MARC: Monitoring and Assessment Research Centre

GEMS: Global Environmental Monitoring System

MARC REPORTS NUMBERS 16-18

PROGRESS REPORTS IN ENVIRONMENTAL MONITORING AND ASSESSMENT
1. LEAD

Technical Reports

Prepared by:
MONITORING AND ASSESSMENT RESEARCH CENTRE
Chelsea College, University of London

With the support of:
UNITED NATIONS ENVIRONMENT PROGRAMME and
THE ROCKEFELLER FOUNDATION

The Monitoring and Assessment Research Centre (MARC), Chelsea College, University of London, became operational on 1 July 1975.

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ISBN 0 905918 15 0

MARC, Chelsea College

Lead pollution of the global environment

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A Technical Report (1980)

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United Nations Environment Programme and
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ABSTRACT

The production and release of lead into the environment is briefly reviewed and some attempt is made to quantify the movement of lead from atmosphere to man, both via the soil food chain and the respiration pathway. Existing data are analysed to estimate the transfer to man per unit input into the atmosphere. The results indicate that one year's contamination of the atmosphere at 1 $\mu g\,m^{-3}$ would result in an average lifetime lead uptake to blood of 7 mg. A relationship between average daily intake and mean blood levels of lead is given. Dose-response information is presented which indicates that some persons living in more highly polluted environments are probably suffering from deleterious effects.

Foreword

During the last few years, the Monitoring and Assessment Research Centre (MARC) has been involved in the study of environmental pollution problems of global concern. In particular, the exposure commitment method has been applied to non-radioactive pollutants and the relevant exposure-response relationships reviewed.

Recent MARC reports (Nos 12 to 15) illustrated the application of the exposure commitment method to environmental lead and mercury and special attention was devoted to the analysis of errors in exposure predictions.

The first report in this volume, "Lead pollution of the global environment" (No. 16) arose from a request by the Executive Director of the United Nations Environment Programme (UNEP), in response to a UNEP Governing Council decision in 1978 "to undertake a pilot study to illustrate evaluation techniques with respect to one of the priority pollutants". This report brings together a considerable amount of data, and uses the commitment method to estimate the exposure of man to lead pollution via the soil-food chain and respiratory pathways. The mathematical basis for the methodology adopted is described in MARC report No. 13.

MARC is actively involved in the study of exposure-response relationships. In report No. 17, apparent threshold values are derived for various health effects in adults and children which may be a result of exposure to lead.

A valid statistical approach is very important at all stages of designing environmental and health-related experiments and evaluating data. Report No. 18 examines statistical aspects in the establishment of exposure-response and exposure-effect relationships.

The publication of these three MARC reports in one volume emphasizes the common theme running through our research programme. Future MARC reports will develop the main components of this programme: a greatly extended data base, particularly on pollution in various environmental compartments and the interactions within and between compartments will be used to refine estimates of exposure to globally significant pollutants; the resulting risks to human and environmental health will be established, and comprehensive methods of pollution assessment will be reviewed and evaluated.

5 January 1980

T. A. Rafter
Director

Contents

1.0 Introduction

Lead metal has been used by man for some thousands of years. Before the industrial revolution, lead was mainly used for making pipes and various utensils. Since that time there has been a considerable increase in the smelting of lead and in the present century it has found increasing usage as an additive to petrol for use in internal combustion engines. This rapid rise in the use of lead by man has resulted in large increases in the levels of lead prevailing in the environment, even in the most remote corners of the earth.

The present report aims to summarize our present knowledge concerning the contamination of the environment with lead. Present data on lead levels in important environmental reservoirs are reviewed, the transport of lead between reservoirs is considered and the intake of lead by man via important pathways is estimated. By considering what is known about dose-effect relationships, it is possible to make some assessment of possible future health risks.

2.0 Industrial production and emissions of lead

Lead is the most abundant of the heavy metals and its use has been recorded from around 2500 BC onwards (68). Its extensive use in historic time has made it one of the earliest known metal pollutants and this early use may have had some effect on 'baseline' levels in the environment. Between 1968–1977 the world production of refined lead increased from 3.55 to 4.27 million tonnes (58). Approximately 50 per cent of refined lead production is obtained by recycling of lead products. Of the total end use of lead, almost half goes to make batteries and around seven per cent in producing alkyl lead fuel additives – introduced into petrol technology around 1923. The other main uses of lead are cable sheathing, chemicals, alloys and castings for component parts.

The natural emission rate of lead to the atmosphere has been estimated at 24,500 $t\,y^{-1}$ compared with an anthropogenic emission rate of 449,000 $t\,y^{-1}$ in 1975 (65). The greatest single source of anthropogenic emissions of lead comes from the combustion of alkyl lead in motor fuels; global emission rate from this source in 1974–75 was estimated to be 267,000 $t\,y^{-1}$ which is about 60 per cent of the total man-made release of lead to the atmosphere (64).

3.0 Lead in the environment

3.1 Rocks

The commonest lead ore is galena (PbS) which is a polymetallic ore and represents a source of several other metals. Lead in rocks is often found at a concentration of approximately $20 \mu g\,g^{-1}$. Data from various sources (2, 41, 55, 56, 82, 92) for several types of rock are listed in Table 1. The mean value is $22 \mu g\,g^{-1}$ with granitic (acid) rocks tending to have higher levels than basaltic (basic) ones.

3.2 Soils

In general, soils tend to reflect the composition of their parent material. Soils in mineralized areas, therefore, have the highest concentrations of lead. As with the parent material, lead content of soils varies with acidity.

Agreement on a mean concentration or range for lead in soil is poor. Bowen (10) gives a mean of $10 \mu g\,g^{-1}$ with a range of $2–200 \mu g\,g^{-1}$, whereas WHO (96) reported a range of $0.04–1 \mu g\,g^{-1}$. From limited data presented in Table 2, it would appear that the latter estimates are low, most values lying in the range $10–130 \mu g\,g^{-1}$ (4, 63, 70, 74). The data of Archer (4) is an average for 752 samples collected on several hundred farms in the U.K. Based upon this, the average concentration in the top layer of agricultural soils in temperate latitudes is assumed to be $50 \mu g\,g^{-1}$.

Some data on the variation in concentrations of lead in soil with depth are also shown in Table 2. The increased concentration of lead in the top horizon of the Scottish soils has been reported for soils in other areas (46, 48, 98). This is thought to be due to accumulation of lead in plants, the lead being held in the surface layer in an insoluble complex (79).

Concentrations of lead in surface soils of 240 to $540 \mu g\,g^{-1}$ have been reported at eight metres from busy highways in the U.S.A., falling to 60 to $140 \mu g\,g^{-1}$ at a distance of 32 m (64). The variation of soil lead concentration at different distances from busy highways is shown in Figure 1. Although concentrations at distances of less than 50 m tend to be elevated, at distances over 100 m they appear to be about normal (78). High concentrations of lead in surface soil in city parks have been reported in Los Angeles, $3{,}350 \mu g\,g^{-1}$ and

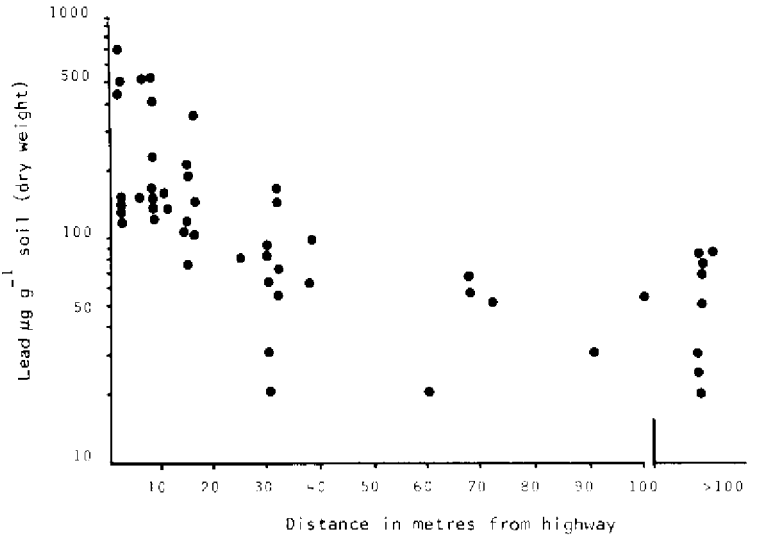

Figure 1 Lead content of roadside surface soils (78)

San Francisco, 560 $\mu g\ g^{-1}$. Even higher average concentrations were reported for dust. In 77 cities in the U.S.A. average lead concentrations in dust in commercial and residential areas ranged from 1,640 $\mu g\ g^{-1}$ to 2,410 $\mu g\ g^{-1}$ (64).

3.3 Atmosphere

Whether or not current "baseline" levels of lead in air are wholly natural or are a composite of natural and anthropogenic sources can be determined through analysis of isotopic composition (6, 26, 27) or by a consideration of enrichment factors[§]. However, it seems certain that even in the remotest sites the lead concentration in air has been considerably elevated above natural levels due to man's impact upon the natural cycle of lead. This is supported by the high enrichment factors obtained for lead even at the most remote sites as indicated in Table 3. Lead enrichment factors for atmospheric

[§]The enrichment factor for lead in an atmospheric aerosol is defined as the ratio of the concentration of lead to that of scandium (or aluminium) in the aerosol divided by the same ratio for average soil.

aerosols collected at a number of sites are shown in this table. If atmospheric lead is mainly from wind blown soil, the enrichment factor would be close to unity. From the burning of fossil fuel, a value of about nine would be expected (8) while for volcanic aerosols values of 100 and 61 are reported (61, 33). The enrichment factors of atmospheric aerosols at both urban and remote sites exceed these values usually by at least an order of magnitude, which indicates that even in more remote regions most atmospheric lead is of anthropogenic origin. The degree of contamination is indicated in the work of Murozumi *et al.* (62) in Greenland and Antarctica. Lead levels in the northern ice-cap have increased from $< 0.0005\,\mu g\,kg^{-1}$ ice in 800 BC to $> 0.20\,\mu g\,kg^{-1}$ ice at the present time (see Figure 3). This is a rise by a factor of over 400 in the past 2,500 years and most of this increase has taken place since 1750. The rise in the southern hemisphere snow and air has not been so dramatic due to the poor interhemispheric mixing of air as well as to lower levels of atmospheric pollution in this hemisphere.

The natural lead aerosol is a product of several sources including volcanism and wind blown soil particulates. It has been proposed that the volatilization of the components of surface rocks adds to the aerosol burden of lead and other metals (42). Further, studies with radioisotopes indicate that, under laboratory conditions at least, plants release particulates containing lead (and zinc) into the atmosphere (7).

Reported levels of atmospheric lead for urban, rural and oceanic sites are given in Table 4. Data from the UKAEA[§] atmospheric trace element survey (16, 17, 18) suggest that rural lead levels in the northern hemisphere range from 50–200 $ng\,m^{-3}$ whereas the more remote continental areas give values around 0.5–1.5 $ng\,m^{-3}$ (36, 62). By comparison, the limited data for analogous areas in the southern hemisphere suggest a level of approximately 20 $ng\,m^{-3}$ for rural (non-urban) zones (38) and 0.5–5.0 $ng\,m^{-3}$ for remote areas (38, 99).

Estimated concentrations of lead in the atmosphere at Chilton U.K. between 1957 and 1974 are shown in Figure 2 (76). The high levels in 1957–1958 are thought to be from an industrial source

[§] United Kingdom Atomic Energy Authority.

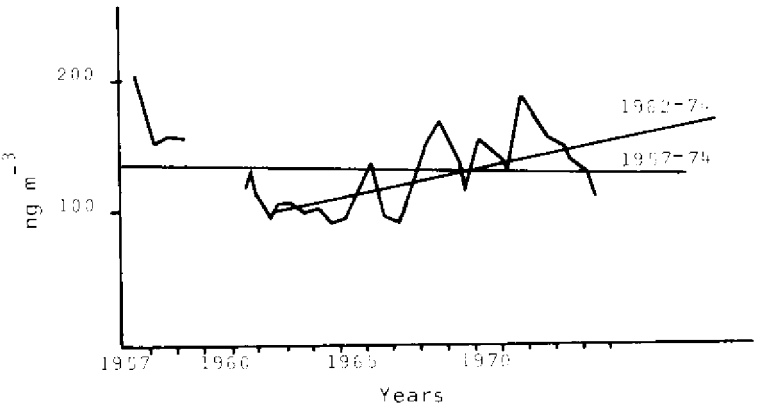

Figure 2 The concentration of lead in the air at Chilton U.K. (76)

which was attenuated as a result of the U.K. Clean Air Act of 1956. The gradual rise in levels since the early 1960s is thought to be mainly due to increasing petrol consumption, which doubled between 1960 and 1970.

Open ocean and coastal levels of atmospheric lead in the northern hemisphere range from 0.2–6.0 ng m^{-3} in the data reviewed (16, 17, 18, 36, 38, 39, 50) with fairly distinct differences between coastal and ocean sites. Elevated levels recorded at two open ocean sites in the Atlantic are almost certainly due to long-distance pollution transport (39). Marine data for the southern hemisphere are very limited but levels recorded are <10 ng m^{-3} at remote sites (36, 38). Coastal sites in South America given in Table 4 show a clear urban influence.

Concentrations of lead in air reported for remote sites (Arctic and Antarctic region, the Pacific and Indian Oceans) are probably spuriously high due to local pollution or sample contamination. Deposition of lead onto snow in the polar regions indicates that average atmospheric concentrations would be of the order of 1 ng m^{-3}.

Urban air lead levels vary with the size of the city, traffic density, etc. During the last decade, lead levels generally exceed 1,000 ng m^{-3} in northern hemisphere cities with populations in excess of 200,000,

but they are not strongly dependent upon the size of the city (64). Extremely high levels of 38,000 ng m^{-3} have been recorded during "rush hours" in Los Angeles (96). Air monitoring in South American cities indicates that lead levels are approximately 850 ng m^{-3} (39). In the U.S.A. average values of lead in air at non-urban sites near cities are about 200 ng m^{-3}, 100 ng m^{-3} in rural areas at intermediate distances from cities and about 20 ng m^{-3} in more remote areas. These values and also average levels in the North Atlantic of 10 ng m^{-3}, and in the North Pacific and Indian Oceans and other remote regions of 1 ng m^{-3} can be accepted as representative.

3.4 Deposition

Average annual deposition of lead at a number of sites is shown in Table 5. Ter Haar *et al.* (84) found an average deposition of 1 μg cm^{-2} y^{-1} in semirural areas of the U.S.A. Wadsworth and Webber (93) reported measurements of lead deposition at six rural sites in the U.K. over a period of five years. The mean annual deposition was 0.89 ± 0.52 μg cm^{-2}, about three times lower than those reported for the UKAEA monitoring stations (19).

Also included in Table 5 are some examples of the annual deposition rate at sites within large cities, near a busy highway and at close proximity to lead smelters (20, 24, 54, 91). In rural areas of Europe and North America the annual deposition rate is typically a few μg cm^{-2} y^{-1} and in less industrialized areas of the world it would be considerably less. In large cities, deposition rates appear to be about 10 times higher than in rural areas. Near busy highways it is higher still, typically some hundreds of μg cm^{-2} y^{-1}. The highest recorded levels of lead deposition occur near smelters where deposition rates in excess of 1,000 μg cm^{-2} y^{-1} have been recorded.

At present, data on atmospheric concentrations of lead are much more extensive than data on deposition. It is possible to estimate deposition rates from measured atmospheric concentrations, using an average deposition velocity for lead particulates. This is defined as the quotient of the deposition rate and the concentration in air at one metre above ground level. Some values are shown in Table 6.

It is possible to estimate the average enrichment factor for lead in deposition using the enrichment factor for lead in atmospheric

particles (Table 3) together with the average deposition velocities for lead and scandium reported by Cawse (19) which are 0.7 and 3.4 $cm\,s^{-1}$ respectively. Taking 1,500 as a typical enrichment factor for lead in atmospheric particulates, a value of about 300 is obtained for the enrichment factor in deposition. This indicates that the current flux of lead to the earth's surface is about 300 times its natural value, in agreement with the estimate of Murozumi *et al.* (62) based upon lead in Arctic snow in 800 BC and 1965 AD, and also with the results of Elias *et al.* (37) based upon Ba/Ca and Pb/Ca ratios in rocks and human bones.

3.5 Hydrosphere

The average concentration of lead in rain water at 32 stations in the U.S.A. was 34 $\mu g\,\ell^{-1}$ (54). At five stations in the U.K. the average over a five-year period was 27 $\mu g\,\ell^{-1}$ whereas a survey carried out in the U.S.S.R. gave an average of 4.6 $\mu g\,\ell^{-1}$ (19, 34). The average lead content of 33 water samples of major U.S.A. rivers was 6.6 $\mu g\,\ell^{-1}$ (64). Tap water in New York was found to have a lead concentration of 4 $\mu g\,\ell^{-1}$ (8).

Concentrations of lead in open ocean and coastal waters tend to decrease with increasing depth. The estimated mean concentration of lead in open ocean waters, both surface and deep, is 0.06 $\mu g\,\ell^{-1}$ (28, 81) whereas in near shore waters the concentration in surface layers is estimated at 0.16 $\mu g\,\ell^{-1}$ and in deep layers 0.03 $\mu g\,\ell^{-1}$ (25, 28, 81). Patterson, by comparing the concentrations of lead, barium and radium in surface ocean waters has concluded that concentrations of lead in surface ocean waters have increased by 0.05 $\mu g\,\ell^{-1}$ because of industrial pollution (68). Because of difficulties experienced in the past in reliably measuring lead in ocean waters, the estimated concentrations reported here should be considered as tentative (23, 95). It is clear that further research is needed on methods of lead analysis. Furthermore, a larger data base for lead in the marine environment needs to be developed.

The residence time of lead in the ocean was estimated by Goldberg (44) to be about 400 years. Elias *et al.* (37) estimate the current anthropogenic input rate of lead to the ocean to be 300,000 $t\,y^{-1}$ of which some 60,000 $t\,y^{-1}$ are assumed to be in soluble form, while

the input rate of lead from natural sources is about 113,000 $t\,y^{-1}$ of which some 13,000 $t\,y^{-1}$ are in soluble form. This indicates that the current input rate of lead into the world's oceans is some four times the natural flux. According to Turekian (87), based upon ^{210}Pb data in the ocean the residence time of dissolved lead in the surface ocean is of the order of a year, much of the removal being due to absorption on sinking particles. This removal process is also important for the deep ocean (30).

3.6 Sediments

Marine sediments, both near shore and open ocean, contain from 20–320 $\mu g\,g^{-1}$ of lead. The data collected on some 50 open ocean sediments give a mean lead level of $148 \pm 21\,\mu g\,g^{-1}$ (22, 31, 43, 80, 88, 94) at depths which were usually greater than 4,500 m. Excluding a few very high values (94), the mean lead level for near shore sediments is approximately 39 $\mu g\,g^{-1}$ (14, 60, 94). This lower concentration in coastal regions probably is a result of the much higher sedimentation rate there. Freshwater sediment data (5, 13, 57, 60, 85, 86) suggest that lead levels are around 20–30 $\mu g\,g^{-1}$ in non-mineralized areas. Geochemical reconnaissance surveys have been carried out in the U.K., based on the analysis of stream sediments taken at an average of one sample per square mile. The resulting geochemical maps have provided "baseline" information on the regional distribution of various heavy metals, including lead, in relation to the surrounding bedrock and soil (5, 85, 86).

4.0 Historic lead levels

Environmental lead levels in past times can be estimated from records preserved in certain media, e.g. permanent snowfields (12, 62), museum samples of moss (74) and lake and marine sediments (29, 35).

Murozumi *et al.* (62) examined lead levels preserved in the annually deposited snowlayers of the Greenland ice sheet; they show that deposition of lead aerosols onto the ice mass has increased considerably in recent times (see Figure 3). Natural lead was estimated to be about 0.0004 $\mu g\,kg^{-1}$ snow in the older samples. However, at the beginning of the Industrial Revolution in 1750 AD, concentrations had risen to about 25 times natural levels and by 1940 this factor

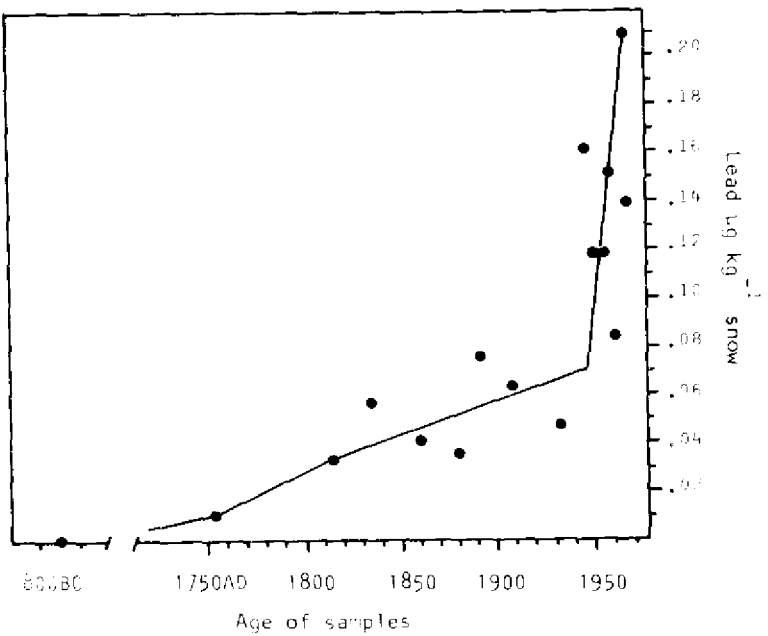

Figure 3 Increase of industrial lead pollution in northern Greenland snow with time, reproduced from Murozumi *et al.* (62)

had increased to about 175. After 1940, levels rose sharply over a short interval to 500 times natural levels. The sources of the industrial lead aerosols removed from the atmosphere in the north polar regions are considered to have originated mainly from lead smelters before 1940 and vehicle exhaust fumes after that date. Levels in the Antarctic ice sheet between 1950 and 1974 show a two- to threefold increase in the more recently deposited snow layers, although actual levels on the whole are 10–12 times lower than those found in the Greenland ice sheet (12). This is evidence that considerable quantities of lead are transported to the open ocean and remote continental land masses by the atmosphere. Lead analysis of museum preserved mosses in southern Sweden reveal trends similar to those found in the Greenland ice sheet. Thus, levels of lead in 1965 specimens of moss of 80–90 $\mu g\, g^{-1}$

contrast with values of 20 $\mu g\,g^{-1}$ dry weight in moss specimens dated 1860–1875 (74).

Edgington and Robbins (35) determined the distribution of stable lead in several Lake Michigan sediment cores. The profiles are all roughly exponential, decreasing to an apparently constant value of about 23 $\mu g\,g^{-1}$ sediment dry weight. Lead concentrations at the top of the cores are variable, ranging from about 100–160 $\mu g\,g^{-1}$. In all sediment cores, lead in excess of the 23 $\mu g\,g^{-1}$ background was found primarily within the 1930–1972 interval, which corresponded to the period of enhanced consumption of gasoline containing lead in the region.

In like manner, Chow *et al.* (29) examined the lead content of dated varved sediment layers from the virtually anoxic shallow basins off the coast of California. The profiles found for the San Pedro and Santa Monica basins are reproduced in Figure 4. The rates of accumulation began to increase in the basins in the 1940s. The authors estimated that the anthropogenic fluxes of lead for the San Pedro and Santa Monica basins were 1.7 and 0.9 $\mu g\,cm^{-2}\,y^{-1}$ compared with the natural fluxes of 0.26 and 0.24 $\mu g\,cm^{-2}\,y^{-1}$ respectively.

An example of the use of human bones to provide an historical record of human exposure is that by Jaworowski (52) (see Table 7). The low concentrations of lead (1–3 $\mu g\,g^{-1}$ bone) in the third century contrast with the high lead content of bones from the 11th to the 19th centuries (5–199 $\mu g\,g^{-1}$ bone). These variations in the lead concentrations were probably caused not by pollution of the atmosphere resulting from industrial activity but rather by dietary habits and contamination of food. Recent samples contained on average 4 $\mu g\,g^{-1}$. In view of the uncertainty of the extent to which lead was used by primitive societies, Elias *et al.* (37) suggest that bones for lead analysis should only be taken from civilizations older than 2500 BC. Of the few analyses available, it appears that levels were about two orders of magnitude lower than those presently found in human bones.

5.0 Transfer of lead from the environment to man

In order to ascertain whether present or future environmental levels of lead will prove detrimental to the health of man, it is necessary

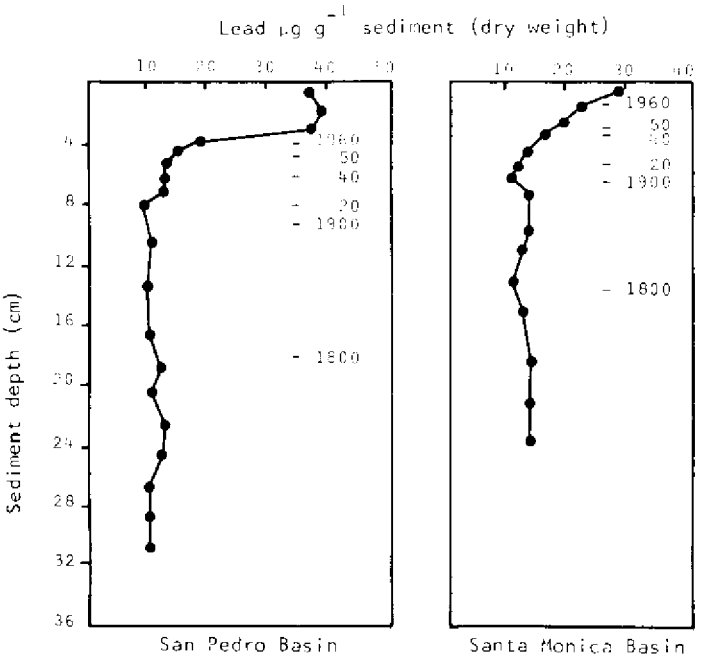

Figure 4 Lead concentrations in sediments from the San Pedro and Santa Monica basins of southern California. Redrawn from Chow *et al.* (29)

to estimate how human lead intake and uptake are related to environmental levels. Since, in general, lead concentrations in underground and river waters are quite low, except in cases of contamination by local industrial wastes, most lead will enter man via inhaled air or ingested food.

The transfer of lead to man, excluding aquatic pathways, can be represented by the diagram in Figure 5. Two main pathways are evident, one direct from air to man by inhalation of air, the other via soil, plants and animals to man by ingestion of food. These two pathways will be considered separately.

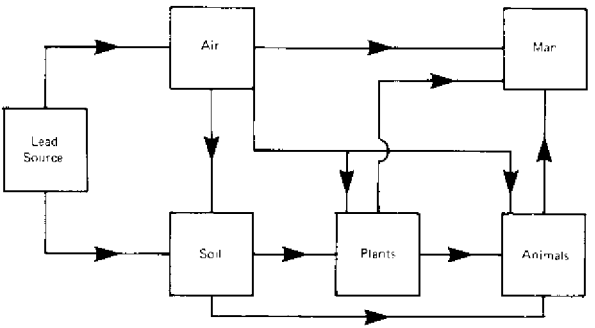

Figure 5 Simplified transfer of lead to man

5.1 Intake of lead by ingestion

Estimates of the average annual intake of lead from food consumption in the United Kingdom and in New York are given in Table 8 which shows the contribution from each of the main food categories (9, 59). The United Kingdom results are based upon the analysis of some 6,000 samples between 1972 and 1974. The New York City lead data are the average of three surveys conducted in 1968–69, 1970–71 and 1972–73 for 19 food categories of the standard U.S.A. diet. In addition, ^{210}Pb was concurrently measured with stable lead in the 1972–73 survey of New York diet and these results, together with the specific activities in the different diet categories, are also shown in Table 8.

All diet categories contribute significantly to the intake of stable lead; cereals, meat and fish and fruit account for the major contribution in both surveys. For ^{210}Pb in New York, cereals provide a larger intake than other food categories.

The U.K. survey (59) indicated that lead levels in canned food were in general higher than those in the fresh product. Concentrations in lean meat were about $0.2\,\mu g\,g^{-1}$ but were about three times this value in heart and liver. Fresh fish contained about $0.9\,\mu g\,g^{-1}$ but shellfish in general had higher levels, in the range of $0.5–4\,\mu g\,g^{-1}$. Goldberg found the average concentration of lead in mussels gathered from both the Atlantic and Pacific coasts of the U.S.A. was $3.1\,\mu g\,g^{-1}$ (45). In the U.K., fish contributes less lead to the average diet than

meat, but people who regularly eat large amounts of shellfish would have a significantly greater intake of lead.

The transfer of lead from soil to plants is complex. Much of the lead present in soil appears unavailable for plant uptake, and experiments in growing plants on soils containing different levels of lead have produced varying results, depending upon both the physico-chemical properties of the soil and on the plant species used (64).

There are a number of possible pathways through which lead deposited onto crops can become part of the food chain. One possibility is that lead deposited onto vegetables or fruit is adsorbed onto or absorbed into these food stuffs. A number of measurements made on leafy vegetables, fruit and berries grown in areas of high lead pollution indicate that surface contamination can add significantly to the total lead content of these foods, but that where the food is washed and/or peeled, this source of contamination becomes much less significant (59). The other pathway is that the lead is absorbed from soil through the root system.

Ter Haar (83) investigated the uptake of lead by plants grown at different distances from busy highways in soils containing different levels of lead. He concluded that the lead content in the edible parts of plants was unaffected by the increased anthropogenic lead in soil, and depended only on the natural lead level in soil. Davies (32) who investigated the uptake of lead from soils in mining districts of the U.K. contaminated to different degrees, found that lead in both ryegrass and potatoes was roughly proportional to the amount of extractable lead in soil. Thornton (85) also found higher levels of lead in pastures grown on lead contaminated soils and also observed that lead uptake was much higher in the spring and autumn than in summer. Richardson (73) reported on the Pb content of plants grown on soils, some of which had been treated with sewage sludge containing elevated levels of lead. Although the concentration of lead in lettuce leaves was strongly influenced by total lead in soil, the effects upon other plants were much less marked. Other work has shown that the concentration of lead in the leafy parts of plants is affected by the direct deposition of lead onto the plant (83).

The relationship between lead in deposition, the concentration and residence time in soil and the uptake by plants can be investigated

by comparison of ^{210}Pb, which is produced in the atmosphere by the decay of radon-222, and is present in the air and in deposition over continental areas in fairly uniform concentrations. The radioactive half-life of ^{210}Pb is 21 years and the mean life is $21 \div ln\ 2 = 30.3$ years.

The average level of ^{210}Pb in air over continents is $0.5\,mBq\,m^{-3}$ (9, 46, 63) which, together with a value of lead in air in rural areas of $0.1\,\mu g\,m^{-3}$, gives a specific activity of $5{,}000\,Bq\,g^{-1}$. The average deposition rate of ^{210}Pb over continents in the northern hemisphere is $7.4\,mBq\,cm^{-2}\,y^{-1}$ (53). Assuming the mean annual deposition of lead in rural areas to be $2\,\mu g\,cm^{-2}\,y^{-1}$, this implies a specific activity of $3{,}700\,Bq\,g^{-1}$. The average activity of ^{210}Pb in soil is about $0.03\,Bq\,g^{-1}$ (89) which, with the mean concentration of lead in soil of $50\,\mu g\,g^{-1}$, gives a specific activity in soil of $600\,Bq\,g^{-1}$.

From Table 8 it can be seen that the specific activity of ^{210}Pb in the New York diet is $530\,Bq\,g^{-1}$. In the U.K. the average dietary intake of ^{210}Pb is $43\,Bq\,y^{-1}$ (49) which, together with the lead intake rate of $50\,mg\,y^{-1}$ (see Table 8), gives a specific activity in the diet of $860\,Bq\,g^{-1}$. Both the New York and the U.K. dietary intake have specific activities about the same as for soil lead, but five to eight times smaller than for lead in air or deposition. This strongly suggests that most dietary lead originates from uptake by plants from soil through their root system. In addition, it implies that the mean residence time of lead in soil before uptake by plants is at least five times the mean radioactive life of ^{210}Pb (30.3 years), or 150 years. This means that lead deposited onto arable land will cause increased dietary intake of lead for future generations of man. Bowen (11) estimated the residence time of lead in soil of the upper Thames basin, U.K., to be between 400 and 3,000 years. We shall assume the mean residence time in soil is 300 years. Using existing data, it is possible to estimate levels of lead in soil resulting from deposition of lead in air and, in turn, levels of lead in diet resulting from the lead concentrations in soil. The ratio of the deposition density rate to soil and the concentration in air defines the deposition velocity. Assuming an average value of the deposition velocity of $0.5\,cm\,s^{-1}$, the deposition rate from $1\,\mu g\,m^{-3}$ of lead in air is

$$1\ \frac{\mu g}{m^3} \times 0.5\ \frac{cm}{s}\ \frac{10^{-2}\,m}{cm}\ \frac{3.15 \times 10^7\,s}{y} = 15.8 \times 10^4\ \mu g\,m^{-2}\,y^{-1}$$

Therefore, a concentration of $1\,\mu g\,m^{-3}$ of lead in air for one year, or equivalently an exposure commitment (i.e. the integral of concentration over time) of $1\,\mu g\,y\,m^{-3}$, gives rise to a cumulative deposition density of $15.8 \times 10^4\,\mu g\,m^{-2}$. This amount of deposition per unit area of soil surface is assumed to be distributed in the upper 10 cm depth region of soil. The soil density is assumed to be $1.4\,g\,cm^{-3}$. The concentration of lead in soil from this deposited amount is therefore

$$\frac{15.8 \times 10^4\ \frac{\mu g}{m^2}}{1.4\ \frac{g}{cm^3}\ 10\,cm\ \frac{10^4\,cm^2}{m^2}} = 1.13\,\mu g\,g^{-1}$$

The exposure commitment to soil depends on the mean residence time of lead in soil. This is most uncertain, but from the discussion of ^{210}Pb specific activities, it has been estimated to be 300 y. The exposure commitment to soil, designated E_2, from the unit exposure commitment to air, E_1, is thus

$$E_2 = 1.13\ \frac{\mu g}{g} \times 300\,y = 340\,\mu g\,y\,g^{-1}$$

The ratio of the exposure commitments (66) defines the transfer coefficient, P_{12}, for lead from air to soil

$$P_{12} = \frac{E_2}{E_1} = 340\,\mu g\,y\,g^{-1}\ \text{per}\ \mu g\,y\,m^{-3}$$

It will be assumed that the level of lead in food is proportional to that in the soil in which it is grown. Using the New York and U.K. dietary data (average intake about $40\,mg\,y^{-1}$) and the average soil concentrations ($50\,\mu g\,g^{-1}$), one can obtain a useful relationship:

$$\frac{40\,mg\,y^{-1}}{50\,\mu g\,g^{-1}} = 800\,\mu g\ \text{per}\ \mu g\,y\,g^{-1}$$

This is the cumulative intake of lead (intake commitment) per unit exposure commitment to soil. This intake commitment can be referred back to the exposure commitment to air (E_1) by multiplication of the air to soil transfer coefficient (P_{12}).

$$340 \frac{\mu g\, y\, g^{-1}}{\mu g\, y\, m^{-3}} \times 800 \frac{\mu g}{\mu g\, y\, g^{-1}} = 2.7 \times 10^5\ \mu g \text{ per } \mu g\, y\, m^{-3}$$

In the steady state, $1\ \mu g\, m^{-3}$ of lead in air can be associated with a lead intake rate in diet of $2.7 \times 10^5\ \mu g\, y^{-1}$[§]. For any other time integral of air concentration, the intake commitment of lead in diet is $2.7 \times 10^5\ \mu g$ per unit exposure commitment to air.

In estimating the transfer coefficients from air and deposition to dietary intake, it has been assumed that the deposited lead is immediately available for uptake, but that its availability steadily decreases with time. However, there is at present no information on how availability actually changes in time.

It is very important to verify whether the uptake rate of lead into food chains is in fact proportional to total lead in soil or to total lead deposition, and over what time the lead remains available for uptake. Monitoring and research programmes should be undertaken to assess this by determining dietary intake, average soil levels and deposition rates for both stable lead and ^{210}Pb in regions with different lead levels in soil and in regions with markedly different deposition rates of anthropogenic lead. Measurements of lead in historical food samples over the last several hundred years would also provide useful information.

5.2 Intake of lead by inhalation

The inhalation rate of air is on average $22\ m^3\, d^{-1}$, applicable to the adult male (51). The inhalation rate and therefore the intake of lead via this pathway is less for women and children. For a lead concentration in air of $1\ \mu g\, m^{-3}$, the inhalation intake rate is

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[§] The correspondence of exposure or intake commitments and steady state values, viewed as alternative associations of the same units (μg per $\mu g\, y\, m^{-3}$ and $\mu g\, y^{-1}$ per $\mu g\, m^{-3}$), is a useful feature of exposure commitment analysis (66).

$$1\ \frac{\mu g}{m^3} \times 22\ \frac{m^3}{d} \times \frac{365 d}{y} = 8000\ \mu g\ y^{-1}$$

Alternatively, for an exposure commitment to air of $1\ \mu g\ y\ m^{-3}$, the inhalation intake commitment is 8,000 μg.

5.3 Absorption of lead into blood

Studies of lead ingestion and excretion indicate that some 10 per cent of ingested lead is absorbed in the gastrointestinal tract of adults. Rabinowitz *et al.* (72) found that the absorption of orally administered ^{204}Pb was a little less than 10 per cent. For young children a much higher degree of lead absorption has been reported, up to 53 per cent (27).

For the adult, the absorption rate to blood via ingestion from $1\ \mu g\ m^{-3}$ in air is thus

$$2.7 \times 10^5\ \frac{\mu g\ y^{-1}}{\mu g\ m^{-3}} \times 0.1 = 2.7 \times 10^4\ \frac{\mu g\ y^{-1}}{\mu g\ m^{-3}}$$

At equilibrium, a continuous level of $1\ \mu g\ m^{-3}$ of lead in air gives rise to an absorption rate of $27\ mg\ y^{-1}$. For single releases of lead to air, the absorption to blood (uptake commitment) in the ingestion pathway from an exposure commitment to air of $1\ \mu g\ y\ m^{-3}$ is 27 mg. This transfer takes place over many years, due to the long residence time of lead in soil. Other transfer times are negligible in comparison. The fractional transfer to any one individual during a 70 year lifetime for a single release of lead to the atmosphere occurring at someone's birth would be

$$\frac{\int_0^{70} e^{-\lambda t}\, dt}{\int_0^{\infty} e^{-\lambda t}\, dt} = \frac{\frac{1}{\lambda}\,(1 - e^{-70\lambda})}{\frac{1}{\lambda}} = 21\%$$

where $\lambda = 1/\bar{t}_m$ and $\bar{t}_m$ is the mean residence time of lead in soil, assumed here to be 300 years. The transfer to blood via ingestion is thus $27\ mg \times 0.21 = 5.7\ mg$ for this individual.

Following inhalation intake, fractional retention of respirable particles in the pulmonary region of the lung is of the order of 30 per cent. Chamberlain *et al.* (21) found values of 32 to 48 per cent, in agreement with other studies. A retention of 35 per cent will be assumed here. Of this only 50 per cent is absorbed into the blood (21).

The transfer relationship for the inhalation pathway is thus

$$8000 \frac{\mu g\, y^{-1}}{\mu g\, m^{-3}} \times 0.35 \times 0.5 = 1400 \frac{\mu g\, y^{-1}}{\mu g\, m^{-3}}$$

For an exposure commitment to air of $1\,\mu g\, y\, m^{-3}$, the absorption to blood from inhalation is 1.4 mg.

The data presented above indicate that one year's contamination of the atmosphere with lead at $1\,\mu g\, m^{-3}$ would give rise to a transfer to blood by inhalation of 1.4 mg which would occur during the year of atmospheric exposure. In addition, a person born in the year when the atmosphere was contaminated would receive another 5.7 mg of lead through the diet, which would be delivered over 70 years following the release. Other persons would receive amounts of lead proportional to the balance of their lifespan. In addition, individuals of future generations would receive progressively smaller amounts via the ingestion pathway. The estimate of transfer from inhalation is reasonably precise; that from ingestion has probably a wide margin of error.

For representative background levels of lead in air, the current absorption rates to blood can be summarized as follows: $0.15\,\mu g\, m^{-3}$ in air gives rise to $50\,\mu g\, g^{-1}$ average concentration in soil (from the transfer coefficient P_{12}). The annual ingestion intake of lead is 40 mg and absorption to blood is 4 mg. The inhalation intake for rural residents from $0.15\,\mu g\, m^{-3}$ of lead in air is $0.2\, mg\, y^{-1}$ and for urban residents from $2\,\mu g\, m^{-3}$ of lead in air is $2.8\, mg\, y^{-1}$. The total absorption rate to blood, therefore, ranges from 4.2 to $6.8\, mg\, y^{-1}$ which even for urban residents is due primarily to the ingestion pathway. Additional intake of lead could occur from other sources, such as from food and drink in contact with lead containers or soiled hands. Additional analysis would be required to estimate the absorption rate to blood for children from these and other sources.

5.4 Concentration of lead in blood and distribution in body

The residence half-time of lead in blood has been determined to be about 16 days (21, 72) giving a mean residence time of 23 days. This result is from relatively short-term studies following oral or inhalation intake and probably does not include redistribution of lead from tissues.

From the assumed residence time of lead in blood and an estimate of blood volume (5.2 litres), the exposure commitment to blood from $1\,\mu g\,y\,m^{-3}$ of lead in air due to inhalation can be determined.

$$1400\ \frac{\mu g}{\mu g\,y\,m^{-3}} \times \frac{23\,d}{5.2\,\ell} \times \frac{1\,y}{365\,d} = 17\,\mu g\,y\,\ell^{-1}\ \text{per}\ \mu g\,y\,m^{-3}$$

or

$$1.7\,\mu g\,y\ (100\,ml)^{-1}\ \text{per}\ \mu g\,y\,m^{-3}$$

Both Rabinowitz *et al.* (72) and Chamberlain *et al.* (21) obtained from their experimental studies on humans a value of $1.2\,\mu g\ (100\,ml)^{-1}$ for the increase of lead in blood due to exposure to air containing $1\,\mu g\,m^{-3}$ of lead. These results may reflect a somewhat lower breathing rate than was assumed above. The absorbed fraction of lead will also depend on the chemical form. WHO (97) has reviewed data on blood lead and atmospheric exposure for occupationally exposed workers and found that an increase of $1\,\mu g\,m^{-3}$ in the average level of lead in air gives rise to an increase in blood lead of 0.5 to $1.5\,\mu g\ (100\,ml)^{-1}$.

For the ingestion pathway, the exposure commitment to blood from $1\,\mu g\,y\,m^{-3}$ of lead in air is

$$2.7 \times 10^4\ \frac{\mu g}{\mu g\,y\,m^{-3}} \times \frac{23\,d}{5.2\,\ell} \times \frac{1\,y}{365\,d} = 330\,\mu g\,y\,\ell^{-1}\ \text{per}\ \mu g\,y\,m^{-3}$$

or

$$33\,\mu g\,y\ (100\,ml)^{-1}\ \text{per}\ \mu g\,y\,m^{-3}$$

The ratio of the exposure commitment to blood and the ingestion intake commitment is

$$0.1 \times \frac{23\,d}{5.2\,\ell} = 0.44\,\mu g\,d\,\ell^{-1} \text{ per } \mu g$$

$$= 0.044\,\mu g\,(100\,ml)^{-1} \text{ per } \mu g\,d^{-1}$$

Several studies aimed at establishing the relationship between oral lead intake and blood lead have been reviewed by WHO (97). The agreement between them is not particularly good. The estimates of the diet to blood transfer coefficient for lead range from 0.044–0.28 $\mu g\ (100\,ml)^{-1}$ per $\mu g\,d^{-1}$ intake. The differences, as indicated by animal studies, may be due to a number of factors, such as level of nutrition, intake of calcium, vitamin D and iron.

Assuming that a representative diet-blood transfer coefficient is 0.1 $\mu g\ (100\,ml)^{-1}$ per $\mu g\,d^{-1}$, current dietary lead intake of 40 $mg\,y^{-1}$ (= 110 $\mu g\,d^{-1}$) would give rise to an average blood lead level of 11 $\mu g\ (100\,ml)^{-1}$. Inhalation intake would add another 0.3 $\mu g\ (100\,ml)^{-1}$ for rural residents, since

$$0.15\,\mu g\,m^{-3} \times 1.7\,\frac{\mu g\,(100\,ml)^{-1}}{\mu g\,m^{-3}} = 0.3\,\mu g\,(100\,ml)^{-1}$$

or

3.4 $\mu g\ (100\,ml)^{-1}$ for urban residents, since

$$2\,\mu g\,m^{-3} \times 1.7\,\frac{\mu g\,(100\,ml)^{-1}}{\mu g\,m^{-3}} = 3.4\,\mu g\,(100\,ml)^{-1}$$

In Table 9 the lead concentrations in blood of selected male individuals are listed. The result for rural residents of 12 $\mu g\ (100\,ml)^{-1}$ is in agreement with the above estimate. Levels two to three times higher are observed for occupationally exposed individuals.

In broad terms, lead in the body can be divided into exchangeable and retained components. In the exchangeable component are those tissues in which lead equilibrates relatively quickly with that in blood. The highest lead concentration in soft tissues (51) is found in the aorta, liver and kidneys. Most of the lead retained by the body is in the skeleton – some 95 per cent of the lead burden of adults is found in bone (77). There is at most only slow exchange of lead

in bone. Some studies indicate that the quantity of lead in human bone increases with age, at least to the age of 40 (72).

6.0 Effects of lead on human health

It is not intended to give here a detailed review of the effects of acute and chronic lead poisoning. These have been summarized in the review by the National Academy of Sciences in 1972 (64) and more recently in the WHO health criteria document on lead (97). What we are mainly interested in is the possible effect on large populations of moderate increases in the intake rate of lead.

Lead poisoning can give rise to several clinical syndromes of illness in man, including anaemia, acute abdominal colic, acute and chronic encephalopathy, peripheral neuropathy and lead nephropathy. At moderately elevated levels in blood, lead interferes with the biosynthesis of haem at several enzymatic steps, resulting in the reduction of amino laevulinic acid dehydratase (ALA-D) in blood and the production of free protoporphyrins.

If we assume that the various effects are related to the level of lead in blood, it is possible to relate the percentage of persons in a population showing a given effect to the level of lead in blood.

The relationship between levels of lead in human blood and the frequency of various observable effects has recently been reviewed by Piotrowski and O'Brien (69). These results which should be regarded as tentative are shown in Figure 6 for adult males and in Figure 7 for children. It should be noted that changes in ALA-D levels in blood do not, as far as is known, represent a deleterious effect, but rather are an indicator of elevated levels of lead in blood. From such curves it should be possible to estimate the increase in the number of persons at risk from any given increase in the average level of blood lead in a given population. The blood levels that give a 10 and 50 per cent response level in adults and children are shown in Table 10 (69). These results indicate that a number of effects manifest themselves at blood lead levels not much in excess of prevailing values in industrialized countries.

7.0 Needs for further monitoring and research

In the above review an attempt has been made to estimate the lead

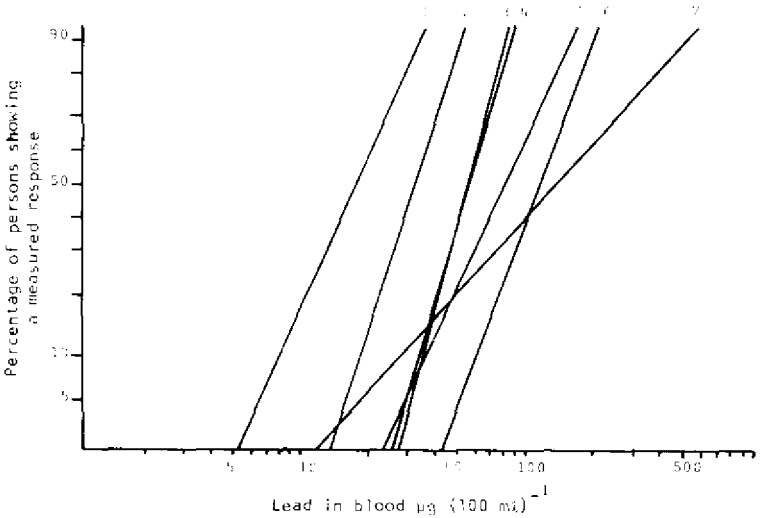

Figure 6 Dose-response relationship for the adult male. The seven curves refer to the following effects:

1. Reduction of erythrocyte ALA-D activity
2. Increase in the free erythrocyte protoporphyrin (FEP) concentration
3. Increase in production of urinary coproporphyrins (CP-U)
4. Rate of ALA-U excretion in urine
5. Inhibition of the peripheral nervous system
6. Anaemia
7. Kidney damage

transfer from its initial release into the atmosphere all the way to human blood. However, at the present time knowledge about certain steps in the processes is not sufficiently precise to estimate with any certainty what future harm will result from the present rate of input of lead into the environment. The data and information needs are as follows:

Better estimates of the transfer of lead from atmospheric deposition into food chains are needed as well as more data on lead concentrations in air and deposition over agricultural land. In addition, more reliable data on lead levels in the surface soils and crops in these areas are required. Such data should be determined for areas

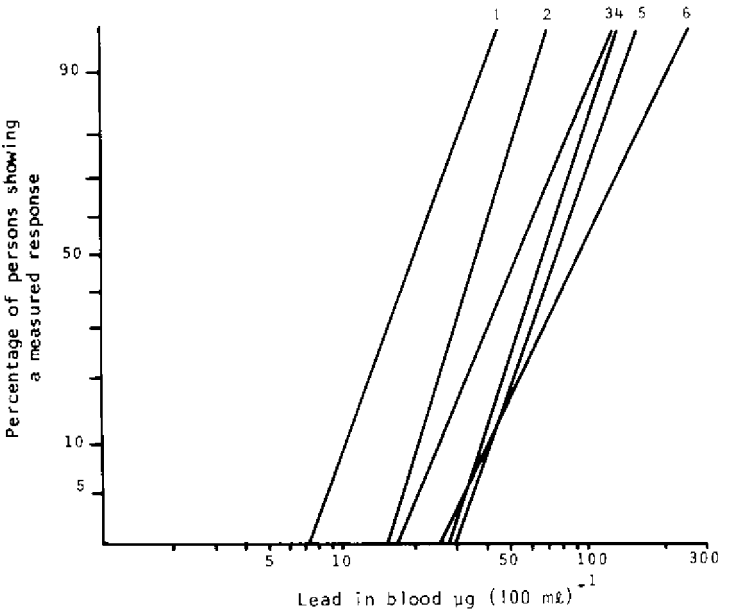

Figure 7 Dose-response relationship for children. The six curves refer to the following effects:

1. Reduction in erythrocyte ALA-D activity
2. Increase in the free erythrocyte protoporphyrin (FEP) concentration
3. Anaëmia
4. Rate of ALA excretion in urine (ALA-U)
5. Increase in production of urinary coproporphyrins (CP-U)
6. Central nervous system dysfunction

with high and low levels of lead in soil and with high and low levels of lead deposition.

There is a need for better data to establish firmly the relationship between lead intake and average blood lead levels. This would involve monitoring blood lead levels in a population together with dietary and respiratory intake. There is also a need for research on lead metabolism, in particular to elucidate to what extent the release of lead from bone affects blood lead levels. In addition, there is a need to quantify more exactly the blood lead effect relationships and

to establish what relationships exist, if any, between the different effects.

8.0 Conclusions

Studies of lead in a variety of historical samples indicate that levels in the general environment have increased several hundred times as a result of additional discharges due to human activity. Lead reaches man via inhalation and through the food chain. For persons living outside large cities and remote from major sources of atmospheric lead, the main contribution is via the food chain. The existing data are insufficient to partition the ingested lead between natural and anthropogenic sources. Data presently available indicate that lead deposited upon agricultural land may remain available for uptake in the food chain for several hundred years at least. However, more information is needed to quantify this further and will need to be obtained from properly assessed data both from monitoring and from research.

The greatest areas of uncertainty at present concern atmospheric concentration, atmospheric deposition, soil concentration and uptake by crops grown on these soils. Complicating these uncertainties is the fact that the comparability of measurements by different authors is often open to question.

There is certainly a need for monitoring lead in ground-level air and deposition in rural agricultural areas, particularly in the vicinity of regions with localized industrial activity. At several sites in such areas there is a need to establish multimedia monitoring and research programmes to measure lead in air, its deposition and its occurrence in locally produced food. In addition, a survey of lead in soil should be conducted and the average lead distribution with depth established. Radioactive or stable lead isotopes should be used to determine the availability of soil lead for plant uptake and to ascertain how this availability changes in time after lead deposition in different soils. Such multimedia monitoring stations could profitably be used for concurrent studies of other pollutants.

There is also a great need for monitoring the levels of lead in human blood in order to determine how this is related to dietary and respiratory intake. The average intake of lead by the subjects

studied will have to be monitored carefully. Long-term experimental studies with a stable lead isotopic tracer would also help to provide this information. Other processes of which a better understanding is needed are the exchange time of lead between blood, other soft tissue, and bone, and what effects nutritional and health conditions have on the uptake of lead from the gastro-intestinal tract and upon reabsorption of lead from bone.

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Table 1 Concentration of lead in rock

Ref.	Rock type	Concentration $\mu g\,g^{-1}$
55	Limestone	9
	Shales	20
	Sandstone	7
2	Granites	14.81
82	Basalts	5
	Granites	20
56	Granitic bedrock	30.2
	Metamorphic bedrock	25.7
	Mineralized veins	37.0
	Mineralized rock	10.8
	Trachybasalt flows	26.7
92	Granitic rocks	21
41	Andesite (AGV-1)	35.1
	Basalt (JB-1)	14
	Basalt (BCR-1)	17.6
	Basalt (BM)	12
	Slate (TB)	7
	Diabase (W-1)	7.8
	Dunite (DTS-1)	14.2
	Granite (G)	38
	Granite (G-1)	48
	Granite (G-2)	31.2
	Granite (GM)	30
	Granodiorite (JG-1)	24
	Granodiorite (GSP-1)	51.3
	Limestone (KH)	7
	Lujavrite (L)	45
	Peridotite (PCC-1)	13.3
	§Sulphide (SU-1)	249
	Syenite (S)	13
	§Syenite (SY-1)	495
	mean	$22 \pm 13\,\mu g\,g^{-1}$

§Excluded from calculation of mean

Table 2 Concentration of lead in soil

Ref.	Soil type	Location	Depth (cm)	Total concentration $\mu g\,g^{-1}$
4	"Mixture" (752 samples from pasture and cropping land)	U.K.	0–15	57
79	Brown earth	Scotland	3–18	40
			25–36	10
			46–66	10
			74–84	10
	Podzol	Scotland	0–18	80
			33–48	50
			61–69	30
			81–97	30
			102–109	70
	Gley (non-calcareous)	Scotland	5–13	40
			13–23	15
			28–36	10
			41–51	20
			61–76	15
			91–107	15
70	Podzol	Belgium	Total profile	17.3
	Grey-brown podzolic	Belgium		22.3
	Grey-brown podzolic	Belgium		28.0
63	Tropical brown soil	Cameroun	Total profile	127
	Ferralitic	Cameroun		16.4
	Ferruginous	Cameroun		31
	Solodized solonetz	Cameroun		17.4
	Vertisol	Cameroun		21.2
	Hydromorphic	Cameroun		12.2

Table 3 Enrichment factors for lead in atmospheric particulates

Ref.	Location	
16, 17, 18	Chilton, U.K.	1520
	Collafirth, U.K.	1300
	Plynlimon, U.K.	1100
	Wraymires, U.K.	1400
15	Petten, Netherlands	380
33	Atlantic 30°N	3100
50	Pacific N	1600
36	Indian Ocean North	130
99	South Indian Ocean	290
99	South Pole	3500

Table 4 Concentration of lead in air

Continental non-urban sites

Ref.	Location	Concentration ($ng\ m^{-3}$)	Duration of sampling years
	Northern Hemisphere		
16	Chilton, U.K.	157.8	4 years
17	Plynlimon, U.K.	68	4 years
18	Wraymires, U.K.	77.2	4 years
36	Salekhard, U.S.S.R.	1.2	1 year
39	Moosonee, Canada	34.6	2 years
	Southern Hemisphere		
99	South Pole	0.63 (±0.3)	7 weeks
38	Puerto Montt (Chile)	22.9	5 years
	Chacaltaya (Bolivia)	23.6	5 years
	South Pole	5.1	5 years

Table 4 (cont.)

Maritime non-urban sites

Ref.	Location	Concentration ($ng\,m^{-3}$)	Duration of sampling years
	Northern Hemisphere		
16	Lerwick, U.K.	27.5	2 years
36	Novaya Zemlya, U.S.S.R.	0.2	1 year
	Dickson Island, U.S.S.R.	0.9	1 year
	Petropavlovsk, U.S.S.R.	15.4	1 year
	Magadan, U.S.S.R.	15.8	1 year
	Indian Ocean (N. latitudes)	4.4	1 year
50	Oahu (Hawaii)	3 (± 3)	1 year
38	Mauna Loa (Hawaii)	4.6	5 years
	Thule (Greenland)	10.7	5 years
17, 18	Collafirth, U.K.	26.9	2 years
39	§Bravo Ocean Stn. (56N 51W)	41.1	1 year
	§Charlie Ocean Stn. (52N 35W)	19.8	1 year
	§Delta Ocean Stn. (44N 41W)	59.4	1 year
	§Echo Ocean Stn. (35N 48W)	101.2	1 year
	Kap Tobin (Greenland)	3.3	1 year
	Bimini, Bahamas	140.8	1 year
	Southern Hemisphere		
36	Indian Ocean (S. latitude)	1	1 year
38	Easter Island	5.7	5 years
39	Antofagasta (Chile)	72.2	1 year
	Punta Arenas (Chile)	53.2	2 years

§approximate locations

Table 4 (cont.)

Urban sites

Ref.	Location	Concentration ($ng\,m^{-3}$)	Duration of sampling years
	Northern Hemisphere		
39	New York	1183	5 years
	Salt Lake City	1346	5 years
	Sterling	324	4 years
	Miami	1404	5 years
	Average of 217 urban sites in the U.S.A.	1100	2 years
	Southern Hemisphere		
39	Balboa, Panama	245	2 years
	Guayaquil, Ecuador	367	2 years
	Santiago, Chile	825	5 years
	Lima, Peru	493	5 years

Table 5 Average annual deposition of lead

Ref.	Location	Deposition rate ($\mu g\,cm^{-2}\,y^{-1}$)
3	Tennessee, USA	2.3
1	Upper Great Lakes, USA	1.2
71	Texel, Holland	1.5
75	Göttingen, W. Germany	2.3
16, 17, 18	Chilton, U.K.	2.9
16, 17, 18	Lerwick, U.K.	3.4
16, 17, 18	Collafirth, U.K.	1.6
16, 17, 18	Plynlimon, U.K.	2.3
16, 17, 18	Wraymires, U.K.	2.5
67	Average at nine towns in South Wales, U.K.	3.8
15	North Sea	1.6
15	Clyde Sea	2.0
91	New York, USA	35
20	London, U.K.	11
54	Chicago, USA (Airport)	17
24	10 m from road with 4000 vehicles/hour	117
20	0.1 km from smelter (Toronto)	1460
20	0.7 km from smelter	580

Table 6 Total deposition velocity for atmospheric lead

Ref.	Location	Years	Deposition velocity ($cm\,s^{-1}$)
16, 17, 18	Chilton, U.K.	1972–75	0.53
16, 17, 18	Plynlimon, U.K.	1972–75	1.1
16, 17, 18	Wraymires, U.K.	1972–75	0.98
24	San Diego, USA		0.50
26	La Jolla, USA		0.19

Table 7 Lead in human bones

Time period	Concentration ($\mu g\,g^{-1}$ dry weight) USA	Peru	Italy	Denmark	Poland
4000–1000 BC			< 0.1	< 0.2	
300 AD					2.4
1–1700 AD		2	5	0.2–6.8	
1100–1800 AD					5.8–199.0
Recent	20	20		1.4–19	3.9
Reference	77	37	37	47	52

Table 8 Annual human intake of Pb and ^{210}Pb in food

	Intake stable lead ($mg\,y^{-1}$)		^{210}Pb ($Bq^{\S}\,y^{-1}$)	Specific activity $Bq\,mg^{-1}$
Food	U.K.¶	New York#	New York	New York
Cereals	11.7	5.8	5.66	0.96
Meat and fish	10.6	6.5	2.15	0.33
Fruit	10.2	8.3	1.89	0.23
Root vegetables	6.9	3.8	2.18	0.57
Green vegetables	7.6	3.5	2.29	0.65
Milk	2.9	3.2	2.15	0.67
Total Diet	49.9	31.1	16.32	0.53

§one becquerel = 1 disintegration per second i.e. one curie equals 3.7×10^{10} Bq
¶ref. 59
#ref. 9

Table 9 Lead concentration in blood of selected groups of males (90)

Mean lead concentration in blood mg/(100 ml)$^{-1}$	No. of subjects	Group
0.011	9	Suburban non-smokers, Philadelphia
0.012	16	Residents of rural California county
0.013	10	Commuter non-smokers, Philadelphia
0.015	14	Suburban smokers, Philadelphia
0.019	88	City employees, Pasadena
0.021	33	Commuter smokers, Philadelphia
0.021	36	City health department employees, Cincinnati
0.021	155	Policemen, Los Angeles
0.022	11	Live and work downtown, non-smokers, Philadelphia
0.023	140	Post Office employees, Cincinnati
0.024	30	Policemen, non-smokers, Philadelphia
0.025	191	Firemen, Cincinnati
0.025	123	Policemen, Cincinnati
0.025	55	Live and work downtown, smokers, Philadelphia
0.026	83	Policemen, smokers, Philadelphia
0.027	86	Refinery handlers of gasoline, Cincinnati (1956)
0.028	130	Service-station attendants, Cincinnati (1956)
0.030	40	Traffic policemen, Cincinnati
0.030	60	Tunnel employees, Boston
0.031	17	Traffic policemen, Cincinnati (1956)
0.031	14	Drivers of cars, Cincinnati
0.033	45	Drivers of cars, Cincinnati (1956)
0.034	48	Parking-lot attendants, Cincinnati (1956)
	1,434	Total

Table 10 Blood lead levels at which 10 and 50 per cent of persons show a response (69)

Effect	Concentration (μg (100 ml)$^{-1}$)			
	Adults		Children	
	10%	50%	10%	50%
ALA-D	9	18	11§	20§
FEP	19	33	21	36
ALA-U	34	58	38	66
CP-U	37	58	41§	74§
Anaemia	63	120	25	54
CNS	–	–	40§	90§
PNS	37§	84§	–	–
Kidney injury	28§	140§	–	–

§preliminary figures based on inadequate number of data.

Analysis of the effects of lead in tissue upon human health using dose-response relationships

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A Technical Report (1980)

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With the support of:
United Nations Environment Programme and
The Rockefeller Foundation

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ABSTRACT

A survey was made of available data in the literature on quantitative effects of inorganic lead in humans. Data were converted into response and no-response (quantal) form. Dose-response functions were calculated by regression analysis of probit values and by standard probit analysis. Apparent threshold values for various health effects were then estimated. The apparent thresholds, defined at the 10 per cent response rate, differed largely with regard to various effects, and expressed as blood lead levels (μg Pb (100 ml)$^{-1}$) ranged from about 10 for ALA-D to about 20 for FEP and to about 30—40 for other effects, except for anaemia. For anaemia the threshold did show a difference between adults (men) and children, being 63 and 25 μg Pb (100 ml)$^{-1}$ respectively. Since the pathways of haem synthesis do not account for this difference in susceptibility, it is assumed that the action of lead on the globin component in children is more likely to be the cause. Some of the computed values are only tentative due either to an inadequate amount of or large scatter in the available data. The results indicate that a large proportion of the population not occupationally exposed to lead is already at some risk as far as the critical effect (increase of free erythrocyte protoporphyrin) is concerned.

Contents

LIST OF ABBREVIATIONS

ALA	δ-aminolevulinic acid
ALA-D	δ-aminolevulinic acid-dehydratase
ALA-U	δ-aminolevulinic acid excretion in urine
CNS	Central nervous system
CP-U	Coproporphyrin III in urine
ED_{10}, ED_{50}	Effective dose (concentration) yielding 10 and 50 per cent response respectively
FEP	Free erythrocyte protoporphyrin
IQ	Intelligence quotient
LD_{50}	Median lethal dose (at which 50 per cent mortality of test organisms occurs)
Pb-B	Blood lead concentration
Pb-U	Urine lead concentration
PBG	Porphobilinogen
PNS	Peripheral nervous system
RBC	Red blood cells
TLV	Threshold limit value
ZPP	Zinc-protoporphyrin

I SCOPE AND TECHNIQUES

1.0 Introduction

In setting guidelines regarding acceptable levels of toxic substances in the human environment, the risk/benefit approach has recently gained increasing support. To evaluate properly the risk resulting from an existing level of a toxic agent in the environment, not only have the various toxic effects to be recognized, but for each of the effects a threshold level has to be estimated. Obviously, the choice of a guideline would be one recommending that environmental levels of a contaminant should be kept below the threshold of any individual adverse biological effect. Moreover, a reasonable safety margin would be desired.

Lead is an example of a contaminant for which the above ideal solution is difficult to meet. The existing range of lead levels in the human body, even under conditions of no recognizable abnormal exposure, differs by less than one order of magnitude from those causing overt toxic effects. Moreover, the critical biological effect of lead in humans, deterioration of the pathways of haem synthesis, is characterized by a series of physiological changes of which the first is the inhibition of δ-aminolevulinic acid-dehydratase (ALA-D) in blood. This latter effect can be observed even at blood lead levels typical of the general population in industrial countries. Other, probably more meaningful effects appear in sequence as the blood lead level (Pb-B) increases, leading eventually to anaemia due to a low level of blood haemoglobin.

Guidelines must be based on clear recognition of threshold levels for the critical and as many as possible other biological effects. The aim of this study has been, therefore, to contribute to the recognition of threshold levels for the various toxic effects of lead in humans, based on available published information.

2.0 Toxicology of lead

The toxicology of lead in humans has been recently reviewed in a series of reports (25, 83, 38, 130, 131, 132, 128).

Lead induces a variety of biological impairments and the problem can be categorized in the following way:

(a) Haematological effects (preceded by a sequence of biochemical changes of the haem-synthesis pathways)
(b) Other effects
(c) Critical groups

(a) Haematological effects

Lead interrupts the biosynthesis of haem at several stages (see Figure 1 and recent review by Labbé, 1977 (63)).

At the first of these stages, the enzyme ALA-D, which catalyzes the conversion of δ-aminolevulinic acid (ALA) into porphobilinogen (PBG) (Figure 1, Pb 1) is partly inhibited even at very low lead concentrations. Most published information refers to ALA-D localized in the erythrocytes. These, however, do not represent an important site of haem biosynthesis. Hence it is believed that the effect is of no biological importance *per se* and has value only as an indirect indicator. Attention has been drawn recently, however, to the discovery that inhibition of ALA-D activity in blood occurs in parallel with that in other tissues, e.g., liver (100) and brain (76). This might be of importance since the metabolic reaction in question represents the initial step of the biosynthesis of not only haemoglobin, but also other haemoproteins (such as cytochromes) which play a key role in cellular metabolism.

The partial inhibition of ALA-D results in an increased excretion of the excess (unused) ALA in urine. This effect is observed only at levels of lead in blood (Pb-B) much in excess of those producing ALA-D inhibition in blood. It probably reflects, therefore, inhibition at major sites of porphobilinogen (PBG) formation.

The second site of lead action seems to be the inhibition of the enzyme coproporphyrinogen oxidase (which converts coproporphyrinogen III into protoporphyrinogen IX) resulting – in an indirect way – in increased urinary excretion of coproporphyrin III (CP-U) (Figure 1 Pb 2).

The third stage at which lead may act is the inhibition of the enzyme ferrochelatase which catalyzes the incorporation of iron into the protoporphyrin (Figure 1, Pb 3). This effect is manifested by an increase in the level of the free protoporphyrins observed in the erythrocytes. The free erythrocyte protoporphyrins (FEP) are known

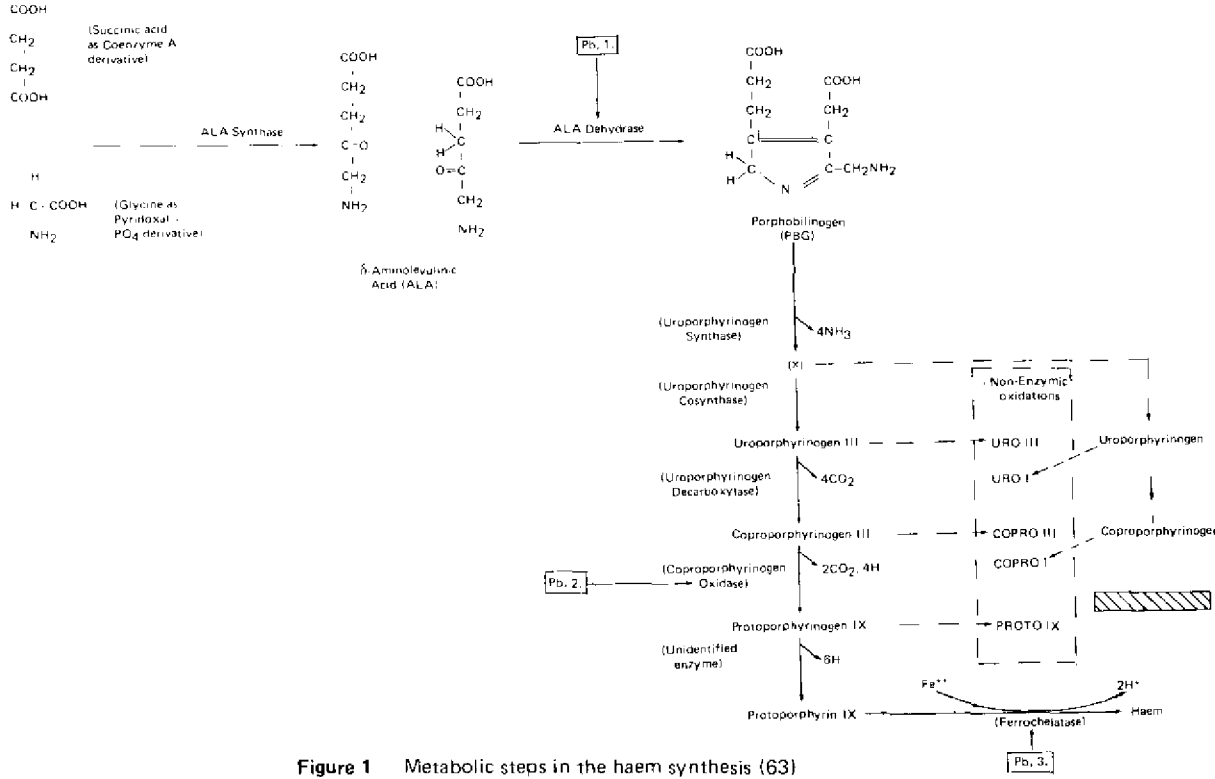


Figure 1 Metabolic steps in the haem synthesis (63)

to occur in a complex with zinc; thus, depending on the applied method of measurement, the name zinc-protoporphyrins (ZPP) may be used concurrently with FEP or PROTO (28, 65, 51). The same effect is described by morphologists as an increased level of fluorizing erythrocytes (fluorocytes) in the blood (124, 85, 64, 65, 30).

None of the above effects is biologically important *per se* — unless the degree of impairment is serious enough to be reflected in a decreased yield in the synthesis of final products of the metabolic pathway for haemoglobin or other haemoproteins. Assuming a sufficiently severe inhibition at the three sequential steps of the metabolic pathway mentioned above, a diminished output of haemoglobin is to be expected. However, it seems to be commonly assumed that lead-induced anaemia may manifest itself only at rather high Pb-B levels, much in excess of those needed to produce the effects discussed above (131). Obviously the existence of lead-induced anaemia is a "bone of contention" among specialists, and both adherents and opponents can present sufficient evidence in support of their views. It has to be strongly stressed, however, that effects of lead, related to the final cellular levels of important haemoproteins other than haemoglobin, have not yet been recognized and, in the absence of any evidence in this area, more emphasis should be placed on those effects recognized so far, even if direct evidence of their biological importance is missing.

(b) Other effects

Lead is known or suspected to be the cause of several other health effects; the most abundant information concerns the central and the peripheral nervous system, disorders of the gastro-intestinal tract and kidney damage.

The effects of lead on the central nervous system (CNS) have been studied mainly in children. Information regarding adults is still at a preliminary stage (132). In children, increased body burden of lead can cause mental retardation which manifests itself by changes in behaviour (hyperactivity) and a decrease in intelligence (IQ), especially within the range of performance tests. Whereas most authors agree that the risk exists, quantitative details are controversial (89, 35, 5, 77, 84).

Effects of lead on the peripheral nervous system have been recognized mainly in adults, especially workers exposed professionally. Increased Pb-B results in a decreased nerve conduction velocity. The effects observed by various authors[§] seem highly dependent upon the method used: e.g. the slower motor fibres of *n. ulnaris* seem especially suitable for the study of early effects. Preliminary data on children show similar trends (39).

Kidney damage in its clinical form is now rarely observed and only at Pb-B levels much in excess of those currently found in industrial workers (132). The possible severity of the problem, on the other hand, is recognized from reports on delayed effects of high lead exposure (34) as well as delayed sequelae of childhood plumbism, manifesting themselves in the form of severe renal failure many years later (37, 53, 81). The existing body of information is insufficient to prove the above cause-effect relationship quantitatively since the Pb-B levels at the time of onset of symptoms do not correspond to those which had possibly initiated the pathologic process in question. In the Australian cases of renal failure, childhood scarlatina was suspected to be a factor or at least a co-factor.

It seems probable that clinically defined renal damage is preceded by aminoaciduria, proteinuria, impaired clearance of urea and uric acid. Such information seems available primarily regarding adults (males) occupationally exposed to lead.[¶]

Effects of lead on the gastro-intestinal tract have been clearly recognized in the past when the exposure to lead happened to be very high. The acute form of this effect is known as "lead colic". Quantitative information regarding this effect is meagre. It would seem reasonable to assume that the effect in question may occur at rather high Pb-B levels; however, effects at lower levels cannot be entirely ruled out (9, 1). A more frequent form of this effect, possible at much lower lead levels, is constipation. These effects, however, hardly lend themselves to objective assessment.

Apart from these well known toxic effects of lead, several authors have reported biological impairments of various other kinds:

§ (95, 23, 102).

¶ Reports on health impairment resulting from excess consumption of lead-containing wine or moonshine whisky are not being considered here because of the uncertainties involved.

cardiological changes, impairments of the hormonal system and of a variety of biochemical processes, and also mutagenic effects manifested in chromosome aberrations. The existing body of information regarding all these effects is far too limited, however, to allow any dose-response relationships to be proposed.

(c) Critical groups

It is well recognized at the present time that there are two populations at high risk: workers exposed in industry (mostly males) and children exposed through a habit referred to as "pica" (eating and chewing various non-edible materials). This latter habit is especially important in environments abundant in lead (lead-based paints used in the past are the most common example). It is also suspected that the risk to children could be additionally increased due to their higher sensitivity to lead.

Women are considered as another possible sensitive group (109, 131). However, their relative importance in terms of numbers is probably low owing to legal limitations imposed on women working in industries involving lead exposure, and to the absence of the "pica" habit in adults.

3.0 Dose-effect and dose-response relationships

On a group basis, the toxic effects of a given contaminant may be expressed quantitatively in two ways, viz. dose-effect and dose-response relationships. The following definitions of these terms were compiled by the Task Group on Metal Toxicity (86).

> "The term *effect* is used to mean a biological change caused by an exposure. Sometimes this effect can be measured on a graded scale of severity, although at other times one may only be able to describe a qualitative effect that occurs within some range of exposure levels. When data are available for the graded effect, it is apparent that one may establish a relationship between dose (usually an estimate of dose) and the gradation of the effect in the population; this is the dose-effect relationship. An example may be the relationship between lead concentration in industrial air and the concentration of ALA in urine samples from workers.
>
> Ideally, a dose-effect relationship is established with measurements on many individuals over a range from minimum to

maximum effect. The curvilinear relationship that represents the best fit to all of the data points should be expressed in terms of mean values and their standard deviations at various doses. In other words, the scatter of data will usually lead to confidence limits around the mean values, and these expressions of degree of uncertainty should be estimated wherever possible.

The term *response* is used to mean the proportion of a population that demonstrates a specific effect, and its correlation with estimations of dose provides the dose response relationship. For example, a dose-response relationship might compare different lead concentrations in industial air (estimates of dose) with the per cent of the exposed workers that have greater than 5 mg ALA ℓ^{-1} in urine.

To establish dose-response and dose-effect relationships requires much data, which are often lacking for human beings with regard to many metals. In cases in which only limited data are available, knowledge of general principles governing the action of metals may sometimes permit approximations of such relationships."

In experimental toxicology, dose-response relationships have been used for a long time, originally in the calculation of median lethal dose (LD_{50}) values for various chemicals. Recent interest in the threshold levels for toxic compounds has drawn the attention of toxicologists to this type of presentation of the biological effects in both acute and chronic toxicity.

The most fruitful and outstanding attempt at using this approach to establish threshold levels for chronic toxicity has been that of the Iraq-American group (126) regarding threshold levels of methylmercury in humans. This example has been frequently quoted in various presentations in the field of heavy metal toxicology (86) and this approach has drawn the attention of scientists involved in the environmental toxicology of lead (29, 131, 132). In his extensive report, Zielhuis (131, 132) proposed dose-response relationships for the three basic biochemical responses to lead toxicity, i.e. ALA-D, ALA-U and FEP. The possible relationships regarding other effects were presented in a descriptive way only and no clear distinction was made between adults and children. Regarding the proposed

dose-response functions, these were based on data extracted from a limited number of selected reports. This enabled Zielhuis to draw the dose-response curves in the conventional S-shaped form, using the traditional arrangement whereby the percentage response R(%) is a function of the level of lead in the blood Pb-B (R(%) = f(Pb-B)). These first attempts at applying the dose-response concept to chronic lead poisoning gave promising results.

4.0 The scope of the present project

The aim of the present study has been to examine the approach of the dose-response relationships for lead on a broader basis using a large spectrum of accessible information.

The primary consideration in evaluating data reliability for this project was the possibility of clinical "preselection". The best estimates of lead levels and related health effects could not be used if the group under investigation had been preselected, e.g. as having a given health impairment. This is a frequent occurrence where clinical reports are concerned.

Pooling together all available information regarding a given biological effect would be expected to produce a more reliable basis for assessments and forecasts. However, this approach introduces specific technical problems of data evaluation and treatment, since many sets of data are often inconsistent with each other due to the use of a variety of different measurement techniques. This has been overcome to some extent by converting the often incompatible quantitative data into quantal (yes or no) responses. The latter were assumed to be less dependent on the methods of measurement.

Pooling together data extracted from the reports of various authors can be regarded as an advantage for the following reasons:

(a) Assuming some random errors incorporated in each individual report, pooling many data would be expected to provide a better estimate of the function.

(b) In the case of diverging opinions consensus among the experts could be more easily reached when as many sources of information as possible were used to construct the dose-response function.

(c) A dose-response function could be produced also from

incomplete fragmentary data of various authors of which none was sufficient alone for this purpose.

On the other hand, some reservations regarding the use of pooled data should be mentioned. Usually dose-effect and dose-response functions are calculated for sets of data obtained from one source for a controlled experiment on a given population (usually animals). Such data are usually internally consistent and sufficiently numerous to enable classical methods of probit analysis to be employed. Up to the present time the comparability of data available from many epidemiological studies on lead is rather poor and does not easily lend itself to a complete statistical analysis.

For the above reasons the present report may be regarded as a tentative evaluation, intended not only for computing the individual dose-response functions for lead, but also for assessing the major difficulties and biases inherent in such a procedure.

5.0 Data extraction and elaboration

(a) General assumptions

Following intake by inhalation or ingestion, lead which is absorbed enters the blood stream (erythrocytes mainly). Relatively soon, lead reaches equilibrium with the soft tissues such as the liver, kidneys, lungs, heart, etc. which, together with the blood, form the rapid-exchange compartment for lead. With some time delay, a small percentage of the lead enters the muscles and skin which represents a pool of intermediate turnover rate. Finally, after a further time delay, a percentage of the total intake will be found in bone representing the slow exchange pool for lead. The lead bound in the skeleton may be regarded as being deposited irreversibly (14, 15, 16). When the population is subjected to continuous exposure (including intermittent exposure repeated at frequent and regular intervals), a steady state is expected to occur and then the level of lead in blood (as well as that in the whole rapid exchange pool) may be related to the intake from the environment by applying a proper proportionality factor (126). The same applies to the level of lead in urine which is assumed to be directly proportional to the Pb-B level (130). Thus, the Pb-B level reflects both the level of more recent exposure and also that part of the body burden that is related to the intermediate

exchange pools. Lead contained in bone is not subject to rapid equilibration and, in general, levels are expected to rise with increasing age.

When using Pb-B as a measure of exposure, we should only consider groups of humans characterized by a constant long-term exposure. When anticipating the possible influence of the duration of exposure on the results of this study, a limit of roughly three months was thought adequate. This corresponds to the assumptions drawn from the more recent reports (7, 42). The above prerequisite (three-month exposure) represents only the lower time limit necessary to rely on a given dose-response relationship. It seems adequate for most of the purely biochemical indices; however, it may be much too short to allow for other long-lasting processes to appear. Thus, for effects on the central and peripheral nervous system as well as the kidneys, a minimum of one year's exposure is required.

(b) The independent variable

It is commonly believed that the concentration of lead in the blood represents the most reliable measure of both the more recent systemic uptake of lead and of the actual body burden, at least so far as the rapid exchange pool of lead is concerned. Thus, in most recent reports, the biological effects of lead have been correlated with the corresponding blood lead level. A similar attitude has been adopted in this report. In some reports, particularly earlier ones, data on Pb-B levels were missing and other measurements were used, i.e. the concentration of lead in urine (Pb-U). In some cases, reports containing such information have also been used, since there is a high correlation between Pb-B and Pb-U. For the conversion of Pb-U into Pb-B, use was made of a regression line reported by Zielhuis (130) which agrees well with that given elsewhere (83).

Reports that gave sufficient data within each narrow Pb-B group were chosen. For some biological effects, however, only limited data were available; therefore, rather broad limits of Pb-B in each group had to be used, as can be seen in the tables that present the basic data (Appendix II).

(c) Analysis of the data

The relationship between the dose-effect relationship and the

corresponding dose-response relationship is given in Appendix I. Here we describe in a practical way how the method is applied. It is useful to take a particular example using the data on FEP in blood (88). A plot of the logarithm of FEP in blood versus blood lead concentration is shown in Figure 2A.

The response (R) is estimated in the following way in the case of the data presented in Figure 2A. The mean value of log (FEP), ($\bar{Y}_0$) for Pb-B levels below 20 μg (100 ml)$^{-1}$ is $\bar{Y}_0 = 1.8$ which corresponds to a mean FEP value of 63 μg (100 ml)$^{-1}$ RBC's (dotted line B). The standard deviation, σ, of log (FEP) data is approximately constant with different Pb-B values. Twice the standard deviation, the 95 per cent confidence limit, is about 0.3. The upper limit of log (FEP) is $Y' = \bar{Y}_0 + 2\sigma = 2.1$. This is drawn as the dotted line (A) in Figure 2A and corresponds to an FEP value of 125 μg (100 ml)$^{-1}$ RBC's.

In practice, the location of the upper limit was usually determined from the criteria that only about two per cent of the data points were above this level for blood levels in the no response range, say less than 10 μg (100 ml)$^{-1}$ Pb-B. In some cases it was difficult to locate the upper limit in this way and other methods, described below, were employed.

Once the upper limit has been set, the blood lead level scale is divided into a set of ranges. For the data shown in Figure 2A, each range was 10 μg (100 ml)$^{-1}$ Pb-B, being 15–25, 25–35, etc. Within each Pb-B range the total number of data points, N, and the number of data points above the upper limit, N', are counted. The probability Q of the upper limit being exceeded is estimated by q (the sample probability)

$$q = N'/N$$

In the tables (1–13, Appendix II) this is expressed as the percentage probability $R(\%) = 100\,q = 100(N'/N)$. In this way numerous individual data presented in the dose-effect arrangement (Figure 2A) can be reduced to only few data in the arrangement of dose-response (Figure 2B). Dose-response curves presented in the arrangement $R(\%) = f(D)$ (R = response, D = dose) have an S-shape which is inconvenient for regression analysis. The S-curve is usually also asymmetric since many toxicity phenomena seem to follow the log

Figure 2. Transformation of the dose-effect into dose-response relationship

Description of figures

A. Example of dose-effect data using one author's set of data on log FEP in red blood cells as a function of the blood lead level.

B. Per cent response in groups of subjects at intervals of 10 μg (100 ml)$^{-1}$ of blood lead levels.

C. Data of graph B corresponding to blood lead levels of 20, 30, 40 and 50 μg (100 ml)$^{-1}$, in the arrangement of probit of response as function of log lead concentration.

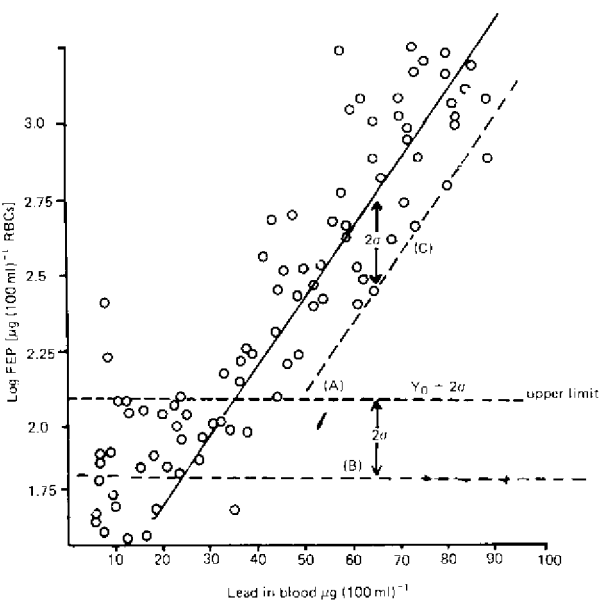


Fig. 2A

Fig. 2B

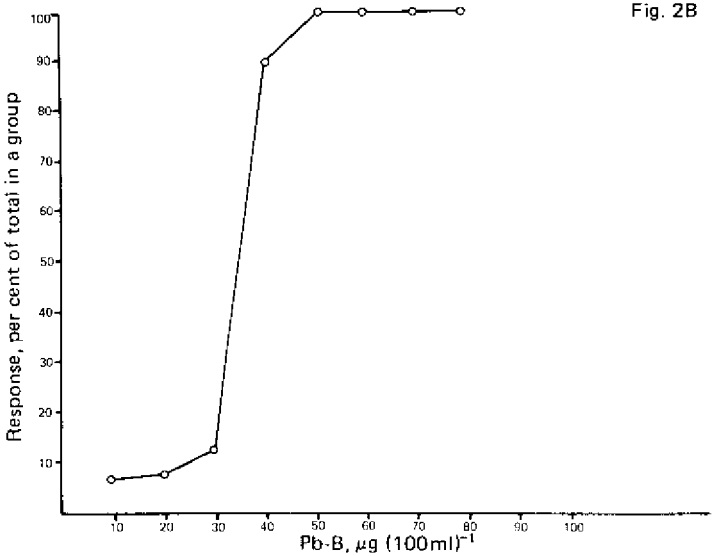
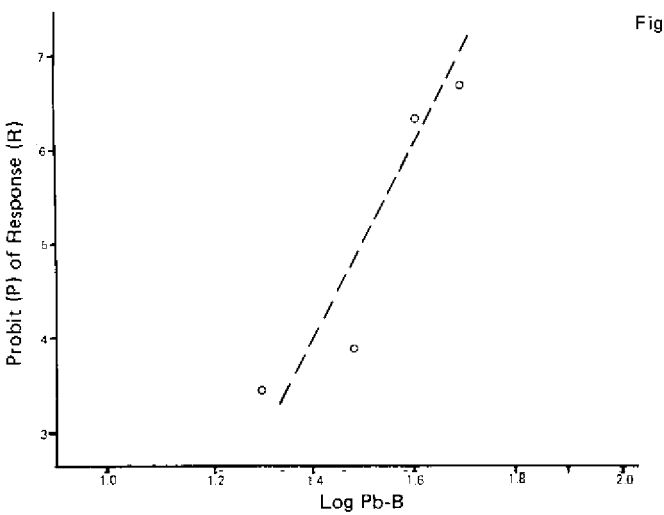

Response, per cent of total in a group
100
90
80
70
60
50
40
30
20
10
10
20
30
40
50
60
70
80
90
100
Pb-B, μg (100ml)⁻¹

Fig. 2C


Probit (P) of Response (R)
7
6
5
4
3
1.0
1.2
1.4
1.6
1.8
2.0
Log Pb-B

normal rather than a normal distribution. It has been common practice in toxicological assays to transform the data into the form (96):

$$P(R) = f(\log D)$$

where P(R) represents the probit of a given response frequency. This transformation has been used in the present report.

Values of the probit P were determined from probit tables (41). Figure 2C, in which the transformation of the data from Figure 2B is presented, shows that (a) in this particular case only a part of the curve (2B) was relevant for further calculations (tailings on both ends had to be cut out); and (b) that much more data in the response range of about 10–90 per cent would be needed to construct a reliable dose-response curve. The final graph based not just on one, but on ten different reports is shown in Figure 5.

Thus, the pairs of data (Pb-B, R) initially reported or calculated from the author's data were transformed into the values log Pb-B and P(R) and, after pooling data from various reports, a straight line was fitted. The parameters of the regression line were obtained together with the coefficient of determination, r^2. At this stage a decision was made as to which of the "no response" and "all positive" ranges should be included. The decision was based on the effect of including additional ranges of the extreme Pb-B levels upon the magnitude of the regression coefficient and the coefficient of determination. An improved correlation, as well as an increased regression coefficient, were regarded as favouring the inclusion of a given range of values. This procedure to some extent would correct for any bias introduced in setting the upper limit, $\bar{Y}_0 + 2\sigma$, in cases where the data were not good.

The results of calculations have been presented in the form

$$y = ax + b$$

where y = P(R); x = log Pb-B; "a" and "b" are constants calculated by regression analysis.

(d) Control groups and their extreme limits

As it follows from the basic assumptions, and as shown by Zielhuis (131) the location of the dose-response curves relative to the axis

of the independent variable is highly dependent upon the accepted extreme "normal" limits. Thus, by applying a limit which is in excess of the "true" one, a definite shift of the dose-response curve towards the right (increased Pb-B range) will occur. The reverse, however, is not necessarily true. When applying limits which are below the "true" ones, one achieves initially increased numerical values of the response, but this artifact may be easily detected, if sufficient data are at hand, through an "unjustified" high and constant response throughout the low-exposure groups. The proper limit value can thus often be found empirically by using successive approximations.

In the present study the upper limit has been determined independently for each set of data. It was considered inadequate to impose a constant value for all the data under investigation since these had often been obtained by different analytical procedures, also the "normal levels" as found in various populations were expected to be dependent upon many other unknown factors. The upper limit is thus established in each case by the criterion that it should allow for about a two per cent "yes" response in the "no response" range.

In several cases, adequate control groups were missing and more arbitrary judgements had to be applied. Wherever possible, the suggestions of the authors were then followed. Otherwise, data from a given report would be categorized according to methodology used, kind of population included, and range of responses obtained, and, wherever possible, an extreme limit of the indicator understudy would then be adopted from another report using similar methodology. In several cases, however, as with many reports containing information regarding haemoglobin, a considered judgement was made to select the extreme "normal" level.

(e) Regression analysis

The location of a dose-response curve depends to some extent upon the inclusion or rejection of data in various subgroups at the "no response" level. This is obvious if one takes into account the whole series of negligible responses in the "no response" range which, if included, would result in curving of the otherwise possibly linear function. This results in a much poorer fit and a smaller regression coefficient. Wherever justified, therefore, the extreme levels of the

"normal" range for the effect considered have been estimated for the lowest range of the available Pb-B values. The individual compartments within the increasing range of the Pb-B values were then checked for per cent response and the last compartment of the "no response" range would only be included for calculation. A final adjustment could be made at the stage of computing the regression equations as explained under (c) above.

(f) Computing the frequency of response

Many reports contain data on each individual under investigation. This allows the assessment of the response to various ranges of the Pb-B level to be easily made. In such cases the initial analysis of the data involved grouping the individuals into appropriate classes according to Pb-B levels (if necessary) and counting the number of "yes" responses against the total.

Several reports contained the basic information in the form of tabular data together with the mean and standard deviation of the effect. The assumption was that the values of the dependent variable (effect) followed a normal distribution. In some cases a log-normal distribution was assumed. With some reservation regarding the latter statement (to be explained below) these data allow the response to be calculated from integrals of the cumulative normal frequency distribution (96). The following example explains this technique.

Suppose there are three groups – A, B and C – of data relating to increasing levels of intermediate Pb-B values, of which the first, A, may be regarded as control ("no response" range). Suppose the effect on group A has been recorded as 100 ± 10 units. This allows the upper level to be accepted as $100 + 2 \times 10 = 120$ units. Suppose the effect in group B is recorded as 120 ± 15 units. In this case it is obvious that, since the mean value of the effect in B is identical with the upper "normal" limit in A, half of the population of group B must fall below and another half above the upper level of A. Hence, the frequency of response is 50 per cent. Suppose group C had the effect recorded as 140 ± 20 units. The difference between the mean of C (140) and the upper "normal" limit of A (120) amounts to 20 units, i.e. 1.0 σ of group C. From statistical tables (96) it is seen that the percentage reacting positively in C (response) amounts to 84 per cent

with respect to A. A similar procedure was used where the log-normal distribution was more appropriate.

The above technique has been used in cases where (a) the effect resulted in an increase of the indicator value (examples FEP, ALA-U); (b) where σ was given for the "plus" and "minus" range separately and where the effect in question resulted in a decrease of the indicator value (examples, ALA-D, Hb). In certain other cases it was obvious that a single standard deviation given in the report would not apply to the "minus" range (for instance, mean minus 2σ = negative) and in these cases a log-normal distribution was used.

In a few cases the percentage response in the "no response" range could not be reduced below about five per cent, despite selecting the extreme limit according to the best judgement available. In such cases it was assumed that a fixed fraction of the data was above the extreme limit. A fixed percentage was subtracted from each data set. Due to this procedure, the percentage of a given symptom in a population corresponds to the increase in frequency assumed to be caused by lead.

If a given compartment (range of Pb-B values) served as a basis for calculation of the upper background level, the frequency at the "no response" level has been recorded as two per cent. The same figure was applied to compartments closer to the "response range" if direct calculation gave values below two per cent. If higher, the calculated figure was recorded. Due to this procedure a linear regression between the independent and dependent variables can be expected only within certain limits of the Pb-B levels.

(g) Cases with all negative and all positive responses

In small groups of observations made either in the very low or in the very high range of Pb-B values, all members of a group often responded in the same way, resulting in an apparent frequency of 0 or 100 per cent respectively. Such values do not lend themselves to statistical calculation in the arrangement accepted in this study. Such extreme values can be regarded as too exaggerated as a result of a computation performed on a small group of subjects (e.g. five). On the other hand, such an extreme response, if recorded at the range of Pb-B values adjacent to the range under investigation, might be of key importance

for locating the position of the dose-response curve. To solve this problem, the following arbitrary assumption was made. A uniform group of all positive responses is assumed to yield one case of negative response upon doubling the number of measurements. Thus, for example, an all positive group of five responses would be recorded as $(2 \times 5 - 1) \div (2 \times 5) \times 100 = 90$ per cent. The same applies to all negative responses. The above solution had been previously proposed by Berlison (cited in (19)).

(h) Alternative technique of computation: probit analysis

The technique generally recommended for the estimation of the dose-response functions is the probit analysis (99). This was developed originally for the computation of the quantal data obtained in animal experiments on biological activity of drugs. It is not certain, therefore, to what extent it is applicable to human data on subtle biological changes pooled from various sources. As compared with the analysis described above it differs in:

1. using the criterion of maximum likelihood of curve location;
2. introducing weighting coefficients for the number of subjects in each group and the level of response;
3. computing the equation coefficients through subsequent iterations in which the all negative and all positive responses are given values defined by specially designed functions (dependent on group size and location in the dose-scale).

For comparison with the analysis of the data as performed above, probit analysis of all sets of data was performed using original numbers of subjects reacting against the total in each group (see data in Appendix II). Whenever the number of subjects reacting was not given, it was calculated and the nearest round numbers were used. In the few cases where the number of subjects in the Tables (Appendix II) is described as 'large', the standard value 100 was assumed. The probit analysis calculations were performed at the University of London Computing Centre using the biomedical statistics package BMD035 (biological assay probit analysis).

II DOSE-RESPONSE RELATIONSHIPS FOR INDIVIDUAL INDICATORS OF HEALTH IMPAIRMENT

The data presented in paragraphs 1–9 are those obtained by regression analysis of probit values. For comparison, data obtained by the standard probit analysis are presented in paragraph 10.

1.0 Delta-aminolevulinic acid dehydratase (ALA-D)

(a) Adults

The evaluation is based on eight reports published between 1970 and 1976: Hernberg *et al.* 1970 (55); Haeger-Aronsen *et al.* 1971 (49); Haas *et al.* 1972 (47); Lauwerys *et al.* 1973 (68); Tomokuni 1974 (113); Haeger-Aronsen *et al.* 1974 (50); Hernberg's data cited by Zielhuis 1975 (131); Wada *et al.* 1976 (119). Of the available reports, only those containing a control group consisting of men having Pb-B levels below 10 μg $(100\,ml)^{-1}$ were used. The whole range of values within the medians of Pb-B between 3 and 50 μg $(100\,ml)^{-1}$ were included for the calculation of the regression function (App. II Tables 1a and 1b) resulting in the equation:

$$y = 4.17\,x - 0.25 \qquad (1)$$

This equation fits the data with a high correlation coefficient of $r = 0.86$ and the data and fit are shown in Figure 3.

(b) Children

The assessment is based on an inadequate number of three reports; therefore it has to be accepted as only preliminary. The reports include: Millar *et al.* 1970 (76); Schaller 1971 as cited by Zielhuis 1975 (131); and Wada *et al.* 1976 (119). The data cover the range of Pb-B values between 3–40 μg $(100\,ml)^{-1}$ similar to that for adults (App. II Table 2). The regression equation

$$y = 5.03\,x - 1.53 \qquad (2)$$

fits the data with a high correlation coefficient, $r = 0.96$ (Figure 4).

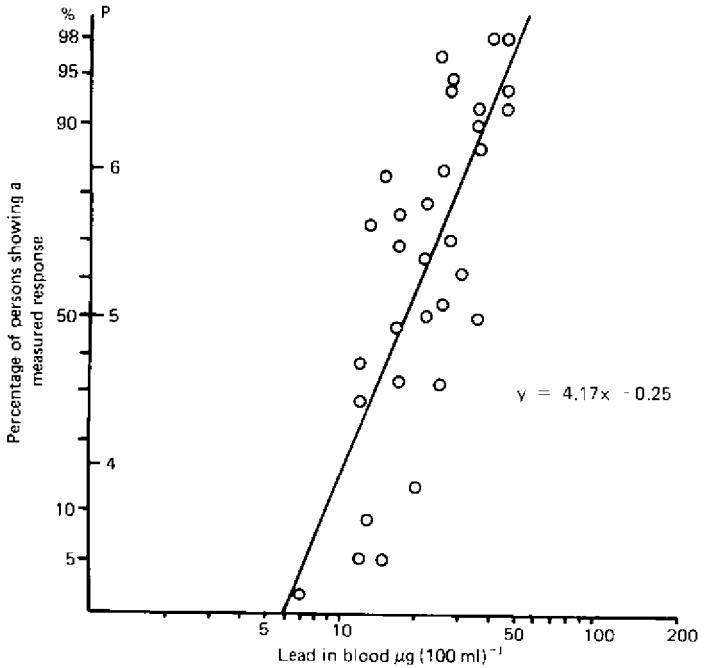


Figure 3 Dose-response of ALA-D in adults

2.0 Free erythrocyte protoporphyrins (FEP)

(a) Adults

The evaluation was based on 10 reports (Appendix II Table 3a) published between 1971 and 1976: Haeger-Aronsen 1971 (48); Piomelli 1973 (88); Roels 1974 as cited by Zielhuis 1975 (131); Roels *et al.* 1975 (93); Vitale *et al.* 1975 (118); Tomokuni *et al.* 1975 (115); Wedeen *et al.* 1975 (121); Lamola *et al.* 1975 (65); Tomokuni and Ogata 1976 (114); and Clarke 1976 (30). The last report (Clark) refers to per cent content of "fluorocytes" in blood. The reports cover a range of median Pb-B values between 10 and 80 μg $(100\,ml)^{-1}$ and the regression analysis (Appendix II Table 3) revealed the optimum range to be between 10 and 60 μg $(100\,ml)^{-1}$.

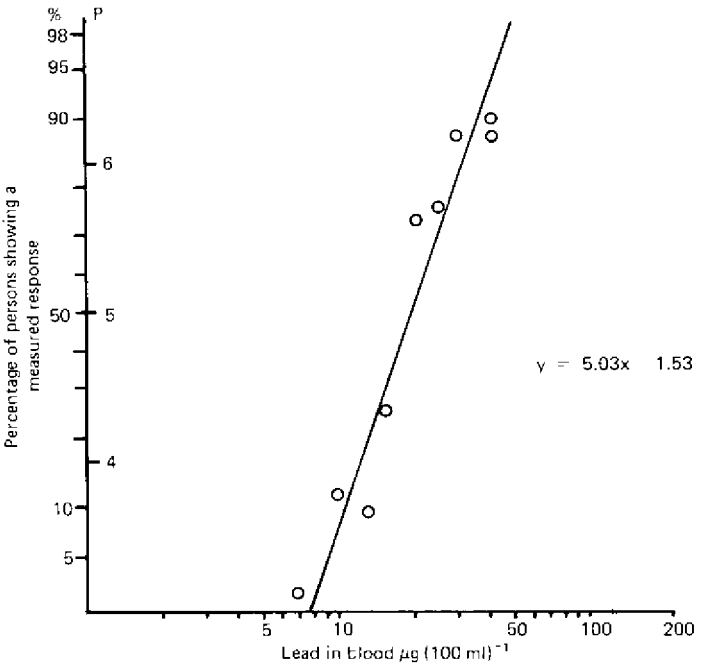


Figure 4 Dose-response of ALA-D in children

Within this range the regression equation is:

$$y = 5.21\,x - 2.93 \qquad (3)$$

which fits the data with a high correlation coefficient, $r = 0.84$ (Figure 5).

(b) Children

The assessment is based on seven reports published between 1972 and 1976 (Table 4a) which include: Kammholz *et al.* 1972 (58); Sassa *et al.* 1973 (95); Chisolm *et al.* 1974 (28); Chisolm *et al.* 1975 (29); Lamola *et al.* 1975 (65); collective data cited by Zielhuis 1975 (131); and Hanna *et al.* 1976. (51). Regression was calculated for the whole range (12–80 μg $(100\,ml)^{-1}$ of Pb-B) (see Appendix II Table

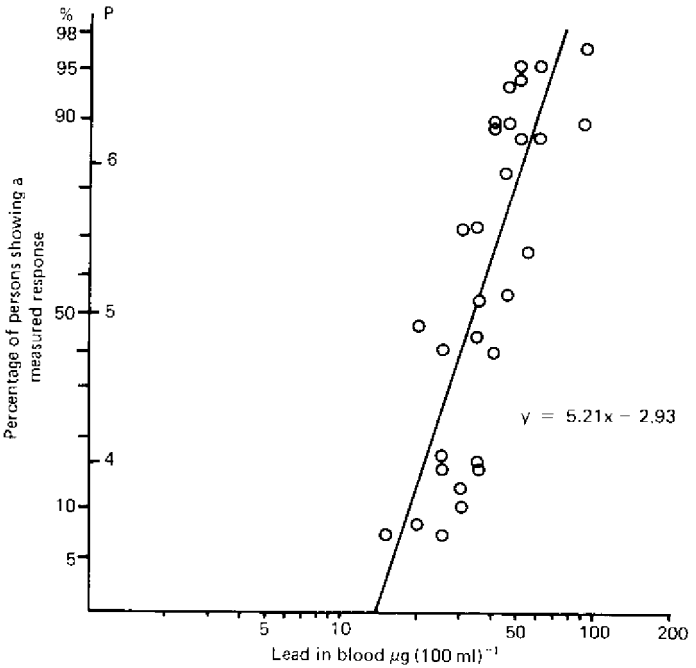


Figure 5 Dose-response of FEP in adults

4b). The equation:

$$y = 5.77\,x - 3.98 \qquad (4)$$

fits the data with a high correlation coefficient, r = 0.88 (Figure 6).

3.0 Urinary delta-aminolevulinic acid (ALA-U)

(a) Adults (male)

Data from 14 reports were included in the assessment (see Appendix II Table 5a): Selander and Cramer 1970 (101); Hernberg *et al.* 1970 (55); Schwanitz *et al.* 1970 (97); data cited in "Airborne Lead", 1972 (83); Goyer *et al.* 1972 (45); Beattie *et al.* 1972 (6); Tola 1973 (111); Cramer *et al.* 1974 (33); Sakurai *et al.* 1974 (94); Vitale *et al.*

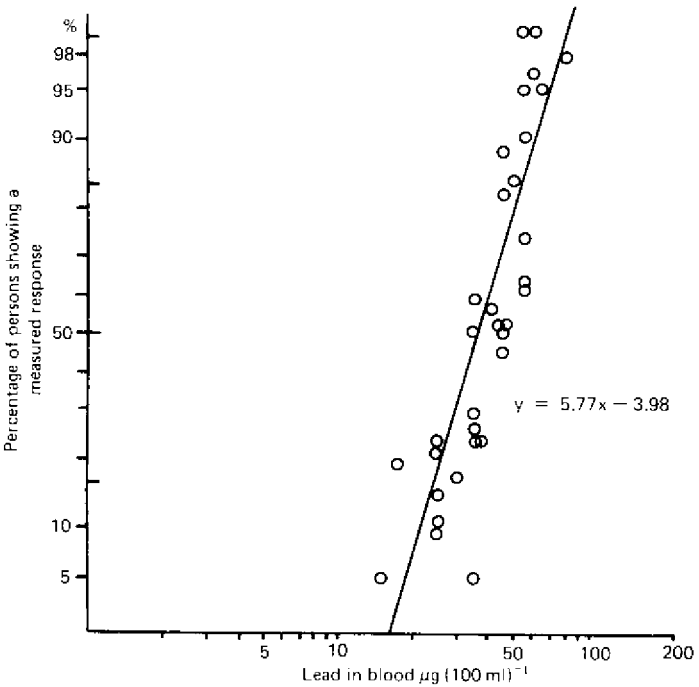


Figure 6 Dose-response of FEP in children

1975 (118); Wedeen *et al.* 1975 (121); Schwanitz *et al.* 1975 (98); Benson *et al.* 1976 (7); and Forni *et al.* 1976 (42). The reports covered the broad range of Pb-B values between 10 and 210 μg $(100\,ml)^{-1}$; however, the regression analysis (Appendix II Table 5b) indicated the optimum range to be between 24 and 105 μg $(100\,ml)^{-1}$. The equation

$$y = 5.55\,x - 4.80 \qquad (5)$$

fitted this data with a high correlation coefficient, r = 0.84 (Figure 7).

(b) Children

The evaluation (Appendix II Table 6a) is based on six reports

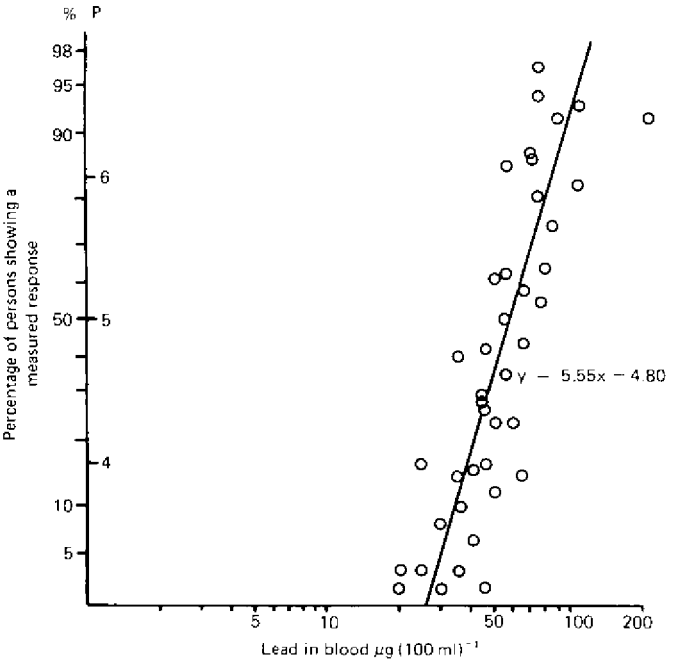


Figure 7 Dose-response of ALA-U in adults

published between 1971 and 1975: Weissberg *et al.* 1971 (122); Murphy and Lepow 1971 (82); data cited in "Airborne Lead" 1972 (83); Lob *et al.* 1972 (70); Blumenthal *et al.* 1972 (13); and Chisolm *et al.* 1975 (29) (Appendix II Table 6a). These reports covered the range of Pb-B values from 15–70 μg $(100\,ml)^{-1}$ of which 30–70 μg $(100\,ml)^{-1}$ appeared to be the optimum for regression analysis (Appendix II Table 6b). The equation

$$y = 5.14\,x - 4.35 \qquad (6)$$

fits the data with a high correction coefficient, $r = 0.88$ (Figure 8).

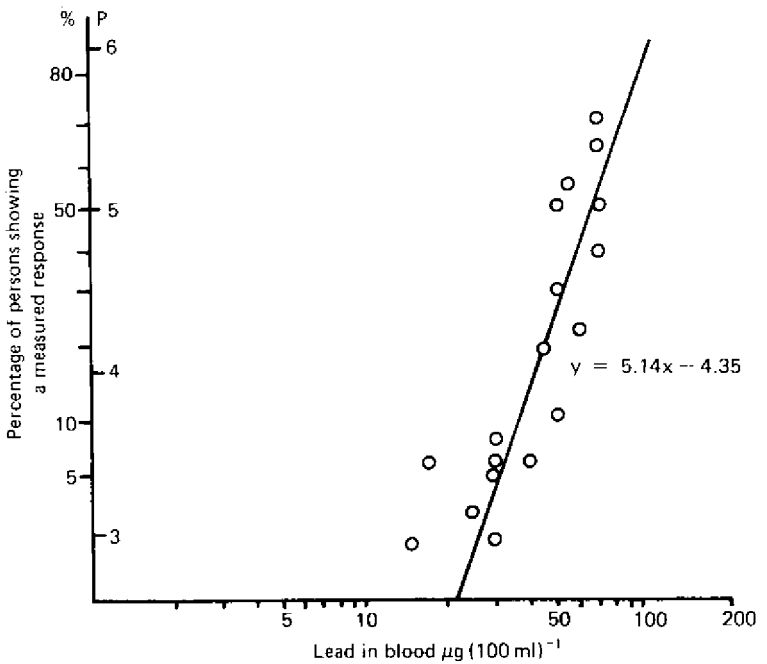


Figure 8 Dose-response of ALA-U in children

4.0 Urinary coproporphyrins (CP-U)

(a) Adults

The evaluation (App. II Table 7a) is based on 10 reports published between 1961 and 1976: King and Thompson 1961 (59); Mehani 1966 (75); de Bruin and Hoolboom 1967 (20); Williams *et al.* 1969 (126); Stankovic *et al.* 1969 (108); Joshua *et al.* 1971 (57); Beattie *et al.* 1972 (6); Wedeen *et al.* 1975 (121); Benson *et al.* 1976 (7); and Forni *et al.* 1976 (42). In four of these reports the Pb-B range had to be determined from the original Pb-U values. These reports covered

the range of median Pb-B values from 15–115 μg $(100\,ml)^{-1}$ of which 24–85 μg $(100\,ml)^{-1}$ appeared optimal for the regression analysis (App. II Table 7b). The equation

$$y = 6.85\,x - 7.06 \qquad (7)$$

fits the data with a high correlation coefficient, r = 0.82 (Figure 9).

(b) Children

An inadequate number of only three reports were used for this

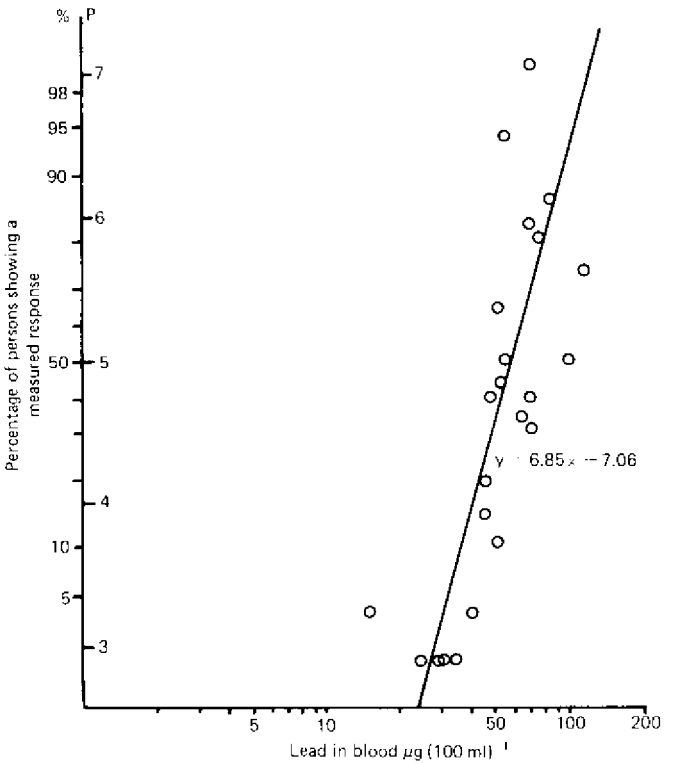


Figure 9 Dose-response of CP-U in adults

assessment: Benson and Chisolm 1960 (8); Joshua *et al.* 1971 (57); and Weissberg *et al.* 1971 (122). Thus, results of this evaluation have to be regarded as preliminary only. The whole range of the median Pb-B values, 30–120 μg (100 ml)$^{-1}$ gave the regression equation

$$y = 5.09\,x - 4.54 \qquad (8)$$

which fits the data with a correlation coefficient, r = 0.78 (App. II Table 8 and Figure 10).

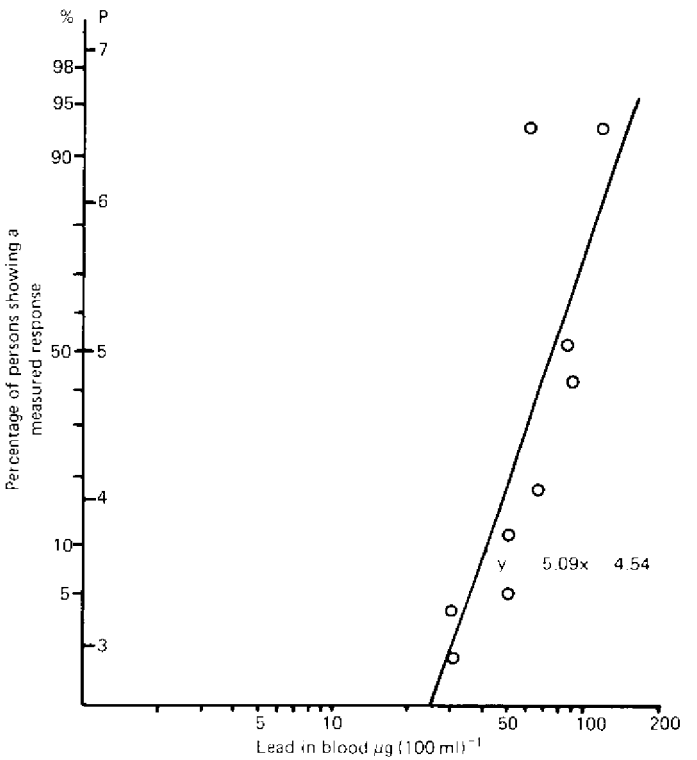


Figure 10 Dose-response of CP-U in children

5.0 Anaemia

(a) Adults

The assessment is based on 19 reports, published from 1961 to 1976 which include: King and Thompson 1961 (59); Kosmider and Petelenz 1962 (62); Mehani 1966 (75); Bonsignore 1966 (17); Williams 1966 (125); de Bruin and Hoolboom 1967 (20); Gibson *et al.* 1968 (43); McCallum *et al.* 1968 (74); Williams *et al.* 1969 (126); Catton *et al.* 1970 (23); Schwanitz *et al.* 1970 (97); Tola *et al.* 1971 (112); Cooper *et al.* 1973 (32); Beattie *et al.* 1972 (6); Tola 1973 (111); Cramer *et al.* 1974 (33); Sakurai *et al.* 1974 (94); Wedeen *et al.* 1975 (121); Clark 1976 (30). In four of these, the range of Pb-B values was obtained through computation from the original Pb-U values. Data (App. II Table 9a) cover a broad range of Pb-B median values from 20 to 220 μg $(100\,ml)^{-1}$. The individual reports show extreme differences in the assessed response. The report of Williams (125) based on a large number of workers under study was unique in failing to discover any response, even at high levels of Pb-B, much in excess of 100 μg $(100\,ml)^{-1}$. Very moderate response was also noted by Tola *et al.* (112) and Tola (111) based on an adequate number of observations which were well below the range of 100 μg $(100\,ml)^{-1}$. The regression analysis (App. II Table 9b) revealed a relatively high correlation, when calculations were limited to the range of 40–110 μg $(100\,ml)^{-1}$. The regression equation was

$$y = 4.48\,x - 4.36 \qquad (9)$$

and the correlation coefficient, $r = 0.52$, was significant at the five per cent level (Figure 11).

(b) Children

Evaluation is based on nine reports published between 1958 and 1973: Watson *et al.* 1958 (120); Moncrief *et al.* 1964 (80); Joshua *et al.* 1971 (57); Qazi and Mahadar 1971 (91); Weissberg *et al.* 1971 (122); Pueschel *et al.* 1972 (90); Kammholz *et al.* 1972 (58); Green *et al.* 1973 (46); Betts *et al.* 1973 (11); (App. II Table 10a). The reports covered the range of median Pb-B values between 15 and 200 μg $(100\,ml)^{-1}$ (App. II Table 10b), of which 15–125 μg $(100\,ml)^{-1}$ appeared optimal for the regression analysis. The equation

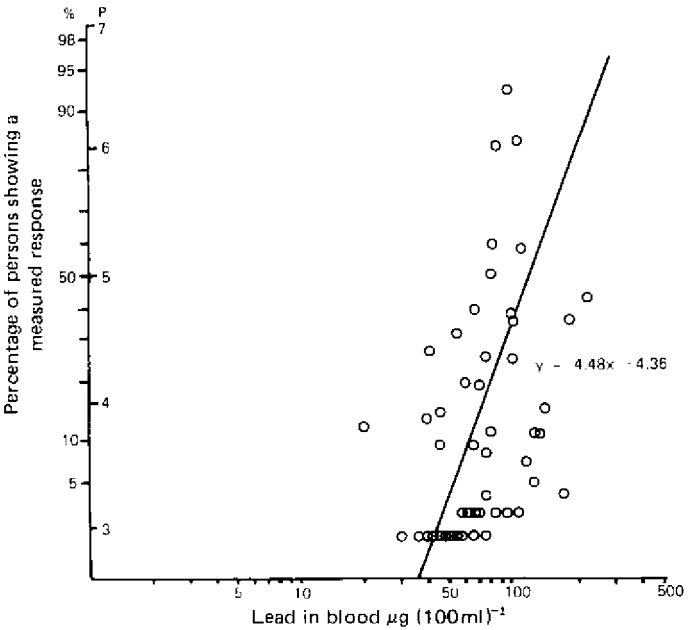


Figure 11 Dose-response of anaemia in adults

$$y = 3.85\,x - 1.76 \qquad (10)$$

fits the data with a relatively high correlation coefficient, $r = 0.77$ (Figure 12).

6.0 Central nervous system: Children

Quantitative evidence regarding effects of lead on the CNS seems to exist only for children; however, even in this case data are too limited to permit of firm judgements. The preliminary evaluation of the dose-response relationship is based on only seven reports which contain data reflecting disturbances of the CNS functions such as mild clinical symptoms, hyperactivity, decreased IQ values (especially the performance IQ), or other motor dysfunctions. All these symptoms have been given equal weight. The following reports constituted the basis

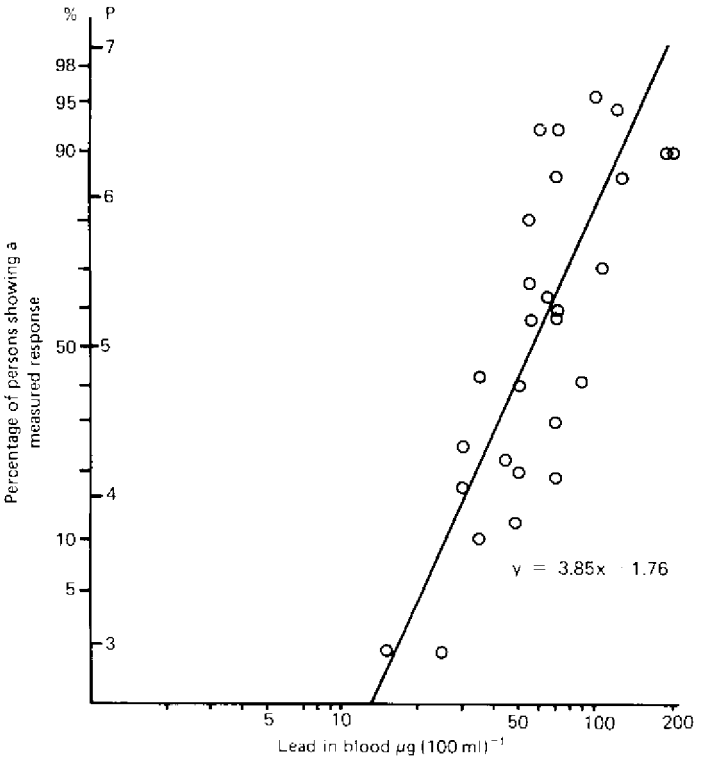


Figure 12 Dose-response of anaemia in children

for the evaluation: Gibson *et al.* 1967 (44); Joshua *et al.* 1971 (57); Pueschel *et al.* 1972 (90); de la Burdé and Choate 1972 (21); Lansdown *et al.* 1974 (67); Baloh *et al.* 1975 (4); and Landrigan *et al.* 1975 (66) (App. II Table 11). These reports cover the range of Pb-B median values from 25 µg (100 ml)$^{-1}$ ("no response" range) to 70 µg (100 ml)$^{-1}$ and the dose-response function is fitted by the equation

$$y = 3.65\,x - 2.15 \qquad (11)$$

with a correlation coefficient, $r = 0.81$, which seems extremely high regarding the type of mixed-symptoms analysis (Figure 13).

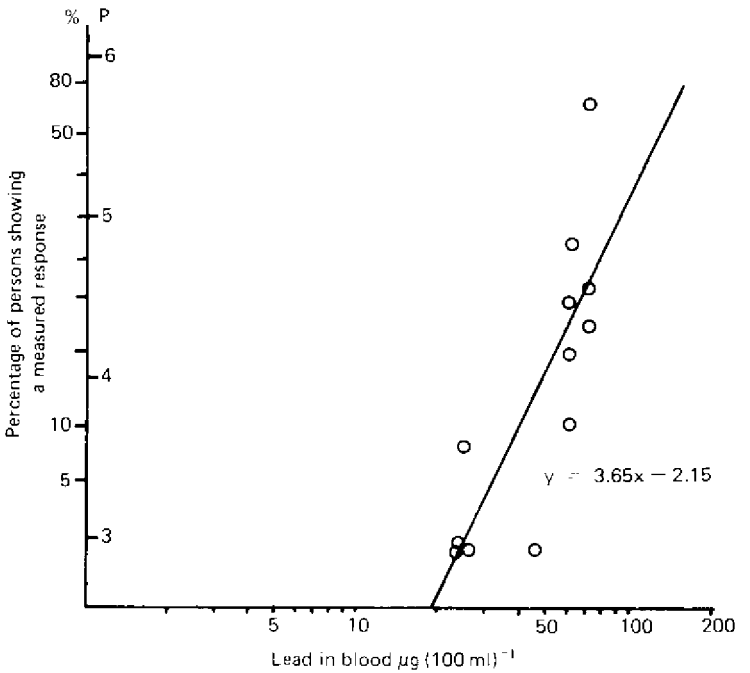


Figure 13 Dose-response of CNS disturbance for children

7.0 Peripheral nervous system (adults)

Regarding the PNS, limited quantitative data seem available for adults only. Relatively consistent information exists for changes in the conduction velocity of the peripheral nerves and the most sensitive technique seems to be that based on measurements performed on the slow motor fibres. Data from only five reports have been used: Sassa *et al.* 1965 (95); Catton *et al.* 1970 (23); Seppalainen and Hernberg 1972 (102); Seppalainen *et al.* 1975 (103); and Araki and Honma 1976 (3) (App. II Table 12). It should be noted that these reports do differ in the experimental techniques used; however, equal

weight has been ascribed to all reported values. The reports cover a rather narrow range of median Pb-B values, 10–100 μg (100 ml)$^{-1}$ of which the range 30–100 μg (100 ml)$^{-1}$ appeared optimal for the regression analysis. The regression equation

$$y = 3.59\,x - 1.89 \qquad (12)$$

fits the data with an unexpectedly high correlation coefficient, r = 0.83 (Figure 14).

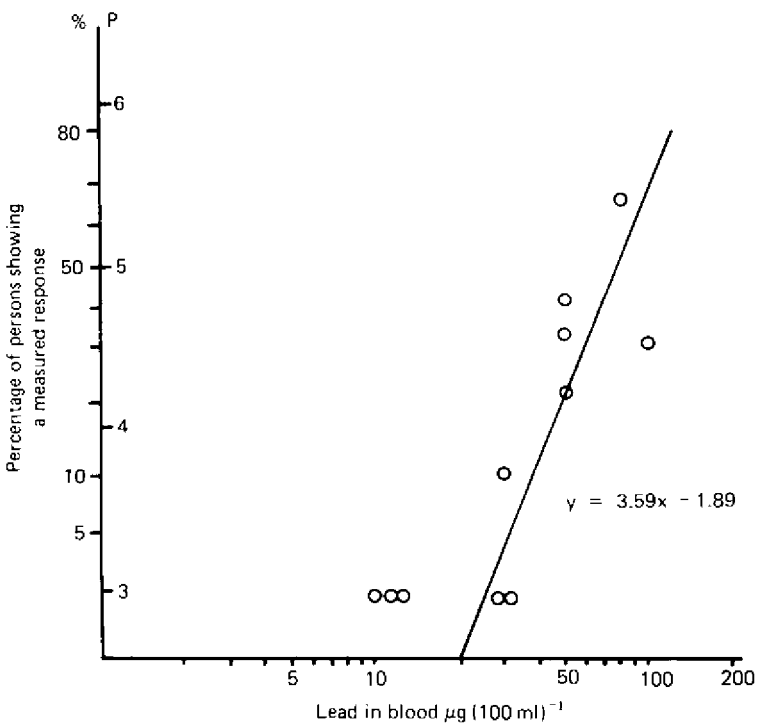


Figure 14 Dose-response for PNS disturbance in adults

8.0 Kidney injury (adults)

This evaluation is based on effects which differ in nature and do not point to similar mechanisms and areas of kidney damage. Thus, for instance, proteinuria may point to impaired glomerular filtration; aminoaciduria to impaired tubular reabsorption; and clearances, if changed, may be indicative of several changes, among others, of a decreased blood flow through the filtering areas of the kidney. Raised blood urea and urate levels would be regarded as an indication of saturnine gout. Such an evaluation is therefore to be regarded as preliminary only. It is based on seven reports: Clarkson and Kench 1955 (31); Richet *et al.* 1964 (92); Borghetti *et al.* 1971 (18); Goyer *et al.* 1972 (45); Cramer *et al.* 1974 (33); Wedeen *et al.* 1975 (121); and Campbell *et al.* 1977 (22) (App. II Table 13a). These reports cover a broad range of the Pb-B values, 30–220 μg $(100\,ml)^{-1}$. In some reports, where data on the control groups did not include Pb-B levels, a standard value of 30 μg $(100\,ml)^{-1}$ was presumed. Regression analysis (App. II Table 13b) yielded best estimates for the range of 30–150 μg $(100\,ml)^{-1}$ within which the regression equation reads:

$$y = 1.78\,x + 1.15 \qquad (13)$$

This regression, based on highly heterogeneous data, yielded a low correlation coefficient, $r = 0.59$, which, however, is significant at the five per cent level (Figure 15).

9.0 Other effects

For other effects, beyond those discussed in detail above, the existing body of information is far from being sufficient for the calculation of the dose-response functions.

Table 1 summarizes those effects for which a preliminary estimation of frequency at known Pb-B levels could be proposed. Changes in the cardiovascular system, as revealed by ECG, or the even more sensitive technique of balistocardiography, call for attention. These have been found at relatively high levels of Pb-B, of the order of 100 μg $(100\,ml)^{-1}$; however, at these levels the frequency is very high.

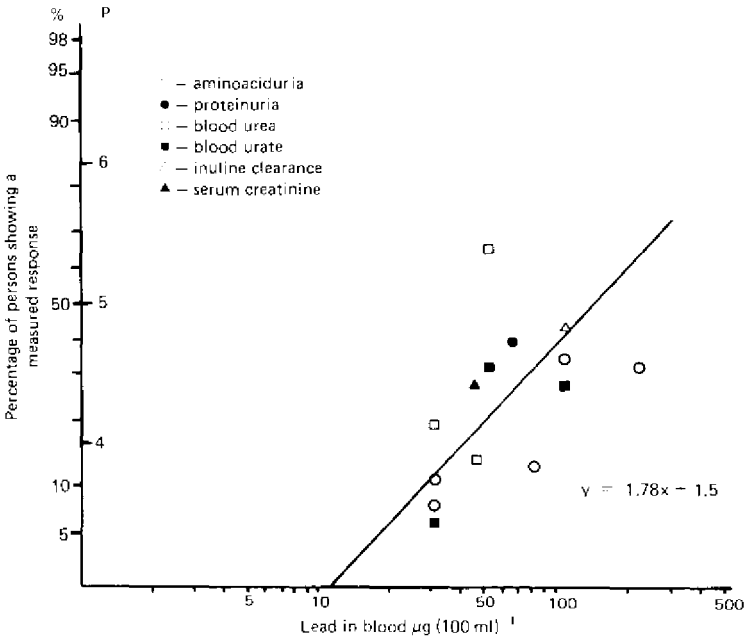


Figure 15 Dose-response of kidney injury.

Table 1 Preliminary data on other possible dose-response relationships [§]

Ref.	Type of effect	Pb-B range ug (100 ml)$^{-1}$	R (%)
(a) Adults			
62	Heart: ECG	70–290[a]	50[dn]
60	Heart: BCG	90[a]	32[d]
60	Heart: BCG	90–180[a]	52[d]
60	Heart: BCG	180	71[d]
17	Colic and other disorders of GI-tract	20– 40[a]	43
17	Colic and other disorders of GI-tract	40– 80[a]	80
17	Colic and other disorders of GI-tract	80–120[a]	70
17	Colic and other disorders of GI-tract	120–240[a]	83
57	Colic and other disorders of GI-tract	48– 61	78[d]
117	Metabolic disorders (HIAA)	90–125[a]	83–92
110	Metabolic disorders (carbonic anhydrase, glutathione, Hb-F)	35	16–60
(b) Children			
106	Heart: ECG	60– 90	65
106	Heart: ECG	100–200	85
57	Colic and other disorders of GI-tract	52– 72	89
58	Colic and other disorders of GI-tract	30– 50	17
58	Colic and other disorders of GI-tract	50– 70	40
58	Colic and other disorders of GI-tract	70–130	83
4	Colic and other disorders of GI-tract	50– 80	12[n]
105	Metabolic disorders (noradrenaline metab.)	59– 68	85[g]

[§] For symbols see Appendix II.

Studies of the cardiovascular system in children have only been initiated but no relation between dose and response can yet be proposed (106). The same seems to apply to the disorders of the gastrointestinal tract, although these are largely subjective in nature and a greater error of estimation is likely to be involved. Metabolic disorders of various kinds seem to be quite frequent at relatively low levels of Pb-B; however, their significance as indicators of health impairment has not yet been recognized.

10.0 Dose-response functions obtained by probit analysis

For purposes of comparison the above data were also analysed using the methods of probit analysis. The results are shown in Table 2.

This gives the values of ED-10 and ED-50, the effective doses corresponding to 10 and 50 per cent response respectively.

Table 2 Dose-response relationships calculated by probit analysis

X — logarithm of Pb-B ($\mu g\ (100\ ml)^{-1}$), y — Probit corresponding to response rate
ED_{10} and ED_{50} — effective doses (levels) corresponding to 10 and 50 per cent response, respectively ($\mu g\ Pb\ (100\ ml)^{-1}$)
A — adult males; C — children; N — degrees of freedom (for evaluation of chi square)

Effect		Equation	N	ED_{10} [§] $\mu g\ (100\ ml)^{-1}$	ED_{50} [§] $\mu g\ (100\ ml)^{-1}$	Chi^2
ALA-D	(A)	$y = -1.050 + 3.172.X$	38	7	18	297
	(C)	$y = -3.533 + 6.869.X$	9	10	18	18
FEP	(A)	$y = -2.370 + 4.815.X$	33	18	34	135
	(C)	$y = -4.514 + 5.932.X$	34	25	40	256
ALA-U	(A)	$y = -4.043 + 5.156.X$	47	31	57	111
	(C)	$y = -2.583 + 4.087.X$	16	31	71	45
CP-U	(A)	$y = -2.692 + 4.061.X$	23	36	78	180
	(C)	$y = -5.703 + 5.621.X$	7	47	80	27
Anaemia	(A)	$y = -0.246 + 2.227.X$	47	67	220	387
	(C)	$y = -1.129 + 3.428.X$	27	26	62	59
CNS	(C)	$y = -1.438 + 3.172.X$	12	42	110	39
PNS	(A)	$y = -0.466 + 2.832.X$	10	30	85	17
Kidney	(A)	$y = -1.910 + 1.356.X$	14	22	190	34

[§] Probit for $ED_{50} = 5$; for $ED_{10} = 3$

III EVALUATION OF RESULTS

1.0 Dose-response relationships for adults

Figure 16 and Table 3 present all the dose response relationships obtained for adults, as based predominantly on male workers exposed in industry. It is seen that the derangement of haem synthesis is represented by a chain of effects each characterized by the Pb-B range necessary to produce them, which follow in sequence: ALA-D, FEP, ALA-U (and CP-U which gives an almost identical dose-response curve) and finally, a fall in haemoglobin level as a sign of anaemia. It is usually agreed (128) that the first of these effects, a fall in the activity of ALA-D in blood, represents a subcritical effect of no direct biological importance. In fact this seems to be a non-threshold effect (see also 25, 79). FEP is accepted as a true critical effect (29) to which some biological role is ascribed and so it is striking that the ED_{10} (threshold level) is reached at an unexpectedly low level of only $19 \pm 3\,\mu g\,(100\,ml)^{-1}$ of Pb-B (Table 3).

Calculations of Zielhuis (131) performed on a smaller group of reports gave the "no response" level at about $20–30\,\mu g\,(100\,ml)^{-1}$. The third indicator in sequence, increase of ALA-U, becomes apparent far ahead of an essential fall of haemoglobin levels. The apparent threshold (ED_{10}) for ALA-U (resp. CP-U) amounts to about $35\,\mu g\,(100\,ml)^{-1}$. This value agrees with the estimates of Zielhuis (131) of $30–40\,\mu g\,(100\,ml)^{-1}$. For anaemia, which represents the final effect in this series of events, the ED_{10} amounts to about $65\,\mu g\,(100\,ml)^{-1}$. This value is close to the range of Pb-B values which follow the threshold limit value, TLV, of $0.15\,mg\,m^{-3}$ in industry (128).

It must be stressed, however, that in the case of adult men, anaemia is not the first recognizable effect of clinical importance. By using sufficiently sensitive techniques, damage to the nervous system may be detected well ahead of signs of anaemia. For the "asymptomatic" signs as manifested by subtle changes in the peripheral nervous system, the apparent threshold (ED_{10}) amounts to only $35–40\,\mu g\,(100\,ml)^{-1}$, a range that has been considered safe not only for individuals exposed in industry, but also for the whole population. This figure, $35–40\,\mu g\,(100\,ml)^{-1}$, is much lower than expected from direct comparisons of responses (131).

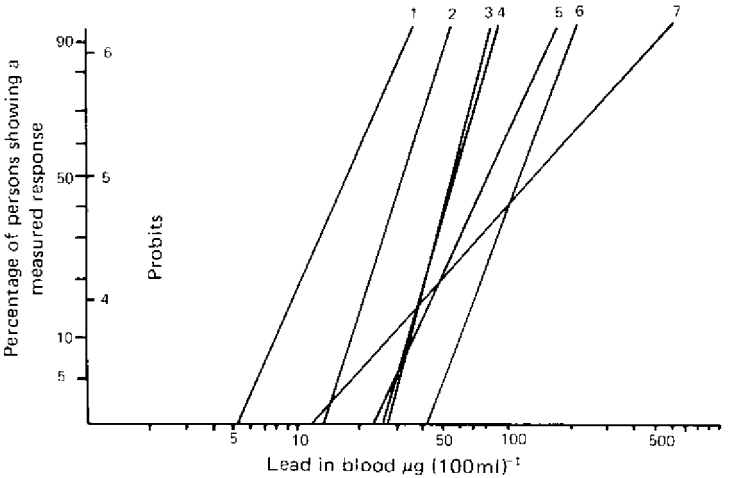


Figure 16 Dose-response relationships for adults

Key: 1 Reduction in erythrocyte ALA-D activity
2 Increase in the free erythrocyte protoporphyrin (FEP) concentration
3 Increase in urinary coproporphyrins (CP-U)
4 Increase of ALA excretion in urine (ALA-U)
5 Dysfunction of the peripheral nervous system
6 Anaemia
7 Kidney injury

As seen from Figure 15 the dose-response curve for the asymptomatic kidney damage differs essentially from all others by a relatively low regression constant (slope). This may either be an artifact, due to the fact that a variety of effects were treated together resulting in a large standard deviation and poor correlation or may be real, i.e. such a function could also be expected if we assume wide limits of individual sensitivity to kidney damage.

Should the latter explanation be true, then the low apparent threshold for this effect, about $30\,\mu g\ (100\,ml)^{-1}$, should be given serious consideration. In view of the uncertainties involved in this study, as well as many of the past reports regarding the probable role of lead in renal insufficiencies (87, 78, 69, 71), this area clearly calls for further studies.

Table 3 Blood lead levels at which 10% and 50% of persons exhibit effects above the upper limit (μg (100 ml)$^{-1}$). The errors shown are two times the standard error.

Effect	Concentration (μg (100 ml)$^{-1}$)			
	Adults		Children	
	10%	50%	10%	50%
ALA-D	9 ± 2	18 ± 3	11[§] ± 2	20[§] ± 2
FEP	19 ± 3	33 ± 5	21 ± 3	36 ± 4
ALA-U	34 ± 4	58 ± 5	38 ± 19	66 ± 47
CP-U	37 ± 5	58 ± 9	41[§] ± 17	74[§] ± 24
Anaemia	63 ± 11	120 ± 52	25 ± 8	54 ± 13
CNS	—	—	40[§] ± 5	90[§] ± 35
PNS	37[§] ± 19	84[§] ± 84	—	—
Kidney injury	28[§] ± 23	140[§] ± 140	—	—

[§] Preliminary figures based on inadequate number of data

Because most of the data concerning adults on which Figure 16 and Table 3 are based stem from industrial exposure of male workers, industrial toxicology seems the first and main field to which implications of this part of the study apply. It should be noted that the normal procedure of health protection in industry contains two important check-points which are of the utmost importance for any evaluation of data in this area. First, workers are subject to a medical examination before entering work connected with lead exposure and those showing signs of vulnerability to lead intoxication are rejected. Second, those admitted to work are subject to periodical medical check-ups, following which subjects showing signs of chronic intoxication would be temporarily removed from exposure. This is why dose-response relationships obtained from studies performed in medically well-managed industries must bear errors of underestimation regarding frequency and severity of health effects. This is especially true for anaemia which serves as a guide in the periodical medical check-ups.

Despite the above reservation, this survey gave unexpectedly low apparent threshold values for all effects under investigation. If, neglecting the critical effect (FEP), we base our findings only on those effects which may be regarded as subclinical indicators of health impairment (such as changes in the peripheral nervous system or

asymptomatic kidney injury), the threshold value to be recommended can hardly exceed 35 μg $(100\,ml)^{-1}$ Pb-B. These conclusions could perhaps be ascribed to analysis in terms of the dose-response utilizing pooled data from a variety of studies, allowing an extrapolation to be made down to a level which could not have been reached from individual studies of lead toxicity.

2.0 Dose-response relationships for children

Figure 17 and Table 3 summarize the dose-response curves for children.

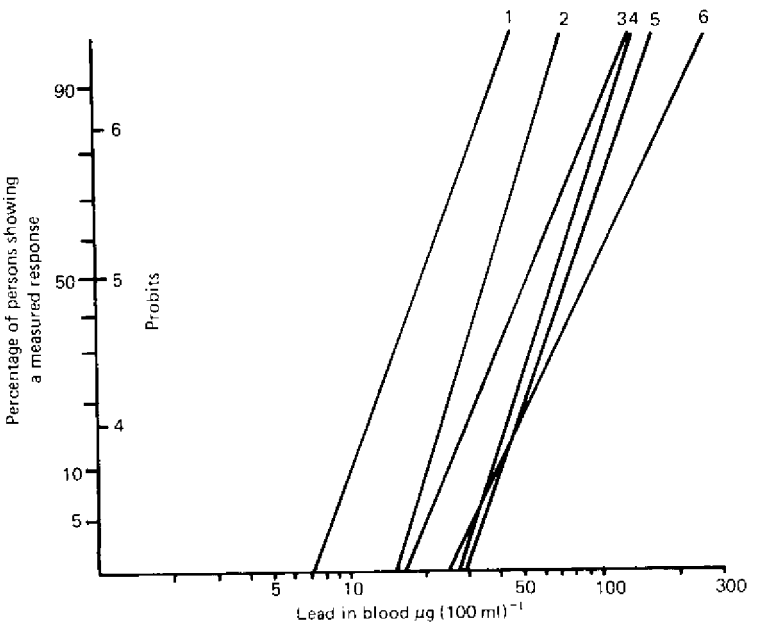


Figure 17 Dose-response relationships for children

Key:
1 Reduction in erythrocyte ALA-D activity
2 Increase in the free erythrocyte protoporphyrin (FEP) concentration
3 Anaemia
4 Rate of ALA excretion in urine (ALA-U)
5 Increase in urinary coproporphyrins (CP-U)
6 Central nervous system dysfunction

The first three stages in the derangement of haem synthesis follow a very similar pattern to that of adults, the dose-response curves for ALA-D, FEP and ALA-U (resp. CP-U) being well separated. Unexpectedly, the dose-response curve for anaemia falls between those of FEP and ALA-U. Thus, ALA-U (and CP-U as well), in the case of children, do not represent indicators of any biological value (see also 107, 12). The apparent threshold for anaemia is unexpectedly low and close to that of FEP, the ED_{10} being noted at 21 and 25 μg $(100\,ml)^{-1}$ respectively. Thus, the FEP as an indicator must be considered a most critical one. The presently accepted borderline, 40 μg $(100\,ml)^{-1}$, equals the apparent threshold (ED_{10}) for the central nervous system. The dose-response curve for the CNS in children is based here on limited evidence and should be regarded as tentative (5, 73) (see Table 3). The results obtained here seem to be supported by several other reports not included in the present analysis (36, 2, 89, 35). Since the changes induced in the CNS are considered largely irreversible, such a borderline (40 μg $(100\,ml)^{-1}$) can no longer be regarded as fulfilling the demands of a safety standard. Existing data on the PNS in children (39, 66) do not yet allow any dose-response relationships to be proposed. The same applies to kidney injury (24, 27).

3.0 Comparison of the dose-response for adults and children and considerations regarding the general population

Table 3 summarizes responses for adults (men) and children regarding the available data on health effects. Both the ED_{10} and ED_{50} blood lead levels are shown together with estimates of twice the standard error. Generally the ED_{10} thresholds are more significant (statistically) than those for ED_{50}. Before starting comparisons, one has to realize that the compared sets of data may bear systematic errors of opposite sign built in because of possible "preselection" during the setting up of the original study. Adults are represented here mainly by men who have been subjected to a "positive" preselection regarding their resistance to the toxic action of lead as noted above. Such "positive" preselection is hardly imaginable regarding children. If any preselection is to be suspected regarding groups of children under investigation, the "negative" one seems more probable. This is

because medical scientists would prefer to select, for studies of a given health effect, subjects reacting positively, i.e. children of lower resistance.

The above explanation is necessary to appreciate fully the importance of the unexpected uniformity in some of the biological responses. Table 3 shows that the response of both groups is almost identical regarding all three biochemical effects on haem synthesis: ALA-D, FEP and ALA-U (CP-U). This conclusion opposes the view of those scientists who have attempted to explain the higher sensitivity of children by differences in these biochemical responses using inadequate sets of data (131). The almost identical dose-response of both groups regarding the nervous system is surprising, if we realize that we do not compare the same systems on both sides (CNS on the one hand and PNS on the other). A more adequate comparison in this respect will probably be possible in the future if the already initiated lines of research into the CNS in adults (61) and on the PNS in children (116, 66, 39) are extended.

The only dramatic difference between adult men and children shown in this study refers to anaemia. This is the only effect of lead in which children have shown a significant difference compared with adults, in that they appear much more vulnerable. Since the effects of lead on the basic pathways of haem synthesis, as evaluated in this report, appear to be similar for children and adults, the different results for anaemia indicate either that the globin component is affected in children or that much excess haem is synthesized in adults.

4.0 Comparison of probit analysis results with those obtained from regression analysis

Probit analysis, which was introduced for purposes of comparison, gave the results shown in Table 2. When comparing this data with that in Table 3 the following observations should be noted.

(a) The probit analysis yielded functions differing in numerical values of coefficients from those generated by regression analysis. The most striking difference, as expected, was found regarding anaemia in adults. This was due mainly to the weighting of responses according to the size of groups, which

especially in this case, seemed to the authors an inappropriate technique. These assumptions gave, namely, *a priori* a higher credit to those few authors who, on vast material, failed to show any serious effects of lead at such lead levels, where most authors would find evident response.

(b) Accordingly, the greatest difference in the computed ED_{50} value was found for anaemia (220 vs 120 μg $(100\,ml)^{-1}$). All other ED_{50} values were found to be similar to those yielded by regression analysis and were within or close to the limits of error estimates given in Table 3.

(c) The change of computation technique did not alter essentially any of the values of ED_{10} and all of them appeared essentially close to those computed by regression analysis, fairly well within the error estimates given in Table 3.

5.0 Problems connected with the computational techniques

Regarding the statistical methods to be used, the authors decided to give priority to procedures which were simple enough and close to the traditional approach of toxicity computations. The classical technique is that elaborated by Finney (40) for quantal responses obtained in pharmacological and toxicological evaluation of drugs on experimental animals. It makes use of the plotting of probits of response versus log dose that is followed by a weighting and iterative procedure known as "probit analysis". This technique has also been recommended for use in problems of environmental toxicology (99). There seem to be, however, several assumptions underlying such a computation technique that does not apply to data of the kind discussed in this report.

(a) The reliability of data taken from various reports is not simply a function of the number of subjects in a group reported: another factor which is probably of the utmost importance, the scientific competence of the reporting laboratory, is difficult to measure and express in terms of numerical values. Therefore, weighting of various groups for their size as inherent in the probit analysis does not seem to solve the question;

(b) Weighting of responses according to their numerical values, with maximum coefficients for the response of 50 per cent (also included in the probit analysis) fulfils the demands of

formal statistics and also in the case where the ED_{50} (e.g. LD_{50}) is to be computed is easily understood on purely logical grounds. This is not necessarily the case with an analysis aiming basically at computing the dose levels corresponding to much lower response rates (e.g. ED_{10}).

For the above reasons the authors gave more credit to a technique of data analysis in which these assumptions were excluded (regression analysis of probit values). For the sake of comparison, however, the classical full probit analysis was also performed and reported in Section II. Both techniques gave very close values of ED_{10}, giving support to the use of these values.

The full probit analysis, however, as performed in this report, using a special computer programme, has revealed a bias regarding data treatment. The high values of chi-square listed in Table 2 (each to be compared with criteria referring to the degrees of freedom) speak against the assumption of log-normal distribution (underlying both methods of data analysis). An alternative plotting of data (probit *vs* dose level) failed to eliminate the bias (results not quoted).

It is concluded that while the functions computed in this report represent a reliable approximation, a much better fit could probably be achieved using other types of functions. Since for the alternative models recommended (see 99) (such as the logistic model, the sine-curve, models based on the "hit theory") no computer programmes were available to the authors at the time of analysis, these possibilities have not been explored further. It seems, however, that the problems discussed here are worthy of study by biostatisticians, and it may be that the basic numerical values included in this report could be used for a first approach. Whitehead (123) has stated that valuable information is lost if dose-effect data is transformed into binary dose-response data and that a better procedure is to fit curves to the dose-effect data by curvilinear regression and in this way to determine threshold levels. However, as he states, it is often impossible to use pooled data with such a procedure. In addition, many sets of dose-effect data used in compiling the present report would have been inadequate for the purpose of making curvilinear dose-effect regression fits.

From informal inspection of various data used in the compilation of this report as reflected in the extreme normal limits shown in

Appendix II Tables 3--15 it is evident that the direct quantitative data on effects are largely incompatible. This is not necessarily the case, however, with regard to the transformed quantal data, if the extreme normal limits are properly selected. The Tables 3 to 15 of Appendix II give several examples, where not only different methods gave compatible quantal responses but also, in some instances, different approaches to the assessment of the same basic biological phenomenon could have been used with no evident aberration in response rate. It is concluded, therefore, that the initial incompatibility of the quantitative data on effects does not represent a serious obstacle in using the transformed quantal data in a system of pooled dose-response analysis.

6.0 Needs for further research

Estimates of threshold values of blood lead for the various biological effects computed in the present paper seriously overlap with the existing published data of blood lead levels in the general population. Guidelines for the future must not be based, therefore, on approximate threshold values alone. Firm experimental data are needed to justify the serious economic measures which would have to be implemented if the input of lead to the human environment is required to be reduced. In the light of the data surveyed in the present report, the following need urgent investigation:

(a) All responses to lead of women, and of elderly people of both sexes.
(b) More abundant, reliable data on the effect of lead on the nervous system as well as on the kidneys.
(c) Effects of lead on the cardio-vascular system.

It would be highly desirable to obtain data of effects of (b) and (c) in a comparable way for children and adult men. This would create a firm basis for the assessment of which effects are identical and which differ regarding susceptibility in these two model groups.

Apart from gathering purely experimental evidence on the dose-response relationships, the statistical technique of constructing the dose-response functions should be given further attention by biostatisticians. The reliability of the statistical procedures should be assessed and standard procedures should be developed. The importance of these more technical questions is emphasized by the present trend

to make a broader use of the dose-response relationships for chemicals in procedures leading to estimates of apparent threshold values as well as health standards.

7.0 Conclusions

(1) For the assessment of the dose-response functions for inorganic lead use may be made of quantitative data contained in various reports. Converting the quantitative data into quantal forms allows relatively compatible information to be obtained from different sources and the final computation may be performed on pooled sets of data.

(2) The traditional analysis of the probits of response rate *vs* log of dose (here lead level in blood) allows simple functions to be calculated by either regression or probit analysis. Such a plot of data, however, does not represent the best fit of functions and further statistical studies on this seem to be warranted.

(3) From the equations of regression or probit functions the apparent thresholds for various toxic effects of lead can be calculated with some credibility. For the sake of this computation the apparent threshold was defined as a lead level in blood, at which 10 per cent of the population under study would respond to the toxic stimulus yielding a discernible effect.

(4) The apparent thresholds, as determined separately for adults (men) and children and expressed in μg Pb per 100 ml of blood respectively, were as follows:

ALA-D: 9 and 11; FEP: 19 and 21; ALA-U: 34 and 38; CP-U: 37 and 41; anaemia: 63 and 25; CNS (children): 40; PNS (adults): 37; kidney injury (adults): 28.

The difference in the apparent thresholds for anaemia point to a higher susceptibility for children. Some of these thresholds are still tentative due either to inadequate number of reports available or broad limits of error estimates.

(5) The similar response of adults and children in all effects related to the haem synthesis speaks against the assumption that this pathway is responsible for the greater susceptibility of children. The action of lead on the globin component seems more likely to be the cause of this phenomenon.

(6) From the value of the apparent threshold for the critical effect (FEP) it follows that a large proportion of the general population is already at some risk.

Acknowledgements
The authors feel deeply indebted to Dr T. A. Rafter who undertook the enormous task of editing this paper in the absence of both authors at the time of editing. Thanks are due also to Dr S. Smith for re-checking the data, and also to Mr J. M. Buchanan for his assistance in the probit analysis and to Dr B. G. Bennett for assistance with editing this paper. The assistance of Dr J. Whitehead in preparing Appendix I is acknowledged.

Appendix I

Relationship between dose-effect data and dose-response data: computational procedure

For a given level of lead in blood (i.e. dose represented by B[§]), there may be associated on average an effect E in an individual measured on some physiological or biochemical basis. The association forms the dose-effect relationship, which might be represented by the equation

$$F(E) = cf(B) + d \qquad (1)$$

where F and f could be any monotonically increasing functions, for example logarithmic or exponential, and c and d are constants. The effect in a specific individual may deviate from the average by an amount ϵ. Thus,

$$F(E) = cf(B) + d + \epsilon \qquad (2)$$

We assume that ϵ is normally distributed over the population with mean zero and variance σ^2.

To simplify the notation, let $y = F(E)$ and $x = f(B)$. Then equation (2) can be written

$$y = cx + d + \epsilon \qquad (3)$$

Further, let B_0 represent a certain low level of blood lead where $x_0 = f(B_0)$. If we let $y_0 = cx_0 + d$ and $y' = y_0 + 2\sigma = cx_0 + d + 2\sigma$ then, according to this model, 97.5% of individuals with a blood lead level of B_0, would have an effect E, such that $y = F(E) \leqslant y'$. Conversely, 2.5%, say Q_0, of individuals in the population would have an effect such that $y \geqslant y'$. The equation representing this model is schematically shown in Figure A.1 in which the relations between the various quantities mentioned above are also depicted.

For individuals with a blood level, B, the assumption of normality allows the proportion, Q, of this group with an effect such that $y = F(E) \geqslant y'$ to be estimated. The value of Q is given by the expression:

$$Q = 1 - \Phi\left(\frac{y' - cx - d}{\sigma}\right) \qquad (4)$$

[§] B is used here instead of Pb-B for simplicity's sake.

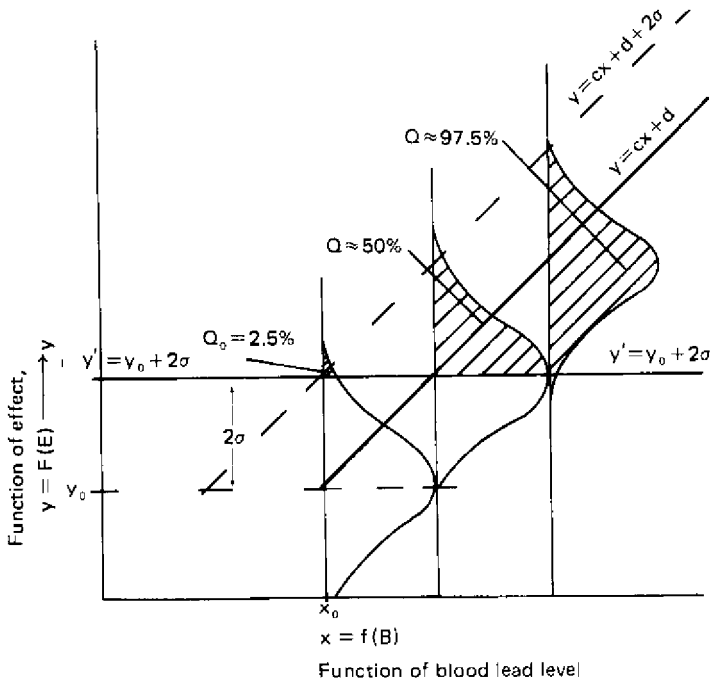


Figure A.1 The relationship between doses and the distribution of effects

where

$$\Phi(x) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{x} e^{-t^2/2}$$

is the standard normal distribution function. The area of the distribution curve corresponding to Q is also dipicted in Figure A.1. The value of Q increases as x increases. In this model it has been assumed that σ, the standard deviation for the distribution, is a constant, independent of the value of x.

In the calculations on which the results in the main text are based,

the sample proportion of individuals, q, with a blood lead level in a given range, who have effects such that $F(E) = y \geqslant y'$ is used. This is transformed into its probit, P, using the transformation

$$q = 1 - \Phi(5 - P) \qquad (5)$$

As q is an estimate of Q, equations (*4*) and (*5*) may be combined to obtain the expression:

$$P = 5 - \frac{y' - cx - d}{\sigma} + \delta \qquad (6)$$

where δ is the residual error. Equation (*6*) can be expressed in a simple notation as:

$$P = ax + b + \delta \qquad (7)$$

Since this is a linear equation, P may be readily fitted to x.

Linear regression and probit-specific methods were both used, reflecting somewhat different optimization objectives — least squares and maximum probability respectively.

In the analysis of data, B_0 was chosen and y' estimated. For each blood level range, q is expressed as the percentage of cases for which $F(E) \geqslant y'$

$$\text{i.e.} \quad q = \frac{N'}{N} \times 100\%$$

where N is the total number of cases in the group and N' is the number of cases for which $y = F(E) \geqslant y'$. The corresponding values of P are calculated using equation (*5*) above or obtained from published tables. When $N' = 0$ or N, it is necessary to modify the procedure to avoid values of q of 0 or 1. In these cases, the following formulae were used:

when

$$N' = N \qquad q = \left(\frac{2N - 1}{2N}\right) \times 100\%$$

and when

$$N' = 0 \qquad q = \frac{100}{2N}\ \%$$

In these ways, sets of data originally given in terms of doses and effects were grouped, pooled and transformed into functions of doses and responses. The analysis of these relations enables the blood lead level corresponding to a particular response to be estimated from the values of the parameters. The response, derived from "dose-effect" data as outlined in Figure A.1, and the probit of the response would, in the framework of the assumed model, be expected to be related to a function of the blood lead level as indicated in Figures A.2 and A.3 which correspond to equations (*4*) and (*7*) above.

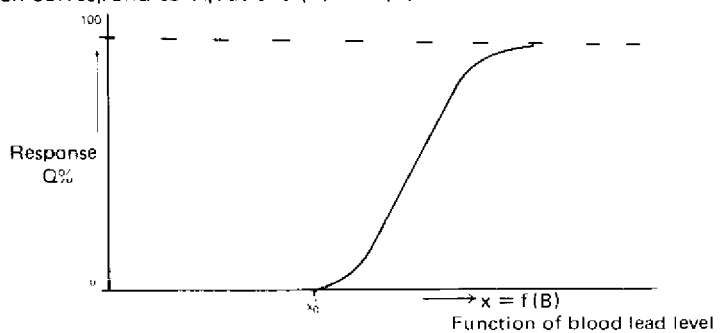


Figure A.2 The relationship between the response and a function of blood lead level

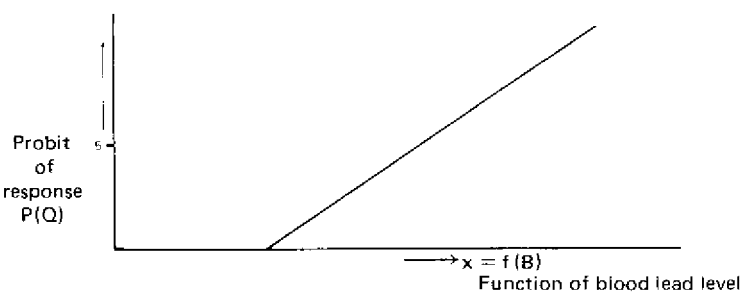


Figure A.3 The relationship between the probit of the response and a function of blood lead level

Appendix II

Tables showing experimental data from literature

Explanatory notes referring to tables

a – Pb-B value calculated from Pb-U data
b – Extreme normal level calculated from authors' data at the lowest exposure level or in an appropriate control group
c – Extreme normal level adopted from another report which matches in method and parameters
d – The per cent above the upper limit used is that applied or suggested by the author of the reference
e – Extreme normal level adopted arbitrarily
f – Response of the "control" group accepted as two per cent following statistical definition
g – All positive response, all negative response
h – Response calculated from means and standard deviations given in reference
i – Rough estimate from authors' graphic data
j – Standard deviation adopted from other similar reports
k – Inconsistent with authors' own data or interpretation
l – Rough estimate of median
m – Additional recalculations were involved
n – Corrected for background frequency
p – Lead level in the control group not reported: arbitrary value adopted

Table 1a ALA-D: Adults

Series No.	Ref.	Extreme normal limit[§]	Pb-B median and range μg (100 ml)$^{-1}$	N total	N +	R (%)
1	(55)	80 units[b]	7 (5–10)	9	–	2[f]
			12 (10–15)	20	1	5
			17 (15–20)	15	7	47
			22 (20–25)	28	14	50
			27 (25–30)	20	14	70
			35 (30–40)	27	25	92
2	(49)	70 units[bk]	7 (5–10)	29	1	3
			15 (10–20)	57	3	5
			25 (20–30)	12	4	33
			35 (30–40)	6	3	50
			45 (40–50)	13	12	92
3	(47)	600 units[b]	7 (5–10)	12	0	2[f]
			12 (10–15)	21	6	28
			17 (15–20)	9	3	33
			22 (20–25)	8	5	63
			15 (10–20)	6	5	83
			25 (20–30)	12	10	84
			35 (30–40)	10	9	90
			45 (40–50)	7	7	93[g]
4	(68)	50 units[bm]	7 (5–10)	22	–	2[f]
			12 (10–15)	36	15	42
			17 (15–20)	22	15	68
			22 (20–25)	28	22	78
			27 (25–30)	15	14	93
5	(113)	0.6 units[b]	3 (0– 5)	7	0	2[f]
			8 (5–10)	10	5	50
			13 (10–15)	15	11	73
			17 (15–20)	12	9	75
			25 (20–30)	18	18	96[g]
6	(50)	500 units[bi]	7 (5–10)	> 20	–	2[f]
			25 (20–30)	15	8	53
			35 (30–40)	8	7	87
			45 (40–50)	15	15	97[g]
7	(131)	60% initial[d]	20 (15–24)	30	4	13[d]
			30 (25–34)	26	16	62[d]
			40 (35–44)	32	31	97[d]
			50 (45–54)	53	53	99[g]

Table 1a continued

Series No.	Ref.	Extreme normal limit [§]	Pb-B median and range $\mu g\ (100\ ml)^{-1}$	N total	N +	R (%)
8	(119)	150 units[b]	8 (5–10)	10	–	2[f]
			13 (11–17)	10	–	11[h]
			27 (15–37)	20	–	94[h]

[§] ALA-D levels in red blood cells were usually reported in some arbitrary units

Table 1b ALA-D: Adults. Parameters of the regression analysis depending on the accepted range of Pb-B values

Pb-B range $\mu g\ (100\ ml)^{-1}$	N	Coefficient of determination r^2	Coefficient of regression a
12–27	22	0.33	4.43
12–40	28	0.41	3.93
7–40	34	0.70	4.56
3–40	35	0.69	4.09
3–50	39	0.74	4.17

Selected range 3–50 $\mu g\ (100\ ml)^{-1}$
Regression equation $y = 4.17\ X - 0.25$
Characteristic values of response
50% – 18 $\mu g\ (100\ ml)^{-1}$
10% – 9 $\mu g\ (100\ ml)^{-1}$
5% – 7 $\mu g\ (100\ ml)^{-1}$

Table 2 ALA-D: Children

Series No.	Ref.	Extreme normal limit	Pb-B median and range µg (100 ml)$^{-1}$	N total	N +	R (%)
1	(76)	400 nmol PBG/hr per 10^{10} RBC[b]	3 (0– 5)	8	0	2[f]
			7 (5–10)	16	0	3[g]
			15 (10–20)	16	4	25
			25 (20–30)	8	6	75
			40[l] (30–50)	4	4	88[g]
2	(131)	40% inhibition[d]	10[l] (< 14)	9	–	11[d]
			20 (15–24)	37	–	73[d]
			30 (25–34)	24	–	88[d]
			40 (35–44)	10	–	90[d]
3	(119)	160 nmol PBG/ml RBC[b]	9 ± 1	10	–	2[f]
			13 ± 2	10	–	9[h]

Regression equation (range 9–40 µg (100 ml)$^{-1}$ Pb-B) $y = 5.03\,X - 1.53$; $r^2 = 0.93$
(Alternative: range 3–40 µg (100 ml)$^{-1}$, $r^2 = 0.86$, $a = 3.72$)
Characteristic values of response

50% – 20 µg (100 ml)$^{-1}$
10% – 11 µg (100 ml)$^{-1}$
5% – 9 µg (100 ml)$^{-1}$

Table 3a FEP: Adults (male)
No. 8 refers to ZPP, no. 10 to Fluorocytes

Series No.	Ref.	Extreme normal limit	Pb-B median and range $\mu g\ (100\ ml)^{-1}$	N total	N +	R (%)
1	(49)	100 µg per 100 ml RBC[c]	30 (20–40)	5	0	10[g]
			45 (40–50)	9	5	55
			55 (50–60)	6	4	66
			65 (60–70)	9	4	45
			80 (70–90)	10	9	90
2	(88)	125 µg per 100 ml RBC[bm]	10 (5–15)	15	1	7[b]
			20 (15–25)	12	1	8
			30 (25–35)	8	1	12
			40 (35–45)	10	9	90
			50 (45–55)	11	11	95[g]
3	(131)	80 µg per 100 ml RBC[d]	15 (11–20)	36	–	2[f]
			25 (21–30)	43	–	7[d]
			35 (31–40)	32	–	19[d]
			50 (40–70)	8	–	94[g]
4	(93)	83 µg per 100 ml RBC[d]	15 (10–20)	15	–	7[d]
			25 (20–30)	27	–	15[d]
			35 (30–40)	18	–	44[d]
5	(118)	25 µg per 100 ml RBC[d]	35 (29–39)	7	5	71

Table 3a continued

Series No.	Ref.	Extreme normal limit	Pb-B median and range μg (100 ml)$^{-1}$	N total	N +	R (%)
	(118)	25 μg per 100 ml RBC[d]	45 (41–48)	10	9	90
6	(115)	120 μg per 100 ml RBC[b]	17 (15–20)	7	0	2[f]
			25 (20–30)	17	7	41
			35 (30–40)	15	8	53
			45 (40–50)	18	15	83
7	(121)	25 μg per 100 ml[d]	45 (29–66)	7	7	95[g]
8	(65)	20 μg per 100 ml[d]	25 (20–30)	6	1	17
			40 (30–50)	5	2	40
			60 (50–70)	10	10	95[g]
9	(114)	100 μg per 100 ml RBC[b]	12 (10–15)	12	0	2[f]
			20 (15–25)	28	13	46
			30 (25–35)	28	20	71
			40 (35–45)	28	25	90
			50 (45–55)	16	14	88
10	(30)	5% Fluorocytes	35 (20–50)	12	2	17
			60 (50–70)	12	10	83
			80 (70–90)	12	12	96[g]

Table 3b FEP: Adults (male). Parameters of the regression analysis depending on the accepted range of Pb-B values

Pb-B range $\mu g\ (100\ ml)^{-1}$	N	Coefficient of determination r^2	Coefficient of regression a
25–45	19	0.54	8.05
15–45	24	0.61	5.76
15–50	27	0.69	6.20
10–50	29	0.71	5.43
10–60	32	0.72	5.21
10–80	35	0.70	4.73

Selected range 10–60 $\mu g\ (100\ ml)^{-1}$
Regression equation $y = 5.21\ X - 2.93$
Characteristic values of response
50% – 33 $\mu g\ (100\ ml)^{-1}$
10% – 19 $\mu g\ (100\ ml)^{-1}$
5% – 16 $\mu g\ (100\ ml)^{-1}$

Table 4a FEP: Children
Nos. 4, 5, 7 refer to ZPP

Series No.	Ref.	Extreme normal limit	Pb-B median and range µg (100 ml)$^{-1}$	N total	N +	R (%)
1	(58)	160 µg per 100 ml RBC[d]	25 (20–30)	7	1	14
			35 (30–40)	12	6	50
			45 (40–50)	11	9	82
			55 (50–60)	11	10	91
			65 (60–70)	11	11	95[g]
			80 (70–90)	16	16	97[g]
2	(95)	140 µg per 100 ml RBC[d]	30 (25–35)	12	2	17
			40 (35–45)	35	20	57
			50 (45–55)	46	39	85
			60 (55–65)	27	27	98[g]
3	(28)	7.3 resp. 10.9 µg per 100 ml blood[d]	25 (20–30)	30	3	10
			35 (30–40)	39	9	23
			45 (40–50)	23	12	52
			60 (50–80)	23	22	96
4	(29)	8.1 µg per 100 ml blood[d]	25[l] (< 30)	34	–	9[d]
			35 (30–39)	54	–	23[d]
			45 (40–49)	38	–	45[d]

Table 4a continued

Series No.	Ref.	Extreme normal limit	Pb-B median and range $\mu g\ (100\ ml)^{-1}$	N total	N +	R (%)
	(29)	8.1 µg per 100 ml blood[d]	55 (50–59)	20	–	95[d]
5	(65)	20 µg per 100 ml blood[bi]	12 (10–15)	7	0	2[f]
			17 (15–20)	15	3	20
			25 (20–30)	49	11	23
			35 (30–40)	55	33	60
			45 (40–50)	64	58	90
			55 (50–60)	34	34	98[g]
6	(131)	–	15[l] (< 20)	87	–	5[d]
		–	25 (21–30)	72	–	21[d]
		–	35 (31–40)	24	–	29[d]
		–	55 (41–70)	36	–	64[d]
7	(51)	80 µg per 100 ml RBC[d]	35[l] (20–39)	large	–	5[d]
			45 (40–49)	large	–	52[d]
			55 (50–59)	large	–	63[d]
			65 (60–69)	large	–	99[gi]
			35[l] (20–39)	large	–	26[d]
			45 (40–49)	large	–	50[d]
			55 (50–59)	large	–	74[d]
			65 (60–69)	large	–	99[gi]

Table 4b FEP: Children. Parameters of the regression analysis depending on the accepted range of Pb-B values

Pb-B range $\mu g\ (100\ ml)^{-1}$	N	Coefficient of determination r^2	Coefficient of regression a
25–50	21	0.61	6.15
12–50	24	0.62	4.22
12–55	30	0.68	4.90
12–65	35	0.74	5.79
12–80	36	0.76	5.77

Selected range 12–80 $\mu g\ (100\ ml)^{-1}$
Regression equation $y = 5.77\ X - 3.98$
Characteristic values of response
50% – 36 $\mu g\ (100\ ml)^{-1}$
10% – 21 $\mu g\ (100\ ml)^{-1}$
5% – 18 $\mu g\ (100\ ml)^{-1}$

Table 5a ALA-U: Adults (male)

Series No.	Ref.	Extreme normal limit	Pb-B median and range μg (100 ml)$^{-1}$	N total	N +	R (%)
1	(101)	4 mg/l[bk]	15[l] (< 20)	10	0	2[f]
			25 (21–30)	10	0	4[g]
			35 (31–40)	20	8	40
			45 (41–50)	35	15	43
			55 (51–60)	22	19	86
			75 (61–90)	23	22	96
2	(55)	13 mg/l[b]	10 (7–15)	13	–	2[f]
			20 (16–25)	33	1	3
			30 (26–35)	30	1	3
			40 (36–45)	18	1	6
			50 (46–55)	8	1	12
			65 (56–75)	16	2	14
			80 (76–85)	14	9	64
			105 (86–125)	6	5	83
3	(97)	4.3 mg per g creatinine	75 (62–89)	8	8	94[g]
4	(83)	2.0 mg/day per m^2[b]	13 (6–15)	13	0	2[f]
			20 (16–25)	23	1	4
			30 (26–35)	13	1	8
5	(45)	3.0 mg/l[b]	30[a] (12–50)	9	0	2[f]
			85[a] (76–100)	4	3	75
			210[a] (150–280)	6	6	92[g]
6	(6)	5.5 mg/l[d]	50 (46–59)	4	1	25
			70 (67–75)	4	4	88[g]
7	(111)	10 mg/l[b]	15 (10–19)	12	–	2[f]
			25 (21–29)	31	–	16[h]
			35 (30–39)	20	–	10[h]
			45 (40–49)	43	–	30[h]
			55 (50–59)	51	–	50[h]
			65 (60–69)	38	–	60[h]
			75 (70–79)	47	–	80[h]
8	(33)	4.0 mg/l[c]	105 (70–140)	7	7	93[g]
9	(94)	5.0 mg/l[bj]	35 (31–40)	27	1	4

Table 5a continued

Series No.	Ref.	Extreme normal limit	Pb-B median and range μg (100 ml)$^{-1}$	N total	N +	R (%)
	(94)	5.0 mg/l[b,i]	45 (41–50)	18	0	3[g]
			55 (51–60)	25	9	36
			65 (61–70)	9	4	44
			75 (71–80)	11	6	55
			90 (81–100)	24	22	92
10	(118)	6.0 mg/l[d]	35 (29–30)	7	1	14
			45 (40–48)	11	3	27
			60 (51–70)	8	2	25
11	(121)	6.0 mg/l[d]	45 (29–66)	7	2	28
12	(98)	4.5 mg/g creatinine[d]	38 ± 21	105[i]	16[i]	15
13	(7)	43 μmol/l[b]	24 (16–44)	17	0	2[f]
			50 (38–52)	5	3	60
			70 (64–76)	8	7	87
14	(42)	8.9 mg/l[b]	34 ± 13	11	–	2[f]
			46 ± 17	6	–	16[h]
			51 ± 12	6	–	30[h]
			57 ± 33	6	–	62[h]

Table 5b ALA-U: Adults (male). Parameters of the regression analysis depending on the accepted range of Pb-B values

Pb-B range µg (100 ml)$^{-1}$	N	Coefficient of determination r^2	Coefficient of regression a
34– 75	31	0.59	6.73
24– 75	37	0.65	5.78
24– 85	39	0.66	5.58
24–105	42	0.71	5.55
20–105	44	0.72	5.15
15–105	46	0.72	4.68
10–105	48	0.70	4.12
10–210	49	0.71	3.94

Selected range 24–105 µg (100 ml)$^{-1}$
Regression equation $y = 5.55\ X - 4.80$
Characteristic values of response
50% – 58 µg (100 ml)$^{-1}$
10% – 34 µg (100 ml)$^{-1}$
5% – 30 µg (100 ml)$^{-1}$

Table 6a ALA-U: Children

Series No.	Ref.	Extreme normal limit	Pb-B median and range $\mu g\ (100\ ml)^{-1}$	N total	N +	R (%)
1	(122)	5 mg/l[d]	50 (40–59)	12	6	50
			70[l] (> 60)	11	7	64
2	(82)	5.5 mg/l[d]	30 (10–40)	60	15	5[n]
			50 (40–60)	10	5	30[n]
			70 (60–80)	5	3	40[n]
3	(83)	1.8 mg/day per m^2[b]	17 (5–25)	36	2	6
			33 (25–40)	16	1	6
4	(70)	4.7 mg/l[b]	15 (12–16)	13	0	2[f]
			25 (21–30)	32	1	3
5	(13)	6.0 mg/l[d]	30	161	21	8[n]
			40	105	12	6[n]
			50	33	5	10[n]
			60	10	3	25[n]
			70	9	5	50[n]
6	(29)	2.0 mg/day per m^2[b]	30 (23–40)	15	0	2[f]
			45 (40–50)	18	4	22
			55 (50–60)	17	10	60
			70 (60–80)	13	9	70

Table 6b ALA-U: Children. Parameters of the regression analysis depending on the accepted range of Pb-B values

Pb-B range $\mu g\ (100\ ml)^{-1}$	N	Coefficient of determination r^2	Coefficient of regression a
40–70	11	0.55	5.52
30–70	15	0.77	5.14
15–70	18	0.72	3.56

Selected range 30–70 $\mu g\ (100\ ml)^{-1}$
Regression equation $y = 5.14\ X - 4.35$
Characteristic values of response
50% – 66 $\mu g\ (100\ ml)^{-1}$
10% – 38 $\mu g\ (100\ ml)^{-1}$
5% – 32 $\mu g\ (100\ ml)^{-1}$

Table 7a CP-U: Adults (male)

Series No.	Ref.	Extreme normal limit	Pb-B median and range μg (100 ml)$^{-1}$	N total	N +	R (%)
1	(59)	negative[i]	15[l] (< 20)	51	–	4[i]
			40[l] (30–50)	192	–	4[i]
			70[l] (60–80)	206	–	32[i]
			100[l] (90–110)	58	–	50[i]
2	(75)	60 μg/l[b]	75[a,l] (35–100)	10	10	95[g]
3	(20)	250 μg/g creatinine[b]	30[a] (15–40)	9	0	2[f]
			50[a] (42–60)	5	0	10[g]
			70[a] (65–75)	5	2	40
			115[a] (100–130)	4	3	75
4	(126)	3.5 Donath units[b§]	29 ± 3.5	10	–	2[f]
			63 ± 8	8	–	60[h]
			63 ± 27	9	–	35[h]
			74 ± 12	6	–	80[h]
5	(108)	60 μg/l[b]	70[a,i]	36	36	98[g]
6	(57)	negative[d]	55 (48–61)	9	9	94[g]
7	(6)	250 μg/l[d]	55 (40–75)	7	3	43
8	(121)	300 μg/day[d]	45 (29–66)	7	1	14
9	(7)	0.33 μmol per litre[b]	24 (16–44)	16	0	2[f]
			48 (38–60)	5	2	40
			70 (60–80)	6	5	83
			85 (80–92)	4	4	87[g]
10	(42)	80 μg/l[b]	34 ± 13	11	–	2[f]
			46 ± 17	6	–	20[h]
	(42)	80 μg/l[b]	51 ± 12	6	–	65[h]
			57 ± 33	6	–	50[h]

§ See (126).

Table 7b CP-U: Adults (male). Parameters of the regression analysis depending on the accepted range of Pb-B values

Pb-B range $\mu g\ (100\ ml)^{-1}$	N	Coefficient of determination r^2	Coefficient of regression a
40— 70	15	0.37	7.57
24— 70	19	0.63	6.81
24— 85	21	0.68	6.85
15— 85	22	0.61	5.27
15—115	24	0.57	4.57

Accepted range 24—85 $\mu g\ (100\ ml)^{-1}$
Regression equation $y = 6.85\ X - 7.06$
Characteristic values of response
50% — 58 $\mu g\ (100\ ml)^{-1}$
10% — 37 $\mu g\ (100\ ml)^{-1}$
5% — 32 $\mu g\ (100\ ml)^{-1}$

Table 8 CP-U: Children

Series No.	Ref.	Extreme normal limit	Pb-B median and range µg (100 ml)$^{-1}$	N total	N +	R (%)
1	(8)	++[e]	30 (20–40)	105	1	2[f]
		"	50 (40–60	65	7	11
		"	85 (70–100)	47	24	51
		"	120 (100–140)	7	7	93[g]
2	(57)	+[d]	60 (52–72)	7	7	93[g]
3	(122)	++[d]	30[k] (< 40)	12	0	4[g]
		"	50 (40–60)	18	1	5
		"	65[k] (60–70)	6	1	17
		"	90[k] (> 80)	7	3	43

Regression equation $y = 5.09 x - 4.54$
Coefficient of determination $r^2 = 0.61$
Characteristic values of the response
50% – 74 µg (100 ml)$^{-1}$
10% – 41 µm (100 ml)$^{-1}$
5% – 35 µg (100 ml)$^{-1}$

Table 9a Anaemia: Adults (male)
(except for 13, all haemoglobin)

Series No.	Ref.	Extreme normal limit	Pb-B median and range μg (100 ml)$^{-1}$	N total	N +	R (%)
1	(59)	90%[bik]	below 20	51	–	8[i]
			40 (30–50)	192	–	13[i]
			70 (60–80)	206	–	19[i]
			100 (90–110)	58	–	26[i]
2	(62)	65%[d]	180 (70–290)	38	14[d]	37
3	(75)	13 g%[e]	60 (35–100)[a]	10	2	20
4	(17)	75%[e]	40 (20–60)[a]	15	4	27
			80 (60–100)[a]	12	6	50
			140 (100–180)[a]	13	2	15
			220 (> 180)[a]	9	4	44
5	(125)	75%[bhk]	45 (40–50)	182	–	2[h]
			55 (50–60)	132	–	2[h]
			65 (60–70)	115	–	2[h]
			75 (70–80)	112	–	2[h]
			85 (80–90)	64	–	3[h]
			95 (90–100)	38	–	3[h]
			105 (100–110)	25	–	3[h]
			115 (110–120)	9	–	7[h]
			125 (120–130)	8	–	5[h]
			170 (130–200)	22	–	4[h]
6	(20)	14 g%[b]	45 (20–60)[am]	9	–	2[f]
			130 (90–200)	9	1	11
7	(43)	13 g%[d]	46 –	20	–	9[j]
			65 –	49	–	40[hj]
			81 –	16	–	60[hj]
			94 –	13	–	93[hj]
8	(74)	12.5 g%[d]	100 wide[a]	225	–	36[d]
9	(126)	95%[b]	30 –	10	–	2[f]
			63 ± 9	17	–	3[g]
			74 ± 5	6	–	8[g]
10	(23)	12.0 g%[d]	100 (40–120)	19	7	37
11	(97)	13.0 g%[e]	75 (62–89)	8	2	25
12	(112)	13.0 g%[b]	35 ± 16	16	–	2[f]

Table 9a continued

Series No.	Ref.	Extreme normal limit	Pb-B median and range $\mu g\ (100\ ml)^{-1}$	N total	N +	R (%)
	(112)	13.0 g%[b]	58 ± 11	11	–	3[h]
			59 ± 11	13	–	2[h]
			64 ± 13	14	–	9[h]
			68 ± 15	36	–	3[h]
			77 ± 20	22	–	11[h]
13	(32)	4.6 10^6 RBC	110[i]	12[d]	7[d]	58
14	(6)	13.0 g%[d]	55 (40–75)	5	2	40
15	(111)	13.0 g%[b]	45 (30–60)	364	–	2[f]
			65 (60–70)	44	–	3[h]
			75 (70–79)	41	–	4[h]
			85 (80–90)	29	–	8[h]
16	(33)	13.0 g%[e]	105 (75–140)	7	6	85
17	(94)	14.0 g%[b]	52 ± 15	20	–	2[g]
18	(121)	13.0 g%[e]	45 (29–66)	7	1	14
19	(30)	12.4 g%[b]	35 (20–50)	12	0	2[f]
			80 (60–150)	27	3	11

Table 9b Anaemia: Adults (male). Parameters of the regression analysis depending on the accepted range of Pb-B values

Pb-B range $\mu g\ (100\ ml)^{-1}$	N	Coefficient of determination r^2	Coefficient of regression a
60–100	23	0.10	3.75
60–130	29	0.04	1.95
60–220	33	0.03	1.19
50–220	38	0.08	1.76
41–220	43	0.13	1.97
31–220	47	0.13	1.97
20–220	49	0.14	1.63
41–100	32	0.25	4.37
41–110	35	0.27	4.48
41–130	39	0.14	2.68

Selected range 41–110 $\mu g\ (100\ ml)^{-1}$
Regression equation $y = 4.48\ X - 4.36$
Characteristic values of response
50% = 120 $\mu g\ (100\ ml)^{-1}$
10% = 63 $\mu g\ (100\ ml)^{-1}$
5% = 52 $\mu g\ (100\ ml)^{-1}$

Table 10a Anaemia: Children (Hb)

Nos. 2, 5, 6, 8, 9 age up to 6 years, 7 up to 5.5 years most below 2 years, 1 up to 3 years, 3 up to 10 years

Series No.	Ref.	Extreme normal limit	Pb-B median and range $\mu g\ (100\ ml)^{-1}$	N total	N +	R (%)
1	(120)	11.0 g%[b]	70 (40–90)	4	4	87[g]
			120 (110–140)	9	9	94[g]
2	(80)	70%[e]	50 (40–55)	5	1	20
			65 (62–72)	8	5	63
			200 (100–380)	5	5	90[g]
3	(57)	10.0 g%[d]	60 (52–72)	7	7	93[g]
4	(91)	9.6 g%[b]	70 (60–80)	22	–	30[h]
			105 (90–120)	10	–	70[h]
5	(122)	9.6 g%[ck]	30 (12–40)	> 10	–	17[h]
			50 (40–60)	> 10	–	10[h]
			70[l] (> 60)	> 10	–	19[h]
6	(90)	11.0 g%[c]	35 (30–40)	5	0	10[g]
			45 (40–50)	9	2	22
			55 (50–60)	5	4	80
			70 (60–80)	7	7	93[g]
			100 (80–120)	11	11	95[g]
7	(58)	10.0 g%[b]	25 (7–47)	14	0	2[f]
			36 (28–40)	12	5	42
			48 (44–50)	8	1	12
			55 (53–60)	6	4	66
			70 (61–93)	7	4	57
8	(46)	11.0 g%[c]	57 (50–68)	16	9	56
			90 (71–105)	12	5	41
			125 (120–141)	4	4	87[g]
9	(11)	11.0 g%[d]	15 (5–20)	9	0	2[f]
			30 (20–37)	12	3	25
			50 (37–60)	25	10	40
			70 (60–80)	5	3	60
			200[l] (> 80)	10	9	90

Table 10b Anaemia: Children. Parameters of the regression analysis depending on the accepted range of Pb-B values

Pb-B range $\mu g\ (100\ ml)^{-1}$	N	Coefficient of determination r^2	Coefficient of regression a
45– 70	15	0.21	5.43
45–125	20	0.33	3.91
30–125	24	0.45	3.62
15–125	26	0.60	3.85
15–200	28	0.62	3.37

Selected range 15–125 $\mu g\ (100\ ml)^{-1}$
Regression equation $y = 3.85\ X - 1.76$
Characteristic values of response
50% – 54 $\mu g\ (100\ ml)^{-1}$
10% – 25 $\mu g\ (100\ ml)^{-1}$
5% – 21 $\mu g\ (100\ ml)^{-1}$

Table 11 Central nervous system (selected symptoms): children

Series No.	Ref.	Pb-B median and range μg (100 ml)$^{-1}$	Indicator	Extreme normal limit	N total	N +	R (%)
1	(44)	25 (0–40)	IQ.	80[b]	17	–	2[f]
		70 (50–100)	IQ.	80[b]	9	–	76[h]
2	(57)	60 (50–70)	Mild clinical symptoms.	–	9	4[d]	44[d]
3	(90)	70 (30–130)	Mild clinical symptoms.	–	58	–	33[d]
		70 (30–130)	Neurol. dysfunction and motor deficits.	–	58	–	25[d]
4	(21)	25[lp]	Low IQ and other psychol. tests.	–	71	–	8[d]
		60[l] (40–100)	Low IQ and other psychol. tests.	–	69	–	20[d]
		25[lp]	IQ alone.	–	71	–	2[f]
		60[l] (40–100)	IQ alone.	–	69	–	10[h]
5	(67)	45 (40–50)	IQ.	–	31	–	2[f]
6	(4)	25 (13–39)	Hyperactivity.	–	27	4	2[dn]
		60 (50–80)	Hyperactivity.	–	27	12	31[dn]
7	(66)	27 (15–39)	Performance IQ.	78[b]	78	–	2[f]
		48 (40–68)	Performance IQ.	78[b]	46	–	13[h]

Regression calculation performed for the whole range, 25–70 μg (100 ml)$^{-1}$
Regression equation $y = 3.65 X - 2.15$
Coefficient of determination $r^2 = 0.66$
Characteristic values of the response — 50% — 90 μg (100 ml)$^{-1}$
10% — 40 μg (100 ml)$^{-1}$
5% — 32 μg (100 ml)$^{-1}$

Table 12 Peripheral nervous system; adults of both sexes

Series No.	Ref.	Pb-B median and range $\mu g\ (100\ ml)^{-1}$	Indicator	Extreme normal limit	N total	N +	R (%)
1	(95)	30[lp]	Ulnar nerve conduction velocity	46 m/sec[cd]	--	--	2[f]
		50 (42–58)[a]					
		50 (42–58)[a]			7	3	43
		85 (65–98)[a]			6	4	66
2	(23)	30[lp]	Muscle action potential, knee/ankle	82%	17	0	2[f]
		100[l] (40–150)			19	6	32
3	(102)	12[l]	Ulnar nerve conduction velocity (slow motor fibres)	40 m/sec[b]	32	0	2[f]
		50[l] (20–70)			34	15	44
4	(103)	12[l]	Ulnar nerve conduction velocity (slow motor fibres)	38 m/sec[b]	22	0	2[f]
		50[l] (20–70)			26	6	22

Table 12 continued

Series No.	Ref.	Pb-B median and range µg (100 ml)$^{-1}$		Indicator	Extreme normal limit	N total	N +	R (%)
5	(3)	10	(0—20)	Maximal motor nerve conduction velocity (MCV), knee/ankle	50 m/sec[bm]	16	0	2[f]
		30	(20—40)			10	1	10
		50	(40—70)			12	4	33

Regression equation (range 30—100 µg (100 ml)$^{-1}$ Pb-B) $y = 3.59\ X - 1.89$
(Alternative: range 10—100 µg (100 ml)$^{-1}$ $r^2 = 0.72$, $a = 2.31$)
Characteristic values of response: 50% — 84 µg (100 ml)$^{-1}$
10% — 37 µg (100 ml)$^{-1}$
5% — 30 µg (100 ml)$^{-1}$

Table 13a Asymptomatic kidney injury: adults

Series No.	Ref.	Pb-B median and range $\mu g\ (100\ ml)^{-1}$	Indicator	Extreme normal limit	N total	N +	R (%)
1	(31)	30[lp]	Urinary alpha-amino nitrogen	73 mg/g creatinine[b]	12	1	8
		105[al]			27	10	36
2	(92)	50[l] (30–65)	Blood urea	40 mg%[c]	6	4	66
		50[l] (30–65)	Blood urate	8 mg%[d]	6	2	33
3	(18)	30[al]	Microproteinuria	120 mg/day[b]	5	0	2[f]
		65[a] (50–85)			15	6	40
4	(45)	30[al] (12–50)	Urinary alpha-amino nitrogen	1 μmol/mg N_2[b]	9	1	11
		80[a] (75–90)			4	0	12[g]
		220[a] (150–280)			6	2	33
5	(33)	105 (75–140)	Inuline clearance	90 ml/min[d]	7	3	43
		105 (75–140)	Serum urate	7.5 mg %[d]	7	2	29
6	(121)	45 (29–66)	Blood urate	7.6 mg %[d]	7	1	14
		45 (29–66)	Blood urea nitrogen	20 mg %[d]	7	1	14
		45 (29–66)	Serum creatinine	1.4 mg %[d]	7	2	28
7	(22)	30 (< 100)	Serum urea	40 mg %[d]	283	57	20
		30 (< 100)	Serum urate	7.1 μg %[d §]	283	20	7

§ Authors' value, inconsistent with others (mg %)

Table 13b Asymptomatic kidney injury: Adults. Parameters of the regression analysis depending on the range of accepted Pb-B values

Pb-B range $\mu g\ (100\ ml)^{-1}$	N	Coefficient of determination r^2	Coefficient of regression a
45–105	10	0.03	0.49
30–105	15	0.35	1.78
30–220	16	0.31	1.32

Selected range 30–105 $\mu g\ (100\ ml)^{-1}$
Regression equation $y = 1.78x + 1.15$
Characteristic values of response
50% — 140 $\mu g\ (100\ ml)^{-1}$
10% — 28 $\mu g\ (100\ ml)^{-1}$
5% — 18 $\mu g\ (100\ ml)^{-1}$

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The establishment and interpretation of dose-effect relationships for heavy metal pollutants

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A Technical Report (1980)

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With the support of:
United Nations Environment Programme and
The Rockefeller Foundation

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ABSTRACT

The modelling of dose-effect relationships involves the application of standard techniques of regression analysis. The relationship between the mean effect and dose may be expressed by a linear, quadratic, exponential or some other form of equation. Several examples for exposure of man to cadmium, lead, and mercury are illustrated. The examples include the use of normal errors, sometimes after transformation, and the use of binary models.

A method is suggested for selecting a reference level, or greatest acceptable dose of a toxic substance. This may be, for example, the level at which 10 per cent of a population shows a response in excess of some predetermined magnitude.

Contents

1. Statistical techniques

1.1 Introduction

The exposure of individuals in a population to a toxic substance may result in the occurrence of changes or effects in a portion of this group.

The effect of a particular amount or dose of the toxic substance on a member of the population will not be fixed, rather it will vary from individual to individual. Thus it is necessary to consider the distribution of effects and its relationship with the dose[§]. This is the dose-effect relationship in its widest sense.

In many studies of lead, cadmium and mercury exposure, dose is measured in terms of the concentration of the metal found in the blood or in the urine. This is the case in all the examples studied in this report.

Dose-effect and dose-response relationships can be found for specific populations of human beings, for example, for adult men, children under the age of eight, and so on.

Certain effects are quantitative and are measured on a continuous scale. In many cases, the distribution can be assumed to be normal with standard deviation not dependent on dose; sometimes a transformation from the original scale of measurement is necessary for this assumption to be valid. Examples of effects of lead exposure for which a continuous scale of measurement is suitable include the decrease in concentration of δ-aminolevulinic acid-dehydratase (ALA-D) in blood, the increase in the level of free erythrocyte protoporphyrins (FEP) and the diminished output of haemoglobin.

Other effects are qualitative, taking one of a finite number of possible states. Most commonly, there are only two possible states; for example, life or death, or in the case of mercury exposure, the absence or presence of symptoms of paresthesia. Such effects will be called binary, and subjects exhibiting the less desirable of the two possible states will be said to be harmed.

[§] The definitions of dose, effect and response given below are those recommended by the World Health Organization Secretariat (21).

Dose: the amount or concentration of a given chemical at the site of the effect.

Effect: a biological change caused by (or associated with) an exposure.

Response: the proportion of a population that demonstrates a specific effect.

The only unknown parameter of the distribution of a binary effect will be the probability that a subject is harmed. In general, this will depend on the dose received. The probability of harm at a particular dose can be estimated by the proportion of subjects harmed amongst a sample who received that dose, that is, by the response of the sample. For this reason, a dose-effect relationship for a binary effect is sometimes called a dose-response relationship.

It is always possible to transform a quantitative effect into a binary one. for instance, the level of FEP, measured in μg $(100\,\text{ml})^{-1}$, is a quantitative effect, whereas the possession or otherwise of an FEP in excess of 40 μg $(100\,\text{ml})^{-1}$ is a binary effect. Dose-response relationships can then be fitted to the binary data generated. This approach has been used by Piotrowski and O'Brien (16) and Roels *et al.* (18) amongst others. However, by reducing quantitative effects to binary ones, a great deal of information is lost, and any inference drawn from the dose-response relationship could be more efficiently drawn from the full dose-effect relationship for the original quantitative data. In Section 1.4, the connexion between dose-effect relationships and such artificially generated dose-response relationships will be considered in more detail.

The distribution of effects for a given dose may follow a distribution other than the normal (with constant standard deviation) or the binary. These two cases have been the most widely used, and are sufficient for the analysis of the examples in Section 2 but studies may exist for which Poisson, exponential or multinomial models are more appropriate.

A word of caution must be given on the interpretation of dose-effect relationships. The definition of effect refers to a change "caused by (*or associated with*) an exposure". The study of dose-effect (or dose-response) relationships can never, by itself, be used to distinguish between these two cases.

1.2 The analysis of normally distributed effects

Consider the distribution of some quantitative effect over some specific population of human beings. Suppose that the effect is measured in such a way (possibly involving a transformation from a more natural scale) that the distribution over all members of the

population with dose x is normal. The mean effect is f(x), a function of x, and the standard deviation is σ, a constant in x. The process of determining the most suitable transformation is one of trial and error, and will be made clearer in the examples in Section 2.

The relationship between the effect, y, exhibited by a subject and the dose, x, to which he has been exposed can be expressed as

$$y = f(x) + \epsilon, \tag{1}$$

where f(x) is the mean effect at that dose, and ϵ the residual variation about the mean peculiar to that individual.

The residual variation may be reduced by identifying causes of variation other than dose, such as age or smoking habit. Thus models such as

$$y = f_1(x) + f_2(a) + f_3(s) + \delta \tag{2}$$

should be considered, where a is age and s is smoking habit. In some cases dependence on other variables may be important. Most papers do not include the data from which such dependence could be evaluated.

Plots of y values against x for a sample of subjects representative of the population under study can be used to suggest the form of f(x). Such plots are called scatter diagrams. The easiest case occurs when f(x) is linear;

$$f(x) = a + bx \tag{3}$$

The parameters a and b and standard deviation, σ, can be estimated using the method of least squares.

Unfortunately, many of the dose-effect relationships encountered in the study of heavy metal pollutants are not linear. Linearizing transformations can sometimes be applied to y, but these often destroy the assumption of a constant variance. The general shape is sigmoid, as shown in Figure 1.

If the range of observed doses falls within AC, or if the curvature is small, then linear methods will be adequate. If the range falls within OB, then relationships of the form

$$f(x) = a + b_1 x + b_2 x^2 \tag{4}$$

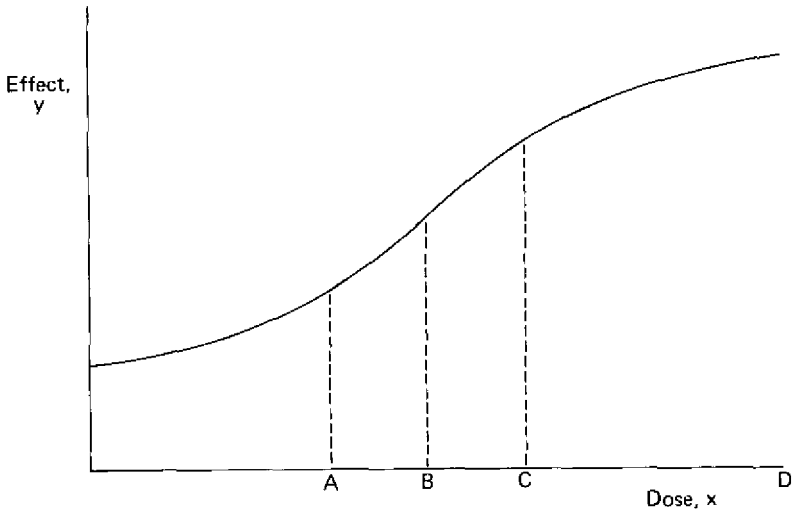

Figure 1 A typical dose-effect relationship

or

$$f(x) = a + be^{cx} \quad (5)$$

might be appropriate. Polynomial regression would be used to fit equation (4) and non-linear least-squares to fit equation (5). Similar curves can be fitted if the range of observed doses falls within BD.

Occasionally the data might display the full sigmoid pattern of Figure 1, because the range of observed doses covers the whole of OD. If a model for this full range is required then one of the relationships

$$f(x) = a + b_1x + b_2x^2 + b_3x^3 \quad (6)$$

or

$$f(x) = a + b/(1 + e^{cx}) \quad (7)$$

might be fitted. Polynomial regression would be used in the case of equation (6) and non-linear least-squares for equation (7).

All these choices are arbitrary, but are chosen in the absence of theoretical models for dose-effect relationships. Because of this

arbitrary nature, extrapolation of the relationship outside the range of observed doses should be avoided.

Full accounts of regression analysis, of which these procedures are examples, are given by Williams (20) and Draper and Smith (8).

1.3 The analysis of binary effects

Consider some binary effect. Let $p(x)$ be the probability that a subject with dose x is harmed; values of $p(x)$ against x will form the dose-response curve. Typically $p(x)$ will be a sigmoid curve, as shown in Figure 2. As x becomes large, harm becomes almost certain, and so $p(x)$ approaches 1. The background frequency of harm, $p(0)$, is not necessarily zero and may have to be estimated from the data. The "corrected dose-response curve" is

$$p^*(x) = \frac{p(x) - p(0)}{1 - p(0)}, \tag{8}$$

and is shown in Figure 3. This does satisfy $p^*(0) = 0$.

The shape of $p^*(x)$ is often similar to one of the family of normal distribution curves

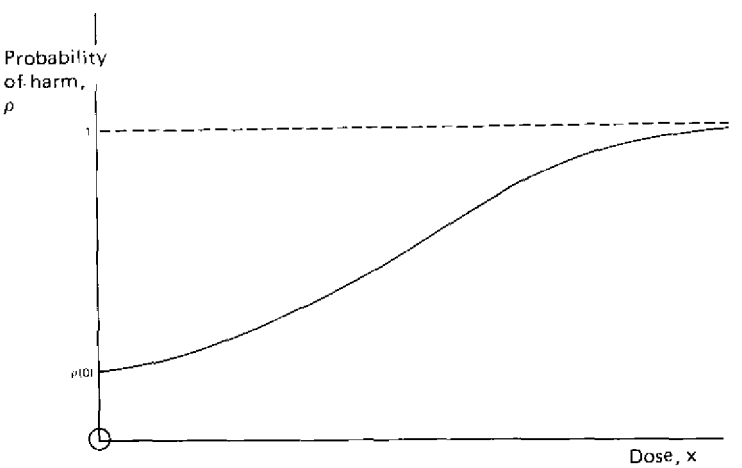

Figure 2 A typical dose-response curve

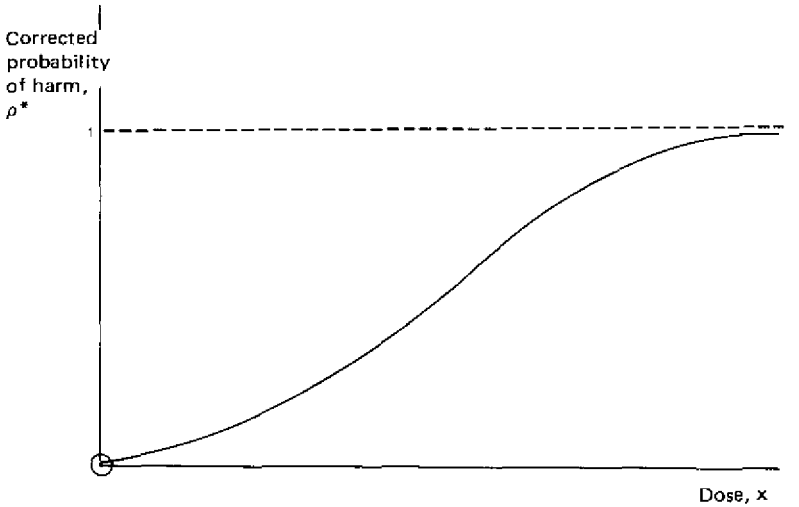

Figure 3 The corrected dose-response curve

$$p^*(x) = \Phi(a + bx - 5), \tag{9}$$

where

$$\Phi(x) = \frac{1}{\sqrt{(2\pi)}} \int_{-\infty}^{x} e^{-t^2/2}\,dt$$

denotes the standard normal distribution function. The parameters a and b are unknown, and the 5 is included to maintain consistency with the traditional notation of probit analysis.

The probit transformation of $p^*(x)$ is defined by

$$P^*(x) = \Phi^{-1}\{p^*(x)\} + 5 \tag{10}$$

where Φ^{-1} denotes the inverse of the function Φ, so that equation (10) is equivalent to $\Phi\{P^*(x) - 5\} = p^*(x)$. If $p^*(x)$ is indeed close in shape to a curve of the family given by equation (9), then, approximately, $P^*(x)$ will be of the form

$$P^*(x) = a + bx \tag{11}$$

In the first instance, one should assume only a model of the form

$$P^*(x) = g(x) \qquad (12)$$

and use graphical techniques in order to check the linearity of g(x).

Before a model of the form given in equations (11) or (12) can be fitted, an estimate $\hat{p}(0)$ of p(0) is required. There may be a sizeable group of subjects amongst the sample examined with zero dose. Then $\hat{p}(0)$ is just the proportion of this group that is harmed. More usually there will be a group of subjects with low doses in the interval $[0, x_0)$, (this notation means that the dose is greater than or equal to zero, but strictly less than x_0) whose dose can be considered negligible or normal. The proportion harmed amonst this group can then be used for $\hat{p}(0)$. The subjects used in estimating p(0) are not used again in the analysis.

To check the linearity of g(x), and if it is confirmed, to begin the estimation of a and b, further grouping is employed. The subjects with non-negligible doses are divided into groups corresponding to the dose intervals $[x_0, x_1), \ldots, [x_{k-1}, x_k)$. All subjects in the ith group are treated as if their dose was $m_i = \frac{1}{2}(x_{i-1} + x_i)$, the mid-point of dose interval $[x_{i-1}, x_i)$. The value $p(m_i)$ is estimated by $\hat{p}(m_i)$, the proportion of subjects who are harmed amongst those in the ith group, and $\hat{p}^*(m_i)$ is estimated as

$$\hat{p}^*(m_i) = \frac{\hat{p}(m_i) - \hat{p}(0)}{1 - \hat{p}(0)}, \qquad (i = 1, \ldots, k). \qquad (13)$$

Finally $P^*(m_i)$ is estimated by the empirical probit,

$$\hat{P}^*(m_i) = \Phi^{-1}\{\hat{p}^*(m_i)\} + 5 \qquad (14)$$

found from tables such as those given by Finney (10). Groups in which all subjects are harmed, or in which no subjects are harmed, give infinite empirical probits and so are ignored at this stage.

The finite $\hat{P}^*(m_i)$ are plotted against the m_i. The linearity of this scatter diagram is assessed by eye. If linearity is accepted, then the plot can be used to give first estimates of a and b. These estimates and that of p(0) can be improved iteratively using the method of probit analysis, which is most conveniently applied using computer packages. Curved relationships must be considered if the scatter diagram indicates that a linear model is not appropriate. Furthermore,

models involving other variables, for example

$$P^*(x, a, s) = g_1(x) + g_2(a) + g_3(s) \tag{15}$$

where a is age and s represents smoking habit, should be considered.

A detailed account of probit analysis is given by Finney (10), and the related technique of logit analysis is described by Ashton (12) and by Cox (7).

1.4. Reducing dose-effect relationships to dose-response relationships

Suppose that the level, y, of some quantitative effect displayed by a subject exposed to dose x can be expressed as

$$y = f(x) + \epsilon. \tag{16}$$

As in Section 1.2, the residual ϵ will be taken to be normally distributed with mean zero and standard deviation σ.

This quantitative effect can be reduced to a binary effect. Choose some value y_0, and consider a subject with a quantitative effect y in excess of y_0 to have been harmed. The true relation between the probability of harm, p(x), and the dose x will be

$$\begin{aligned} p(x) &= P(y \geqslant y_0 \text{ when the dose is } x) \\ &= 1 - \Phi\left\{\frac{y_0 - f(x)}{\sigma}\right\} \end{aligned}$$

as y is normally distributed with mean f(x) and standard deviation σ when the dose is x. Hence

$$p(x) = \Phi\left\{\frac{f(x) - y_0}{\sigma}\right\}$$

and the probit of p is

$$P(x) = \frac{f(x) - y_0}{\sigma} + 5 \tag{17}$$

The most efficient method of estimating the dose-response curve is to use the full quantitative data to estimate f(x) and σ as described

in Section 1.2, and to derive P(x) and p(x) from these estimates using equation (13). If the application of probit analysis to the derived binary data leads to a simpler model, then this only reflects the loss of efficiency involved in reducing the data.

In the reports of Piotrowski and O'Brien (16) and Roels *et al.* (18), y_0 itself is estimated from the data. The value y_0 is supposed to represent the quantitative effect exceeded by only $2\frac{1}{2}$ per cent of subjects with dose x_0. This shifts the problem from one of choosing y_0, to one of choosing x_0. Piotrowski & O'Brien choose x_0 to be a low dose, one which from prior considerations should produce little or no effect. Such a criterion in the author's opinion is unsatisfactory as the choice is made *before* the dose-response relationship is fitted to the reduced data. A reasonable choice might be to make x_0 the normal dose level found in subjects with no unusual exposure to the pollutant.

According to the model equation (16)

$$y_0 = f(x_0) + 1.96\sigma$$

(although the authors cited above approximate this by $y_0 = f(x_0) + 2\sigma$). For such a choice, expression (17) shows that the probit is given by

$$P(x) = \frac{f(x) - f(x_0)}{\sigma} + 3.04.$$

Notice that $P(x_0) = 3.04$.

In conclusion it should be stressed that dose-response relationships are useful only when binary data is the best that is available. When quantitative data can be observed, then a dose-effect relationship, based on the normal assumption or on some other model, should be fitted. Probit relationships such as equation (17) can then be derived, but these in the author's opinion will not be of interest.

2. Examples of data analysis

2.1 Introduction

To illustrate the methods of data analysis, examples presented here are based on data from four publications. Smith (19) discusses the effects of cadmium exposure, while Roels *et al.* (18) and Pueschel *et al.* (17) discuss lead exposure. All these papers provide results

suitable for the fitting of dose-effect relationships via the normal model, although this was not in all cases the primary intention of their authors. Bakir *et al.* (3) report on mercury exposure, and their results have been used to illustrate the fitting of dose-response relationships.

In some of the papers, original values were not quoted but had to be obtained from a printed scatter diagram. This was felt to be adequate for an illustrative analysis. The computing was performed on the CDC6600 at the University of London Computer Centre, using the biomedical computer programs BMD (2).

These examples by no means illustrate all the possible models and analyses that might be employed in the fitting of dose-effect relationships. Much statistical theory is available for this purpose, and it is desirable that environmental scientists receive statistical advice on both the planning and the interpretation of their investigations.

2.2 The effect of cadmium on the lungs

The data of Table 1, obtained from Smith (19, Figure 1) for 29 workers in a cadmium production facility, give the concentration of cadmium found in the urine (Cd-U) of each man, together with his respiratory forced vital capacity (FVC) expressed as a percentage of that predicted for a normal subject with the same height and age.

Figure 4 is a scatter diagram of FVC against Cd-U, showing a distinct trend for FVC to decrease with Cd-U. Furthermore, bearing in mind the higher density of points at lower Cd-U values, the standard deviation about the line appears to be roughly constant.

These preliminary considerations motivate the application of the theory of Section 1.2 taking y to be FVC, x to be Cd-U, and f(x) to be linear so that

$$y = a + bx + \epsilon, \tag{18}$$

where ϵ is normal with mean zero and constant standard deviation σ.

Using the polynomial regression program BMD05R the straight line model

$$y = 103.15 - 0.28x + \epsilon, \tag{19}$$

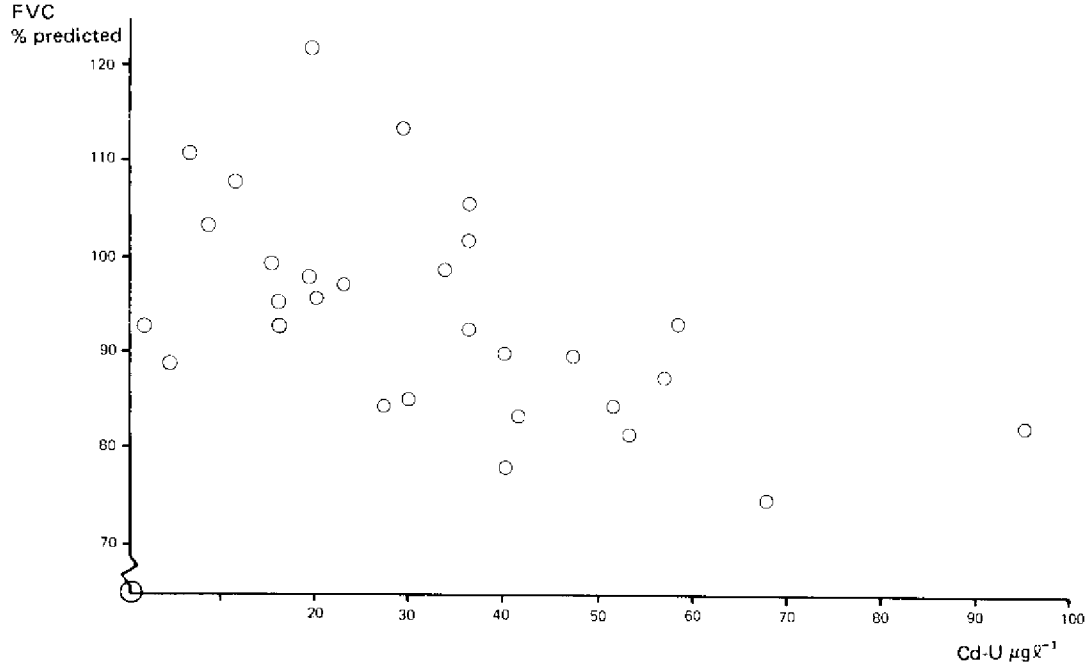

Figure 4 Scatter diagram of FVC against Cd-U

Table 1 Cd-U and FVC for 29 cadmium workers

x, Cd-U $\mu g\,\ell^{-1}$	y, FVC (% of predicted)	x, Cd-U $\mu g\,\ell^{-1}$	y, FVC (% of predicted)
1.3	92.6	33.3	98.6
3.8	88.6	35.9	92.6
5.8	110.5	35.9	101.9
7.7	103.2	35.9	105.9
10.9	107.9	39.7	78.0
14.7	99.2	39.7	90.0
15.4	92.6	41.0	83.3
15.4	95.2	46.8	89.9
18.6	97.9	51.3	84.6
18.6	121.8	52.6	81.9
19.9	95.9	56.4	87.9
22.4	97.2	57.7	93.2
26.9	84.6	67.3	74.6
28.8	113.9	94.9	82.6
29.5	85.3		

with σ estimated by S = 9.41, was fitted. This line is compared with the scatter diagram in Figure 5, and is the same as that found by Smith (19).

The slope, −0.28, is significantly non-zero, ($t = -3.35$, d.f. = 27, $p < 0.01$). The intercept, 103.2, represents the estimated FVC as a percentage of normal exhibited by subjects with a zero dose. This might be expected to be 100, and in fact the estimate is not significantly different from 100, ($t = 0.99$, d.f. = 27, n.s.).

The line could be refitted with the intercept a fixed at 100. However, it is not necessarily true that subjects with a zero dose of cadmium will have a normal FVC. Imbus *et al.* (12) found a mean Cd-U of 1.59 $\mu g\,\ell^{-1}$ in a sample of 100 men with no known unusual exposure to cadmium. Thus the subjects used to establish 'normal FVC' might not have had zero doses of cadmium themselves and to constrain a to equal 100 would be unrealistic.

Having fitted a linear model, various checks on the validity of the assumptions underlying it can be made. These involve the residuals, that is, the differences between observed and predicted FVC values. The residuals are printed in the output of the program BMD05R.

Various residual plots are discussed by Draper and Smith (8,

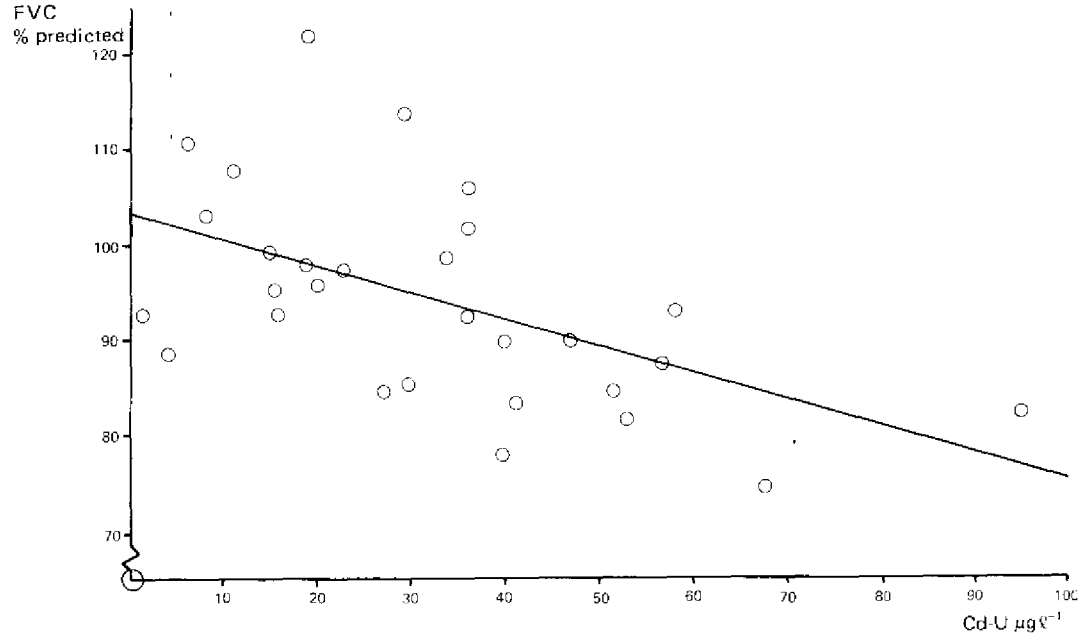

Figure 5 The fitted dose-effect relationship for FVC against Cd-U

Chapter 3), including the plot of residuals against x values. In Figure 6, a variation of this plot is shown in which residuals are plotted against the ranks of the x values, (the smallest dose, $x = 1.3 \mu g \ell^{-1}$, has rank 1, the next smallest, $x = 3.8 \mu g \ell^{-1}$, has rank 2 and so on). This overcomes problems caused by the varying density of points as x increases, and makes examination of the assumption of a constant standard deviation easier.

The points in Figure 6 appear to form a horizontal band of uniform width. The fact that the band is roughly horizontal confirms the adequacy of the linear model, any curvature would indicate that a curve should have been fitted. The uniform width confirms the constancy of standard deviation, the most usual alternatives being a widening or narrowing band of points.

A more technical check of the constancy of the standard deviation can be conducted using Bartlett's test, (14, Section 16). The dose scale is divided into a number of intervals with a roughly equal number of subjects in each. The standard deviations of the residuals corresponding to each group are then calculated and compared, either informally by inspection, or formally by the calculation of Bartlett's M-statistic.

For the present study, three dose intervals, (0, 20], (20, 40], (40, 100] will suffice. These intervals contain 11, 10 and 8 points respectively, and the residuals corresponding to them have standard deviations of 10.25, 10.68 and 6.17 respectively. This is not a very wide spread of values, and indeed $M = 2.28$ which is not even close to significance at the 5 per cent level.

In Figure 7 the residuals are plotted against their own ranks, on normal probability plotting paper. This allows an assessment of the assumption of normality to be made; the degree of linearity in the plot reflecting the degree to which the normal assumption is valid. In this case the plot is satisfactory.

In both Figures 6 and 7 the two largest residuals, 23.9 and 18.8, stand out from the overall pattern. If original records were available, such outliers would be carefully checked. Techniques for excluding extreme observations from the analysis do exist (4) but their use is controversial and we shall not apply them here.

The original selection of the model and its assessment through

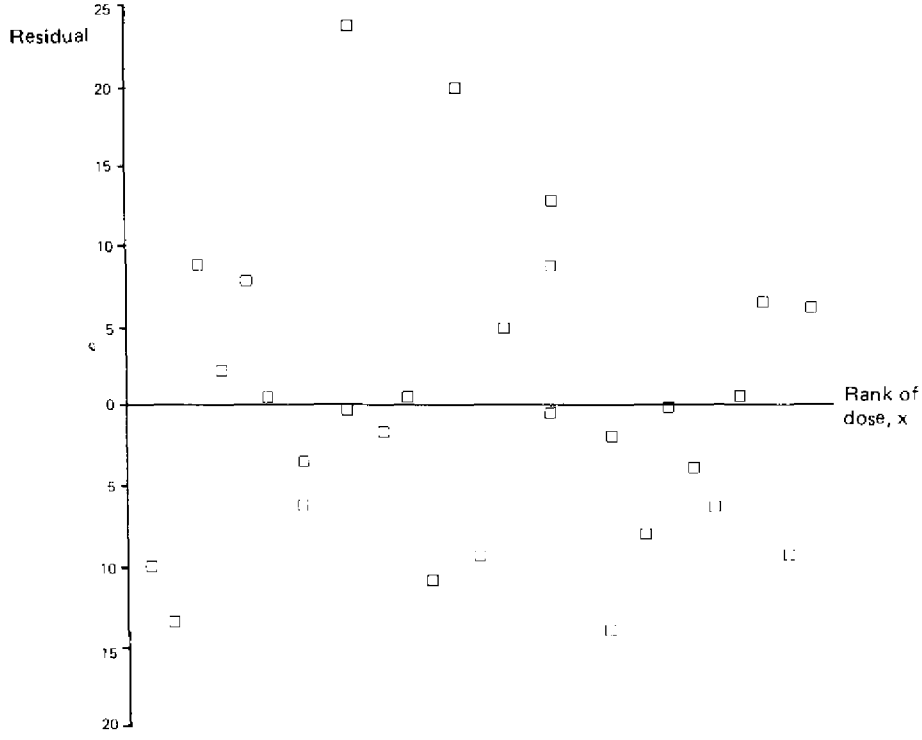

Figure 6 A plot of the residuals against the rank of the doses

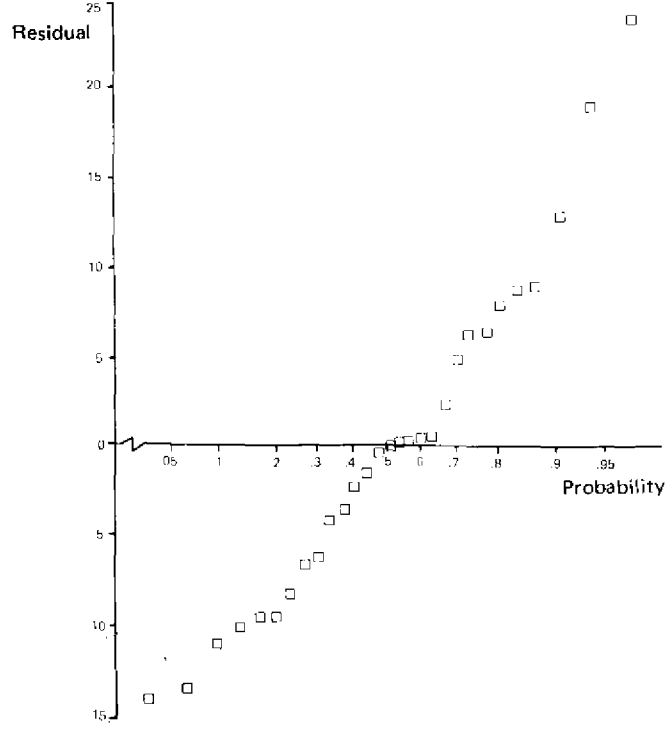

Figure 7 A plot of the residuals on normal probability plotting paper

residual plots are both highly subjective. The assumptions of the model can be assessed from the original scatter diagram of y on x, and with practice an adequate model will be chosen first time, although residual plots should still be used to provide a more reliable check.

2.3 Haemoglobin concentration in children with an increased lead burden

Pueschel *et al.* (17) report a study involving 38 children, sampled to represent children with an increased lead burden from an impoverished area of Boston. The blood-lead (Pb-B in $\mu g\, g^{-1}$) and haemoglobin concentration (Hb in g $(100\,ml)^{-1}$) for each child are listed in Table 2, and a scatter diagram is plotted for these points in Figure 8.

The scatter diagram suggests a decreasing, convex relationship, about which there is a constant scatter. Two points, or possibly three, are outliers. If original records were available they would be consulted to check whether these were errors, or whether there was anything unusual about the observations. A strong argument could be made for neglecting these points on statistical evidence alone, but in the present analysis they have been retained.

The assumption of constant standard deviation will be adequate without transformation, and so models of the form

$$y = f(x) + \epsilon$$

will be fitted, where y is Hb, x is Pb-B, and the residual ϵ is normal with mean zero and standard deviation σ.

Three models have been fitted for comparison. The first two are convex, as suggested by the data: the quadratic curve

$$f(x) = a + b_1 x + b_2 x^2 \qquad (20)$$

and the exponential model

$$f(x) = a + be^{cx} \qquad (21)$$

As the haemoglobin concentration is decreasing with increasing dose, the shape of the curve over the full range of doses might be

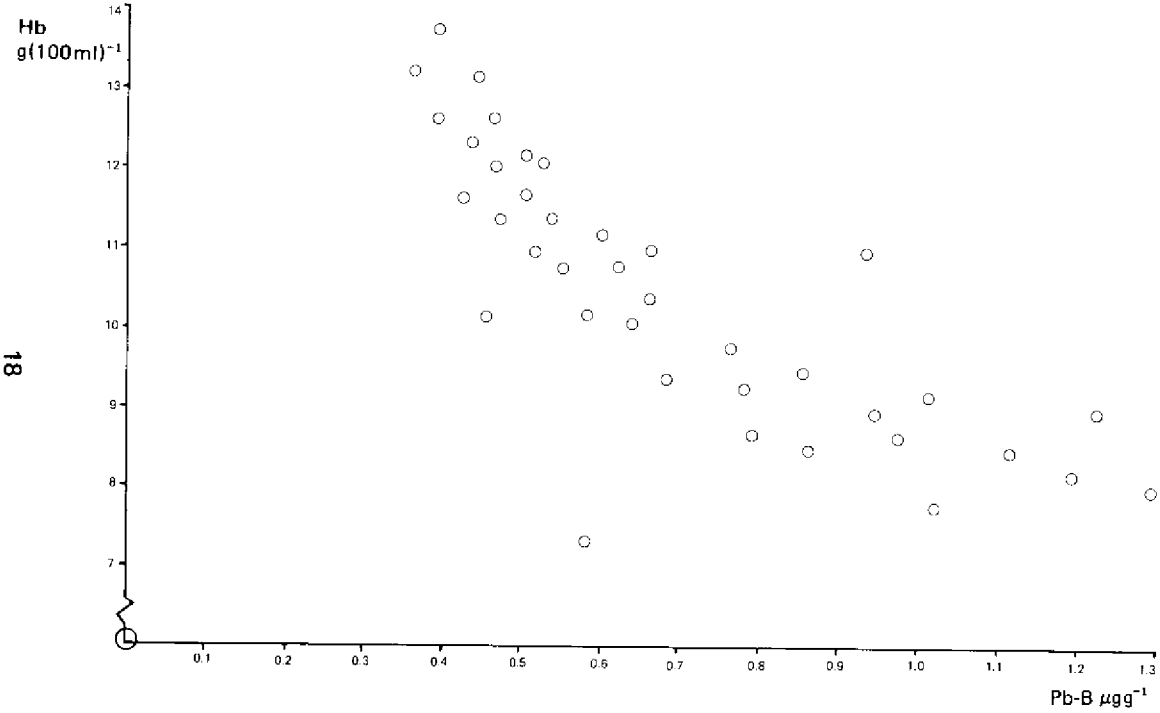

Figure 8 Scatter diagram of Hb against Pb-B

Table 2 Pb-B and Hb for 38 children with increased lead burden

x, Pb-B $\mu g\,g^{-1}$	y, Hb $g(100\,ml)^{-1}$	x, Pb-B $\mu g\,g^{-1}$	y, Hb $g(100\,ml)^{-1}$
0.36	13.2	0.62	10.7
0.39	12.6	0.64	10.0
0.39	13.7	0.66	10.9
0.42	11.6	0.66	10.3
0.43	12.3	0.68	9.3
0.44	13.1	0.76	9.7
0.45	10.1	0.78	9.2
0.46	12.0	0.79	8.6
0.46	12.6	0.85	9.4
0.47	11.3	0.86	8.4
0.50	11.6	0.93	10.9
0.50	12.1	0.94	8.9
0.51	10.9	0.97	8.6
0.52	12.0	1.01	9.1
0.53	11.3	1.02	7.7
0.55	10.7	1.11	8.4
0.58	10.1	1.19	8.1
0.58	7.3	1.22	8.9
0.60	11.1	1.29	7.9

expected to be reverse sigmoid, that is an inverted version of Figure 1, Section 1.2. In an attempt to accommodate such behaviour a cubic model

$$f(x) = a + b_1x + b_2x^2 + b_3x^3 \qquad (22)$$

was also fitted.

Model equations (20) and (22) were fitted using the polynomial regression program BMD05R and equation (21) using the asymptotic regression program BMD06R. The estimated curves were

$$f(x) = 18.15 - 17.27x + 7.64x^2, \qquad (S = 0.920) \qquad (23)$$

$$f(x) = 8.194 + 19.16e^{-3.63x}, \qquad (S = 0.896), \qquad (24)$$

$$f(x) = 24.03 - 42.69x + 41.41x^2 - 13.93x^3, \qquad (S = 0.905) \qquad (25)$$

They are illustrated in Figure 9.

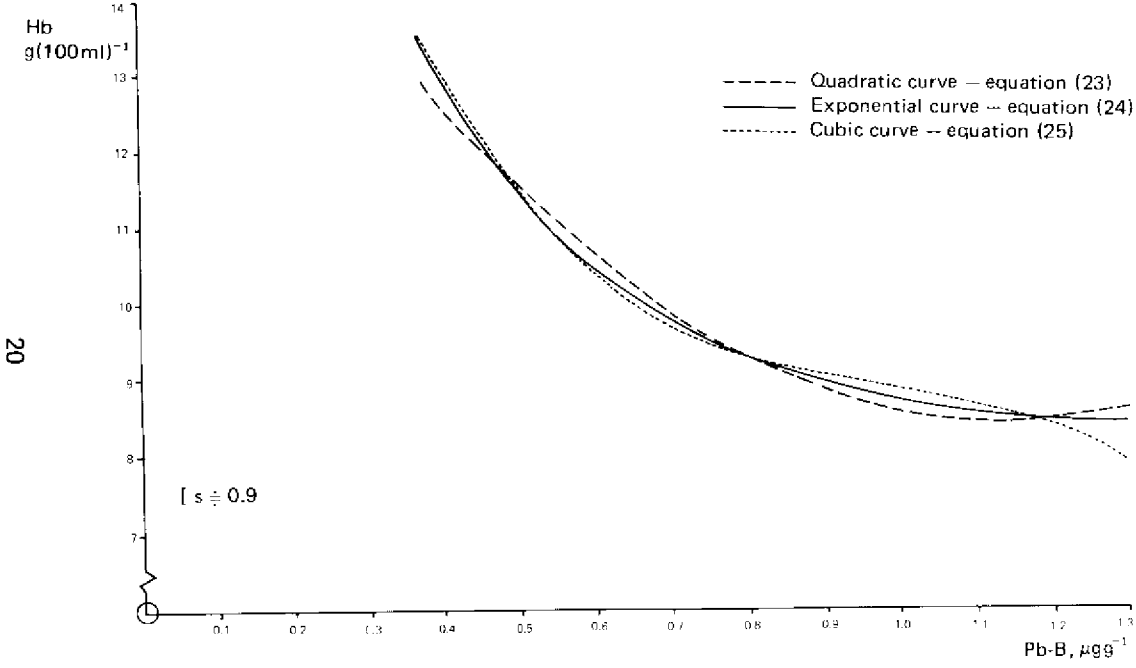

Figure 9 Fitted models for the data of Pueschel *et al.* (17).

Within the range of observed doses all three curves are very close, particularly when considered relative to the estimated standard deviation which in all three cases is approximately 0.9. Outside this range, particularly at the upper end of the Pb-B values, the curves diverge rapidly. This serves as a clear warning against extrapolation outside the range of observed doses.

In the quadratic model, the estimate of the coefficient of x^2, $\hat{b}_2 = 7.64$, is significantly non-zero ($t = 3.17$, d.f. $= 35$, $p < 0.001$). However, the curve does have the unrealistic property of increasing for doses greater than $1.13\,\mu g\,g^{-1}$.

The estimate $\hat{b}_3 = -13.93$ in the cubic model is not significantly different from zero at the 5 per cent level ($t = -1.48$, d.f. $= 34$, n.s.), and the shape is not the reverse sigmoid which motivated the inclusion of the cubic term.

The most satisfactory model is provided by the exponential curve equation (24), and this is also the best fit in the sense of having the smallest estimated standard deviation, S. Nevertheless, the behaviour of this curve for $x < 0.4$ is unlikely to resemble the true dose-effect curve.

Residual plots along the lines of Figures 6 and 7 have been plotted for the model equation (24). Apart from the effect of the three outliers they are satisfactory, and have not been included here.

2.4 Free erythrocyte porphyrin in men and women moderately exposed to lead

This example is based on data from Roels *et al.* (18). Two groups of men and women were studied: 40 men and 26 women were workers moderately exposed to lead and 24 men and 23 women were students and laboratory staff serving as controls.

The concentration of lead in the blood (Pb-B in $\mu g\ (100\,ml)^{-1}$) and the free erythrocyte porphyrins (FEP in $\mu g\ (100\,ml)^{-1}$ erythrocytes) were determined for each subject. The results for men given in Table 3 and for women given in Table 4 were found from Figure 2 of Roels *et al.* (18). Figure 10 shows the scatter of points for the men.

Figure 10 demonstrates an increasing relationship between FEP and Pb-B. Both workers and controls could be accommodated by a

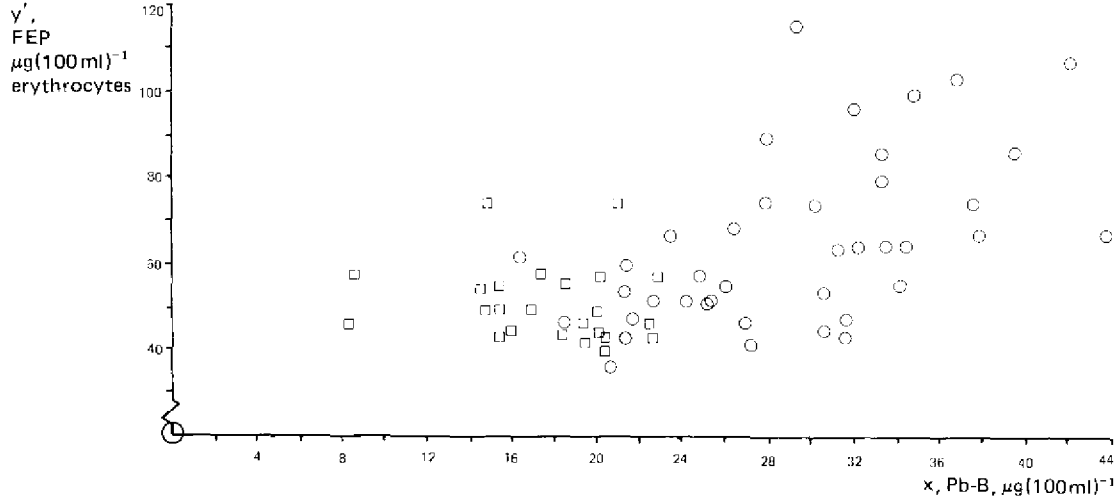

Figure 10 Scatter diagram of FEP against Pb-B for male subjects; □ controls, ○ workers

Table 3 Pb-B and FEP for male subjects

x, Pb-B $\mu g\,(100\,ml)^{-1}$	y', FEP $\mu g\,(100\,ml)^{-1}$	x, Pb-B $\mu g\,(100\,ml)^{-1}$	y', FEP $\mu g\,(100\,ml)^{-1}$	x, Pb-B $\mu g\,(100\,ml)^{-1}$	y', FEP $\mu g\,(100\,ml)^{-1}$
			Controls		
8.1	45.6	15.9	43.8	20.0	48.9
8.4	56.8	16.9	48.9	20.0	56.8
14.4	53.0	17.2	56.8	20.3	39.3
14.7	48.9	18.4	43.8	20.3	42.1
14.7	73.7	18.4	54.6	20.9	73.7
15.3	48.9	19.4	45.6	22.5	42.1
15.3	54.6	19.4	40.9	22.5	45.6
15.3	42.1	20.0	43.8	22.8	56.8
			Workers		
16.3	60.9	26.3	68.0	33.1	79.0
18.4	45.6	26.9	45.6	33.1	85.6
20.6	35.2	27.2	40.9	33.4	63.4
21.3	42.1	27.8	73.7	34.1	54.6
21.3	53.0	27.8	88.2	34.4	63.4
21.3	59.1	29.1	114.4	34.7	98.5
21.6	47.0	30.0	73.7	36.6	102.5
22.5	50.9	30.6	43.8	37.5	73.7
23.4	66.0	30.6	53.0	37.8	66.0
24.1	50.9	31.3	63.4	39.4	85.6
24.7	56.8	31.6	42.1	41.9	106.7
25.3	50.9	31.6	47.0	43.8	66.0
25.3	50.9	31.9	95.6		
25.9	54.6	32.2	63.4		

Table 4 Pb-B and FEP for female subjects

x, Pb-B $\mu g\,(100\,ml)^{-1}$	y', FEP $\mu g\,(100\,ml)^{-1}$	x, Pb-B $\mu g\,(100\,ml)^{-1}$	y', FEP $\mu g\,(100\,ml)^{-1}$	x, Pb-B $\mu g\,(100\,ml)^{-1}$	y', FEP $\mu g\,(100\,ml)^{-1}$
			Controls		
9.4	68.3	11.6	37.8	12.8	56.8
10.6	63.4	11.6	54.7	13.4	58.9
10.6	63.4	11.6	76.3	13.4	54.7
11.3	43.8	11.6	70.9	14.4	49.0
11.3	50.8	12.5	50.8	15.0	63.4
11.3	58.9	12.5	63.4	15.6	73.6
11.3	70.8	12.5	73.6	18.4	63.4
11.3	85.3	12.8	56.8		
			Workers		
18.8	52.7	24.1	52.7	33.1	106.5
19.1	42.2	25.3	68.3	33.1	258.8
19.4	50.8	25.9	40.7	36.2	110.5
19.7	50.8	27.5	58.9	38.4	91.8
20.6	148.6	29.4	76.3	41.2	223.2
23.1	143.2	30.0	172.3	41.9	223.2
23.1	45.5	32.2	76.3	43.4	258.8
23.8	148.6	32.2	199.7	48.1	403.4
23.8	63.4	32.2	215.1		

single convex dose-effect curve, but the standard deviation about such a curve is likely to be increasing with dose. To overcome this a transformed effect will be used. This is y, the natural logarithm of the FEP. Data from workers and controls will be pooled, and the adequacy of this assumption checked using the residuals at the end of the analysis.

The considerations above also apply to the data on women given in Table 4, and Figure 11 is a scatter diagram of y against dose for both sets. The overall impression is of an increasing convex dose-effect curve, common to both men and women, and satisfying the constant standard deviation assumption. However, at least one group of points, those in the region labelled B on Figure 11, do not conform to the general pattern.

The seven points in region B all relate to women. There are too many of them to neglect, or to treat as outliers. The four points in region C are also suspicious, the dose-effect curve might rise steeply for x greater than 36 and pass close to these points, on the other hand they might be behaving in the same way as those in region B. To these atypical points might be added some or all those in and around region A.

Roels *et al.* (18) fitted separate models to the male and female data, and concluded that, at equal doses, women had significantly higher FEP values. From Figure 11 a more reasonable interpretation might be that men and the majority of women follow the same dose-effect relationship, but that some subgroup of women have higher FEP values. Original records, and possibly new observations, should be studied in an attempt to identify this subgroup.

One possibility is that the atypical points are spurious, being the results of a different investigator using different equipment for samples from some of the women. If this involved a clear error, such points might be neglected in the analysis. A more interesting possibility is that there is something special about the atypical points, perhaps relating to menstruation which Roels *et al.* (18) mention as a factor in this relationship. Any hypothesis suggested by the data in this way must be verified using a second, independent sample.

For the men's data the quadratic model

$$y = 3.9894 - 0.0169x + 0.0007x^2 + \epsilon, \quad (S = 0.2248) \quad (26)$$

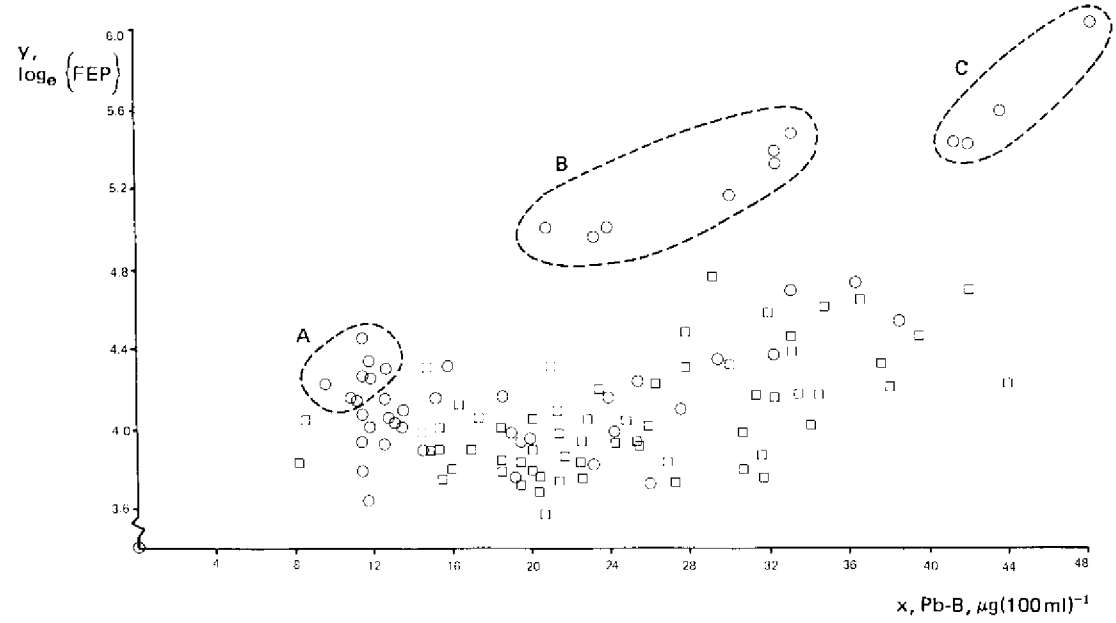

Figure 11 Scatter diagram of y on dose for male and female subjects; □ male subjects, ○ female subjects

was fitted, using BMD05R. The coefficient of x^2 is not significantly different from zero at the 5 per cent level, although it is at the 10 per cent level ($t = 1.84$ d.f. $= 61$, $p < 0.1$). The quadratic term has been retained in the model because of the curvature shown over this range of doses in the women's data, and in other studies (for example, Piomelli (15)), and because of the expected overall sigmoid shape discussed in Section 1.2. The quadratic model is close to, and a slightly better fit than the best exponential model.

The residuals are plotted against the ranks of the doses in Figure 12. No curvature is exhibited indicating that the model defined by equation (26) has the right shape. The scatter does appear to grow wider as dose increases, and the standard deviation of the residuals relating to workers is larger than that of those relating to controls. This is not significant at the 5 per cent level ($F = 2.04$, d.f. $= 37,21$, n.s.; the test is approximate as the residuals are not independent). This trend in the standard deviation could be reduced by a further transformation of the effect, or avoided by fitting separate models to controls and workers. Alternatively, explanatory variables might be sought and a model such as equation 2 of Section 1 fitted. As it is the workers who exhibit the wider scatter, length of exposure to lead might be tried in the model.

A quadratic model can be fitted to the women's data; this is

$$y = 4.2261 - 0.0284x + 0.0014x^2 + \epsilon, \qquad (S = 0.3633). \quad (27)$$

The standard deviation is significantly larger than that for the men's model. ($F = 2.61$, d.f. $= 46,61$, $p < 0.01$). The residuals are plotted against their own ranks on normal probability paper in Figure 13. The lack of linearity on the upper part of this plot is caused by the seven atypical points in region B of Figure 11. A chi-squared test applied to the residuals found them significantly non-normal at the 5 per cent level ($\chi^2 = 9.86$, d.f. $= 4$, $p < 0.05$; this test, and the F test above, are approximate as the residuals are not independent).

It would be unwise to use the model defined by equation (27). The first approach to a better model would be an attempt to identify a subgroup of women with high FEP values as discussed earlier. If quadratic models with comparable standard deviations could be found to fit both men's and women's data, tests for equality of the various parameters

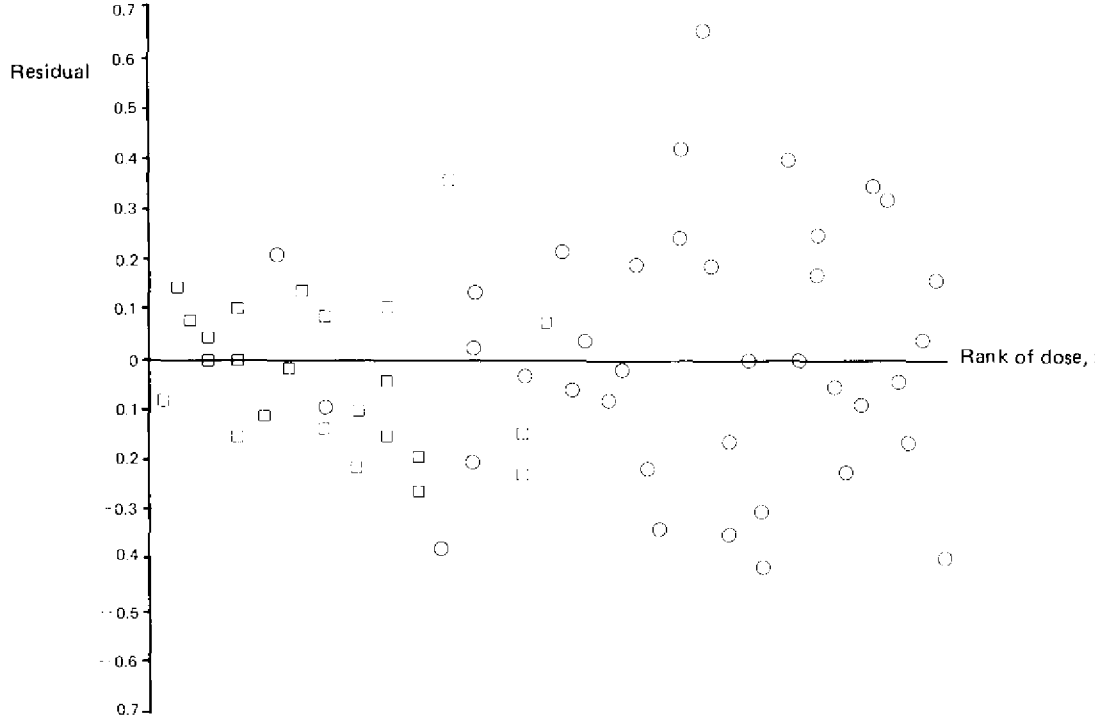

Figure 12 Residual plot for the men's data; □ controls, ○ workers

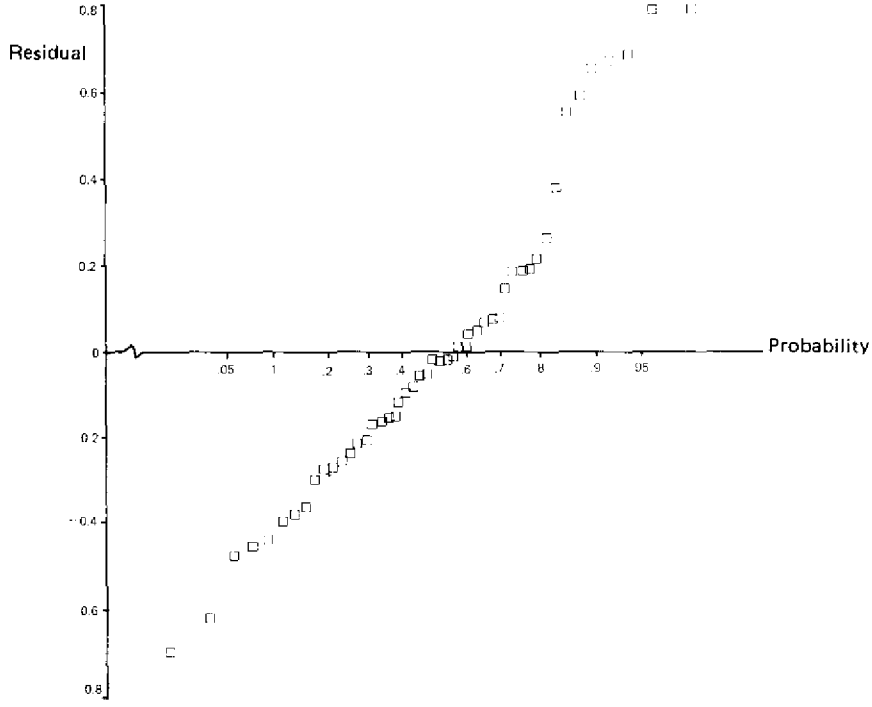

Figure 13 A residual plot on normal probability paper for the women's data

could be conducted. This would establish whether or not separate models were necessary.

2.5 Methylmercury poisoning in Iraq

In 1973, following a serious outbreak of mercury poisoning in Iraq, a report (3) on the effects of the poisoning was prepared by a joint Iraqi – American team. One of the effects studied was paresthesia, this being a binary effect as subjects were classified as either reporting symptoms of paresthesia or not.

Table 5 presents a summary of the data on paresthesia. The 122 subjects are classified into seven groups according to dose, measured as the concentration of mercury in the blood (Hg-B) in $ng\,ml^{-1}$. The subjects with doses less than $100\,ng\,ml^{-1}$ seem to be treated as controls by Bakir *et al.* (3), the two subjects in the group reporting symptoms being regarded as either victims of a background frequency of the condition or as falsely claiming symptoms which were widely known at the time. In the present analysis the subjects with doses in the interval [0, 100] are treated as controls and the background frequency p(0) is estimated first as 9 per cent, the percentage found in the control group.

Corrected percentages have been obtained from

$$\hat{p}^* = \frac{\hat{p} - 9}{100 - 9}$$

in accordance with the presentation in Section 1.3. The empirical probit, $\hat{P}^*$ satisfies

$$\hat{P}^* = \Phi^{-1}(\hat{p}^*/100) + 5$$

and was found directly from Table 1 of Finney (10).

Figure 14 shows a plot of $\hat{P}^*$ against $x(= \log_{10}$ of the midpoint of the dose interval). Only the four finite values of $\hat{P}^*$ are plotted. The transformation to log dose can hardly be justified in terms of a plot of only four points, but it is made on the basis of its successful application to other, similar problems. With 101 subjects not in the control group a larger number of points could have been produced by use of a finer grouping, say 9 or 10 dose intervals with about

Table 5 A summary of the paresthesia data

Dose interval ng m^{-1}	Midpoint of interval, m	$\log_{10}$ m, x	No. of subjects, n	No. with paresthesia, r	Percentage 100r/n, $\hat{p}$	Corrected percentage, $\hat{p}^*$	Empirical probit, $\hat{P}^*$
(4000, 5000]	4500	3.65	4	4	100	100	∞
(3000, 4000]	3500	3.54	17	14	82	80	5.84
(2000, 3000]	2500	3.40	25	20	80[1]	78	5.77
(1000, 2000]	1500	3.18	17	10	60	56	5.13
(500, 1000]	750	2.88	19	8	42	36	4.64
(100, 500]	300	2.48	19	1	5	−4	$-\infty$
Controls	(50)	(1.70)	21	2	9	–	–

[1] Bakir *et al.* (3) quote 79 per cent for this group, but 20 out of 25, corresponds to exactly 80 per cent

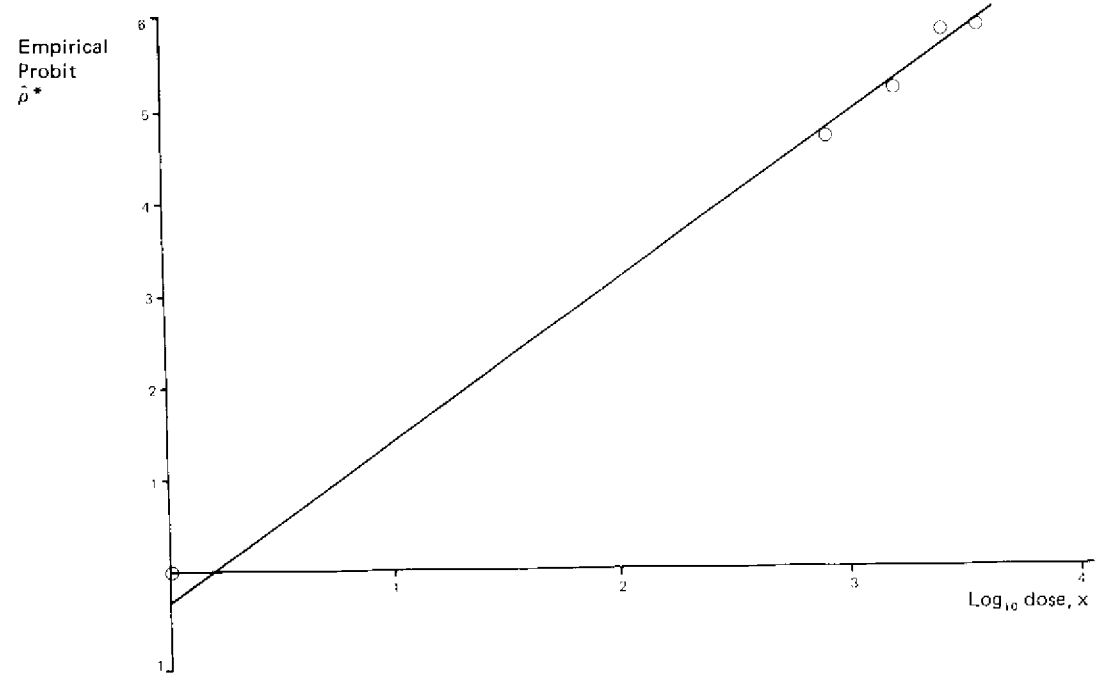

Figure 14 The probit line fitted by eye

10 subjects in each. The linear probit model

$$P^*(x) = a + bx$$

was fitted taking x to be $\log_{10}$ dose; certainly Figure 14 does not suggest that a more complicated model is necessary.

The probit line shown was fitted by eye, and gives the estimates $\hat{a} = -0.35$ and $\hat{b} = 1.75$. These, together with $\hat{p}(0) = 9$ could be used as starting values in an iterative fit. The program BMD03S provides its own more accurate starting values which were used in the present analysis. The final estimates produced by the program were $\hat{p}(0) =$ 7.2 per cent, $\hat{a} = -2.85$ and $\hat{b} = 2.53$. These are based on the information from all six groups, not just the four plotted in Figure 14. The fitted dose-response curve, expressed in terms of percentage probabilities, is

$$\begin{aligned}\hat{p}(x) &= \hat{p}(0) + \{1 - \hat{p}(0)\}\,\Phi\{\hat{P}^*(x) - 5\} \\ &= 7.2 + 92.8\Phi(-7.85 + 2.53x), \qquad (28)\end{aligned}$$

using equations (8) and (10) of Section 1.3.

The adequacy of the model is checked by the χ^2 value quoted by the program. In this case the value is non-significant and so the assumptions underlying the model are not called into question, ($\chi^2 = 2.37$, d.f. = 4, n.s.). The ED50, that is the dose which would cause paresthesia in 50 per cent of those exposed to it, is estimated as 1267 ng ml^{-1}, with 95 per cent confidence limits of (213, 7549). The fitted dose-response curve is shown in Figure 15.

Notice that the model does not involve a threshold dose below which the exposure to mercury has no effect on the susceptibility to paresthesia. The question of whether a threshold exists cannot be settled by the type of data given here, and so the safer and more reasonable assumption of no threshold has been adopted. The straight line fitted by Bakir *et al.* (3) and the threshold estimated from it are not valid, especially as background frequency is not allowed for.

A more accurate analysis could have been performed had the full data been available. The values given in Table 6 have been constructed artificially, in keeping with Table 5 in order to illustrate this full analysis. The dose of every subject is recorded, and those

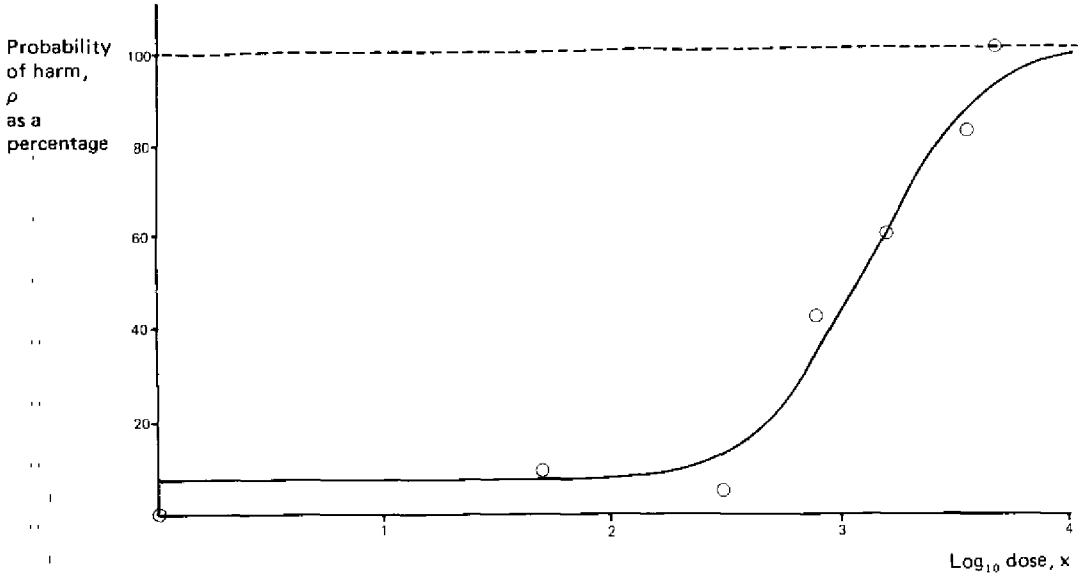

Figure 15 The fitted dose-response curve, $p(x) = 7.2 + 92.8\Phi(-7.85 + 2.53x)$

corresponding to subjects reporting symptoms of paresthesia are followed by the letter P.

Of the 122 doses in Table 6, 113 are distinct. These are entered into the program BMD03S together with the number responding and the number of subjects at each level. As most groups now have either zero or 100 per cent response, starting values must be provided for the iteration. These could be taken from the line drawn on Figure 14, but we used the final values from the analysis of the grouped data; $\hat{p}(0) = 7.2$, $\hat{a} = -2.85$ and $\hat{b} = 2.53$. None of the subjects were treated as controls but background frequency was estimated. Fitted values were $\hat{p}(0) = 6.7$, $\hat{a} = -2.56$ and $\hat{b} = 2.46$. The χ^2 value was non-significant ($\chi^2 = 117.86$, d.f. = 110, n.s.). The ED50 was estimated as 1196 ng ml^{-1} with 95 per cent confidence limits of (191, 7513).

The data of Bakir *et al.* (3) provide a good illustration of the method of probit analysis, but wider use of the model equation 28 with these specific parameter values may be limited. This is because of the original sampling procedure. Of the 122 subjects, 90 were chosen from amongst hospital patients suffering from the effects of mercury poisoning. To establish a model applicable to the general population the sample should have been drawn *at random* from the affected region, following chosen subjects to hospital when necessary. The estimates of the probability of harm for a given dose given by equation (28) will be overestimates of the probabilities valid in the general population. In general it is valid to select patients because they are likely to have high doses but *not* because they are likely to have been badly affected. For further information on sampling theory see Cochran (6).

3. Reference levels from dose-effect relationships

3.1 Introduction

Documents such as the EEC Council Directive on Lead (9) and the British Medical Journal (5) categorization of lead exposure quote reference levels for Pb-B based on clinical experience and judgement. In this section procedures for deriving reference levels from dose-effect relationships will be studied. At first sight the introduction of a statistical method appears to remove the subjectivity involved in

Table 6 Fictitious doses to illustrate the full analysis. Doses relating to subjects reporting symptoms of parasthesia are marked 'P'.

(0, 100]	(100, 500]	(500, 1000]	(1000, 2000]	(2000, 3000]	(3000, 4000]	(4000, 5000]
6	106	520	1086 P	2068	3143 P	4035 P
6	107	551	1090 P	2071	3146	4167 P
11	121	563	1130 P	2082 P	3183	4631 P
13	139	589	1175	2195 P	3280 P	4910 P
14	150	600 P	1177	2280 P	3296 P	
20	150	603 P	1178	2285 P	3333 P	
20	178	603	1193 P	2295	3391	
20	230	650	1207 P	2305 P	3409 P	
21	237	671 P	1253	2361	3568 P	
23	289	679 P	1261 P	2397 P	3677 P	
25	290	705 P	1289	2480 P	3682 P	
31	311	729	1453 P	2572 P	3693 P	
33 P	333	733	1498 P	2573 P	3693 P	
42	367 P	771	1600 P	2761 P	3810 P	
47	452	775 P	1689	2783 P	3889 P	
51 P	468	891	1982 P	2785 P	3930 P	
60	473	905 P	1995	2801 P	3950 P	
60	497	955 P		2876		
89	499	967		2882 P		
90				2937 P		
94				2945 P		
				2945 P		
				2945 P		
				2980 P		
				2989 P		

setting reference levels; however, as we shall see, it merely transfers it to an earlier stage in the procedure.

For a given pollutant and a given population of individuals an *acceptable dose* will be one giving rise to an effect exceeding y_0 with probability less than α. The *greatest acceptable dose* will give rise to an effect exceeding y_0 with probability exactly equal to α. The greatest acceptable dose would then be used as a reference level; i.e. as a yardstick by which observed dose levels could be assessed. The choice of y_0 and α are, of course, subjective.

If y_0 were taken to be the zero effect and α were put equal to zero, then an acceptable dose could realistically be described as "safe", and the greatest acceptable dose as a "threshold". However, in many cases the only dose likely to satisfy such a stringent definition of safety is the zero dose. Even if a non-zero threshold exists, it will not usually be possible to estimate it reliably.

In Section 3.2 which follows, the selection of y_0 and the estimation of the greatest acceptable dose will be discussed for normally distributed effects. When effects are binary y_0 can be set at the zero effect, so that only subjects who are harmed will have effects exceeding y_0. Estimation in this case is considered in Section 3.3.

3.2 Reference levels for normally distributed effects

Suppose that the model introduced in Section 1.2 is appropriate. Thus the level, y, of the effect is related to the dose, x, by

$$y = f(x) + \epsilon \qquad \textit{equation (1)}$$

where ϵ is normally distributed with mean zero and constant standard deviation σ.

In Section 1.4 a binary effect was derived from such a quantitative effect by considering a subject to be harmed if he had an effect exceeding y_0. Then the probability of harm at dose x was shown to be

$$p(x) = \Phi\left\{\frac{f(x) - y_0}{\sigma}\right\}. \qquad (29)$$

Denoting the greatest acceptable dose by G, we have

$$\alpha = \Phi\left\{\frac{f(G) - y_0}{\sigma}\right\}$$

so that

$$f(G) = y_0 - \sigma\Phi^{-1}(1-\alpha). \tag{30}$$

Roels *et al.* (18) and Piotrowski and O'Brien (16) quote reference levels which appear to fit into the framework above, although the authors give no explicit definitions. The value of y_0 is chosen as the effect exceeded by only 100β per cent of subjects with dose x_0, both sets of authors choosing $\beta = 0.025$. Hence

$$y_0 = f(x_0) + \sigma\Phi^{-1}(1-\beta). \tag{31}$$

The choice of x_0 is also subjective, but it might represent a normal or control dose level. With such a choice of y_0, equation (30) becomes

$$f(G) = f(x_0) + Q\sigma \tag{32}$$

where

$$Q = \Phi^{-1}(1-\beta) - \Phi^{-1}(1-\alpha). \tag{33}$$

The relationship between the distribution of effects at x_0 and G is illustrated in Figure 16.

So far it has been assumed that large values of y correspond to serious effects. In some examples it is more convenient to allow small values of y to be the serious ones. This requires that subjects receive effects *less* than y_0 with small probability and it is then useful to define

$$y_0 = f(x_0) - \sigma\Phi^{-1}(1-\beta).$$

The relation equation (32) will be generally valid if Q is re-defined as

$$Q = \begin{cases} \Phi^{-1}(1-\beta) - \Phi^{-1}(1-\alpha) \\ \text{if } \textit{large} \text{ values of y correspond to serious effects,} \\ -\{\Phi^{-1}(1-\beta) - \Phi^{-1}(1-\alpha)\} \\ \text{if } \textit{small} \text{ values of y correspond to serious effects.} \end{cases} \tag{34}$$

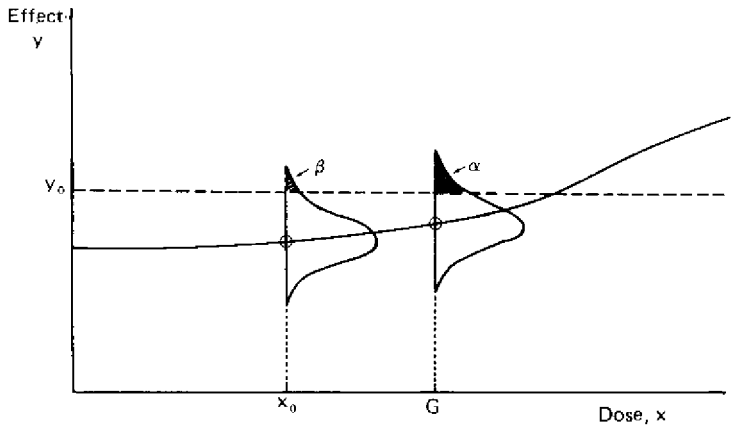

Figure 16 At dose x_0, 100β per cent of the population would have an effect exceeding y_0. At dose G, the greatest acceptable dose, this percentage has risen to 100α per cent.

The estimates of G, from either equation (30) or (32), can be derived from fitted values of f(x) and σ. In the latter case the model must be a good fit for doses between x_0 and G, and so the range of observed values must include these points. Other authors have estimated G from binary data generated from the original quantitative observations, but this is inefficient, and obscures the importance of finding the right form for f(x) and of the constant standard deviation assumption.

The use of equation (32) will be illustrated using the examples of Section 2. Following Piotrowski and O'Brien (16) the values $\alpha = 0.10$ and $\beta = 0.025$ will be used, so that $Q = 0.68$ when large values of y correspond to serious effects. For the dose level x_0, values estimated from normal, unexposed populations will be used. As such estimates are generally based on only small samples, and have not been determined by the same investigators or for the same target populations, the calculations should be treated only as illustrations. Future applications of this method should include large control groups of normal individuals, both for accurate estimation of the

normal dose x_0, and then for reliable fitting of the dose-effect curve around x_0.

For the three principal models of Section 2 the following forms for G can be derived from equation (32).

$$\text{Linear: } f(x) = a + bx$$

$$G = x_0 + Q\sigma/b \tag{35}$$

$$\text{Quadratic: } f(x) = a + b_1x + b_2x^2$$

$$G = \frac{-b_1 + \{(b_1 + 2b_2x_0)^2 + 4b_2Q\sigma\}^{1/2}}{2b_2} \tag{36}$$

$$\text{Exponential: } f(x) = a + be^{cx}$$

$$G = \frac{\log_e(e^{cx_0} + Q\sigma/b)}{c} \tag{37}$$

For the data of Smith (19), relating lung function (FVC) to cadmium level in urine (Cd-U), the model

$$f(x) = 103.15 - 0.28x, \qquad (S = 9.41)$$

was fitted. Imbus *et al.* (12) quotes a value of $1.59\,\mu g\,\ell^{-1}$ as normal Cd-U, and so $x_0 = 1.59$ is used. As the effect, FVC as a percentage of normal, becomes *smaller* as dose increases, $Q = -0.68$ is used. Hence G can be estimated by

$$\hat{G} = 1.59 + 0.68 \times 9.41/0.28$$

$$= 1.59 + 22.85$$

$$= 24.44\,\mu g\,\ell^{-1}$$

and the 95 per cent confidence limits are (9.75, 39.13). Smith (19) quotes a value of $25\,\mu g\,\ell^{-1}$ as "a level of approximate no-effect" but gives no details as to how it was obtained.

The exponential model fitted to the data of Pueschel *et al.* (17), relating haemoglobin concentration to blood lead levels in children, was

$$f(x) = 8.194 + 19.16e^{-3.63x}, \qquad (S = 0.896)$$

From Goldwater and Hoover (11) normal values of Pb-B would appear to be of the order of $0.2\,mg\,\ell^{-1}$ for adults; normal values for children might be smaller than this. However, the range of doses observed by Pueschel *et al.* (17) and used in the fitting of the exponential model, does not include $0.2\,mg\,\ell^{-1}$ or smaller values. Application of equation (37) would imply an extrapolation of the fitted model to cover lower doses, and thus would not lead to a reliable conclusion.

For the men's data from Roels *et al.* (18), relating FEP in blood to Pb-B levels, the quadratic model

$$f(x) = 3.9894 - 0.0169x + 0.0007x^2, \qquad (S = 0.2248)$$

was fitted. The normal level of lead in blood from Goldwater and Hoover (11) in the units required is about $20\,\mu g\,(100\,ml)^{-1}$ and $x_0 = 20$ is used. The effect, $\log_e$ (FEP), is large when serious, and $Q = 0.68$ is used. This gives

$$\hat{G} = \frac{0.0169 + \{(-0.0169 + 2 \times 0.0007 \times 20)^2 + 4 \times 0.0007 \times 0.68 \times 0.2248\}^{1/2}}{2 \times 0.0007}$$

$$= 28.85\,\mu g\,(100\,ml)^{-1}$$

with 95 per cent confidence limits of (25.87, 31.83).

3.3 Reference levels for binary effects

For a binary effect the greatest acceptable dose, G, is that dose which will harm a subject with probability α. The choice of α is subjective and will depend upon the nature of the harmful effect. In testing the safety of potential carcinogens, where the harmful effect is the contraction of cancer, this definition of G is used with α set as low as 10^{-9}, (13).

In the notation of Section 1.3, p(x) is the probability that a subject receiving a dose, x, is harmed. Then G satisfies

$$p(G) = \alpha$$

If a background response is present then clearly α must be greater than p(0). The corrected probability $p^*(G)$ will satisfy

$$p^*(G) = \alpha^*$$

where

$$\alpha^* = \frac{\alpha - p(0)}{1 - p(0)}$$

It may then be easier to set α^* rather than α itself. In cancer studies, when there is a positive background response, it is α^* which is set equal to 10^{-9}.

If the linear probit model

$$P^*(x) = a + bx, \qquad \textit{equation (11)}$$

in which x denotes $\log_{10}$ (dose) is valid, then with equation (10) of Section 1.3 we have

$$\Phi^{-1}(\alpha^*) + 5 = a + b \log_{10} G$$

that is

$$\log_{10} G = \left\{ \frac{1}{b} \phi^{-1}(\alpha^*) + 5 - a \right\}. \qquad (38)$$

Unless α^* is quite large, the relation to equation (11) will only be fitted to higher doses which give positive responses. The dose G can only be determined by extrapolation. Thus it is rarely valid to estimate G from equation (38).

The method used by Mantel and Bryan (13) in cancer studies gives a very conservative underestimate of G. When used for setting standards for new potential carcinogens, this wide safety margin can be accommodated, but it may produce impractical requirements when applied to pollutants which are already widespread.

When applied to the data of Bakir *et al.* (3), the Mantel and Bryan (13) procedure with $\alpha = 10^{-9}$ gives as an estimate of G, $\hat{G} = 0.00256\,\text{ng ml}^{-1}$. Raising α to 10^{-6}, 10^{-3}, and 10^{-1} gives $\hat{G} =$ 0.0186, 0.851 and 54.95 respectively. Only the last of these values is a remotely practical reference level. Using equation (38) for $\alpha = 10^{-1}$ gives as an estimate of G, $\hat{G} = 394.5\,\text{ng ml}^{-1}$. Even for such a comparatively large value of α, this estimate involves extrapolation and is not reliable.

4. Discussion

In this report we have fitted dose-effect relationships to existing data. Sometimes the data have not been ideal for this purpose, and certain questions have been left unanswered. When planning future studies, statistical advice on how many and what kind of observations to take should be sought at an early stage. To answer these questions the statistician will need to know the purpose of fitting the model and the accuracy required. The scope of the investigation may need modification, in the light of the statistical requirements.

Often dose-effect curves will be fitted just as a descriptive summary of the data. Alternatively, the experimenter may have specific aims such as a comparison of effects on men and women, and investigation of the role of a smoking habit in the relationship, or the setting of reference levels.

If these methods are applied to two or more different sets of data, both observed to study the same relationship, it may be desirable to combine the results. Unfortunately, the values obtained by different investigators, possibly using different techniques and sampling different populations, will usually not be directly comparable. A literal pooling of such sets of data is inadvisable.

It is possible to make a qualitative comparison of different studies, noting, for example, whether they all give increasing dose-effect curves and whether they are all concave or sigmoid. Otherwise it is best to analyse them all separately and to combine the results informally, weighting reports by the reliability of the analyses and the size of samples studied.

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Price
U.K. £5.00
Overseas U.S. $10.00
Printed in Great Britain at the Alden Press
Oxford, London and Northampton

ISBN 0 905918 15 0