

CHAPTER 6

Human Health Concerns of Lead, Mercury, Cadmium and Arsenic

M. HUTTON

*Monitoring and Assessment Research Centre,
The Octagon Building, King's College London,
University of London, 459A Fulham Road,
London SW10 0QX, United Kingdom*

ABSTRACT

The trace elements lead, mercury, cadmium and arsenic have caused major human health problems in several parts of the world. Concern over such incidents has prompted numerous investigations into the metabolism and toxic effects of these four elements. This chapter outlines their contrasting metabolism and describes the major health effects and the relative scale of such incidents. Attention is paid to the environmentally important chemical species of mercury and arsenic, the overall health significance of early biochemical effects and the limitations of certain epidemiological studies. Comparisons are made between the exposure threshold for the initial effects of each element and the exposure levels seen in the general population.

INTRODUCTION

The three metals, lead, mercury and cadmium, and the metalloid arsenic have all caused major human health problems in various parts of the world. The overt toxicity of these elements has been recognized for many years; indeed, the harmful effects of lead were known as far back as the second century BC in ancient Greece (Waldron, 1973). Over the years, physicians became increasingly familiar with the symptoms of metal poisoning arising in occupationally exposed workers and in individual cases of poisoning. In more recent times, toxicologists concerned with metal poisoning attempted to elucidate the metabolism and range of effects induced by metals in these two populations. Such studies revealed that certain effects only become ap-

parent at particular stages of the exposure scale. In cases of high exposure, clinical signs and symptoms can be observed. At lower exposure levels clinical manifestations may be absent but effects may be observed at the physiological or biochemical level.

From the mid-1950s to the early 1960s it was recognized that poisoning by these four elements was not restricted to occupationally exposed workers or to the occasional individual. In the USA, detailed studies by health officials revealed that many hundreds of cases of childhood lead poisoning occurred every year in the dilapidated housing areas of the older cities (Lin-Fu, 1980). At about the same time in Japan, major environmental poisoning incidents caused by methylmercury and by cadmium were the subject of intense scientific investigation and attracted public attention and concern. Possibly less well known but also occurring in Japan over the same time period were two mass incidents of arsenic poisoning (WHO, 1981). These major episodes have prompted numerous studies of other populations considered to be subjected to elevated exposure levels from a variety of sources. Such studies, employing increasingly sophisticated techniques, revealed that effects could be detected at exposure levels which had previously been considered safe.

This chapter reviews the current state of knowledge regarding the health effects induced by the four elements in environmentally exposed populations. Attention is paid to the significance of the observed effects, the scale of such incidents and the limitations of recent epidemiological studies. By reference to dose response relationships, a comparison is made between the exposure threshold for the initial effects of each element and the exposure levels seen in the general population.

METABOLIC FACTORS

Before discussing the health effects caused by the four elements, it is worthwhile to consider the major metabolic factors associated with environmental exposure, as this will allow a greater understanding of the basis for the observed effects. The relevant factors are summarized in Table 6.1. In the cases of mercury and arsenic, the chemical species of importance in environmental exposure need to be distinguished. For mercury these are the short chain alkyl compounds, particularly methylmercury. In the case of arsenic, both inorganic compounds, as arsenates (As^{5+}) or as arsenites (As^{3+}), and organic compounds, such as arsenobetaine and arsenocholine, are of importance.

Uptake

Generally, the predominant route of exposure for all four elements is ingestion, although inhalation is an important source of lead, particularly in

Table 6.1 Major metabolic factors associated with environmental exposure to lead, mercury, cadmium and arsenic

	Lead	Mercury	Cadmium	Arsenic
Major routes of entry	Ingestion and inhalation	ingestion	Ingestion and inhalation (tobacco)	Ingestion
Gastrointestinal absorption (%)	~ 10	~ 95	~ 5	> 80
Organs of accumulation	Bone, kidney and liver	Brain, liver and kidney	Kidney and liver	Keratinous tissue
Major routes of excretion	Urine	Faeces	Urine	Urine
Biological half-life	~ 20 years	~ 70 days	> 10 years	10–30 hours

urban-dwelling populations. In addition, the smoking of tobacco can be an important source of cadmium. Great differences exist between the four elements in the fractional absorption by the gastrointestinal tract.

Methylmercury and the various arsenic compounds are absorbed efficiently. Gastrointestinal absorption of cadmium is enhanced considerably in individuals with iron deficiency (Flanagan *et al.*, 1978) while lead absorption may be much higher than 10% in children (Alexander *et al.*, 1973).

Behaviour in the Body

Both inorganic arsenic and methylmercury exhibit a relatively even tissue distribution, but arsenic does accumulate in hair, skin and nails, while methylmercury displays considerable affinity for the brain. About 90% of the body burden of lead is stored in the skeleton, while in soft tissues the liver and kidneys have high concentrations. Cadmium is selectively accumulated in the kidney and liver, particularly in the renal cortex. In these organs cadmium is bound specifically to a low molecular weight protein, metallothionein. Both lead and methylmercury show significant transplacental transfer. In the latter case this transfer is particularly efficient.

With the exception of methylmercury, the major route of excretion of the elements is via urine. In humans inorganic arsenic is methylated to methylarsonic acid and dimethylarsinic acid and these are rapidly excreted. The organic arsenic compounds present in seafood are excreted unchanged.

The principal route of excretion for methylmercury occurs by biliary excretion into the gastrointestinal tract. Most of the methylmercury excreted in this manner is subsequently reabsorbed, resulting in an enterohepatic cir-

ulation. In the case of cadmium, the binding to metallothionein is thought to be responsible for both the very low excretion rates of this metal and the observed accumulation with age, particularly in the renal cortex.

HEALTH EFFECTS AND POPULATIONS AFFECTED

Lead

The major health effects of lead are manifest in three organ systems; the haematological system, the central nervous system (CNS) and the renal system. Table 6.2 summarizes the various effects in these systems which have been attributed to lead in environmentally exposed populations.

Table 6.2 Major health effects attributed to lead in environmentally exposed populations

Organ affected	Range of effects reported
Haematological system	Inhibition of ALA-D (δ -aminolevulinic acid dehydratase) and haem synthetase and corresponding accumulation of ALA and FEP (free erythrocyte protoporphyrin). At higher levels of exposure, reduced haem synthesis and anaemia.
Nervous system	CNS impairment at moderate exposure in children, reflected by inattention, cognitive difficulties, fine motor dysfunction and altered EEG patterns. Under heavy exposure, encephalopathy may arise. Effects on the peripheral nervous system (PNS) indicated by reduced nerve conduction velocity.
Renal system	Functional impairment of the tubular region characterized by mild aminoaciduria, glucosuria and hyperphosphaturia. Morphological effects include mitochondrial damage and intranuclear inclusion bodies. Long-term heavy exposure may result in irreversible nephropathy.

The haematological effects of lead have been recognized for many years and the biochemical basis for such changes are now reasonably well established. Two of the most sensitive effects on this system arise at the first and final steps of the haem synthesis pathway. The enzyme catalysing the first step, δ -aminolevulinic acid dehydratase (ALA-D) is uniquely sensitive to lead, and erythrocyte ALA-D is often reported to be inhibited in the general population (Hernberg and Nikkanen, 1970). This partial inhibition is

not considered to be a deleterious effect because the enzyme exhibits a large reserve capacity (Zielhuis, 1975). In addition, erythrocyte ALA-D in mammals has no function as such because mature erythrocytes do not participate in haem synthesis. The inhibition of ALA-D in other, haem-forming tissues will, if exposure is sufficiently high, result in an increased concentration of the substrate ALA in the body and urine (Selander and Cramer, 1970).

Lead also interferes with the last stage of haem synthesis, the incorporation of iron into protoporphyrin, catalysed by haem synthetase (ferrochelatase). This step takes place in the inner matrix of the erythroid cell mitochondria in the bone marrow. It is now thought that lead does not interfere with the enzyme but rather inhibits the transmitochondrial transfer of iron (Piomelli 1980). This effect results in the accumulation of protoporphyrin in the mitochondria, its incorporation into the globin molecule in place of haem and the presence of elevated levels of free erythrocyte protoporphyrin (FEP) in the peripheral blood.

When devising an ambient air quality standard for lead in the late 1970s, the US EPA identified the elevation of FEP as the earliest adverse effect of lead (EPA, 1977). This was based on the fact that, unlike the inhibition of ALA-D, the insertion of protoporphyrin occurs within the mitochondrial matrix and elevated levels of FEP represent an impairment of a specific mitochondrial function. In addition, there is a possibility that other mitochondrial functions will also be affected.

Some investigators now consider that the systemic accumulation of ALA is not without significance and may be involved in the neurotoxic effects associated with lead exposure (Moore, 1980). This is based on the findings that ALA can pass the blood-brain barrier (McGillion *et al.*, 1974), while administration of ALA causes neuromuscular and neurophysiological effects (Moore and Meredith, 1976; Cutler *et al.*, 1979). Lead may also induce the development of anaemia but this effect only arises at high levels of exposure (Zielhuis, 1975). Indeed, Piomelli (1980) considers that children may die from the neurological effects of lead without even developing anaemia.

Acute effects of lead on the central nervous system (CNS) are generally seen in children heavily exposed from pica and are manifest by severe encephalopathy which can culminate in coma and death. More controversial is the reported association between certain subtle neuropsychological and neurobehavioural effects and lead exposure in otherwise asymptomatic children. It is this issue which is of most concern in the environmental toxicity of lead because these effects have been reported to occur in children from the general population subjected to commonly occurring exposure regimes. Further concern relates to the greater susceptibility of children to lead resulting from the higher intake and uptake together with the greater sensitivity of the developing CNS. The major study relevant to this issue was carried out on children in the USA by Needleman *et al.* (1979) using dentine lead as the

index of exposure. The study involved numerous tests of performance and intelligence in the children, classified according to their dentine lead levels. The classroom behaviour of the children was rated by the teacher. Needleman *et al.* (1979) reported that children from the high lead group showed significantly lower verbal IQ and performed less well on other behavioural tasks, after controlling for five covariates in an analysis of covariance. In addition, the teacher's assessments of classroom behaviour were reported to show a dose-dependent increase in poor ratings (Needleman, 1980). Since the Needleman study, other investigations in children from the Federal Republic of Germany (Winneke, 1983) and the United Kingdom (Yule and Landsdown, 1983) have reported an association between increased lead exposure and decreases in measurements of intelligence and behaviour. The evidence from these and other investigations may reflect a causal relationship but could also be indicative of the effects of confounding factors. Indeed, the only area where the two divergent opinions on this issue appear to agree is that the study design of retrospective epidemiological investigations will never fully be able to control for confounding factors.

Despite this, an influential paper by Rutter (1983) argued that these and other studies provide sufficient evidence to infer a cause and effect relationship. In contrast, an expert Committee concluded that the results of the study by Needleman *et al.* (1979) 'neither confirm nor refute the hypothesis that low lead exposure in children leads to neuropsychologic deficits' (EPA, 1983). The Committee concerned not only criticized the study of Needleman *et al.* (1979) for failure to control confounding variables but, moreover, noted deficiencies in data handling. In addition, a question of possible bias was raised, as large numbers of eligible subjects were rejected from analysis. However, reanalysis of the data in response to the Committee's recommendations still produced a significant association between dentine lead and signs of intelligence deficit (Needleman, 1984).

The functional morphological effects of lead on the kidneys listed in Table 6.2 occur at exposure levels rarely encountered outside of the occupational setting. Acute lead intoxication in children may elicit renal dysfunction but little is known of the extent and reversibility of this effect.

From the above, it is clear that children represent the critical group with respect to environmental lead exposure. The particular populations considered to be at most risk, based on either observed effects or elevated exposure levels, are the following:

- (i) certain pre-school children from the general population living in urban areas, particularly in those countries where lead is added to petrol;
- (ii) children living in proximity to point sources of lead such as smelters and scrap yards;

- (iii) children living in areas with lead plumbing and served by plumbosolvent water. In this population, exposure takes place before and after birth;
- (iv) children living in housing with high leaded paintwork in poor condition, particularly those individuals which exhibit pica.

Mercury

Methylmercury intoxication is characterized by effects on the CNS and the areas mainly affected are those associated with the sensory, visual and auditory functions and those concerned with co-ordination (WHO, 1976). Early effects are paraesthesia in the tongue, lips and distal extremities, while in more severe cases, blurred and constricted vision and ataxia may appear (Piotrowski and Inskip, 1981). The developing nervous system of the fetus is more sensitive to methylmercury than the adult and pre-natal exposure can result in neurotoxic effects in the infant in the absence of effects in the mother (WHO, 1976). Pregnant women are apparently more sensitive to methylmercury than are other adults (Marsh *et al.*, 1979).

In the last thirty years, there have been several outbreaks of methylmercury intoxication of two distinct types. The first, termed Minamata disease, took place in Japan in the 1950s and 1960s and was caused by long-term ingestion of contaminated fish. There is disagreement over the number of poisonings caused by Minamata disease but one study estimates about 1000 cases, 3300 suspected cases and about 100 deaths (Tsubaki *et al.*, 1978).

Several studies have examined the health of various communities of Canadian Indians because of their elevated methylmercury intakes from fish. The most recent investigation (Methylmercury Study Group, 1980) reported an association between several neurological parameters and methylmercury exposure. However, Piotrowski and Inskip (1981) question this conclusion and note the important influence of confounding factors on the putative association. Piotrowski and Inskip (1981) conclude that the evidence for a neurological effect of methylmercury in the study population is equivocal but that the exposure regimes in question may be at the threshold for effects.

Other populations with heavy fish consumption have also been identified in the Mediterranean, particularly in Italy, in Papua New Guinea, Peru, New Zealand and the Seychelles (WHO, 1976; T. Kjellström, personal communication; M. Berlin, personal communication). In some of these areas no health-related studies have been undertaken, or they are currently still under way. Those studies which have been completed have failed to provide clinical evidence of methylmercury intoxication.

The other type of intoxication is characterized by the Iraqi epidemic in 1971-72 where exposure resulted from consumption of bread prepared from grain dressed with alkylmercury fungicides. The incident in question resulted

in the poisoning of about 6000 individuals (Clarkson, 1977) and the deaths of over 500 in hospital (Bakir *et al.*, 1973). Previous outbreaks of this type together with the number of poisonings are as follows: Iraq (1956), about 100; Iraq (1960), about 1000; Pakistan (1969), about 100; Guatemala (1963-65), about 45; and Ghana (1967), about 150 (Clarkson, 1977). Clearly the inadvertent ingestion of seed treated with organic mercury as a fungicide is a hazard, despite a coloured dye being used and seed bags being marked in several languages.

Cadmium

The kidney is the critical organ of intoxication after long-term exposure to cadmium. One of the initial signs of renal dysfunction is an increased urinary excretion of proteins. Cadmium-induced proteinuria is generally considered to be characterized by the excretion of low molecular weight proteins, particularly α_2, β_2 and γ -globulins. This form of proteinuria, caused by an impaired reabsorption function of the proximal tubules, is not specific for the metal and may be found in hereditary forms of tubular dysfunction.

Some recent studies (Bernard *et al.*, 1979) indicate that a glomerular pattern of dysfunction may also be an early effect of cadmium exposure, as evidenced by an increased excretion of high molecular weight proteins. Later effects on renal function are manifested by aminoaciduria, phosphaturia and glucosuria (Friberg *et al.*, 1974). Recent investigations of cadmium and renal tubular injury have used sensitive radio-immunoassay techniques to measure urinary concentrations of the low molecular weight proteins, β_2 -microglobulin (β_2 -m), and retinol-binding protein (RBP) as indicators of early effect. Of these two proteins, most use has been made of β_2 -m but some studies have also measured RBP.

The precise significance of an increased excretion of β_2 -m is still unclear, especially as markedly elevated β_2 -m levels correspond to relatively small reductions in the tubular reabsorption efficiency. Furthermore, there is no significant transport of low molecular weight proteins back to the blood after tubular uptake; instead these proteins are degraded *in situ* (Cooper and Plesner, 1980). Apparently, the significance of this tubular lesion is the loss of those amino acids which are salvaged by a normal individual. However, increased urinary excretion of β_2 -m is generally considered to be irreversible and is indicative of an impairment of tubular function and, as such, is considered by some workers to constitute a health effect.

Until recently, reports of health effects of cadmium in populations not occupationally exposed to cadmium were confined to Japan. Many areas of Japan are contaminated with cadmium, as a result of discharges from numerous non-ferrous metal mines and smelters. Long-term consumption of rice grown in these areas has resulted in elevated cadmium exposure

levels and signs of renal dysfunction in several localities (Friberg *et al.*, 1974). A syndrome termed 'itai-itai disease' has also been identified in one area characterized by severe renal dysfunction and damage to bone structure. The disease predominantly affected elderly multiparous women with poor nutritional status, who had lived in the contaminated area for many years.

A recent investigation also examined elderly females (>60 years) from a city in Belgium subjected to long-term cadmium contamination (Roels *et al.*, 1981). These women were reported to have larger cadmium burdens and a higher prevalence of signs of renal dysfunction compared with controls from a city with lower levels of cadmium contamination. The cadmium exposure levels in this population were much lower than those encountered in contaminated areas of Japan and the corresponding signs of renal dysfunction were also less pronounced. This study suggests that cadmium may exacerbate the age-related decline in renal function at moderate exposure levels to the metal.

The mortality statistics of the two Belgian cities have also been examined (Lauwerys and De Wals, 1981). Overall mortality rates were similar in the two populations but mortality from nephritis and nephrosis was higher in the cadmium 'polluted' city. However, mortality rates from uremia were similar in the two populations, a surprising finding given the apparent disparity in mortality rates from nephritis and nephrosis.

Mortality studies carried out in cadmium-contaminated areas of Japan have produced conflicting results. One investigation (Nogawa *et al.*, 1981) of a small population reported a significant increase in overall mortality for males with proteinuria. As in the Belgian study, this population was reported to show a large excess of deaths due to nephritis and nephrosis.

Arsenic

Long-term exposure to inorganic arsenic can give rise to health effects in a large number of organs. Those effects reported to occur in populations environmentally exposed to arsenic are shown in Table 6.3 The information depicted in Table 6.3 has been extracted from WHO (1981) and Pershagen (1983).

The most characteristic effects following chronic arsenic exposure are hyperkeratosis of the palms and soles of the feet together with hyperpigmentation, particularly in areas not exposed to the sun. Skin tumours have also been commonly reported and these are often located on the hands and feet.

Haemangioendothelioma of the liver, a very rare form of cancer, has been associated with long-term arsenic exposure in several instances. Most of the reported cases refer to individuals which had been prescribed Fowler's solution, a trivalent arsenic medication.

Table 6.3 Health effects in environmentally exposed populations attributed to arsenic

Organ affected	Effects
Skin	Hyperpigmentation Hyperkeratosis Skin tumours
Lungs	Lung cancer*
Liver	Liver dysfunction Haemangioendothelioma
Cardiovascular system	Peripheral vascular disturbances leading to gangrene
Nervous system	Peripheral neuropathy Hearing defects
Haematopoietic system	Disturbed erythropoiesis with anaemia
Reproductive system	Increased frequency of spontaneous abortions*

* The role of arsenic in these effects is equivocal.

Other effects of arsenic include peripheral vascular disturbances resulting in gangrene and a disease termed 'Blackfoot disease' (Tseng, 1977).

Some studies have reported an increased prevalence of lung cancer and increased rate of spontaneous abortion in communities close to point sources of atmospheric arsenic (Newman *et al.*, 1976; Pershagen *et al.*, 1977; Nordström *et al.*, 1978). However, several detailed evaluations of these and other studies concluded that without further evidence it is not possible to say whether arsenic was the causative agent in those incidents (IARC, 1980; WHO, 1981; Pershagen, 1983).

Those populations affected by arsenic, outside the occupational setting, may be divided into four categories, as shown in Table 6.4. The most serious of the two food poisoning incidents in Japan resulted from the accidental use of arsenic-contaminated sodium phosphate in the preparation of dried milk for infants (Nakagawa and Ibuchi, 1970). A follow-up study of the survivors of this incident revealed severe hearing loss in about 20% of the sample (Yamashita *et al.*, 1972).

The most important cause of environmental arsenic impact relates to the consumption of arsenic-contaminated drinking water. In most cases, the arsenic is of natural origin but in some instances mining activities are responsible. Studies of several affected populations, particularly those in Argentina and Chile, have revealed a close association between skin cancer and arsenic exposure. Similarly, the incidence of Blackfoot disease in Taiwan, manifest by gangrene of the extremities, was found to increase in a dose-dependent manner with arsenic (Tseng, 1977).

Table 6.4 Large scale cases of poisoning associated with exposure to inorganic arsenic

Type of incident	Episodes
Food inadvertently contaminated during preparation (acute and subacute effects)	Morinaga milk incident, Japan (1955). > 12 000 cases, 130 deaths Soy sauce incident, Japan (1956). > 400 cases
Drinking water exposure (chronic effects)	Numerous incidents, with reports from Argentina, Chile, Taiwan, U.S.A., Canada and Japan. In excess of 0.25 million people exposed for several decades in Chile.
Communities close to point sources of airborne arsenic (chronic effects)	Evidence for effects on morbidity and mortality around copper smelters and pesticide plants. Single report of hearing effects in children living near a power plant in Czechoslovakia where a high As (~ 1000 $\mu\text{g/gm}$) lignite was burnt.
Exposure via medications (chronic effects)	Sodium arsenite (Fowler's solution) previously used in the treatment of psoriasis and leukaemia, resulting in severe effects in hundreds of patients.

Several epidemiological investigations of populations living close to point sources have reported an increased mortality from lung cancer but it is not possible to assign this effect to arsenic exposure. Minor hearing loss was reported in children residing close to a power plant in Czechoslovakia burning lignite with an arsenic content of about 1000 $\mu\text{g/gm}$ (Bencko *et al.*, 1977). A similar study found no change in hearing in children subjected to elevated arsenic exposure levels from a large copper smelter (Milham, 1977).

The long-term consumption of Fowler's solution has resulted in the severe poisoning of large numbers of individuals. Examination of the victims has provided valuable information on the toxicity of arsenic. However, this form of contamination is not considered to be an example of environmental contamination.

EXPOSURE THRESHOLDS

One way of assessing the risk to the general population from exposure to a particular chemical is by making a comparison between the actual exposure and the exposure threshold for initial effects. This has been done for the four elements in question using data derived from dose-response analysis;

the values obtained are shown in Table 6.5. In the case of lead, no formal dose-response analyses appear to have been carried out for neurobehavioural and neuropsychological effects. The blood lead level which represents the threshold values for elevated FEP in children is similar to the actual values encountered in many children from the general population particularly those living in urban areas.

This finding and the recent evidence for the neurotoxic effects of lead in young children both show that exposure regimes experienced by the general population commonly exceed the threshold for effects. It is for this reason that of the four elements considered in this workshop, lead is the greatest cause of public health concern.

Table 6.5 Estimated threshold values for chronic exposure to lead, methylmercury, cadmium and inorganic arsenic

Metal	Effect	Estimated threshold	Reported values in the general population or background	Notes and authorities
Lead	ALA-D FEP	11 $\mu\text{g/dl}$ 15–20 $\mu\text{g/dl}$ Blood lead	10–20 $\mu\text{g/dl}$	Data refer to children Value for ALA-D is for a 10% prevalence rate (Piotrowski and O'Brien, 1980; Piomelli <i>et al.</i> , 1982).
Methylmercury	Earliest signs and symptoms	20 $\mu\text{g/gm}$ hair 80 ng/ml blood	2 $\mu\text{g/gm}$ 10 ng/ml	Thresholds refer to non-pregnant adults. The threshold for the fetus is considered to be lower. Background values strongly influenced by fish consumption (Piotrowski and Inskip, 1981).
Cadmium	β_2 -m cancer	150 $\mu\text{g/day}$ dietary intake	20–70 $\mu\text{g/day}$	Threshold refers to 50-year daily intake needed to cause elevated urinary β_2 -m in 10% of the population with average body weight of 70 kg (Kjellström, 1980; Hutton, 1983).
Arsenic (inorganic compounds)	Skin cancer	200 $\mu\text{g/litre}$ in drinking water	2 $\mu\text{g/litre}$	Threshold refers to 5% prevalence after lifetime (70 years) exposure (WHO, 1981).

Exposure levels of methylmercury in the overwhelming majority of the general population are significantly lower than those considered to be at the threshold for early effects. It is only certain sub-groups within the general population, particularly fishing communities, which are likely to be exposed to elevated levels.

The dose response analyses for cadmium were based on data from elderly females whose diet may have been nutritionally inadequate. This should be borne in mind when extrapolating the findings of these analyses to other populations. The 10% response value for cadmium exposure, at 150 $\mu\text{g/day}$ is considerably higher than the average intakes reported for most countries around the world. Japan is one notable exception and average values for 'uncontaminated' areas can approach this threshold. It should also be borne in mind that dietary intake of cadmium displays a log-normal distribution and individuals at the upper end of the distribution will be exposed to considerably larger amounts than average.

Exposure information for early effects of arsenic are considered to be inadequate for dose-response analysis (WHO, 1981). Table 6.5 depicts the threshold value for skin cancer, derived from populations exposed to arsenic in drinking water. It is clear that the arsenic levels commonly found in drinking water pose no realistic cancer hazard to the general population.

REFERENCES

- Alexander, F. W., Delves, H. T., and Clayton, B. E. (1973). The uptake and excretion by children of lead and other contaminants. *Proc. Int. Symp. Environmental Health Aspects of Lead*, pp. 319-330, Commission of the European Communities, Luxembourg.
- Bakir, F., Damluji, S. F., Amin-Zaki, L., Murtadha, M., Khalidi, A., Al-Rawi, N. Y., Tidriti, S., Dhahir, H. I., Clarkson, T. W., Smith, J. C., and Doherty, R. A. (1973). Methylmercury poisoning in Iraq. *Science*, **181**, 230-241.
- Bencko, V., Symon, K., Chladek, V., and Pihrt, J. (1977). Health aspects of burning coal with a high arsenic content. II. Hearing changes in exposed children. *Environ. Res.*, **13**, 386-395.
- Bernard, A., Buchet, J. P., Roels, H., Masson, P., and Lauwerys, R. (1979). Renal excretion of proteins and enzymes in workers exposed to cadmium. *Eur. J. Clin. Invest.*, **9**, 11-22.
- Clarkson, T. W. (1977). Mercury poisoning. In Brown, S. S. (Ed.) *Clinical Chemistry and Chemical Toxicology of Metals*, pp. 189-200, Elsevier/North-Holland Biomedical Press, Amsterdam.
- Cooper, E. H., and Plesner, T. (1980). Beta-2-microglobulin review: its relevance to clinical oncology. *Med. Pediatr. Oncol.*, **8**, 323-334.
- Cutler, M. G., Moore, M. R., and Ewart, F. G. (1979). Effects of delta-aminolaevulinic acid administration on social behaviour in the laboratory mouse. *Psychopharmacology*, **61**, 131-135.
- EPA (1977). Lead: ambient air quality standard. *Fed. Regist.*, **42**, 63076.
- EPA (1983). *Independent Peer Review of Selected Studies Concerning Neurobehavioural Effects of Lead Exposures in Nominally Asymptomatic Children: Official*

- Report of Findings and Recommendations of an Interdisciplinary Expert Review Committee.* EPA-600/8-83-028A US Environmental Protection Agency, North Carolina.
- Flanagan, P. R., McLellan, J. S., Haist, J., Cherian, G., Chamberlain, H. J., and Valberg, L. S. (1978). Increased dietary cadmium absorption in mice and human subjects with iron deficiency. *Gastroenterology*, **74**, 841-846.
- Friberg, L., Piscator, M., Nordberg, G. F., and Kjellström, T. (1974). *Cadmium in the Environment*, 2nd edition, CRC Press, Cleveland, Ohio.
- Hernberg, S., and Nikkanen, J. (1970). Enzyme inhibition by lead under normal urban conditions. *Lancet*, **1**, 63-64.
- Hutton, M. (1983). Evaluation of the relationships between cadmium exposure and selected indicators of renal function. In *Heavy Metals in the Environment, Heidelberg, September 1983*, pp. 274-277, CEP Consultants Ltd, Edinburgh.
- IARC (1980). *Monographs. Arsenic and Arsenic compounds; Volume 23*, Lyons, International Agency for Research on Cancer, pp. 39-141.
- Kjellström, T. (1980). Epidemiological aspects of the dose-response relationship of cadmium induced renal damage. In *International Cadmium Conference, Cannes*, pp. 118-122, Metal Bulletin Ltd, London.
- Lauwerys, R., and De Wals, Ph. (1981). Environmental pollution by cadmium and mortality from renal diseases. *Lancet*, **1**, 383.
- Lin-Fu, J. (1980). Lead poisoning and undue lead exposure in children: history and current status. In Needleman, H. L. (Ed.), *Low Level Lead Exposure: The Clinical Implications of Current Research*, pp. 5-16, Raven Press, New York.
- McGillion, F. B., Thompson, G. G., Moore, M. R., and Goldberg, A. (1974). The passage of δ -aminolaevulinic acid across the blood-brain barrier of the rat: effect of ethanol. *Biochem. Pharmacol.*, **23**, 472-474.
- Marsh, D. O., Myers, G. J., Clarkson, T. W., Amin-Zaki, L., Tikriti, S., Majeed, M. A., and Dablagh, A. R. (1979). Dose-response relationship for human fetal exposure to methylmercury. International Congress of Neurotoxicology, Varese, Italy.
- Methylmercury Study Group (1980). *Methylmercury Study*. McGill University, Montreal, Canada.
- Milham, S. (1977). Studies of morbidity near a copper smelter. *Environ. Health Perspect.*, **19**, 131-132.
- Moore, M. R. (1980). Prenatal exposure to lead and mental retardation. In Needleman, H. L. (Ed.), *Low Level Lead Exposure: The Clinical Implications of Current Research*, pp. 53-65, Raven Press, New York.
- Moore, M. R., and Meredith, P. A. (1976). The association of δ -aminolevulinic acid with the neurological and behavioral effects of lead exposure. In Hemphill, D. D. (Ed.), *Trace Metals in Environmental Health*, pp. 363-371, University of Missouri, Columbia.
- Nakagawa, Y., and Ibuchi, Y. (1970). On the follow-up investigation of Morinaga milk arsenic poisoning. *Igaku no Ayumi*, **74**, 1-3.
- Needleman, H. L. (1980). Lead and neuropsychological deficit: finding a threshold. In Needleman, H. L. (Ed.), *Low Level Lead Exposure: The Clinical Implications of Current Research*, pp. 43-51, Raven Press, New York.
- Needleman, H. L. (1984). Comments on chapter 12 and appendix 12C, Air Quality Criteria for Lead (external review draft no. 1). Available for inspection at: US Environmental Protection Agency, Central Docket Station, Washington, DC. Docket No. ECAO-CD-81-2 IIA. E. C.1.20.
- Needleman, H. L., Gunnoe, C., Leviton, A., Reed, R., Peresie, H., Maher, C., and

- Barrett, P. (1979). Deficits in psychologic and classroom performance of children with elevated dentine lead levels. *New Eng. J. Med.*, **300**, 689-695.
- Newman, J. A., Archer, V. E., Saccomanno, G., Kuschner, M., Auerbach, O., Grondahl, R. D., and Wilson, J. C. (1976). Histologic types of bronchogenic carcinoma among members of copper mining and smelting communities. *Ann. N. Y. Acad. Sci.*, **271**, 260-268.
- Nogawa, K., Kawano, S., and Nishi, M. (1981). Mortality study of inhabitants in a cadmium polluted area with special reference to low molecular weight proteinuria. In *Heavy Metals in the Environment*, Amsterdam, pp. 538-540, CEP Consultants Ltd, Edinburgh.
- Nordström, S., Beckman, L., and Nordenson, I. (1978). Occupational and environmental risks in and around a smelter in northern Sweden. III: Frequencies of spontaneous abortion. *Hereditas*, **88**, 51-54.
- Pershagen, G., (1983). The epidemiology of human arsenic exposure. In Fowler, B. A. (Ed.), *Biological and Environmental Effects of Arsenic*, pp. 199-232, Elsevier/North-Holland Biomedical Press, Amsterdam.
- Pershagen, G., Elinder, C-G., and Bolander, A. M. (1977). Mortality in a region surrounding an arsenic emitting plant. *Environ. Health Perspect.*, **18**, 133-137.
- Piomelli S. (1980). The effects of low-level lead exposure on heme metabolism. In Needleman, H. L. (Ed.), *Low Level Lead Exposure: The Clinical Implications of Current Research*, pp. 67-74, Raven Press, New York.
- Piomelli, S., Seaman, C., Zullo, D., Curran, A., and Davidow, B. (1982). Threshold for lead damage to heme synthesis in urban children. *Proc. Natl. Acad. Sci.*, **79**, 3335-3339.
- Piotrowski, J. K., and O'Brien, B. J. (1980). *Analysis of the Effects of Lead in Tissue upon Human Health Using Dose-Response Relationships*. MARC Report No. 17, Monitoring and Assessment Research Centre, Chelsea College, University of London: 88 pages.
- Piotrowski, J. K., and Inskip, M. J. (1981). *Health Effects of Methylmercury*. MARC Report No. 24, Monitoring and Assessment Research Centre, Chelsea College, University of London: 82 pages.
- Roels, H. A., Lauwerys, R. R., Buchet, J. P., and Bernard, A. (1981). Environmental exposure to cadmium and renal function of aged women in three areas of Belgium. *Environ. Res.*, **24**, 117-130.
- Rutter, M. (1983). Low level lead exposure: sources, effects and implications. In Rutter, M., and Russell Jones, R. (Eds.), *Lead versus Health: Sources and Effects of Low Level Lead Exposure*, pp. 333-370, J. Wiley, Chichester.
- Selander, S., and Cramer, K. (1970). Interrelationships between lead in blood, lead in urine and ALA during lead work. *Br. J. Ind. Med.*, **27**, 28-39.
- Tseng, W. P. (1977). Effects and dose-response relationships of skin cancer and Blackfoot disease with arsenic. *Environ. Health Perspect.*, **19**, 109-119.
- Tsubaki, T., Hirota, K., Shirakawa, K., Kondo, K., and Sato, T. (1978). Clinical, epidemiological and toxicological studies on methylmercury poisoning. In Plaa, G. L., and Duncan, W. A. M. (Eds.), *Proceedings of 1st International Congress on Toxicology*, pp. 339-357, Academic Press, New York and London.
- Waldron, H. A. (1973). Lead poisoning in the ancient world. *Med. Hist. (Lond.)*, **17**, 391-399.
- WHO (1976). *Environmental Health Criteria 1. Mercury*. World Health Organization, Geneva: 131 pages.
- WHO (1981). *Environmental Health Criteria 18. Arsenic*. World Health Organization, Geneva: 174 pages.

- Winneke, G. (1983). Neurobehavioural and neuropsychological effects of lead. In Rutter, M., and Russell Jones, R. (Eds), *Lead versus Health: Sources and Effects of Low Level Lead Exposure*, pp. 219–266, J. Wiley, Chichester.
- Yamashita, N., Doi, M., Nishio, M., Hojo, H., and Tanaka, M. (1972). Current state of Kyoto children by arsenic tainted Morinaga dry milk. *Jpn. J. Hyg.*, **27**, 364–399 (in Japanese).
- Yule, W., and Landsdown, R. (1983). Lead and children's development: recent findings. In *Heavy Metals in the Environment*, Heidelberg, September 1983, pp. 912–916, CEP Consultants Ltd, Edinburgh.
- Zielhuis, R. L. (1975). Dose–response relationships for inorganic lead. 1 Biochemical and haematological responses. *Int. Arch. Occup. Health*, **35**, 1–18.