied by corresponding long-term changes in the rest of the exchangeable pool.

Nuclear inclusion bodies containing lead have been found in man subjected to lead exposure (Cramer et al., 1974; Galle & Morel-Maroger, 1965; Richet et al., 1966) as well as in experimental animals (see section 7.1.3). Although most frequently reported to occur in the kidney, they have been found in other organs as well. There is a suggestion from limited data that inclusion bodies are associated with short-term lead exposure and not with long-term exposure (Cramer et al., 1974).

The concentration of lead in deciduous teeth has received special attention because they are readily available from young children and because they provide a long-term record of lead exposure, much as is the case with bone. Dentine in the area adjacent to the pulp is particularly useful in this respect because it is laid down from the time of eruption to the time the tooth is shed. It has been reported that the concentration of lead in dentine is considerably lower in suburban schoolchildren than it is in children in areas of high lead exposure (Needleman & Shapiro, 1974).

There has been some interest in the possible use of hair lead as an index of exposure. Unfortunately, there is no reliable information, as yet, to indicate just how hair analyses should be interpreted in relation to the frequency and degree of exposure.

6.2.2 Studies in animals

Animal studies have been particularly useful in defining more precisely the nature of the kinetics of lead distribution and removal from various

tissues. Following administration of a single dose of lead to rats, the concentration of lead in soft tissues is relatively high and falls rapidly, mainly as a result of transfer into the bone (Hammond, 1971). The distribution characteristics of lead were found to be independent of the dose of lead over a wide range. The rate constants for the elimination of lead from various tissues in rats following a single dose of lead have been described by Castellino & Aloj (1964). The rate of elimination was much slower from bone than from other tissues. In studies on rats, Bolanowska et al. (1964) noted that the rate of elimination of a single dose of lead from the body by spontaneous excretion became slower with time, reflecting progressively decreasing mobility of the residual body burden. This is no doubt mainly due to the fact that as lead becomes progressively more deeply buried in the bone matrix, its exchangeability with other compartments and its availability for excretion decrease.

Rather striking age-related differences have been observed concerning the distribution and retention of lead in rats (Momčilović & Kostial, 1974). The rate of elimination of a single tracer dose of ^{203}Pb from the whole body, blood, and kidney was faster in adults than in sucklings. In the case of the brain, there was actually a slight increase in the ^{203}Pb content of the brain of the sucklings while the content was falling in other soft tissues. Numerous animal studies have also demonstrated placental transfer of lead to the fetus (see Carpenter, 1974, for relevant literature).

The intracellular distribution of lead has been studied in rat tissue, mainly by cell fractionation techniques (Castellino & Aloj, 1969; Barltrop et al., 1971). Lead has an affinity for membranes of the cell, particularly mitochondria. These organelles undergo functional and ultrastructural changes in organs showing lead effects, e.g. renal tubular cells (Goyer & Krall, 1969). Little lead is found in lysosomes (Barltrop et al., 1971) in contrast with the intracellular distribution of many other metals, e.g. mercury, copper, iron.

There are few studies indicating the concentration of lead in target organs that will produce effects. Formation of nuclear inclusion bodies is observed in rats with renal lead concentrations of about 10 mg/kg (wet weight) of kidney (Goyer et al., 1970a). Other effects of lead were found to occur at higher levels of organ concentration. Death in cattle is associated with lead levels of about 50 mg/kg of kidney cortex (wet weight) (Allcroft & Blaxter, 1950).

The concept of estimating the lowest level of metal accumulation that results in adverse effects in a target organ has not been well-explored in the case of lead. This is in contrast with cadmium where estimates have been made of the minimum concentrations of cadmium in the kidney cortex at which evidence of renal damage appears (Friberg et al., 1974).

6.3 Elimination of Lead

The elimination of lead from the body is thought to be mainly by way of the urine and the gastrointestinal tract. Little is known about the miscellaneous routes of excretion such as sweat, exfoliation of skin, and loss of hair.

6.3.1 Human studies

An approximation of the relative contributions of the various routes to lead excretion in man has been given by Rabinowitz et al. (1973). This study refers to only one non-occupationally exposed human subject. Excretions via the kidneys and the gastrointestinal tract were measured directly. Loss via other routes, e.g. hair, fingernails, and sweat, was estimated from data on the efflux of ^{204}Pb from the blood compartment. Losses per day were as follows:

urine	38 μg (76 %)
gastrointestinal secretions	8 μg (16 %)
hair, nails, sweat, other	4 μg (8 %)

The figure of 38 μg for daily urinary excretion is consistent with the data of Teisinger & Srbova (1959). They reported an average daily urinary lead excretion of 31 μg.

The mechanism of urinary lead excretion in man is not well understood. However, the studies of Vostal (1966) provide strong evidence that the process of renal clearance of lead is essentially glomerular filtration. Extrapolation of a curve of glomerular filtration rate plotted against lead excretion rate resulted in zero lead excretion at zero filtration. The form of lead appearing in the urine has not been defined. One study suggests that the form in which lead appears in the urine depends on whether exposure to lead is normal or elevated. Thus, in lead workers with high urinary lead excretion, it has been found that only one-half to two-thirds of the urine lead can be precipitated with co-precipitating agents such as oxalate, phosphate, or carbonate. By contrast, virtually all the lead in the urine of people with normal lead exposure can be co-precipitated (Dinischiotu et al., 1960). This suggests that a stable lead chelate species arises with elevated exposure. Nuclear inclusion bodies or lead–protein complexes are found in the urine of children with acute lead poisoning (Landing & Nakai, 1959).

The rate of biliary excretion of lead in man is not known.

The biological half-time of lead is extremely difficult to estimate. The constantly decreasing availability of the major stores of lead in osseous tissue makes it virtually impossible to describe the rate of loss from the body in simple terms. It is at least clear that, in man, clearance of one-half of a body burden of lead would require a number of years.

6.3.2 Animal studies

Animal data on the routes of lead excretion suggest a considerable species variation. In rats (Castellino et al., 1966) and in sheep (Blaxter & Cowie, 1946) excretion by biliary and transmucosal routes is greater than urinary excretion. On the other hand, the ratio of urinary to gastrointestinal lead excretion in the baboon is 2:1 (Eisenbud & Wrenn, 1970). Vostal (1966) studied the mechanism of lead excretion in dogs. In mild chronic intoxication, excretion was by glomerular filtration, without evidence of any tubular secretion or reabsorption. With more severe poisoning, there was evidence of renal tubular reabsorption. Evidence was also presented for a tubular secretory mechanism in the chicken.

6.4 The Metabolism of Alkyllead Compounds

The characteristic toxic effects of tetraethyllead and tetramethyllead are not caused by the tetraalkyl compounds themselves, but rather by the trialkyl derivatives formed by dealkylation in the liver (Cremer, 1959; Cremer & Callaway, 1961). Tetraethyllead is initially converted mainly to triethyllead and partly to inorganic lead (Bolanowska, 1968). The triethyllead concentration in organs then falls only slowly. Even after several days, there is no significant reduction. The behaviour of tetramethyllead is quite similar to the behaviour of tetraethyllead. Tetramethyllead is much less toxic probably because it is dealkylated to the trialkyl toxic form much more slowly than is the case with tetraethyllead (Cremer, 1965).

Since both these compounds have toxic and biochemical effects unlike those of inorganic lead, it is not to be expected that the biochemical tests used in assessing inorganic lead exposure would have the same significance as in exposure to organic lead. Indeed, in severe cases of tetraethyllead poisoning, urinary coproporphyrins and ALA excretion are usually not elevated, and free erythrocyte porphyrins are only moderately and inconstantly elevated (Gutniak et al., 1964; Beattie et al., 1972b). These biochemical tests are therefore of little use in short-term exposure situations. But, in long-term exposure situations, it is possible that some of them may be useful. Indeed, Robinson (1974) has shown that in workers industrially exposed to tetraethyllead, the urinary excretion of ALA is increased, but not to the same degree as in workers exposed to inorganic lead who have equivalent levels of total urinary lead excretion (organic plus inorganic). This suggests that some portion of total urinary lead is reflecting alkyllead exposure. Bolanowska et al. (1967) demonstrated that,

in three fatal cases of tetraethyllead poisoning, the ratio of inorganic lead to triethyllead ranged from 67:1 to 18:1 in the urine. But this ratio did not reflect the ratio of inorganic to triethyllead in tissues at all accurately. In tissues, including the brain, the ratios were approximately 1:1.

7. EXPERIMENTAL STUDIES ON THE EFFECTS OF LEAD

The major part of published experimental work on animals describes or aims to explain pathological or pathophysiological changes caused by lead. It does not contribute much to the understanding of the relationship between the dose administered, its distribution in a period of time, and the biological effect. The doses used in most animal experiments have, as a rule, been far above the levels that can occur in environmental or occupational contact with lead, with the exception of accidental ingestion of soluble lead compounds.

7.1 Animal Studies

7.1.1 Haemopoietic system

Experimental studies on the effects of lead on blood and haemopoiesis have been carried out essentially to study pathogenic mechanisms. There are few studies dealing with the relationship between the lead dose and blood changes.

There is a great deal of evidence showing that lead inhibits several enzymes that participate in haem synthesis. Inhibition of these enzymes is invoked to explain the rises in haem intermediates that occur as a result of lead exposure. Thus, the rise in erythrocyte protoporphyrin is readily explained on the basis of the well known inhibitory effect of lead on the mitochondrial enzyme ferrochelatase (EC 4.99.1.1) (haem synthetase). This action was first proposed by Rimington (1938) as the probable explanation for the anaemia in lead poisoning. Numerous studies have since confirmed that lead is indeed a rather potent inhibitor of haem synthetase (Dresel & Falk, 1954; Goldberg et al., 1956; Klein, 1962).

Although specific inhibition of the enzyme haem synthetase is usually invoked to explain the accumulation of protoporphyrin, it is also possible that the availability of iron for coupling with protoporphyrin is inhibited by lead. It has been shown that lead interferes with the transfer of iron from transferrin to human reticulocytes (see section 8.2.1). Further support for

the idea that lead interferes with the availability of iron is to be found in studies showing that lead causes accumulation of iron as "ferruginous micelles" in developing erythrocytes (Bessis & Jensen, 1965). Mitochondrial damage was evident in these studies, suggesting the possibility that globin synthesis may be compromised, along with haem synthesis.

The increased excretion of coproporphyrin III in urine is suggestive of an inhibition by lead of the enzyme coproporphyrinogen oxidase (EC 1.3.3.3), which converts coproporphyrinogen III to protoporphyrin IX (PP) (Goldberg, 1972). There is no supportive evidence showing a direct inhibitory effect on this enzyme. One would imagine that inhibition of coproporphyrinogen oxidase (EC 1.3.3.3) would result in decreased blood levels of protoporphyrin IX, however, the opposite is true. Perhaps the concurrent rise in erythrocyte protoporphyrin, ALA excretion, and excretion coproporphyrin III in urine can be explained on the basis of δ-aminolevulinate synthase (EC 2.3.1.37) (ALAS) stimulation. Stimulation of ALAS activity by lead acetate *in vivo* has been demonstrated in the avian hepatocyte, probably due to impairment of haem synthesis (Strand et al., 1972). By contrast, Gajdos & Gajdos-Török (1969) found no change in the ALAS activity of bone marrow or liver in experimental lead intoxication of rabbits.

Animal studies have been reported concerning ALAD inhibition by lead in tissues concurrently with inhibition in the circulating erythrocytes. This has been shown in the blood, brain, and liver of suckling rats (Miller et al., 1970). After 30–40 days of exposure, erythrocyte ALAD underwent an 80–90% reduction. The blood lead concentration in these rats is not given but can be estimated from data in the report. It is stated that a maximum of 3 ml of blood was obtained from each rat. It also appears that the blood specimens each contained about 4.5 μg of lead. Therefore the blood lead concentration must have been at least 150 μg of lead per 100 ml of blood, and was probably nearer to 200.

In other studies, in which long-term lead exposure of rats resulted in about 50% inhibition of erythrocyte ALAD, there was no inhibition of brain or liver ALAD (Coulston et al., 1972a): this may be due to the fact that the exposure levels were lower in this study than in the others cited.

The question of the significance of lead exposure in relation to haemoglobin formation has been studied in dogs by Maxfield et al. (1972). These authors were mainly concerned with the question of whether the depression of ALAD activity in the peripheral blood was in any way associated with depressed formation of haemoglobin. Dogs were given lead over a period and the ALAD activity fell to a very low level. But the ability of the dogs to regenerate haemoglobin after removal of half of the circulating blood volume remained essentially normal. Although this

indicates that the inhibition of ALAD activity in peripheral blood may not be significant, it should be pointed out that the lead exposure was not sufficiently high to cause any substantial rise in ALA excretion in the urine. ALA excretion was only approximately two–three times the baseline level.

There is evidence that the synthesis of globin is affected by lead in animals as well as in man. In an *in vitro* study, it was shown that the incorporation of ^{14}C-glycine into globin in duck erythrocytes was reduced by 25% by a lead concentration of 5×10^{-4} M (Kassenaar et al., 1957). The reduction of ^{14}C-glycine incorporation into haem was considerably greater.

Relatively little is known about the effects of lead on the formation or activity of other haem-containing compounds in the body. There is some evidence, however, that lead can inhibit formation of cytochrome P-450, a haemoprotein intimately involved in the drug-metabolizing mixed function oxidase system of hepatic microsomes (Alvares et al., 1972). Long-term lead administration has also been shown to affect the activity of cytochrome *c* oxidase (EC 1.9.3.1) (Makašev & Verbolovič, 1967; Verbolovič, 1965). The effects seen were of a mixed nature, involving first stimulation then depression of activity. A decrease was also observed in the myoglobin concentration of some muscle groups. It is not clear from these studies whether the effects were due to inhibition of haem synthesis or of protein synthesis.

Administration of lead to rats (over a period of 6 months) in doses of 2–4 g per rat, resulted in a change in cytochrome *c* oxidase (EC 1.9.3.1) activity and in the amount of haemoglobin. The magnitude of the change increased with larger doses (Verbolovič, 1965). Dogs were given a solution of lead acetate over a 2-year period resulting in a reduction in the activity of cytochrome *c* oxidase (EC 1.9.3.1) that was in proportion to the dose of lead administered (Makašev & Verbolovič, 1967).

By means of electron microscopy, Pernis et al. (1964) showed grossly swollen mitochondria in the erythrocytes of lead-poisoned guinea-pigs, diverse vacuolar formations, and aggregates of molecules of ferritin. Electron microscopy of erythrocytes of rabbits receiving an intravenous dose of 20 mg/kg of 2% lead acetate solution showed vacuolization of the cytoplasm and swelling of the plasma membrane. An intensive vacuolization in thrombocytes and a reduction in the quantity of organelles, particularly those containing serotonin, also took place. In addition, a swelling of mitochondria after the complete disruption of cristae was noted (Hačirov, 1972). An experiment on rats showed ultramicroscopic changes of mitochondria in the red bone marrow cells in the early stages of poisoning.

7.1.2 Nervous system

7.1.2.1 *Inorganic lead*

In view of recent concern about subtle impairments of cerebral function at sub-encephalopathic levels of lead exposure, there has been a renewed interest in lead and its toxic effects. High doses of lead will produce encephalopathy; this has been reported in cats (Aub et al., 1926) and dogs (Staples, 1955).

The brains showed histopathological features similar to those described in human encephalopathy. Others have since reproduced this syndrome in the rat (Thomas et al., 1971; Michaelson, 1973; Clasen et al., 1974) and in the mouse (Rosenblum et al., 1968; Silbergeld & Goldberg, 1974). The effects may be explained on the basis of retardation of brain development (Michaelson, 1973; Krigman et al., 1974).

Paraplegia was reported in suckling rats by Pentschew & Garro (1966). The disease was produced by transfer of lead from the mother's milk until weaning, with subsequent post-weaning feeding of lead to the young.

Behavioural abnormalities such as excessive self-grooming and aggressiveness occur, even when the lead intake is reduced to a point where paraplegia no longer occurs (Michaelson & Sauerhoff, 1974). It was estimated that the minimum daily lead intake causing behavioural effects (Michaelson & Sauerhoff, 1974) rose from 0.08 mg/kg body weight at birth to 3 mg/kg at day 16 as a result of suckling. Post-weaning, this minimum intake rose from 50 mg/kg at day 20 to 60 mg/kg at day 28. From day 16 to day 20, intake was difficult to estimate since the infant rats were eating and suckling to different degrees. Other studies in rats (Snowdon, 1973) and sheep (Carson et al., 1974) indicate that offspring of mothers exposed to lead during pregnancy show learning defects. Older animals are refractory to this type of effect (Brown et al., 1971).

Future behavioural studies should probably be extended to include subhuman primates since it has been shown that the histological and clinical features of lead encephalopathy can be produced in both infant and adult baboons (Cohen et al., 1972; Hopkins & Dayan, 1974).

Studies of lead neuropathy in animals indicate that demyelination and axonal degeneration are more consistent findings than neuronal damage in the anterior horn cells or dorsal root ganglia of the spinal cord (Lampert & Schochet, 1968; Schlaepfer, 1969; Fullerton, 1966). This is consistent with findings in man. The slowing of nerve conduction found in man has also been produced experimentally in the guinea-pig (Fullerton, 1966).

It is known that lead interfers in some manner with synaptic transmission in the peripheral nervous system and that the effects can be reversed by calcium (Kostial & Vouk, 1957). But, in addition, an increased

frequency of miniature end-plate potentials has been reported (Manalis & Cooper, 1973). Neuromuscular blockade has also been demonstrated in the rat phrenic nerve-hemidiaphragm preparation (Silbergeld et al., 1974). Again, as in the other studies, the effect was antagonized by calcium. The significance of these findings with regard to the central nervous system remains to be determined.

Studies at the biochemical level have been very limited. It has been shown, using the "Pentschew model", that incorporation of ^{14}C-glucose carbon into dicarboxylic amino-acids of the brain is reduced (Patel et al., 1974a, 1974b). These results were interpreted to indicate delayed brain maturation.

Recent work in dogs (Stowe et al., 1973) has mapped the variation in lead concentrations in different parts of the brain of lead-poisoned dogs. The studies show a relationship between areas of the most marked histological change and high lead concentration. Male pups from the same litter were fed a purified diet, low in calcium and phosphorus, with and without 100 mg/kg of lead as lead acetate from the age of 6–18 weeks. The concentration of lead in the various brain segments is given in Table 21.

Table 21. Distribution of lead in the brains of control and lead-intoxicated dogs[a]

Brain segment	Lead concentration (mg/kg of wet tissue)	
	Control	Lead intoxicated
Cerebellum	0.160 ± 0.052	0.587 ± 0.113
Medulla	0.155 ± 0.007	0.713 ± 0.112
Frontal white	0.053 ± 0.027	0.920 ± 0.156
Thalamus	< 0.10	1.023 ± 0.142
Occipital white	0.020 ± 0.012	1.030 ± 0.115
Caudate	0.120 ± 0.083	1.613 ± 0.345
Frontal grey	0.033 ± 0.015	1.767 ± 0.254
Occipital grey	0.080 ± 0.071	2.357 ± 0.181

[a] Adapted from Stowe et al., 1973.

7.1.2.2 *Alkyllead compounds*

Unlike the case with inorganic lead, intoxication by tetraethyllead in juvenile or adult rats caused a characteristic encephalopathy, involving restlessness, ataxia, combativeness progressing to convulsions, coma, and death (Davis et al., 1963). In dogs there was extensive muscular tremor and twitching, which progressed to convulsions, coma, and death.

Biochemical studies of the respiration of brain slices incubated with inorganic lead compared with triethyllead (the active metabolite of tetraethyllead) have substantiated the fundamental difference in the action of alkyllead compounds on the brain (Cremer, 1959). The toxic moieties in

tetraethyllead and tetramethyllead poisoning are the trialkyl metabolites and not the inorganic lead ion.

Essentially there is no qualitative difference between the toxic effects of tetramethyllead and tetraethyllead. However, there is a quantitative difference in that the inhalation LC_{50} for tetramethyllead (8870 mg/m^3) is about 10 times higher than that for tetraethyllead (850 mg/m^3) (Cremer & Callaway, 1961). The intravenous LD_{50} for tetraethyllead is about 10 mg of lead per kg of body weight in the rat (Cremer, 1959). This is in contrast to the intravenous LD_{50} for inorganic lead, which is approximately 70 mg/kg in the rat (Fried et al., 1956). The precise manner in which the trialkyllead ion acts to cause altered brain function is not clearly known but the mechanism may involve inhibition of amine oxidase (flavin-containing) (EC 1.4.3.4) (monoamine oxidase) (Galzigna et al., 1964). In rabbits, administration of toxic doses of tetraethyllead results in a loss of copper, iron, and zinc in certain areas of the brain (Niklowitz & Yeager, 1973), suggesting that triethyllead may act by displacing certain essential trace metals from metalloenzymes in the brain.

Tetramethyllead injected into rats in overtly neurotoxic doses did not depress ability to learn a simple task (Bullock et al., 1966).

7.1.3 Renal system

Animal studies have contributed to an understanding of the order of appearance of the various manifestations of renal toxicity in lead exposure. The spectrum and train of events as related to the exposure time and to the dose of lead have recently been reviewed (Goyer & Rhyne, 1973). In the earliest stage of renal response to lead exposure, reversible tubular effects occur. These include the appearance of intranuclear inclusion bodies, which is probably a mechanism for sequestration of lead. These bodies have been isolated and found to be composed of a lead–protein complex. The protein is insoluble in physiological solutions and is rich in acidic amino acids. It has not been characterized further (Moore & Goyer, 1974). The intranuclear inclusion bodies appear to have a high and specific affinity for lead compared with that for calcium, iron, zinc, copper or cadmium and about 90% of the lead in the kidney is associated with them (Goyer et al., 1970a; 1970b).

The appearance of these bodies is accompanied by amino aciduria, glycosuria, and hyperphosphaturia. Morphological and functional changes in tubular epithelial cells also occur at this stage, including impaired respiratory and phosphorylative ability.

After further lead administration, more severe changes occur in the renal tubular epithelium such as hyperplasia and cystic changes. There is a

progressive increase in interstitial fibrous tissue and atrophy of tubular cells. These are irreversible changes that lead to a third stage of renal failure, manifested by azotaemia and hyperuricaemia. Sclerotic glomeruli appear, but the hypertension seen in some cases of chronic lead nephropathy in man has not been reproduced in experimental animals

The sequence described above in animals is probably generally valid for man.

7.1.4 Gastrointestinal tract

The effects of lead on the gastrointestinal tract have been studied in some detail in the guinea-pig (Mambeeva & Ahmiedova, 1967). Spastic contractions occurred from the stomach to the jejunum. Inhibitory effects were also noted, accounting for the frequent constipation seen to accompany lead colic.

7.1.5 Cardiovascular system

Experimental animal data on the question of hypertension are conflicting. Among rats given 70 mg of lead acetate per day orally, only a few survived 40 days and all were hypertensive (Griffith & Landauer, 1944). Hypertension has also been produced in the rabbit (Beckmann, 1925). Others have not seen hypertension with lead exposure in rats (Padilla et al., 1969) or dogs (Fouts & Page, 1942). From all the above animal studies it seems that hypertension can occur with heavy lead exposure.

There are conflicting reports regarding whether lead can cause atherosclerosis in experimental animals. Sroczynski et al. (1967) observed increased serum lipoprotein, cholesterol, and cholesterol deposits in the aortas of both rats and rabbits receiving large doses of lead. On the other hand, Přerovská (1973) did not produce atherosclerotic lesions in rabbits using similar doses of lead given over an even longer period of time.

Cardiac myopathy has also been shown experimentally in lead-intoxicated rabbits (Kosmider & Sroczynski, 1961). The mechanism for this effect is not known.

Kuz'minskaja (1964) and Mirončik & Timofeeva (1974) observed that rabbits receiving lead after a cholesterol load showed more intense sclerotic changes in the aorta and myocardium than rabbits on a normal diet without lead, or than rabbits given cholesterol alone.

Makašev & Krivdina (1972) observed a phased change in the permeability of blood vessels (first phase—increased permeability; second phase—decreased permeability) in rats, rabbits and dogs, that received a solution of lead acetate. A phased change in the content of catecholamines

in the myocardium and in the blood vessels was observed in subacute lead poisoning in dogs (Mambeeva & Kobkova, 1969). This effect appears to be a link in the complex mechanism of the cardiovascular pathology of lead poisoning.

7.1.6 Respiratory system

Alveolar macrophages from guinea-pigs are damaged *in vitro* by inorganic lead compounds (3 μg/1 × 10^6 cells) thus releasing a rapidly occurring lysis and a slowly developing, coarsely blistered vacuolization. More than 90 % of the cells are damaged within 20 hours (Beck et al., 1973).

Similar effects seem to occur in the organism, since in rats that had inhaled 10 μg lead/m^3 for 3–12 months, the number of macrophages that could be flushed from the lungs was reduced by 60 % (Bingham et al., 1968).

Electron microscope investigations of the lungs of rats that had been exposed for 14 days to concentrations of 100–200 μg of lead oxide/m^3 revealed toxic effects in the alveolar macrophages and the type I alveolar epithelial cells. The structures of the endoplasmatic reticulum and mitochondria were changed (Bruch et al., 1973).

In the lungs, the alveolar macrophages have the capacity to degrade noxious substances and are important for other defence reactions. The ability of alveolar macrophages of guinea-pigs that had inhaled concentrations of 70–170 μg of lead per m^3 of air for four days, to degrade benzo[a]pyrene was distinctly decreased, the benzopyrene 3-monooxygenase (1.14.14.2) activity being only about 10 % of the original value. The activity returned to normal after three days without any lead exposure (Bruch et al., 1975). The elimination of bacteria from the lungs was also reduced, when rats were exposed to 70 μg of lead per m^3 of air (Schlipköter et al., 1977).

7.1.7 Reproductive system

Animal studies support the contention that behavioural deficiencies can occur in infants and newborn as a result of intrauterine exposure to lead via their mothers (see section 7.1.2). Others have shown a reduction in the numbers and size of offspring (Dalldorf & Williams, 1945; Puhae et al., 1963). Data in rabbits (Cole & Bachhuber, 1914), guinea-pigs (Weller, 1915), and rats (Stowe & Goyer, 1971) indicate that paternally-transmitted effects can occur, including reductions in litter size, weights of offspring, and in survival rate. Several investigators have reported that oral administration of lead to animals even at doses in the microgram per kilogram range can cause changes in spermatogenesis (Egorova et al., 1966;

Golubovič et al., 1968), and an increase in testicular RNA and DNA content (Golubovič & Gnevkovskaja, 1967; Golubovič et al., 1968).

7.1.8 Endocrine organs

The effects of lead on thyroid function that have been reported in man have also been demonstrated experimentally in rats (Zel'tser, 1962; Sandstead, 1967).

7.1.9 Carcinogenicity

7.1.9.1 *Inorganic lead compounds*

The carcinogenic risk to man of lead salts and the relevant studies in animals have recently been discussed in an IARC publication (IARC, 1972).

The induction of benign and malignant renal neoplasms has been observed in both Swiss mice and rats fed on diets containing 100 or 1000 mg of basic lead acetate ($Pb(C_2H_3O_2)_2.2Pb(OH)_2$) per kg of diet (Van Esch & Kroes, 1969; Van Esch et al., 1962; Mao & Molner, 1967; Azar et al., 1973). Similar results were observed in rats fed 1000 mg of lead acetate ($Pb(C_2H_3O_2)_2.3H_2O$) per kg of diet (Boyland et al., 1962). In addition to renal neoplasms, tumours of the testes, the adrenal, thyroid, pituitary, and prostrate glands and of the brain have been reported in rats fed lead acetate or basic lead acetate, but the results await confirmation (Zawirska & Medras, 1968; Oyasu et al., 1970). Rats given intraperitoneal or subcutaneous injections of lead phosphate also developed renal tumours. Total doses of 120–680 mg of lead were effective (Zollinger, 1953; Roe et al., 1965). No kidney tumours were reported in hamsters fed 100 or 500 mg of basic lead acetate per kg of diet for up to 2 years (van Esch & Kroes, 1969).

In Syrian golden hamsters given a combination of lead oxide and benzo[a]pyrene intratracheally once weekly for 10 weeks, lung adenomas occurred in 11/26 animals within 60 weeks. One adenocarcinoma of the lung was also observed. Such tumours did not occur in animals given the same dose of lead oxide or benzo[a]pyrene alone (Kobayashi & Okamoto, 1974).

7.1.9.2 *Alkyllead compounds*

Epstein & Mantel (1968) reported that subcutaneous injection of 0.6 mg of tetraethyllead (given as 4 equally divided doses) to Swiss mice between birth and 21 days of age produced malignant lymphomas in 1/26 males and 5/41 females, compared with 1/39 and 0/48 controls. In treated females, the

tumours were observed between 36 and 51 weeks after the first injection. The significance of this finding in female mice is difficult to assess since this tumour occurs frequently and with variable prevalence in untreated mice of this strain.

7.1.10 Mutagenicity

Chromosomes from leukocyte cultures from mice fed 1 % lead acetate in the diet showed an increased number of gap-break type aberrations (Muro & Goyer, 1969). These changes involved single chromatids, suggesting that injury followed DNA replication.

7.1.11 Teratogenicity

There have not been any adequate animal studies to provide evidence to support the suggestion that lead may have a teratogenic effect.

7.2 Acquisition of Tolerance to Lead

Although human studies suggest that there is no acquired tolerance in regard to haem-synthesis mechanisms, there may be for other toxic effects. In this regard, it is interesting to note that the blood lead level at which cattle develop severe encephalopathy from eating paint is often less than 80 µg/100 ml (Hammond et al., 1956). However, in cattle receiving 5–6 mg of lead per kg per day orally, the concentration of lead in the blood exceeded 100 µg/100 ml within 2–4 months and remained at about that level for as long as four years with continuous administration, without any apparent harm to the animals (Allcroft, 1951). In these studies, haemoglobin did not fall until a terminal illness developed. Hapke (1974) found that in cattle and sheep the sensitivity to acutely toxic amounts of lead was reduced by a pretreatment with lead for 5 months. Goyer et al. (1972) have suggested from their studies on rats that the intranuclear inclusion bodies that develop during lead exposure serve as a protective mechanism by binding lead in the kidney, making it less toxic. But in the recent study of Cramer et al. (1974) (see section 7.1.3) it was shown that renal intranuclear inclusion bodies are present only in workers exposed to lead for a relatively short period of time. Thus, if inclusion bodies serve some protective function, it is only during a limited period of exposure. The formation of the cadmium-binding protein, metallothionein, which appears to have a protective role in cadmium exposure, is induced by a number of metals but not by lead (Webb, 1972).

7.3 Factors Influencing Lead Toxicity

7.3.1 Age and sex

It has recently been reported that the intraperitoneal lethal dose of lead in rats is significantly lower for adult male rats than for adult female rats (Kostial et al., 1974). In the same study, it was observed that the lethal dose in mg/kg body weight for 3-week-old rats was about the same as for adult females.

7.3.2 Seasonal variations

The same seasonal pattern of high incidence of poisoning has been reported in dogs belonging to urban families as has been reported in children (Zook et al., 1969). It has also been shown experimentally in rats and mice (Baetjer, 1959; Baetjer & Horiguchi, 1963) and in rabbits (Blackman, 1937; Horiuchi et al., 1964) that susceptibility is greater at high ambient temperatures than at normal temperatures.

7.3.3 Nutrition

Experimental studies have shown that nutritional factors may influence the absorption of lead from the gastro-intestinal tract and thus alter susceptibility to the toxic effects of lead (Goyer & Mahaffey, 1972). Low phosphorous and calcium in the diet (Sobel et al., 1938b; Six & Goyer, 1970), high vitamin D (Sobel et al., 1938a), and low iron (Mahaffey, 1974) all enhance lead absorption. The amount and the composition of dietary protein may also influence lead toxicity. Low protein diets appear to increase the susceptibility to lead intoxication as compared to high protein diets (Baernstein & Grand, 1942; Goyer & Mahaffey, 1972).

The significance of these findings for the susceptibility of people to lead poisoning has not been established. However, many children, even in developed countries like the USA, have sub-optimal dietary intakes of calcium, iron, and other nutrients (US Department of Health, Education and Welfare, cited by Mahaffey, 1974). This may have a bearing on the problem of increased lead absorption frequently found in children in poor, urban areas.

7.3.4 Intercurrent disease, alcohol, and other metals

High lead exposure increases the susceptibility of mice to *Salmonella typhimurium* infection (Hemphill et al., 1971). Lead administration also increases the susceptibility of rats (Filkins & Buchanan, 1973; Selye et al.,

1966; Erve & Schumer, 1972), mice (Clercq de & Merigan, 1969), and baboons (Hoffman et al., 1974) to endotoxin shock, but such studies have been performed using extremely large intravenous doses of lead simultaneously with the endotoxin.

Administration of ethanol (10% *ad libitum* in drinking water) had no effect on the toxicity of lead to rats as measured by urinary ALA excretion, renal weight, or lead concentration in the kidneys, liver, or bones (Mahoffey, 1974).

Very little is known about metal interactions and how they might affect the toxicity of lead, except at the nutritional level (see section 7.3.3). Beyond that, a synergistic effect has been noted between lead and cadmium with regard to experimental teratogenesis (Ferm, 1969). It was also found that zinc, given in the diet with lead, protected horses against the toxic effects of lead. Probably, this effect was not due to inhibition of lead absorption. Zinc supplementation actually caused an increase in the lead content of liver and kidney, but a decrease in the lead content of brain and bone (Willoughby et al., 1972). It might be inferred that zinc displaced lead from lead-inhibited enzymes that are zinc-dependent, such as ALAD (Cheh & Neilands, 1973). A dose-dependent effect of zinc, antagonistic to the depression of ALAD by lead, has recently been shown *in vivo* and *in vitro* as well as an *in vitro* antagonism of zinc on the cytotoxic effect of lead on macrophages (Schlipköter et al., 1975; Ruiter de et al., 1977).

7.4 Human Studies

Planned experimental studies on the effects of lead in man are sparse. Kehoe (1961), in his famous experimental studies, in which human volunteers were exposed to a known amount of lead over various periods of time, confined himself to studying the lead balance only, and did not report on the effects of lead.

Three subjects ingested 1 and 3 mg of lead daily, in the form of lead (II) nitrate, for 33 weeks. The ALA-U, CP-U, and erythrocyte protoporphyrin IX were measured regularly while Pb-B and Pb-U measurements were performed at irregular intervals (Schlegel et al., 1973). Exposure from food and ambient air was not controlled during the experiment. A rise in FEP was obtained with both doses and a rise in ALA-U and CP-U only with the 3 mg dose. Evaluation of the results obtained in this study is difficult, partly because of the small number of subjects studied and partly because the results were rather erratic.

Coulston et al. (1972b; 1972c) conducted two exposure chamber experiments on male volunteers (see section 6.1.1.2). The volunteers were exposed to air lead concentrations with an average of 10.9 and 3.2 $\mu g/m^3$

for up to 17 weeks. In the 10.9 μg/m^3 exposure study, 24 volunteers participated, 6 of whom served as controls. In order to control dietary lead exposure, total diet for one full day was collected at intervals of eight days; the results indicated an average lead intake of about 110 μg/day only. The variables measured were the Pb-B, ALAD, ALA-U, and CP-U. Blood lead levels increased in all of the exposed men and appeared to stabilize after about 12 weeks of exposure. The mean Pb-B level at that time was about double the pre-exposure mean, i.e., an increase from 19 to 37 μg/100 ml. A concomitant increase of the urinary excretion of lead was reported; the faecal excretion remained unchanged however. The rise in blood lead levels was followed by a decrease in ALAD activity, which after 5 weeks of exposure was about 50% of the pre-exposure level. No change in ALA-U and CP-U was reported. Five months after the termination of the exposure, all but one of the participants had Pb-B values similar to those before exposure. The ALAD activity returned to normal almost immediately after cessation of exposure. No changes in the haemoglobin level were noted during the experiment. In the 3.2 μg/m^3 experiment a rise in the Pb-B level from 20 to 26 μg/100 ml was obtained, followed by a slight decrease in ALAD activity, which after five weeks of exposure was about 85% of the pre-exposure level. Other changes were not reported.

In a recent experimental study, a greater susceptibility to inorganic lead was demonstrated in females (Stuik, 1974; Stuik & Zielhuis, 1975). The volunteers were healthy male and female students aged 18–26 years. Groups of 5 males and 5 females received 20 μg of lead per kg per day orally for 21 days. Lead was administered as lead acetate in glycerol.

The control blood lead levels remained fairly constant at approximately 17 μg/100 ml during the experiment. The exposed male subjects showed an increase from 20.6 μg/100 ml to 40.0 μg/100 ml at the end of the second week of exposure (40.9 μg/100 ml in the third week). The blood lead in females rose from 12.7 μg/100 ml to 30.4 μg/100 ml, the highest level being reached in the first part of the third week.

The protoporphyrin IX content of the erythrocytes showed no change in either the control or the exposed male group. However, in the female group, it showed a rise beginning in the third week and rising to 48.0 μg/100 ml erythrocytes. The findings were confirmed in a second experiment.

It is suggested that the increase of the erythrocyte protoporphyrin IX was a result of interference in the use of iron in the formation of haemoglobin. The synergism of lead exposure and iron deficiency might be suggested as being responsible for the increased response of FEP in females but this will have to be tested further in experimental and epidemiological work.

8. EFFECTS OF LEAD ON MAN— EPIDEMIOLOGICAL AND CLINICAL STUDIES

Two types of study characterizing the effects of lead on man have been reported:

— retrospective studies of the causes of mortality and morbidity in lead-exposed populations compared with unexposed populations, and

— studies of the effects of lead on specific organs and systems.

The findings from these two types of study will be considered separately. In both cases, the main objective will be to establish, as far as possible, the dose of, or exposure to lead which is associated with specified effects, and the frequency of such effects.

From the toxicological point of view, "the dose should be defined as the amount or concentration of a given chemical at the site of effect, i.e. where its presence leads to a given effect" (Nordberg ed., 1976). The application of this definition is difficult because the dose as defined above can rarely be measured directly and has to be estimated in various ways. In experiments, it is estimated from the amount injected or ingested or from dermal and other topical applications (using appropriate absorption factors and body distribution factors). In inhalation experiments it is estimated from the concentration as measured in air, the time of exposure, and the relevant deposition, retention, and absorption factors (if available). The same considerations apply for dose estimation from occupational exposure where, in addition to inhalation, the possible dermal exposure, ingestion during work-time, and exposure which workers are subject to as members of the general population, should be taken into account. The dose for the general population is estimated from inhalation of air, ingestion of food, water, and other beverages, and various other contacts, including drugs and consumer products, smoking, and in children, ingestion of soil, settled dust, and paint chips. A more direct way of estimating the dose is from measurements in body tissues and fluids such as blood, urine, faeces, sweat, or hair. Other organs, tissues, cells, and subcellular elements can be used for this purpose in animal experiments or in autopsy or biopsy material.

Although the biological effects of lead on man have been characterized in some detail, the precise doses of lead responsible for the effects are rarely, if ever, known. With all its acknowledged shortcomings, the Pb-B level is the vital link between exposure and an effect. In section 6, an effort was made to define, as far as possible, the relationship between the lead in air and in the diet and Pb-B levels. The main objective of this section is to establish the relationship between Pb-B levels and biological effects. Only

in this way is it possible to estimate the possible biological consequences of specific levels of lead in environmental media.

Some biological effects of lead bear a close relationship to concurrent Pb-B levels, others do not. Thus, the degree of ALAD inhibition in peripheral blood rises and falls more or less concurrently with the Pb-B level, while some renal effects of lead are the consequence of an exposure to lead that may have occurred at a point remote in time and which is not reflected in the Pb-B level at the time the effect is first manifested clinically. The fidelity with which the Pb-B level reflects lead concentrations in target organs is subject to serious problems of analytical error as described in section 3.

Beyond these considerations, there is the additional problem of variation in the inherent susceptibility of individuals, and the influence of co-existent variables that may modify this susceptibility, such as nutritional status, age, and presence or absence of diseases such as alcoholism. For all the above reasons, the Pb-B level cannot be used as a reliable indication of dose or exposure in dealing with individual patients. They should be used only in assessing population group exposures at which effects may occur in a certain proportion of individuals.

Other tests for assessing dose have been proposed, e.g. lead excretion in response to chelating agents. Regardless of potential merits and special applications, most information relating health effects to dose has been obtained using Pb-B levels as an estimate or index of dose.

8.1 Retrospective Studies of Lead-exposed Populations

8.1.1 Epidemiology of lead poisoning in industry

In many countries there has been a considerable improvement over the past forty years with respect to hygienic conditions in the lead-using industries. The exposure of workers to lead was considerably higher before 1930 than after. In the United Kingdom, the number of reported cases of poisoning fell dramatically in the decade 1920–30 (Lane, 1964). Against this background, it is useful to consider the studies of Dingwall-Fordyce & Lane (1963). They found a higher than expected incidence of death due to cerebrovascular disease among men with past high lead exposure. The men studied retired from work between 1926 and 1960. All those studied had at least 25 years of service. Men in the heavy exposure category had an average urine lead concentration of 100–250 µg/litre[a] over the last 20 years

[a] 100 µg/litre corresponds to a Pb-B level of approximately 60 µg/100 ml and 250 µg/litre corresponds to a Pb-B level of approximately 120 µg/100 ml (Williams et al., 1969).

of employment. Men in the moderate exposure group had urine lead concentrations in the normal range. The third group had no exposure. As can be seen from Table 22, in the heavy exposure group deaths from cerebrovascular diseases (cerebral haemorrhage, thrombosis, and arteriosclerosis) were much higher than normal.

Table 22. Deaths from cerebrovascular disease in retired and employed workers from a lead industry[a]

Status	Year of death	Grade of exposure					
		None		Medium		Heavy	
		Expected incidence	Observed incidence	Expected incidence	Observed incidence	Expected incidence	Observed incidence
Retired	1926–50	0.7	0	0.2	3	0.8	5
	1951–61	7.2	6	3.2	3	8.5	19
	1926–61	7.9	6	3.4	6	9.3	24[b]
Employed	1946–61	3.2	3	3.1	3	5.6	9

[a] Adapted from Dingwall-Fordyce & Lane, 1963.
[b] $P < 0.001$.

The data also suggest that in this group the excessive death rate was most pronounced among men who retired prior to 1951 when exposure conditions were probably considerably worse than they were later. In the same study, it was found that the death rate from malignant neoplasms was not above the expected rate in any exposure grade. Unfortunately, the incidence of death due to chronic nephritis was not reported. A very similar survey was reported by Malcolm (1971) in which the subjects studied had, with few exceptions, been exposed to lead at moderate levels (average Pb-B level—65 μg/100 ml). There was no statistically significant excess mortality in any of the following disease categories: heart disease, chest disease, cerebrovascular accidents, cancer, renal disease, and "miscellaneous".

A recent American study is in general agreement with the conclusions of the British investigators concerning longevity and causes of death in the lead industries as they have operated over the last 25–30 years (Tabershaw & Cooper, 1974; Cooper & Gaffrey, 1975). The subjects were 1356 workers employed in the lead battery and smelter industries from 1946 to 1970. Both blood lead levels and urinary lead excretion were quite high. For example, 78.7% of 47 smelter workers had Pb-B levels of 80 μg/100 ml or more, from 1946 to 1961. The figure was still 13.5% after 1965 (489 total workers sampled). The percentage of battery workers with Pb-B levels above this was somewhat lower. But for all the various categories of duration of employment and type of work, 81.5–95.7% of the Pb-B levels were equal to or greater than 40 μg/100 ml. About 50% of the workers were employed for more than 10 years. The total mortality in this group was approximately the same as in the general population. The authors

concluded that there was no evidence that work associated with lead increased the risk of death due to the major categories of cardiovascular and renal diseases. However, when chronic renal disease (chronic nephritis or other renal sclerosis) was segregated as a separate cause of death, there did appear to be a significant excess number of deaths. Thus, among smelter workers, the ratio of observed deaths to expected deaths was 7:2.8 and among the battery workers the ratio was 14:8.6. A similar association was found for a category of death classified as "other hypertensive disease": 7:1.9 among smelter workers and 13:6.3 among battery workers. For the two disease categories this adds up to 21 excess deaths out of 1267 for whom cause of death was listed. The authors emphasize that many of the workers in the study group were probably exposed to air lead concentrations considerably in excesss of 0.15 mg/m^3.

Table 23. Urine and blood lead content of persons in the Wenatchee study according to severity of exposure[a]

Group	Urine lead content			Blood lead content		
	No. analyses	Average, µg/litre	S.D. µg/litre	No. analyses	Average, µg/100 ml	S.D. µg/100 ml
Low exposure						
men	146	35	21	148	26	11
women	123	28	19	124	26	10
Intermediate exposure						
men	102	43	30	108	30	11
women	25	27	15	27	22	10
High exposure						
men	386	88	60	329	44	16
women	61	46	25	58	34	13
Children under 15 years						
boys	81	53	39	17	37	15
girls	65	54	40	14	36	10

[a] From Neal et al. (1941)

Although most epidemiological studies on occupational exposure have been carried out on industrial populations, one extensive study on orchard workers in the Wenatchee area of the state of Washington, has been reported (Neal et al., 1941). This study was somewhat complicated by the fact that exposure was to lead arsenate. In view of the known toxicity of arsenic, studies were included on the combined toxicities of lead and arsenic in animals. No synergism was found in these animal studies (Fairhall & Miller, 1941). The blood lead concentrations of the orchard workers and their families are summarized in Table 23.

This study may have been crude in comparison to some more recent ones, but it had the rather unique merit of examining health effects not only in men, but also in women and children. Furthermore, the exposure levels,

as reflected in the urine and blood data of Table 23, were only slightly higher than the approximate upper limit for people living in highly polluted cities today. The study was concerned with weight, blood pressure, diseases of the cardiovascular system, skin disorders, eye irritation, chronic nervous diseases, blood dyscrasias, kidney diseases, neoplastic diseases, and fertility. There was no evidence, based on data available at the time, that the health profile of these people was any different from that of the general population.

In 1968, a follow-up study was undertaken of the people who had participated in the original study (Nelson et al., 1973). Over 97% of the original participants were successfully traced. There had been 452 deaths among the 1231 original participants. A life table method of analysis of the standard mortality ratio was used. The overall mortality was less than the average for the state of Washington. The standard mortality ratios of exposed groups were not consistent with the exposure gradient. The mortality pattern for increasing duration of exposure was not consistent either.

8.1.2 Epidemiology of lead poisoning in the general adult population

Adequate studies of the relationship between lead exposure and health status in the general adult population have not been carried out. The limitations that apply to the epidemiological studies of occupational groups are magnified when applied to the general population. The range of exposure levels is smaller between sub-groups of the general adult population and their socioeconomic, physiological, and health profiles are probably more diverse.

8.1.3 Epidemiology of lead poisoning in infants and young children

There has been only one study reported of general mortality and disease-specific morbidity rate in children exposed to lead. The Wenatchee study referred to in section 8.1.1 included 146 children under the age of 15. As with the adults in this study, no abnormal pattern of disease incidence was noted. These children had moderately high lead exposure (see Table 23).

8.2 Clinical and Epidemiological Studies of the Effects of Lead on Specific Organs and Systems

In the following discussion of the effects of lead on various organs and systems, consideration will be given to dose–effect and dose–response

relationships. The word "dose" as used here will refer to Pb-B levels, as described in the introductory remarks of this chapter.

The diversity of the effects of lead on haemoglobin formation and the complexity of the process itself make it difficult to determine which inhibitory effect is most sensitive and what is their relative importance at different levels of exposure (or dose).

Dose–effect refers to the relationship between dose and the intensity of a specified effect in an individual, e.g. Pb-B level *versus* percentage inhibition of blood ALAD.

Dose–response refers to the relationship between the dose and the proportion of a population showing a defined effect, specified as to the level of intensity, e.g. the proportion of a population showing more than 50% inhibition of blood ALAD at a Pb-B of 20 μg/100 ml.

Some effects of lead are not graded, for example, the effects on the kidney and the central nervous system are usually reported in all-or-none terms, i.e. a certain proportion of individuals in a population are reported to have shown the effect at a given range of Pb-B concentrations. With many effects of lead it is difficult to specify a dose–response or a dose–effect relationship because the available data are inadequate.

8.2.1 Haemopoietic system

The evidence for disturbances in haem synthesis is clearly shown in man by the appearance of abnormal concentrations of haem precursors in blood and urine. The levels of lead exposure at which these various manifestations of disturbed haem synthesis first appear have been studied extensively in man. The sequence of reactions affected by lead, and the consequences thereof, are shown in Fig. 5.

Lead interferes with the biosynthesis of haem at several enzymatic steps, with the use of iron, and with globin synthesis in erythrocytes. Inhibition of ALAD and haem synthetase is well documented, and accumulation of the substrates of these enzymes (ALA and PP) is characteristic of human lead poisoning. Inhibition of ALAS is based on experimental evidence only. Whether there is enzymatic inhibition or whether other factors affect the conversion of coproporphyrinogen III (CPG) to protoporphyrin IX (PP) is not clear; nevertheless, increased urinary excretion of coproporphyrin III is prominent in human lead poisoning. Minor increases in porphobilinogen (PBG) and uroporphyrins in urine are occasionally reported in severe lead poisoning. Although the *in vivo* mechanisms are not clear, nonhaem iron (ferritin and iron micelles) accumulates in red blood cells with damaged mitochondria and other fragments not found in normal mature erythrocytes. Serum iron may be increased in persons with lead

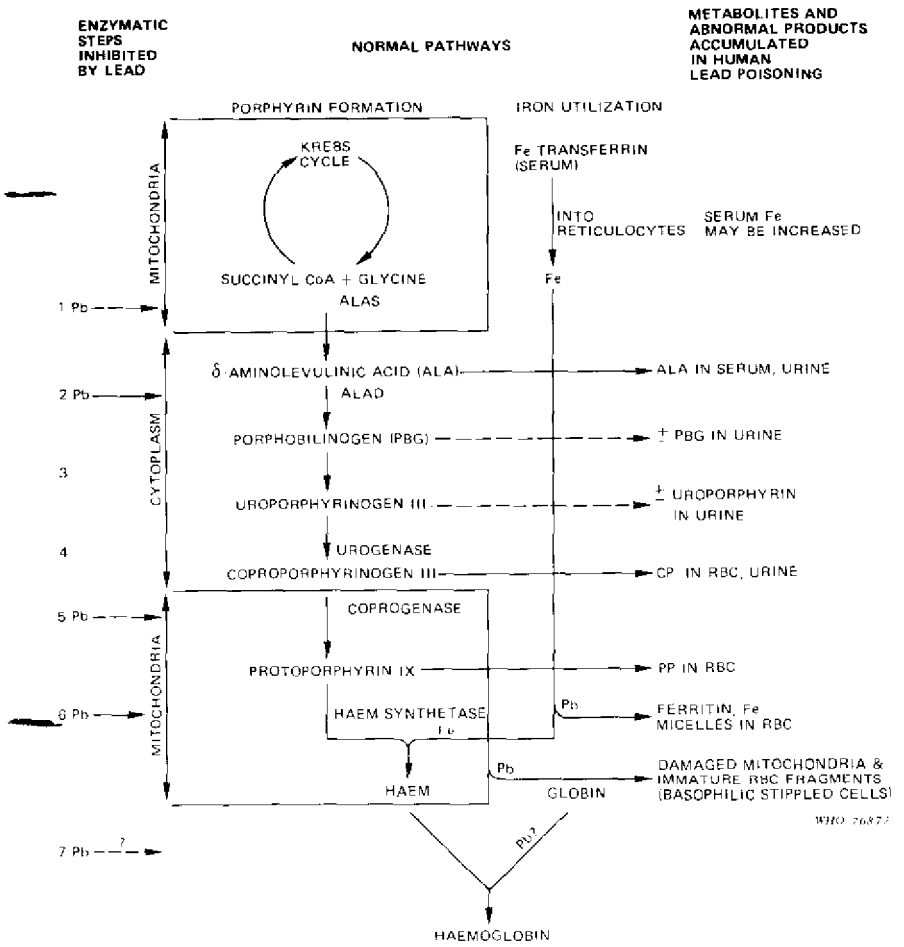

Fig 3 Lead interference with the biosynthesis of haem (NAS-NRC 1972).

poisoning, but without iron-deficiency states. Globin synthesis in red blood cells is apparently impaired, although the mechanisms responsible for reduced globin synthesis remain unknown.

The evidence available suggests that mild anaemia with a small reduction in blood haemoglobin may occur at, or slightly above, dose levels that are associated with minimal increases in urinary excretion of ALA, (Tola et al., 1973).

Increased urinary excretion of ALA is accompanied by an elevation of the concentration in plasma in adults (Cramer et al., 1974) and in children (Chisolm, 1968a). This could indicate either an increased rate of ALA

formation or a decrease in the rate of use of ALA. In view of the well-known inhibition of the enzyme ALAD, most authorities favour the view that elevated plasma levels reflect decreased use of ALA. The alternative possibility is that ALA formation is increased, presumably by increased formation or activity of the enzyme ALA-synthetase (ALAS). This may in fact be a significant factor. Berk et al. (1970) studied the rate of haem labelling in one case of lead poisoning with anaemia. They observed an increase in the rate of ^{14}C-glycine incorporation into the "early labelled peak" of stercobilin, and into haemin, indicating an increased rate of haem synthesis in response to an anaemia due to increased erythrocyte destruction. Coproporphyrin (CP) and ALA excretion were both elevated. This indicates that haem biosynthesis may be increased in lead poisoning in spite of increased excretion of haem precursors.

It is also possible that the rate-limiting step in the pathogenesis of lead-induced anaemia may involve globin synthesis rather than haem synthesis. White & Harvey (1972) reported that the incorporation of ^{3}H-leucine into α- and β-chain globins of reticulocytes was differentially affected in a pair of 3-year-old twins with clinical lead poisoning accompanied by anaemia. The radioactivity associated with the different globin chains shifted systematically as the blood haemoglobin values of the children returned towards normal.

The major effects of lead on haemopoiesis that are readily measured in man, are on the rate of excretion of ALA or CP in the urine, on the concentration of PP in the blood, and on the degree of inhibition of ALAD in the blood. None have been evaluated in relation to the fidelity with which they reflect the actual amount of lead absorbed per unit time, but they have been evaluated extensively with reference to their correlation with the concentration of lead in the blood. The literature since 1955, concerned with these interrelationships, has been reviewed recently by Zeilhuis (1971).

8.2.1.1 *δ-aminolevulinic acid dehydratase (ALAD)*

The effect of lead that most closely correlates with the concentration of lead in the blood is the inhibition of erythrocyte ALAD activity. Within the range of lead exposure encountered in the general population, the higher the concentration of lead in the blood, the lower the activity of the enzyme. Above this range, enzyme inhibition is almost complete and changes little with increasing dose. The relationship between Pb-B levels and ALAD activity was first reported by Makao et al. (1968) in a group of twelve men industrially exposed to lead. Later, Hernberg et al. (1970) reported on a much larger population of adults having a wide range of lead exposures. Granick et al. (1973) suggest the interesting possibility of correcting for individual variations in total ALAD by calculating the ratio of activity

with, *versus* activity without, enzyme reactivation using dithiothreitol as a reactivator. This calculation presumably expresses the inhibitory activity of lead for the particular sample. The normalization procedure improved the correlation between ALAD and blood lead. They found that the average no-effect Pb-B level for inhibitory effects in children, using this correction procedure, was about 15 µg/100 ml. Tola (1973) reached a similar conclusion from his study of 1370 workers. His observations suggested that the average threshold was at a Pb-B level of 10–20 µg/100 ml. However, a recent study on the Finnish general population puts the existence of a no-effect level into some doubt. In their study, Nordman & Hernberg (1975) obtained a statistically significant correlation between ALAD activity and Pb-B values not exceeding 10 µg/100 ml (Pb-B mean value 8.4 µg/100 ml).

Based on data concerning male workers and children, Zielhuis (1975) calculated a dose–response relationship for over 40% and over 70% inhibition of ALAD (see Table 24).

Table 24. Percentage of adults and children with more than 40% and 70% inhibition of the mean ALAD activity found in control subjects with Pb-B <14 µg/100 ml[a]

Pb-B level (µg/100 ml)	adults			children		
	No.	>40%	>70%	No.	>40%	>70%
14	—	—	—	9	11	0
15–24	30	13	3	37	73	8
25–34	26	62	12	24	88	13
35–44	32	97	22	10	90	50
45–54	53	100	68	—	—	—
55–64	37	100	92	—	—	—
65–74	43	100	95	—	—	—
	221			80		

[a] From Zielhuis (1975).

8.2.1.2 *Free erythrocyte porphyrins (FEP)*

The most recently identified biochemical correlate of blood lead concentration is the erythrocyte protoporphyrin concentration. Some of the analytical methods in use (see section 2.2.3) measure the protoporphyrin IX concentration in erythrocytes, while others measure the free erythrocyte porphyrins, more than 90% of which, however, consists of protoporphyrin IX (Baloh, 1974). A correlation between FEP and Pb-B levels has been reported for industrial workers (Haeger-Aronsen, 1971). The dose–effect relationship is linear if log FEP is plotted against Pb-B. Two reports have appeared showing this relationship (Piomelli, 1973; Sassa et al., 1973). In both cases, the subjects were young children with a wide range of blood lead values. For the data reported by Sassa et al. (1973)

the correlation of the logarithm of the protoporphyrin IX values and the blood lead concentrations was fairly good ($r = 0.72$). When only the data for children having had a constant blood lead level for three months or longer were used, the correlation was much better ($r = 0.91$). The point was made by the authors that the elevation of erythrocyte protoporphyrin IX reflected an inhibitory effect of lead on haem synthesis that occurs in erythroid cells in the bone marrow, whereas the absorption of lead by blood elements takes place both in circulating cells and in erythroid cells.

Table 25. Percentage of adult female subjects with FEP levels that exceeded those found in control subjects with Pb-B <20 µg/100ml.

Pb-B level (µg/100 ml)	No.	% with FEP level higher than normal
11–20	28	4
21–30	9	33
31–40	8	90
41–50	4	100
51–60		
61–70		
	49	

[a] From: Zielhuis, 1975.

Table 26. Percentage of adult male subjects with FEP levels that exceeded those found in control subjects with Pb-B <20 µg/100 ml.

Pb-B level (µg/100 ml)	No.	% with FEP level higher than normal
11–20	26	0
21–30	43	7
31–40	32	19
41–50	4	
51–60	2	100
61–70	2	
	109	

[a] From: Zielhuis, 1975.

In recent years, it has become evident that the increase of FEP occurs at lower Pb-B levels than the increase in ALA in the urine (Stuik, 1974; Roels et al., 1975). In addition, the same authors observed that women were more sensitive than men with regard to the effect of lead on erythrocyte protoporphyrin IX. In women the effect was evident at a lower Pb-B level than in men, and the rate of increase in erythrocyte protoporphyrin IX with increasing Pb-B was greater than in men. From the results of a recent preliminary survey, children appear to display an FEP response to lead resembling that of women (Roels et al., 1975). Based on these limited data, for 109 men, 49 women, and for 219 children, Zielhuis (1975) calculated the dose–response relationship (see Tables 25, 26, and 27).

8.2.1.3 *δ-aminolevulinic acid excretion in urine (ALA-U)*

The rate of ALA excretion in urine has long been used as a measure of a biological effect of lead. The most recent studies of this relationship in industrially exposed subjects indicate that the logarithm of the ALA concentration in urine increases linearly with Pb-B levels from 40 μg/100 ml (Selander & Cramer, 1970; Haeger-Aronsen, 1971; Soliman et al., 1973). Chisolm (1973) reported a good correlation in children of log ALA excreted in urine per 24 hours per m^2 of body surface and Pb-B levels

Table 27. Percentage of children with FEP levels that exceeded those found in control subjects with Pb-B < 20 μg/100 ml.

Pb-B level (μg/100 ml)	No.	% with FEP level higher than normal
20	87	5
21–30	72	21
31–40	24	29
41–50	14	
51–60	12	64
61–70	10	
	219	

[a] From: Zielhuis, 1975.

Table 28. Percentage of male adults with ALA-U levels > 5 mg/litre and > 10 mg/litre according to Pb-B level

Pb-B level (μg/100 ml)	No.	ALA-U level (mg/litre)	
		>5	>10
11–20	17	0	0
21–30	27	0	0
31–40	36	14	3
41–50	55	33	11
51–60	38	74	37
61–70	34	88	50
	207		

[a] From: Zielhuis, 1975.

over a wide range of blood lead values. In occupational exposure, the excretion of ALA in urine, at a given Pb-B level was higher in women than in men (Roels et al., 1975).

Using diagrams published by Haeger-Aronsen (1971) and by Selander & Cramer (1970) for 207 adult males, Zielhuis (1975) calculated the dose–response relationships for levels of ALA excretion greater than 5 mg/litre and greater than 10 mg/litre (see Table 28). Some of the dose–response relationships shown in Tables 24–28 are illustrated in Fig. 4.

8.2.1.4 *Coproporphyrin excretion in urine (CP-U)*

Although there is some uncertainty, ALA-U is probably somewhat more sensitive to the effects of lead exposure than CP-U (Haeger-Aronsen, 1960; Djurić et al., 1966). ALA-U is also more lead-specific than CP-U. Data are insufficient for estimating dose–response relationships.

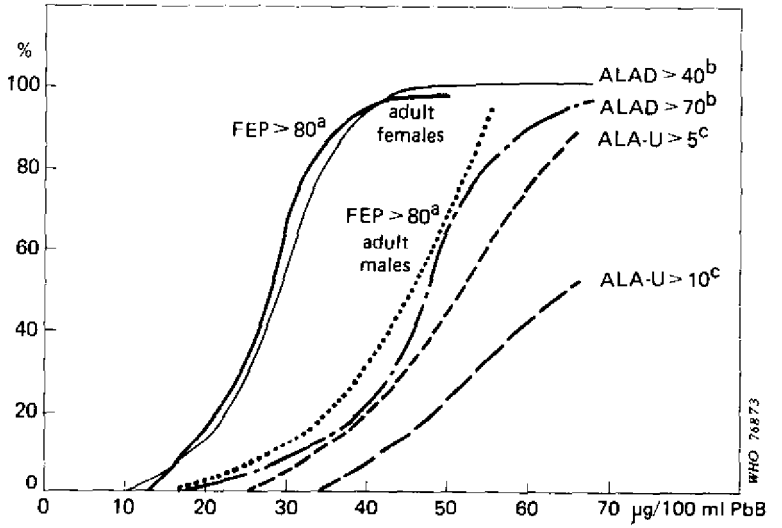

Fig. 4 Dose response relationships for some effects of lead. a = µg/100 ml of erythrocytes; b = % inhibition; c = mg/litre.

8.2.1.5 *Effects of lead on cell morphology*

Punctate basophilia occurs in lead poisoning, but a quantitative relationship between the number of stippled cells and Pb-B levels is not to be expected (Zielhuis, 1971). Too many variables are involved in the preparation of smears. The same is probably true of reticulocyte counts.

8.2.1.6 *Effects of lead on erythrocyte survival*

Increased rate of erythrocyte breakdown (decreased erythrocyte life) is often, but not consistently, seen in cases of anaemia due to lead poisoning. When erythrocytes are exposed to lead *in vitro*, they exhibit increased osmotic resistance and increased mechanical fragility (Waldron, 1966). They also show inhibition of Na-K-ATPase with increased loss of intracellular potassium (Hasan & Hernberg, 1966; Secchi et al., 1973). These effects have been cited to explain the fact that in many instances the anaemia in lead poisoning is accompanied by a shortening of the erythrocyte life span. It is presumed that one or more of these effects is responsible for the sensitivity of erythrocytes to spontaneous haemolysis. Erythrocyte survival time was reduced on the average by 20% in 17

occupationally-exposed workers, only 3 of whom showed clinical signs of poisoning (Hernberg, 1967). The author postulated that shortened cell life was due to the loss of membrane integrity secondary to Na-K-ATPase inhibition. Anaemia does not necessarily accompany a shortened red cell life span, and the correlation between blood haemoglobin and life span was not good in this particular study. The kinetics of disappearance of labelled cells indicated a shortening of life span by increased random destruction of cells of all ages. Leikin & Eng (1963) determined erythrocyte survival in 7 cases of lead poisoning in children. In 3 cases the erythrocyte survival time was shortened. All patients were mildly to moderately anaemic. It would seem from these and other studies that the anaemia in lead poisoning cannot be explained solely on the basis of reduced erythrocyte survival time.

8.2.1.7 *Effects of lead on haem synthesis*

The two general points of attack that have been identified are on haem synthesis and on globin synthesis. Of the two, the effects on haem synthesis are better understood. It is generally recognized, too, that manifestations of disturbed haem synthesis often occur in the absence of frank anaemia. These disturbances may also be significant for the numerous other haem-dependent enzymatic reactions essential for normal body functions. Thus, cytochromes, cytochrome *c* oxidase (EC 1.9.3.1), and hydroperoxidases are all part of electron transfer systems requiring haem.

Little is known about the effects of lead on the formation or activity of other haem-containing compounds. It has been reported that treatment with EDTA reversed the prolonged antipyrine half-life seen in two cases of clinical lead poisoning (Alvares et al., 1975). The authors suggested that in these cases, lead may have significantly inhibited the synthesis of cytochrome P-450.

8.2.1.7 *Relationship between lead exposure and anaemia*

It is well known that anaemia is a characteristic early toxic effect of lead in man. The Pb-B threshold level for this effect is still not certain. Williams (1966) reported that anaemia did not occur in industrial workers with Pb-B levels below 110 μg/100 ml. Cooper et al. (1973) reported that the average haemoglobin level (Hb) was not decreased at Pb-B levels of up to 100 μg/100 ml and Sakurai et al. (1974) did not observe any decrease of Hb or erythrocyte concentrations in workers at Pb-B levels of up to 50 μg/100 ml. On the other hand, Tola et al. (1973) reported a slight effect of lead on Hb at an average Pb-B level of about 50 μg/100 ml. This conclusion was drawn from analysis of the sequential change in Hb among workers newly introduced into an "industrial lead environment". This approach to the analysis of the effect of lead on Hb is certainly more

sensitive for detecting an interaction between Pb-B levels and Hb than is a single Hb determination in a population of lead-exposed persons. Allowance must, however, be made for the possibility that sequential change in Hb may be due to seasonal effects independent of lead exposure (Coulthard, 1958).

Children appear to be more sensitive to lead anaemia than adults. Thus, Betts et al. (1973) found a significant negative correlation between Hb and Pb-B levels; a decrease in Hb was evident in 36% of children with Pb-B levels from 37 to 60 μg/100 ml, compared with only 14% in children with Pb-B levels less than 37 μg/100 ml. Pueschel et al. (1972) observed a curvilinear decrease in Hb between Pb-B levels of 40 and 130 μg/100 ml in children between 1 and 6 years old. On the other hand, McNeil & Ptaznik (1975) found no anaemia in children with Pb-B levels considerably higher than 40 μg/100 ml. Nutritional differences may explain the discrepancy. But this does not invalidate the proposition that for some groups of children a reduction in Hb may occur at a Pb-B level of approximately 40 μg/100 ml.

8.2.2 Nervous system

8.2.2.1 *Central nervous system*

Inorganic lead compounds. The effects of lead on the nervous system vary with the duration and intensity of exposure. Distinction must also be made between the effects on the central nervous system and the effects on peripheral nerves. Further questions have been raised concerning the inherent differences in the sensitivity of the nervous system of adults and the nervous system of infants and young children. There is no doubt that lead effects on the brain are much more commonly associated with childhood lead poisoning than with poisoning as it is seen in adults. But it is also possible that these differences are related to the intensity of exposure at the time the cases are identified rather than to any difference in inherent sensitivity.

With chronic lead exposure, striking effects may occur referred to as lead encephalopathy. There are numerous detailed descriptions of adult lead encephalopathy (Crutcher, 1963; Whitfield et al., 1972; Teisinger & Styblova, 1961; Aub et al., 1926; Cantarow & Trumper, 1944). The major features are dullness, restlessness, irritability, headaches, muscular tremor, hallucinations, and loss of memory and ability to concentrate. These signs and symptoms may progress to delirium, mania, convulsions, paralysis, and coma. The signs and symptoms of encephalopathy in infants and young children are quite similar to those reported to occur in adults.

The brain lesions in fatal cases of lead poisoning are cerebral oedema and changes in cerebral blood vessels. The normal convolutions of the

cerebral hemispheres are often obliterated. Capillary endothelial cells are usually swollen (Pentschew, 1965). Extravasation of red blood cells and perivascular haemorrhage occur rather commonly and patchy neuronal loss, serous exudate, glial proliferation, and occasional areas of demyelinization are all characteristic of lead poisoning (Blackman, 1937; Okazaki et al., 1963; Whitfield et al., 1972). But not all deaths due to lead encephalopathy are accompanied by histological lesions of the central nervous system (Pentschew, 1965).

Neurological sequelae can occur in severe or repeated episodes of lead encephalopathy. The sequelae are no different qualitatively from those that occur following traumatic or infectious cerebral injury. The occurrence of permanent sequelae seems to be much more common among young children than among adults. Approximately one-fourth of the children who survived an attack of acute lead encephalopathy sustained permanent sequelae (Byers, 1959; Chisolm & Harrison, 1956; Smith, 1964). At least this was true prior to the introduction of current therapeutic practices such as those described by Chisolm (1968a). The incidence of sequelae appears to have been substantially reduced in recent years, but central nervous system sequelae may still occur if therapy is initiated only after the onset of encephalopathy (Chisolm, 1973). The most severe sequelae are cortical atrophy, hydrocephalus, convulsive seizures, and idiocy. More commonly, the sequelae are of a more subtle nature. Learning ability may be impaired due to motor incoordination, lack of sensory perception, or inability to concentrate. Such subtle disturbances have also been claimed to occur in children with high lead exposure, but in the absence of a history of encephalopathy (Byers & Lord, 1943; Cohen & Ahrens, 1959).

The major concern today is that young children with elevated lead exposure, as reflected in Pb-B levels of 40–80 μg/100 ml, may be experiencing subtle neurological damage without ever exhibiting classical signs of lead encephalopathy. Studies have been reported of the neurological status of children with Pb-B values in this range. In view of the possible long-term effects of lead on the brain, association between Pb-B and neurological status at the time of evaluation may give a false impression concerning the level of lead exposure when the damage was initiated. Exposure levels at the time of examination may be lower than at the time toxic effects occurred. Thus, the Pb-B level–effect association may underestimate the dose responsible for the effect.

Burdé de la et al. (1972) and Peuschel et al. (1972) observed dysfunction of the central nervous system (irritability, clumsiness, fine motor dysfunction, impaired concept formation, etc.) in 70 and 58 children, respectively, whose Pb-B levels were always, in all cases, above 40 μg/100 ml. Albert et

al. (1974) studied the psychological profiles and educational performances of children, 5–15 years of age, who had histories of lead exposure early in childhood. Those who had been treated for lead poisoning, with or without encephalopathy, exhibited a higher incidence of diagnosed mental disorders and of poor school performance than those who had no such history, even when their history showed elevated lead exposure early in childhood.

Kotok (1972) established that development deficiencies (using the Denver Development Screening test, which, according to the author is a somewhat insensitive measure of development) in a group of asymptomatic children with elevated lead levels (58–137 μg/100 ml) were identical to those of a control group similar in age, sex, ethnic group, environment, neonatal condition, and presence of pica, but whose Pb-B levels were lower (20–55 μg/100 ml). The deficiencies could be correlated with inadequacies in the children's environment. Klein et al. (1974) pointed out that in many studies, pica is not used as a controlled variable. In his view, pica may be part of a behavioural deficiency syndrome. In such a case the child would have the behavioural deficiency regardless of whether or not he ingested lead-containing objects. Indeed, there is evidence that among mentally subnormal children whose mental deficiency is unrelated to excessive lead absorption there is a high incidence of both pica and of moderately elevated Pb-B levels (Bicknell et al., 1968). In this study, 67% of the children, whose subnormal state antedated pica, had Pb-B levels from 39 to 88 μg/100 ml, with a mean of 48 μg/100 ml. By contrast, among the subnormal group without pica all but one had a Pb-B level of less than 36 μg/100 ml. The study did not exclude the possibility that an excessive lead exposure could have aggravated the pre-existent subnormal state.

Recently McNeil & Ptasnik (1975) published an initial evaluation of the long-term effects of elevated Pb-B levels in asymptomatic children, living in El Paso, USA. In 138 out of 206 children aged from 21 months to 18 years (median 9 years), who volunteered (possibility of selection) to participate, the authors could not find any evidence of non-specific complaints, hyperactivity, or of abnormal psychometric testing values, if compared with a matched control group. There existed a significant difference in one personality test; however this was explained by geographic isolation and other factors and not by lead exposure. The average Pb-B levels were, respectively, 50 μg/100 ml (range 14–93) and 16 μg/100 ml (range 10–28).

More recently another psychological evaluation of the El Paso subjects was published by Landrigan et al. (1975a). Forty-six children, aged from 3 to 15 years, with Pb-B levels of 40–60 μg/100 ml were compared with 78 ethnically and socioeconomically similar controls with Pb-B levels below 40 μg/100 ml. The "Wechsler Intelligence Scale" showed that the age adjusted I.Q. was significantly lower in the first group. In addition, the lead

exposed group also showed a significant slowing in the finger-wrist tapping test. The full-scale I.Q., verbal I.Q., and the behavioural and hyperactivity ratings did not differ. In this study, unfortunately, there were differences in age and sex between the study and control group which might account for the positive findings. It seems therefore that we have two studies of this situation that come to different conclusions regarding the possible effects of lead on neurological and psychological functions.

Another approach has been to identify children with neurological or behavioural disorders of obscure etiology and to determine whether they show evidence of current or past elevated lead exposure (David et al., 1972; Moncrieff et al., 1964; Gibson et al., 1967).

The work of David et al. (1972) is of particular interest because the neurological abnormality described was one that was reproduced experimentally in animals (see section 7.1.2). These workers reported occurrence of hyperactivity among children who had essentially normal blood lead concentrations, but who excreted abnormally large amounts of lead when treated with penicillamine. The children had no history of earlier lead encephalopathy. This study has been criticized because of statistical inadequacies (Bullpitt, 1972).

Lansdown et al. (1974) examined a population of schoolchildren in London (less than 17 years of age); there was no relationship between Pb-B levels and intelligence (Wechsler test), reading (Burt test), and behaviour (e.g. hyperactivity as rated by the teachers). The authors suggested that social factors were more important than exposure to lead in determining mental development. The design of the study has also been criticized. Neither Landsown's nor David's study are conclusive.

Morgan & Repko (1974) reported preliminary results of an extensive study of behavioural functions in 190 lead-exposed workers (Pb-B = 60.48 $\pm$ 16.96 µg/100 ml). In 68 % of the subjects the Pb-B level was less than 80 µg/100 ml. The majority of the subjects were exposed for between 5 and 20 years. The authors examined 36 non-independent measures of general performance. In addition, 44 measures of sensory, psychomotor, and psychological functions were obtained. Preliminary analysis suggested that Pb-B levels correlated with several reaction-time measures and ALAD correlated with measures from strength-endurance-recovery tasks. Both Pb-B levels and ALAD correlated with eye-hand co-ordination. This study, therefore, suggested that below a Pb-B level of 80 µg/100 ml some behavioural changes did occur in adult workers. In addition, variability of performance increased with increasing Pb-B levels. Only during periods of high-demand performance did a worker's capacity decrease due to lead exposure. The authors themselves stressed that this preliminary analysis still has to be confirmed by further work.

Alkyllead compounds. The encephalopathy of alkyllead intoxication is somewhat different from that due to inorganic lead exposure. In documented adult cases of poisoning the most frequent findings suggest a psychiatric problem. Hallucinations, tremor, delirium, insomnia, delusions, headaches, and violent mood swings are the most commonly reported symptoms (Boyd et al., 1957; Machle, 1935). The course of the intoxication runs from 1 to 10 weeks. Although alkyllead compounds are notorious for their high lethality, recovery is fairly complete among survivors (Akatsuka, 1973). Convulsions and coma apparently occur only in the most severe cases. There is insufficient information to establish dose–effect and dose–response relationships.

8.2.2.2 *Peripheral nervous system*

Inorganic lead has toxic effects on the peripheral nervous system. The older lead literature cites the frequent occurrence of lead palsy in occupational exposure to lead. The manifestations are mainly weakness of the extensor muscles, particularly those used most heavily. While motor function is mainly affected, hyperaesthesia, analgesia, and anaesthesia of affected areas have also been reported.

Catton et al. (1970) found evidence of reduced nerve conduction velocity in about one-third of a group of 19 occupationally-exposed men of whom only one showed any other overt signs of lead toxicity.

The most prominent finding of Seppäläinen & Hernberg (1972) in lead workers (Pb-B levels 80–120 µg/100 ml) without any clinical neurological signs was reduced motor conduction velocity of the slower fibres of the ulnar nerves; electromyographic changes included a diminished number of motor units on maximum contraction and fibrillations. Similar although less pronounced effects were reported by Seppälainen et al. (1975) in 26 workers whose Pb-B levels had never exceeded 70 µg/100 ml (exposure time 13 months–17 years). Furthermore, in lead workers with Pb-B levels of 2–73 µg/100 ml, Araki & Honma (1976) reported statistically significant negative correlations between nerve conduction velocity and Pb-B, ALAD, and lead mobilization test values, respectively. More recently, Seppäläinen et al. (unpublished results[a]) reported a dose-response relationship between abnormally low conduction velocities, defined as values 2 standard deviations below the mean of an unexposed reference group, and the highest Pb-B recorded during employment (2–20 years). The results indicate that nerve conduction impairment is induced in some workers at Pb-B's exceeding 50 µg/100 ml.

[a] Reported at the Second International Workshop Permissible Levels for Occupational Exposure to Inorganic Lead, 21–23 September 1976, University of Amsterdam, The Netherlands. To be published shortly in *Int. Arch. Occup. Health.*

8.2.3 Renal system

The effects of lead on the kidney have been studied extensively. Two general types of effect have been described. The first is rather clear-cut renal tubular damage characterized by generalized aminoaciduria, hypophosphataemia with relative hyperphosphaturia, and glycosuria, which has been studied in some detail in children with clinical lead poisoning (Chisolm, 1962). The condition is characterized by decreased tubular reabsorption of glucose and α-amino acids and therefore reflects proximal tubular damage. Aminoaciduria was seen more consistently in Chisolm's studies than the other two manifestations of tubular damage. Thus, the amino acid transport system is probably more sensitive to the toxic actions of lead than the transport systems for glucose and phosphate. Limited data indicate that aminoaciduria is terminated by chelation (Chisolm, 1968b).

In a group of children with slight lead-related neurological signs, generalized aminoaciduria was found in 8/43 children with Pb-B levels of 40–120 μg/100 ml (Pueschel et al., 1972). A similar renal tubular syndrome has been reported to occur in industrially exposed adults (Clarkson & Kench, 1956; Goyer et al., 1972). In neither of these studies were Pb-B levels reported. However, Clarkson & Kench observed signs of lead poisoning (colic and punctate basophilia) in conjunction with aminoaciduria.

In a group of 7 carefully studied lead-exposed workers, aminoaciduria was not present. Inulin clearance and renal blood flow were also normal at the time of examination. For these cases, the average Pb-B level was 100 μg/100 ml and the minimum was 71 μg/100 ml. These workers had been exposed for up to 20 years (Cramer et al., 1974). All had markedly elevated urinary ALA excretion. Interestingly, some of these workers with prolonged exposure had diffuse interstitial and peritubular fibrosis as determined by renal biopsy. These pathological findings are associated with quite a different kind of renal effect which is seen with prolonged lead exposure. It is commonly referred to as chronic lead nephropathy. Chronic nephropathy is characterized by slow development of contracted kidneys with arteriosclerotic changes, interstitial fibrosis, glomerular atrophy, and hyaline degeneration of the vessels. This progressive disease sometimes ends in renal failure. There is evidence that it occurs in industrially exposed workers, in long-term drinkers of lead-contaminated whisky, and among middle-aged people who had developed clinical lead poisoning much earlier in life. Currently, it is only rarely encountered in occupational exposure.

This renal syndrome can develop and progress to renal failure long after abnormal lead exposure has terminated. As early as 1897, it was noted that deaths from chronic nephritis were much more frequent among people

under 30 years of age in Queensland than in other sections of Australia. The first serious attempt to document a suspected relationship to earlier childhood lead poisoning was reported by Nye (1929). Further evidence of a causal relationship between chronic nephropathy and childhood lead exposure was provided later (Henderson, 1958). It was shown that people dying of chronic nephropathy in Queensland usually had a high concentration of lead in their bones (Henderson & Inglis, 1957). Emmerson (1963) later demonstrated abnormally elevated lead excretion in response to EDTA among surviving middle-aged cases of chronic nephropathy. Tepper (1963), however, was unable to find evidence of chronic nephropathy among young American adults with a history of childhood lead poisoning. The Americans had probably been exposed for a much shorter period of time than the Australians. Other unknown factors may also have played a role.

The Australian cases involved childhood exposure with an apparent latency of 10–30 years for the development of renal insufficiency. But there is evidence that the same effect can result from continuous, prolonged high lead exposure among adults (Lilis et al., 1968; Richet et al., 1966; Danilović, 1958; Morgan et al., 1966; Albahary et al., 1965; Albahary, 1964). In these cases, lead exposure was higher than is commonly encountered in industry today.

In a series of 102 cases of lead poisoning studied by Lilis et al. (1968), 18 cases of clinically verified chronic nephropathy were found. For the whole series, the mean Pb-B level was approximately 80 µg/100 ml with a range of 42–141 µg/100 ml. Nephropathy was more common among patients who had been exposed to lead for more than 10 years than among those who had been exposed for less than 10 years.

In the Danilović (1958) study 7/23 cases had Pb-B levels of about 100–200 µg/100 ml. In the studies of Albahary et al. (1965) Pb-B levels were not reported. But exposure levels must have been quite high since the mean ALA excretion was about 37 mg/24 h for 29 workers.

It seems likely, from all available evidence, that a prolonged high-level lead exposure is necessary, even in childhood, to produce this progressive chronic nephropathy.

One interesting feature of this syndrome of chronic renal insufficiency is the frequent association with gout (Emmerson, 1963; Morgan et al., 1966). Although uric acid excretion is largely dependent upon tubular secretion, it is not at all certain that tubular secretion is inhibited. As a matter of fact, a study by Emmerson et al. (1971) of 13 cases of renal insufficiency due to lead nephropathy failed to reveal any alteration in uric acid secretion. The authors suggested an increased tubular reabsorption to account for the observed decreased clearance of uric acid.

In summary, proximal tubular effects can occur in children and adults with subtle signs of lead poisoning.

Prolonged exposure to lead leading to a Pb-B level of more than 70 μg/100 ml may give rise to chronic irreversible nephropathy. However, little is known about dose–effect relationships or about time–effect relationships for lead-induced chronic interstitial nephritis.

8.2.4 Gastrointestinal tract

As a symptom of lead poisoning, colic is a fairly consistent early warning of potentially more serious effects likely to occur with prolonged periods of exposure. It is most commonly encountered in industrial exposure. But it is probably also common in lead-poisoned infants and young children. The occurrence of colic at relatively low exposure levels in industry is well-known. Although it has been reported that 13/64 industrially exposed men with presumably lead-related colic and constipation had blood lead levels from somewhat less than 40 μg to 80 μg/100 ml (Beritić, 1971), it was also reported that in every case the diagnosis of lead colic was confirmed by the findings of high CP-U, excessive basophilic stippling, reticulocytosis, and various degrees of anaemia. This is consistent with the general observation that lead colic seems to be accompanied by other signs of poisoning. There are not enough data available to establish a dose–response relationship for this lead effect.

8.2.5 Liver

There is no definite evidence for the effects of lead on the liver. Dodić et al. (1971) reported signs of impaired liver function in 11 out of 91 patients hospitalized for lead poisoning. Liver damage was more frequent in cases of severe lead poisoning in 7 out of 18 patients. However, the authors did not provide any information on Pb-B levels or on indices of disturbed porphyrin metabolism which would enable the assessment of the stage of lead poisoning. In a laboratory study of 301 workers in lead smelting and refining, Cooper et al. (1973) found 11.5% increased aspartate aminotransferase (EC 2.6.1.1), (SGOT)[a] values (above 50 U/litre[b]) in subjects with a Pb-B level below 70 μg/100 ml, 20% in those with a Pb-B level of about 70 μg/100 ml, and 50% in workers with a Pb-B level above 100 μg/100 ml. The correlation between Pb-B levels and SGOT values was statistically significant. However, in the absence of information on the possible

[a] Formerly known as serum glutamic oxaloacetic transaminase.

[b] $= 50 \times 1.67 \times 10^{-5}$ mol/(m^3.s)

influence of diet, infections, or personal habits, the authors did not draw any definite conclusions concerning the etiology of these changes.

8.2.6 Cardiovascular system

Increased capillary permeability occurs in acute lead encephalopathy (section 8.2.2.1). Under conditions of long-term lead exposure at high levels, arteriosclerotic changes have been demonstrated in the kidney (section 8.2.3). Dingwell-Fordyce & Lane (1963) reported a marked increase in the cerebrovascular mortality rate as compared with the expected rate among heavily exposed lead workers (section 8.1.1). This observation applied to men exposed to lead during the first quarter of this century, when working conditions were quite bad. There was no similar increase in the mortality rate for men employed more recently. Hypertension is an important element in the etiology of cerebrovascular deaths. Cramer & Dahlberg (1966) studied the incidence of hypertension in a population of 364 industrially-exposed men, 273 of whom had a long-term exposure to lead. They subdivided these workers into "lead affected" and "non-lead-affected" groups, on the basis of the urinary coproporphyrin test. There was no statistically significant difference between the groups. Nor was the incidence higher than expected for non-exposed men in Sweden. This is contrary to the earlier findings of Vigdortchik (1935) and to the observations of Monaenkova & Glotova (1969). The disparity may have been due to differences in lead exposure. Other reports on the question do not show hypertension to be unduly prevalent among workers exposed to lead (Dressen et al., 1941; Lane, 1949). It is not clear whether vascular effects of lead in man are the result of an action on blood vessels directly, or whether the effects are secondary to renal effects.

There is a good evidence that signs of clinical lead poisoning sometimes include evidence of a toxic action on the heart. Cases have been described in adults and in children, always with clinical signs of poisoning. There is of course the possibility that the coexistence of lead poisoning and myocarditis is coincidental. But in many cases the electrocardiographic abnormalities disappeared with chelation therapy, suggesting that lead may have been the original etiological factor (Myerson & Eisenhauer, 1963; Silver & Rodriguez-Torres, 1968; Freeman, 1965). In a review of 5 fatal cases of lead poisoning in young children, heart failure was concluded to be the proximate cause of death in 2 cases (Kline, 1960). Kosmider & Petelenz (1962) examined 38 adults over 46 years of age with chronic lead poisoning. They found that 66 % had electrocardiographic changes, which was four times the expected rate for that age group. Orlova (1954) also reported electrocardiographic abnormalities in cases of lead poisoning. Dimitrova

(1972) reported cardiac abnormalities in workers with undefined degrees of lead intoxication. There was a correlation of urinary excretion of lead with duration of systolic contraction and with isometric tension. Lead mobilization by EDTA accentuated these effects on the heart. No dose–effect relationships are apparent from the limited data available.

8.2.7 Reproduction

There is no epidemiological evidence of an effect of lead on the fertility of women or on *in utero* fetal development, but there are numerous reports in the older literature of stillbirths and miscarriages among women working in the lead trade (Cantarow & Trumper, 1944; Oliver, 1914). These reports probably contributed to the promulgation of legislation forbidding the employment of women in the lead trades in many countries. Panova (1972) reported that women working in lead industries had a higher incidence, compared with a control group, of ovulatory dysfunction—mainly anovulatory cycles and cycles with luteal abnormality. A relationship was reported between ALA-U and the incidence of anovulatory cycles. The effect was seen at 8–10 mg ALA/litre of urine.

There are not any reliable data to indicate that infertility in women results from exposure of the male partner to lead.

Some of the early reports on lead poisoning (Oliver, 1914) suggested that reproductive failures such as sterility and miscarriages occurred even among the non-working wives of industrially-exposed men. The reproductive capability of 150 occupationally exposed men was recently studied by Lancranjan et al. (1975). The results indicated that both lead poisoning and moderately increased lead absorption decreased the fertility of men. An increased frequency of asthenospermia, hypospermia, and teratospermia was found. No interference with the hypothalamopituitary axis was demonstrated; thus, hypofertility was thought to be due to the toxic effect of lead on the gonads.

8.2.8 Endocrine organs

Impairment of thyroid function and of adrenal function has been reported in cases of lead poisoning (Monaenkova, 1957; Sandstead et al., 1969; Sandstead et al., 1970; Pines, 1965).

There is some evidence suggesting that lead may cause a derangement of tryptophan metabolism. This is based on the observation that urinary excretion of 5-hydroxyindoleacetic acid was increased in 227 children living near a lead smelter (Ghelberg, 1966). Unfortunately, the 5-hydroxyindoleacetic acid determinations were not quantitative. Furthermore, blood

lead values or other indices of exposure were not determined. Urbanowicz et al. (1969) noted a rise in 5-hydroxyindoleacetic acid excretion in workers heavily exposed to lead (ALA-U—33.7 mg/litre of urine). The rise preceded the rise in ALA-U and CP-U. Dugandžić et al. (1973) also noted a rise in 5-hydroxyindoleacetic acid excretion in moderately exposed workers (ALA-U—28.2 ± 22.6 mg/litre of urine). More recently Schiele et al. (1974a), using another analytical method, reported that they were unable to find any significant elevation in 5-hydroxyindoleacetic acid excretion in workers with relatively high blood lead levels (88.5 ± 16.1 µg/100 ml).

8.2.9 Carcinogenicity

Dingwall-Fordyce & Lane (1963) did not find any evidence of an increased incidence of malignant diseases in their follow-up study of 267 workers (section 8.1.1).

In a more recent study of the causes of mortality among lead smelter and lead battery workers, it was concluded that while the incidence of malignant neoplasms was somewhat greater than expected, the difference was not statistically significant (Tabershaw & Cooper, 1974; Cooper & Gaffey, 1975). This seems to support the conclusion of a IARC Working Group that there is no evidence to suggest that exposure to lead salts causes cancer of any site in man (IARC, 1972).

8.2.10 Effects on chromosomes

The literature is controversial as regards chromosomal abnormalities induced by exposure to lead. On the one hand, chromosomal aberrations have been reported to result from lead exposure corresponding to mean Pb-B values of 38–75 µg/100 ml in various groups studied (Forni & Secchi, 1973; Schwanitz et al., 1970). Moreover, Deknudt et al. (1973) reported chromosomal aberrations in a group of 14 male workers with signs of lead poisoning. The authors concluded that, although the workers were exposed to zinc and cadmium as well as lead, the lead ought to be considered responsible for the aberrations. On the other hand, Schwanitz et al. (1975) were not able to corroborate their own findings among occupationally exposed workers and O'Riordan & Evans (1974) did not find any significant increase in chromosomal aberrations in shipbreakers with Pb-B values ranging from 40 to over 120 µg/100 ml. Schmid et al. (1972) did not find any evidence of lead-induced chromosome aberrations in a study on human peripheral lymphocytes *in vivo* and *in vitro*; furthermore, Bauchinger et al. (1972) did not find any abnormalities in the chromosomes of policemen with elevated Pb-B levels.

In a recent report, Bauchinger et al. (1976) found that chromosomal aberrations were significantly increased in a group of 24 male workers occupied in zinc electrolysis and exposed to zinc, lead, and cadmium. The workers had clearly elevated Pb-B and blood cadmium levels in comparison with a control group. The authors pointed out the similarity between this group and the group studied by Deknudt et al. (1973) as regards combined exposure. However, referring to studies indicating mutagenicity of cadmium (Oehlkers, 1953; Shiraishi et al., 1972; Shiraishi, 1975), Bauchinger and his colleagues were inclined to consider cadmium as being mainly responsible for the aberrations. They also emphasized the possibility of a synergistic effect of several metals on the chromosomes. Thus, the question as to whether chromosomal abnormalities occur as a result of lead exposure in man remains open. Furthermore, the human health significance of chromosomal abnormalities seen in lymphocyte cultures, as observed in some of these studies, is not yet known.

8.2.11 Teratogenicity

There is practically no information in the literature to suggest that lead is teratogenic for man (Wilson, 1973). Only one case has been reported of neuromuscular abnormalities and failure to grow in a child attributed to lead poisoning as a result of the consumption by the pregnant mother of illicit whisky (Palmisano et al., 1969).

8.3 Factors influencing Lead Toxicity

8.3.1 Acquisition of tolerance to lead

Experience in industry does not suggest that, with continuous lead exposure, the human body becomes less reactive to lead. There have been two studies in which the biochemical parameters of lead exposure were followed for a long period after the initiation of industrial lead exposure. Tola et al. (1973) found that erythrocyte ALAD fell to a stable level in about 21 days, as the concentration of lead in the blood increased correspondingly. Then both blood lead and blood ALAD remained essentially stable for the next three months. There was no return toward normal values to suggest development of tolerance. Urbanowicz (1971) followed ALA-U and CP-U levels in 60 workers for 24 months after they first became industrially exposed. There was a build-up of both biochemical effects for several months. But the levels then stabilized for the remainder of the two-year period. These studies suggest that the

toxicologically-active fraction of the body burden during steady, long-term exposure remains essentially unchanged.

8.3.2 Age

Young children absorb lead more readily than older people. It also seems that children are more susceptible than adults in the sense that toxic effects occur at lower blood lead concentrations. The susceptibility of old people in comparison with younger adults has not been studied.

8.3.3 Seasonal variations

It has long been recognized that the incidence of severe lead intoxication in children is highest during the summer months (Baetjer, 1959; NAS-NRC, 1972). The observation that urinary excretion of lead increases in late summer may have some bearing (Kehoe, 1961).

8.3.4 Nutrition

There are few reports of studies that point to nutritional variables as having a distinct effect on lead toxicity in man (NAS-NRC, 1972; Goyer & Rhyne, 1974). Iron deficiency and lead exposure both affect porphyrin metabolism at the point where protoporphyrin IX is converted to haem. An additive effect results.

8.3.5 Intercurrent disease, alcohol, and other metals

Little is known about the effects of intercurrent diseases on the toxicity of lead or about the effect of lead on the susceptibility of people to other diseases. People with haemoglobin and erythrocyte anomalies, such as sickle cell anaemia and thalassaemia, would probably be more sensitive to the effects of lead exposure, as would perhaps people with renal damage. It is also possible that an interaction may exist between lead exposure and infectious disease processes, although reliable human data are not available to prove the point.

The effect of ethanol on lead toxicity is of some interest because the encephalopathy of illicitly-distilled whisky drinkers could conceivably involve an interaction of lead and the alcohol consumed. Furthermore, it has been suggested that heavy drinkers among industrially-exposed men may be more prone to lead toxicity than non-drinkers (Cramer, 1966; Candani & Farina, 1972).

9. EVALUATION OF HEALTH RISKS TO MAN FROM EXPOSURE TO LEAD AND ITS COMPOUNDS

The evaluation of health risks to man from exposure to lead and its compounds involves the following considerations:

(1) the significance of different environmental sources of lead and of pathways of exposure;
(2) the probability of occurrence of biological effects at different levels and rates of lead intake;
(3) the significance for human health of the various known biological effects of lead;
(4) the validity and limitations of various indicators of lead exposure and of resultant effects.

These considerations have been used in arriving at the conclusions which are summarized in this chapter.

9.1 Relative Contributions of Air, Food, Water, and Other Exposures to Total Intake

9.1.1 Adult members of general population groups

For the general population, the major contribution of lead to the total daily intake is from food, but water and air may provide significant contributions under certain conditions. Separate consideration must be given to occupationally-exposed persons in whom both the total lead intake and the relative contributions of dietary and airborne lead are quite different.

The inhalation of airborne lead contributes comparatively little to the Pb-B level in the general population. This follows from the fact that the lead concentration in ambient air seldom exceeds 3 $\mu g/m^3$ when averaged over months and from the conclusions reached in section 6 that the contribution of airborne lead to Pb-B levels is probably within the range of 1.0 to about 2.0 $\mu g/100$ ml for every 1 $\mu g/m^3$ of air. Although deposition and retention of different forms of lead in air may vary, estimates of Pb-B levels from the concentrations of lead in air are similar for the ambient air and for the air in the work environment.

Even if we assume a concentration of 1 μg of lead per cubic metre of air contributes as much as 2.0 $\mu g/100$ ml of blood, and that the ambient air concentration of lead is as high as 4.5 $\mu g/m^3$, the total contribution of airborne lead would not exceed 9.0 $\mu g/100$ ml. This is still less than two-thirds of the value estimated by a WHO Expert Committee (1973). The

discrepancy arises from the different approaches used in making the estimate. The WHO Expert Committee's estimate was based on lung deposition figures for lead obtained using the ICRP model (Task Group on Lung Dynamics, 1966). However, the ICRP lung model probably overestimates deposition for particles smaller than 0.5 μm (aerodynamic diameter) (Mercer, 1975), and the assumption that all the lead that is deposited is absorbed is probably also incorrect.

Dietary intake of lead varies with eating habits and the lead content of water sources. The majority of estimates from various countries suggest that the daily oral lead intake from food by adults ranges from approximately 100 μg to more than 500 μg; most studies show lead intake from dietary sources to be 200–300 μg/day. Relating blood lead levels to known daily oral lead intake suggests that each 100 μg of oral lead intake contributes about 6–18 μg of lead/100 ml of blood. This source of lead therefore accounts for a very large fraction of the blood lead levels found in the general adult population with Pb-B values below 25 μg/100 ml.

The quantity of lead intake directly related to the lead content of drinking water is difficult to estimate. Assuming a lead concentration in drinking water of 50 μg/litre (which is the upper limit generally found in the absence of lead pipes or other lead contributing factors) and a daily intake of one litre of water, 50 μg of total dietary lead could be attributed to water. This may be regarded as an upper limit but it must also be pointed out that lead in water ingested independently of food may be more readily absorbed and may provide a relatively greater contribution to the blood lead level than lead in food.

In assessing the relative contributions of air and diet to Pb-B levels, attention is called to the possibility that air may be a significant source of dietary lead through fallout. However, there are no data to confirm this assumption.

Improperly glazed pottery and illicit whisky have been cited as potential sources of excessive lead exposure for members of the general population.

Smoking one packet of 20 cigarettes would result in the direct inhalation of about 1–5 μg of lead but this only indicates the order of magnitude.

9.1.2 Infants and children

Infants and preschool children are a high-risk group with regard to lead intake and absorption. Relative contributions from food, water, and air are difficult to estimate because of the different diet (e.g. milk) and more active metabolic rate of young children. Also, intestinal absorption of lead

by young children and, in particular, by infants may be greater than by adults. Tolerable intake of lead for preschool children should be less than the 3 mg/week recommended provisionally for adults by a WHO Expert Committee on Food Additives (1972).

A special hazard for young children is the ingestion of non-food items, particularly lead-containing paint from surfaces in homes and lead-contaminated dust and soil.

9.1.3 Occupationally exposed population groups

Because of the variability of occupational exposure, no general conclusions are possible but precautions against excessive exposure must be exercised in view of the possibility of extremely high occupational lead exposures, as cited in section 5.

9.2 Evaluation of Haematological Effects

Based on information presented in section 8, the following conclusions have been reached concerning the significance of different effects on haematopoiesis.

Inhibition of ALAD activity in erythrocytes. The health significance of decreased ALAD activity is still open to discussion. Although inhibition of ALAD in erythrocytes is to a certain extent paralleled by a decrease in other organs, e.g. liver and brain, no effect on health of this decrease has ever been established. Inhibition of ALAD is generally regarded as a good indicator of lead absorption but not of health impairment.

Increased excretion of ALA and CP in urine, and increase of FEP are indicators of impaired haematopoiesis. Although at moderate levels of increase, no evidence has been brought forward to show that the vital functions of haematopoiesis are impaired, resulting, for example, in a reduced life-span of erythrocytes or anaemia, any increase should be regarded with suspicion and particularly so when it is more than twice the level found in non-exposed population groups. Because free erythrocyte protoporphyrins are also increased in the case of iron deficiency, this test may provide a better indication of impaired haematopoiesis in exposed iron deficient population groups (especially children) than the excretion of ALA and CP. Moreover, females and children appear to have an earlier and steeper increase of FEP than males for the same levels of Pb-B.

Effects on erythrocyte membrane, as evidenced by shortened life-span and a decrease of Na-K-ATPase clearly can result in adverse health effects since anaemia may occur. *Anaemia*, expressed by decreased haemoglobin level, may be regarded as a consequence of disturbed haem and globin synthesis and of the decreased life-span of erythrocytes and has clear adverse health consequences.

9.3 Dose–Effect Relationships

At present Pb-B levels are the best available indicator of the dose. It should, however, be recognized that Pb-B does not reflect the type of exposure. The dose–effect relationships based on Pb-B levels should generally be used for long-term exposure.

As stated in section 8 (page 99) a dose–effect relationship refers in this report to the relationship between the dose as estimated by Pb-B levels and the intensity of a specified effect in *individual* subjects. For most effects, not enough data are available to present adequate dose–effect curves; however, for some effects, some points on the dose–effect curve can be tentatively estimated; for other effects, the data available only permit a statement referring to the Pb-B level below which such an effect has not been reported. This level is referred to as the no-detected-effect level. The degree of confidence that can be placed on such estimates will vary depending on the sample size and the number of studies reporting no effect.

ALAD activity in erythrocytes. There is a negative linear relationship between the logarithm of ALAD and Pb-B levels. Increase in Pb-B levels is paralleled by a decrease in ALAD levels in the Pb-B range up to about 60 µg/100 ml. For higher Pb-B values, the ALAD activity levels off at a very low level of enzyme activity. The no-detected-effect level for Pb-B is probably about 10 µg/100 ml but may be even lower.

ALA and CP in urine; PP in erythrocytes. There is a positive linear relationship between the logarithm of ALA (CP, FEP) and Pb-B levels; the no-detected-effect level for ALA and CP is about 40 µg/100 ml; for FEP the no-detected-effect level in females is about 20–30 µg/100 ml, in males it is about 25–35 µg/100 ml; and in iron-deficient children in particular, it may be about 20–25 µg/100 ml.

Effects on the erythrocyte membrane start to occur at higher Pb-B levels, probably higher than 50–60 µg/100 ml; a study by Secchi et al. (1974), on Na-K-ATPase, however, reports a lower no-detected-effect level of between 30 and 40 µg/100 ml.

Anaemia. Some authors maintain that the no-effect level in workers is above a Pb-B level of 100 μg/100 ml; others, however, report a slight decrease in the haemoglobin level, at a mean level of Pb-B of about 50 μg/100 ml. In some population groups and particularly in iron-deficient children, the no-detected-effect level is at an approximate Pb-B level of 40 μg/100 ml.

Nervous system effects. The data on effects of lead compounds on the nervous system lead to the following tentative conclusions in regard to prolonged exposures:

(1) From Pb-B levels of approximately 40 μg/100 ml, the probability of the occurrence of subclinical peripheral electrophysiological changes increases.

(2) From approximately 50 μg/100 ml in children, the probability of noticeable brain dysfunction increases; in adults the level is probably somewhat higher (60–70 μg/100 ml).

(3) From approximately 60 μg/100 ml in children the probability of acute or chronic encephalopathy increases; in adults this level is higher, probably above 80 μg/100 ml.

(4) The potential effects of lead on the nervous system constitute one of the main concerns, particularly in children. More carefully considered prospective studies should be carried out taking into account various interacting variables such as nutrition, socioeconomic status, and parental care in order to establish better founded dose–effect and dose–response relationships.

(5) No dose–effect or dose–response relationships can be established for alkyllead exposure on the basis of currently available information.

The present no-detected-effect level for sub-clinical neuropathy appears to be a Pb-B value of 40–50 μg/100 ml. For minimal brain dysfunction it is probably 50–60 μg/100 ml in children and 60–70 μg/100 ml in adults, and for acute or chronic encephalopathy, 60–70 μg/100 ml in children, and over 80 μg/100 ml in adults. The establishment of relationships between Pb-B levels and effect is especially difficult in children because the effect may be detected months or years after the critical exposure occurred.

Renal function. Apparently prolonged exposure to Pb-B levels greater than 70 μg/100 ml is necessary to produce nephropathy; a no-detected-effect level cannot be given. The problem is non-correspondence in time between the determination of Pb-B level and the detection of effect.

Aminoaciduria, reflecting impaired amino acid transport through the

renal tubules may occur in children and adults with increased lead absorption. The present data do not allow a no-detected-effect level to be estimated, but indicate that this effect is unlikely to be found in association with Pb-B levels below some 90–100 μg/100 ml (Chisolm, 1968b, Cramer et al., 1974).

Changes in blood constituents such as calcium, phosphorus, glucose, cholesterol, total proteins, serum albumins, alkaline phosphatase (EC 3.1.3.1), lactate acid dehydrogenase, and urea nitrogen, could not be found in male workers with a median Pb-B level of 63 μg/100 ml; 37% showed an effect with a Pb-B level greater than 70 μg/100 ml (Cooper et al., 1973). There was an indication of increased bilirubin at a Pb-B level of about 70 μg/100 ml. An increased pyruvate level after glucose administration was reported in 50% of children with Pb-B levels of 40–60 μg/100 ml (Moncrieff et al., 1964).

The general pattern of morbidity and mortality in workers does not appear to be affected if the Pb-B level never exceeds 70 μg/100 ml.

In assessing reported dose–effect relationships and no-detected-effect levels, one should take into account the fact that the available data are limited. Even from a theoretical viewpoint, the establishment of a definite no-effect level is not possible, because one can hardly ever expect to cover the whole range of susceptibility in human populations. Nevertheless, the available data suggest that the no-detected-effect levels given above are on the conservative side.

Table 29 summarizes the no-detected-effect levels discussed. For some of these effects, it is possible to elaborate dose–response relationships. These cases are considered in section 9.4.

Table 29. No-detected effect levels in terms of Pb-B (μg of lead per 100 ml of blood)

No detected effect level	Effect	Population
<10	Erythrocyte ALAD inhibition	adults, children
20–25	FEP	children
20–30	FEP	adult, female
25–35	FEP	adult, male
30–40	Erythrocyte ATPase inhibition	general
40	ALA excretion in urine	adults, children
40	CP excretion in urine	adults
40	Anaemia	children
40–50	Peripheral neuropathy	adults
50	Anaemia	adults
50–60	Minimal brain dysfunction	children
60–70	Minimal brain dysfunction	adults
60–70	Encephalopathy	children
>80	Encephalopathy	adults

9.4 Dose-response Relationships

A dose–response relationship considers the observed relative frequency of occurrence of a specified *effect*[a] in a group of subjects at a given dose level. As in the case of dose–effect relationships, the data available to evaluate a dose-response relationship are either limited or non-existent. The available information on dose-response relationships has been presented in section 8. In this section, attention is paid to the 5% response levels, i.e. that level of Pb-B at which not more than 5% of the group considered is expected to show the specified intensity of a specified effect. The 5% level has had to be stipulated, because not enough data are available to state the Pb-B levels for 0.5%, 1%, etc. Further investigations have to be carried out to enlarge the amount of data available. For further discussion see Zielhuis (1975). His review suggests the 5% response levels recorded in Table 30, which are in accordance with the data discussed in section 8. These response levels are also in agreement with those suggested by Hernberg (1975).

Table 30. Pb-B levels at which no more than 5% of the population will show the indicated intensity of effect

Biochemical effect	Intensity of effect	Population	Pb-B (µg/100 ml)
ALAD inhibition	perceptible inhibition	adult, children	10
	>40% inhibition	adults	15–20
	>70% inhibition	adults	30
	>70% inhibition	children	25–30
ALA-U	perceptible increase	adults, children	40
	>10 mg/litre	adults, children	50
FEP	perceptible increase	adult males	30
		adult females	25
		children	20

[a] From: Zielhuis, 1975.

9.5 Diagnosis of Lead Poisoning and Indices of Exposure and/or Effects for Epidemiological Studies

For epidemiological studies and for the detection of the early effects of lead in occupational exposure of individuals, the following tests have been used:

(1) Lead levels in blood.

[a] Graded effects may be specified in terms of their intensity.

(2) Excretion of lead in urine spontaneously or after administration of chelating agents.

(3) Lead levels in tissues (teeth, bones, hair, etc.).

(4) Activity of ALAD in blood.

(5) Indices of disturbed porphyrin metabolism:
ALA and/or CP in urine,
Protoporphyrin IX in erythrocytes.

(6) Haematological indices such as basophilic stippling and haemoglobin levels.

(7) Early (sub-clinical) symptoms and signs of other damage (e.g. to the nervous system or the kidneys).

(8) Clinical evidence of poisoning.

The criteria used by individual investigators correspond to the premises and purposes of their studies, for example, Pb-B for evaluating lead levels in the general population, and clinical signs of poisoning to assess morbidity caused by occupational exposure.

The following considerations should be kept in mind when using and interpreting the results.

9.5.1 Concentration of lead in blood (Pb-B)

Pb-B reflects the current state of the dynamic equilibrium between the amounts of lead entering the organism, transported in the blood, and deposited in the tissues (including the bones). To date, insufficient information has been collected about the quantitative aspects of these processes, but from the data available, it may be stated that:

(*a*) After a single inhalation of a soluble lead compound, the concentration of lead in the body will change in the same way as after an intravenous injection, i.e. there will be a rapid increase in Pb-B levels followed by a slower decrease; initially there will be a rapid elimination in the urine and a slow deposition in the tissues with subsequent redistribution according to the metabolism of lead in the various organs and systems.

(*b*) During long-term exposure at a constant rate, an equilibrium between the amount of lead absorbed, deposited, and excreted develops over a long period (weeks to months, according to the daily doses received), which can be considered as a steady state.

(*c*) There are only limited data as to how quickly this equilibrium (and Pb-B) changes when irregular variations in the dose of lead received (e.g. air lead concentrations) occur.

A long-term steady state probably exists normally in non-occupationally exposed general adult populations, at least in the Pb-B level. However, no direct evidence for this assumption is available.

In occupationally exposed persons, a steady state cannot be assumed because of the well known and marked variations of air lead concentrations in the working environment and of Pb-B levels in occupationally exposed individuals from one time to another and among the individuals in the same work place. Occasional exposure to a high lead concentration in the air could raise the Pb-B level for some time without contributing significantly to the body burden and to the biological effects.

If Pb-B is to be used as an indicator of the degree of environmental lead exposure the above-mentioned facts must be taken into account, as well as the analytical method used and the limitations (accuracy, precision, sensitivity, limits of detection).

9.5.2 Aminolevulinic acid dehydratase (ALAD)

For ALAD the same conditions can apply as for Pb-B. The behaviour of ALAD activity will follow closely the level of Pb-B up to 50–60 μg/100 ml.

9.5.3 Aminolevulinic acid (ALA) and coproporphyrin (CP) excretion in the urine

ALA and CP in urine are not so dependent on the current state of lead exposure and absorption as the Pb-B, although their excretion diminishes relatively quickly when exposure ceases; they reflect more the average short-term level of lead exposure and have proved useful in this way. ALA and CP estimates have found broad recognition as indices of lead absorption and as indicators of early effects they reflect individual susceptibility to lead.

9.5.4 Lead excretion in the urine

An elevated rate of spontaneous lead excretion in the urine is indicative of high lead absorbed, but a normal rate of excretion does not serve as a reliable means of excluding the possibility of excessive absorption. Lead excretion in urine is dependent on the Pb-B level but is also influenced by other—mostly unknown—factors, so that no direct conclusions about exposure and the extent of absorption can be derived from lead levels in urine (even in a 24-hour sample).

The excretion of lead provoked by chelating agents such as calcium

disodium ethylenediamintetraacetate is thought to reflect the biologically active portion of the body burden. It is probably a more sensitive index of over exposure and excess absorption than the Pb-B level since clearly elevated values have been reported in cases of only marginally elevated Pb-B levels.

9.5.5 Haematological changes (stippled cells, anaemia)

These are not sensitive indices of over-exposure or excess absorption. They are not very useful for the early detection of possible health impairment.

9.5.6 Lead in tissues (teeth and hair)

These have been used as indicators of integrated long-term exposure and have the advantage that samples are easy to procure. As yet, the amount of information concerning the interpretation of the values obtained is inadequate for their evaluation as indices of exposure or dose.

9.5.7 Some practical aspects

9.5.7.1 *General population studies*

The Pb-B level is the epidemiological index of choice, assuming that a reasonable approximation of a steady state exposure exists. ALAD activity estimates are equally useful for such studies or as epidemiological indices of lead absorption. The decision to use Pb-B or ALAD depends on the laboratory facilities available. Signs of lead effects other than ALAD inhibition are not to be expected at Pb-B levels below 20 µg/100 ml. Lead in deciduous teeth and hair is potentially useful as an indicator of integrated exposure in infants but needs more study.

9.5.7.2 *Occupationally-exposed persons*

For screening the exposure of groups of workers, any method can be used that has the required sensitivity and specificity. Economic and time factors will determine the choice of test. When using the Pb-B level, the conditions of sampling must be well defined, taking into account the factors influencing the variations of the Pb-B concentrations. ALA and CP estimations in urine are widely used since they are simple, avoid the possibility of external contamination, and may provide a better picture of the integral exposure. ALAD activity is only useful at Pb-B levels below about 60 µg/100 ml. For early detection of the signs of lead effects in individuals, ALA-U or CP-U tests are the best established screening

methods. When abnormal values are found, further tests (including clinical and laboratory investigations) will have to be applied to evaluate the kind of disturbance and the degree of health risk (WHO Study Group, 1975).

9.5.7.3 *Reliability of sampling and analytical methods*

The evaluation of the pollution of the environment by lead and of the health effects on man which might result, depends on the reliability of sampling procedures and analytical methods used.

The methods of sampling for different environmental media, and the possible exposure pathways of man have been discussed in section 3. The great spatial and temporal variability of these environmental media and their diversity make the accurate assessment of total exposure a difficult task. Unless elaborate schemes are set up and extreme precautions are taken, the total exposure of a population group cannot be evaluated with an error of less than about 50%, taking into account the analytical uncertainties.

In the determination of the dose received or the effects on haematopoiesis observed, the sampling problem is relatively minor but the accuracy and precision of analytical techniques play an important role. An evaluation with up to 20% relative precision is seldom achieved under normal operational conditions.

9.6 The Problem of Alkyllead Compounds

The principal risk of alkyllead compounds is in occupational exposure, either by inhalation or by absorption through the skin. Acute toxicity results in an encephalopathy that differs greatly from the effects of inorganic lead on the central nervous system. Some components of the toxic effects are probably due to the alkyl compound as a whole rather than its lead component. Workmen at greatest risk are those involved in mixing fuel additives, although other workmen engaged in related occupations such as the cleaning of storage tanks where inhalation is possible, are also at high risk. Over-exposure of the general population to alkyllead compounds has not been documented.

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