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Lead in Drinking-water

Background document for development of
WHO *Guidelines for Drinking-water Quality*

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Preface

One of the primary goals of WHO and its member states is that "all people, whatever their stage of development and their social and economic conditions, have the right to have access to an adequate supply of safe drinking water." A major WHO function to achieve such goals is the responsibility "to propose regulations, and to make recommendations with respect to international health matters ...."

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as International Standards for Drinking-Water. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO Guidelines for drinking-water quality (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects reviewing selected microorganisms was published in 2002.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of public drinking-water quality is accordingly prepared/updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants examined in drinking-water.

For each chemical contaminant or substance considered, a lead institution prepared a health criteria document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Denmark, Finland, France, Germany, Italy, Japan, Netherlands, Norway, Poland, Sweden, United Kingdom and United States of America prepared the requested health criteria documents.

Under the responsibility of the coordinators for a group of chemicals considered in the guidelines, the draft health criteria documents were submitted to a number of scientific institutions and selected experts for peer review. Comments were taken into consideration by the coordinators and authors before the documents were submitted for final evaluation by the experts meetings. A "final task force" meeting reviewed the health risk assessments and public and peer review comments and, where appropriate, decided upon guideline values. During preparation of the third edition of the GDWQ, it was decided to include a public review via the world wide web in the process of development of the health criteria documents.

During the preparation of health criteria documents and at experts meetings, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health

Criteria monographs and Concise International Chemical Assessment Documents, the International Agency for Research on Cancer, the joint FAO/WHO Meetings on Pesticide Residues, and the joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO internet site and in the current edition of the GDWQ.

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GENERAL DESCRIPTION

Identity

Lead is the commonest of the heavy elements, accounting for 13 mg/kg of the earth's crust. Several stable isotopes of lead exist in nature, including, in order of abundance, ^{208}Pb, ^{206}Pb, ^{207}Pb, and ^{204}Pb.

Physicochemical properties

Property	*Value*
Physical state	Soft metal
Melting point	327 °C

Major uses

Lead is used in the production of lead acid batteries, solder, alloys, cable sheathing, pigments, rust inhibitors, ammunition, glazes, and plastic stabilizers (*1*). Tetraethyl and tetramethyl lead are important because of their extensive use as antiknock compounds in petrol, but their use for this purpose has been almost completely phased out in North America and western Europe, though not in eastern Europe or many developing countries. From a drinking-water perspective, the almost universal use of lead compounds in plumbing fittings and as solder in water-distribution systems is important. Lead pipes may be used in older distribution systems and plumbing (*2*).

ANALYTICAL METHODS

Atomic absorption spectrometry and anodic stripping voltammetry are the methods most frequently used for determining the levels of lead in environmental and biological materials. Detection limits of less than 1 µg/litre can be achieved by means of atomic absorption spectrometry (*3*). Because corrosion of plumbing systems is an important source of excessive lead in drinking-water, lead levels in water should be measured at the tap, rather than at the drinking-water source, when estimating human exposure.

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Air

Concentrations of lead in air depend on a number of factors, including proximity to roads and point sources. Annual geometric mean concentrations measured at more than 100 stations across Canada declined steadily from 0.74 µg/m^3 in 1973 to 0.10 µg/m^3 in 1989 (*4,5*), reflecting the decrease in the use of lead additives in petrol. Typical quarterly averages for urban areas without significant point sources in the USA in 1987 were in the range 0.1–0.3 µg/m^3; in the vicinity of major point sources, such as lead smelters and battery plants, air levels typically ranged from 0.3 to 4.0 µg/m^3 (*6*). Levels at three locations in Barcelona (Spain) during the winter of 1985 ranged from 0.9 to 2.5 µg/m^3 (*7*), presumably reflecting heavy use of leaded petrol. The overall means in London and in a rural area of Suffolk in 1984–85 were 0.50 µg/m^3 (range 0.23–0.82) and 0.10 µg/m^3 (range 0.05–0.17), respectively (*8*). Levels of lead in 1983 in the Norwegian Arctic, an area remote from urban influences, varied between 0.1–0.3 and 0.3–9.0 ng/m^3 (*9*).

If an average concentration in air of 0.2 µg/m^3 is assumed, the intake of lead from air can be calculated to range from 0.5 µg/day for an infant to 4 µg/day for an adult.

Water

With the decline in atmospheric emissions of lead since the introduction of legislation restricting its use in fuels, water has assumed new importance as the largest controllable source of lead exposure in the USA (*10*).

Lead is present in tapwater to some extent as a result of its dissolution from natural sources but primarily from household plumbing systems in which the pipes, solder, fittings, or service connections to homes contain lead. PVC pipes also contain lead compounds that can be leached from them and result in high lead concentrations in drinking-water. The amount of lead dissolved from the plumbing system depends on several factors, including the presence of chloride and dissolved oxygen, pH, temperature, water softness, and standing time of the water, soft, acidic water being the most plumbosolvent (*11,12*). Although lead can be leached from lead piping indefinitely, it appears that the leaching of lead from soldered joints and brass taps decreases with time (*10*). Soldered connections in recently built homes fitted with copper piping can release enough lead (210–390 µg/litre) to cause intoxication in children (*13*). The level of lead in drinking-water may be reduced by corrosion-control measures such as the addition of lime and the adjustment of the pH in the distribution system from <7 to 8–9 (*14,15*).

In 1988, it was estimated that a lead level of 5 µg/litre was exceeded in only 1.1% of public water-distribution systems in the USA (*16*). A more recent review of lead levels in drinking-water in the USA found the geometric mean to be 2.8 µg/litre (*10*). The median level of lead in drinking-water samples collected in five Canadian cities was 2.0 µg/litre (*17*). A recent study in Ontario (Canada) found that the average concentration of lead in water actually consumed over a one-week sampling period was in the range 1.1–30.7 µg/litre, with a median level of 4.8 µg/litre (*18*). In the United Kingdom in 1975–76, there was virtually no lead in the drinking-water in two-thirds of households, but in 10% of homes in England and 33% in Scotland levels were above 50 µg/litre (*2*). In Glasgow (Scotland), where the water was known to be plumbosolvent, the lead concentration in about 40% of the samples exceeded 100 µg/litre (*19*).

If a concentration of 5 µg/litre in drinking-water is assumed, the total intake of lead from this source can be calculated to range from 3.8 µg/day for an infant to 10 µg/day for an adult.

Food

Prepared food contains small but significant amounts of lead. Lead content is increased when the water used for cooking or the cooking utensils contain lead, or the food, especially if acidic, has been stored in lead-ceramic pottery ware or lead-soldered cans. The intake of lead from lead-soldered cans is declining as the use of lead-free solders becomes more widespread in the food processing industry (*2,20*).

A number of estimates based on figures for per capita consumption have been made of the daily dietary lead intake, e.g. 27 µg/day in Sweden (*21*); 66 µg/day in Finland (*22*); and 23 µg/day for a 2-year-old in the USA (*23*). Estimates obtained from duplicate diet studies are in the same range and include a mean dietary intake for all food and drink of about 40 µg/day for mothers and 30 µg/day for children aged 5–7 years in England (*8*) and 53.8 µg/day (0.8 µg/kg of body weight per day) for the intake of lead from food for adolescents and adults in Canada (*17*). Lead intakes for adults were 90 µg/day in Belgium, 24 µg/day in Sweden, and 177 µg/day in Mexico, based on faecal monitoring of lead (*24*). In some countries, dietary intakes as high as 500 µg/day have been reported (*20*). The regular consumption of wine can also result in a significant increase in lead intake; an average level of 73 µg/litre has been reported (*25*).

Other routes of exposure

Soils and household dust are significant sources of lead exposure for small children (*6,26,27*), but the levels are highly variable, ranging from <5 µg/g to tens of milligrams per gram in contaminated areas. As lead is immobile, levels in contaminated soil will remain essentially unchanged unless action is taken to decontaminate them (*28*). The highest lead concentrations usually occur in surface soil at depths of 1–5 cm.

In a 2-year study in England during 1984 and 1985, the geometric mean concentrations of lead in road dust collected in the vicinity of two London schools and in a rural area were 1552–1881 and 83–144 µg/g, respectively. For household dusts in London and in a rural area of Suffolk for 3 consecutive years (1983–85) the geometric mean concentrations were 857 and 333 µg/g, respectively (*8*). Household dust concentrations were 332 µg/g in an Edinburgh study (*29*) and 424 µg/g in one in Birmingham (*30*).

The amount of soil ingested by children aged 1–3 years is about 40–55 mg/day (*27,31,32*). A comprehensive study of a group of 2-year-old urban children indicated an intake of lead from dust of 42 µg/day, almost twice the dietary lead intake (*30*). Studies in inner-city areas in the USA have shown that peeling paint or dust originating from leaded paint during removal may contribute significantly to children's exposure to lead (*33*).

Estimated total exposure and relative contribution of drinking-water

More than 80% of the daily intake of lead is derived from the ingestion of food, dirt, and dust. At 5 µg/litre, the average daily intake of lead from water forms a relatively small proportion of the total daily intake for children and adults but a significant one for bottle-fed infants. Such estimates have a wide margin of error, as it is not known to what extent the general public flushes the system before using-tap water; in addition, the stagnation time (and hence the lead levels) is highly variable (*10*). The contribution of ingested dust and dirt to the total intake is known to vary with age, peaking around 2 years (*32*).

KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Adults absorb approximately 10% of the lead contained in food (*6*), but young children absorb 4–5 times as much (*34,35*); the gastrointestinal absorption of lead from ingested soil and dust by children has been estimated to be close to 30% (*26*). Absorption is increased when the dietary intakes of iron or calcium and phosphorus are low (*36–38*). Iron status is particularly important, as children from disadvantaged homes are more likely to suffer from anaemia, further increasing their absorption of lead (*39*).

The principal vehicle for the transport of lead from the intestine to the various body tissues is the red blood cell (*40*), in which lead is bound primarily to haemoglobin and has a special affinity for the beta, delta and, in particular, fetal gamma chains (*41*). Following its absorption, lead appears both in a soft tissue pool, consisting of the blood, liver, lungs, spleen, kidneys, and bone marrow, which is rapidly turned over, and in a more slowly turned over skeletal pool. The half-life of lead in blood and soft tissues is about 36–40 days for adults (*42*), so that blood lead concentrations reflect only the intake of the previous 3–5 weeks. In the skeletal pool, the half-life of lead is approximately 17–27 years (*42,43*). In adults, some 80–95% of the total body burden of lead is found in the skeleton, as compared with about 73% in children (*44,45*). The biological half-life of lead may be considerably longer in children than in adults (*46*). Under conditions of extended chronic exposure, a steady-state distribution of lead between various organs and systems usually exists (*6*), and the blood lead concentration can therefore be used as a reasonably good indicator of exposure from all sources (*47*); the relationship between them is generally thought to be curvilinear in character (*2,19*).

Placental transfer of lead occurs in humans as early as week 12 of gestation, and uptake of lead by the fetus continues throughout development (*48*). The concentration of lead in umbilical cord blood is 80–100% of the maternal blood lead level; the same applies to blood lead in the fetus (*49–52*).

Inorganic lead is not metabolized in the body. Unabsorbed dietary lead is eliminated in the faeces, and lead that is absorbed but not retained is excreted unchanged via the kidneys or through the biliary tract (*53*). Metabolic balance studies in infants and young children indicated that, at intakes greater than 5 µg/kg of body weight per day, net retention of lead averaged 32% of intake, whereas retention was negative (i.e. excretion exceeded intake) at intakes less than 4 µg/kg body weight per day (*35*). No increases in blood lead were observed in infants with low exposure to other sources of lead and mean dietary intakes of 3–4 µg/kg of body weight per day (*54*), thus confirming the metabolic data.

EFFECTS ON LABORATORY ANIMALS AND *IN VITRO* TEST SYSTEMS

Neurological effects

Research on young primates has demonstrated that exposure to lead results in significant behavioural and cognitive deficits, e.g. impairment of activity, attention, adaptability, learning ability, and memory, as well as increased distractibility. Such effects have been observed following postnatal exposure of monkeys to lead for 29 weeks in amounts resulting in blood lead levels ranging from 10.9 to 33 µg/dl (*55*). These effects persisted into young adulthood, even after levels in the blood had returned to 11–13 µg/dl, and were maintained for the following 8–9 years (*56*). Studies on small groups of monkeys dosed continuously from birth onwards with 50 or 100 µg/kg of body weight per day showed that at 7–8 years of age there were still significant deficits in both short-term memory and spatial learning (*57*).

Reproductive toxicity, embryotoxicity, and teratogenicity

Effects on sperm counts and on the testicles (testicular atrophy) in male rats and on estrous cycles in female rats have been observed at blood lead levels above 30 µg/100 ml (*58,59*).

Mutagenicity and related end-points

Results of studies on the genotoxicity of lead are conflicting (*54,60–62*), but most suggest that some lead salts are genotoxic. Lead chloride, ethanoate, oxide, and tetroxide were inactive in mutagenicity tests on a number of prokaryotes and fungi, including *Salmonella typhimurium* and *Saccharomyces cerevisiae*. *In vitro* tests on human cells were positive for chromosomal damage in one case and negative in two others. *In vivo* short-term tests on mice, rats, cattle, and monkeys were positive in three cases (dominant lethal test and chromosome damage to bone marrow cells) but negative in five others (*60,61*).

Carcinogenicity

Renal tumours have been induced in rats, mice, and hamsters exposed orally to high levels of lead ethanoate, subacetate, or phosphate in the diet. In one study, 5, 18, 62, 141, 500, 1000, or 2000 mg of lead per kg of diet (about 0.3, 0.9, 3, 7, 27, 56, and 105 mg/kg of body weight per day) were fed to rats for 2 years. Renal tumours (mostly tubular epithelial adenomas) developed in male rats at 500, 1000, and 2000 mg/kg, but only at 2000 mg/kg in female rats (*53,62,63*).

EFFECTS ON HUMANS

Lead is a cumulative general poison, infants, children up to 6 years of age, the fetus, and pregnant women being the most susceptible to adverse health effects. Its effects on the central nervous system can be particularly serious.

Acute and long-term exposure

Overt signs of acute intoxication include dullness, restlessness, irritability, poor attention span, headaches, muscle tremor, abdominal cramps, kidney damage, hallucinations, and loss of memory, encephalopathy occurring at blood lead levels of 100–120 µg/dl in adults and 80–100 µg/dl in children. Signs of chronic lead toxicity, including tiredness, sleeplessness, irritability, headaches, joint pain, and gastrointestinal symptoms, may appear in adults at blood lead levels of 50–80 µg/dl. After 1–2 years of exposure, muscle weakness, gastrointestinal symptoms, lower scores on psychometric tests, disturbances in mood, and symptoms of peripheral neuropathy were observed in occupationally exposed populations at blood lead levels of 40–60 µg/dl (*6*).

Renal disease has long been associated with lead poisoning; however, chronic nephropathy in adults and children has not been detected below blood lead levels of 40 µg/dl (*64,65*). Damage to the kidneys includes acute proximal tubular dysfunction and is characterized by the appearance of prominent inclusion bodies of a lead–protein complex in the proximal tubular epithelial cells at blood lead concentrations of 40–80 µg/dl (*66*).

There are indications of increased hypertension at blood lead levels greater than 37 µg/dl (*67*). A significant association has been established, without evidence of a threshold, between blood lead levels in the range 7–34 µg/dl and high diastolic blood pressure in people aged 21–55, based on data from the second US National Health and Nutrition Examination Survey (NHANES II) (*68,69*). The significance of these results has been questioned (*70*).

Lead interferes with the activity of several of the major enzymes involved in the biosynthesis of haem (*6*). The only clinically well-defined symptom associated with the inhibition of haem biosynthesis is anaemia (*40*), which occurs only at blood lead levels in excess of 40 µg/dl in children and 50 µg/dl in adults (*71*). Lead-induced anaemia is the result of two separate processes: the inhibition of haem synthesis and an acceleration of erythrocyte destruction (*40*). Enzymes involved in the synthesis of haem include d-aminolaevulinate synthetase (whose activity is indirectly induced by feedback inhibition, resulting in accumulation of d-aminolaevulinate, a neurotoxin) and d-aminolaevulinic acid dehydratase (d-ALAD), coproporphyrinogen oxidase, and ferrochelatase, all of whose activities are inhibited (*6,40*). The activity of d-ALAD is a good predictor of exposure at both environmental and industrial levels, and inhibition of its activity in children has been noted at a blood lead level as low as 5 µg/dl (*72*); however, no adverse health effects are associated with its inhibition at this level.

Inhibition of ferrochelatase by lead results in an accumulation of erythrocyte protoporphyrin (EP), which indicates mitochondrial injury (*47*). NOAELs for increases in EP levels in infants and children exist at about 15–17 µg/dl (*73–75*). In adults, the NOAEL for increases in EP levels ranged from 25 to 30 µg/dl (*76*); for females alone, the NOAEL ranged from 20 to 25 µg/dl, which is closer to that observed for children (*74,77,78*). Changes in growth patterns in infants younger than 42 months of age have been associated with increased levels of EP; persistent increases in levels led initially to a rapid gain in weight but subsequently to a retardation of growth (*79*). An analysis of the NHANES II data showed a highly significant negative correlation between the stature of children aged 7 years and younger and blood lead levels in the range 5–35 µg/dl (*80*).

Lead has also been shown to interfere with calcium metabolism, both directly and by interfering with the haem-mediated generation of the vitamin D precursor 1,25-dihydroxycholecalciferol. A significant decrease in the level of circulating 1,25-dihydroxycholecalciferol has been demonstrated in children whose blood lead levels were in the range 12–120 µg/dl, with no evidence of a threshold (*81,82*). Tissue lead content is increased in calcium-deficient persons, a fact that assumes great importance in the light of the increased sensitivity to lead exposure that could result from the calcium-deficient status of pregnant women. It has also been demonstrated that interactions between calcium and lead were responsible for a significant portion of the variance in the scores on general intelligence ratings, and that calcium influenced the deleterious effect of lead (*83*). The regulatory enzyme brain protein, kinase C, is stimulated *in vitro* by picomolar lead concentrations (an effect similar to that produced by micromolar calcium concentrations), levels that could be expected from environmental exposure (*84*).

Several lines of evidence demonstrate that both the central and peripheral nervous systems are the principal targets for lead toxicity. The effects include subencephalopathic neurological and behavioural effects in adults, and there is also electrophysiological evidence of effects on the nervous system of children at blood lead levels well below 30 µg/dl. Aberrant electroencephalograph readings were significantly correlated with blood levels down to 15 µg/dl (*85,86*). Significant reductions in maximal motor nerve conduction velocity (MNCV) have been observed in children aged 5–9 years living near a smelter, with a threshold occurring at a blood lead level around 20 µg/dl; a 2% decrease in the MNCV was seen for every 10 µg/dl increase in the blood lead level (*87*). The auditory nerve may be a target for lead toxicity, in view of reports of reduced hearing acuity in children (*88*). In the NHANES II survey in the USA, the association with blood lead was highly significant at all levels from 5 to 45 µg/dl for children 4–19 years old, with a 10–20% increased likelihood of an elevated hearing threshold for persons with a blood lead level of 20 µg/dl as compared with 4 µg/dl (*89*). The NHANES II data also showed that blood lead levels were significantly associated with the age at which infants first sat up, walked, and started to speak. Although no threshold existed for the age at which the child first walked, thresholds existed at the 29th and 28th percentile of lead rank for the age at which the child sat up and spoke, respectively (*89*).

Reproductive effects

Gonadal dysfunction in men, including depressed sperm counts, has been associated with blood lead levels of 40–50 µg/dl (*90–93*). Reproductive dysfunction may also occur in females occupationally exposed to lead (*6,61*).

Epidemiological studies have shown that exposure of pregnant women to lead increases the risk of preterm delivery. In a study of 774 pregnant women in Port Pirie who were followed to the completion of their pregnancy, the relative risk of preterm delivery was more than four times higher among women with blood lead levels above 14 µg/dl than in those with 8 µg or less per dl (*94*).

Elevated cord blood lead levels were associated with minor malformations, such as angiomas, syndactylism, and hydrocele, in about 10% of all babies. The relative risk of malformation doubled at blood lead levels of about 7–10 µg/dl, and the incidence of any defect increased with increasing cord lead levels over the range 0.7–35.1 µg/dl (*95*).

Mutagenicity

Cytogenetic studies in humans exposed to lead (blood lead levels >40 µg/dl) have given conflicting results; chromatid and chromosomal aberrations, breaks, and gaps were reported in 9 of 16 studies but not in the remainder (*60,61*).

Carcinogenicity

The carcinogenicity of lead in humans has been examined in several epidemiological studies, which either have been negative or have shown only very small excess mortalities from cancers. In most of these studies, there were either concurrent exposures to other carcinogenic agents or other confounding factors such as smoking that were not considered (*60,61*). A study on 700 smelter workers (mean blood level 79.7 µg/litre) and battery factory workers (mean blood level 62.7 µg/litre) indicated an excess of deaths from cancer of the digestive and respiratory systems (*96*), the significance of which has been debated (*97,98*). There was also a nonsignificant increase in urinary tract tumours in production workers. In a study on lead smelter workers in Australia, no significant increase in cancers was seen, but there was a substantial excess of deaths from chronic renal disease (*99*). IARC considers that the overall evidence for carcinogenicity in humans is inadequate (*60*).

Neurological effects in infants and children

A number of cross-sectional and longitudinal epidemiological studies have been designed to investigate the possible detrimental effects that exposure of young children to lead might have on their intellectual abilities and behaviour. These studies have been concerned with documenting effects arising from exposure to "low" levels of lead (i.e. blood lead <40 µg/dl), at which overt clinical symptoms are absent. Several factors affect the validity of the conclusions drawn from them (*100*), including the statistical power of the study, the effect of bias in the selection of study and control populations, the choice of parameter used to evaluate lead exposure, the temporal relationship between exposure measurement and psychological evaluations, the extent to which the neurological and behavioural tests used can be quantified accurately and reproducibly, which confounding covariates are included in any multiple regression analysis, and the effect of various nutritional and dietary factors, such as iron and calcium intake (*39*).

Cross-sectional studies

A number of cross-sectional studies have been carried out in which many of the above factors were taken into account. In one such study in the USA, a group of 58 children aged 6–7 years with "high" dentine lead levels (corresponding to a blood lead level of approximately 30–50 µg/dl) performed significantly less well than 100 children from a “low” lead group (mean blood lead level 24 µg/dl). The children's performance was measured using the Wechsler intelligence test in addition to other visual and auditory tests and teachers' behavioural ratings (*101*). There was a significant difference of 4 points and a uniform downward shift in IQ scores. Although this study found that a child in the group with "high" dentine lead was three times more likely to have an IQ of 80 or lower than one in the "low" lead group, it was claimed in a 1986 review that the effect was statistically significant only for children with the highest lead levels in dentine (blood lead >40 µg/dl) (*6*).

A similar study in which lead in dentine was used as the indicator of exposure was carried out on a cohort of 400 children in the United Kingdom (*102*). There were several consistent but nonsignificant differences between the high- and low-lead groups similar to those observed in the American study, including IQ decrements of about 2 points and poorer scores in behaviour indices. In the British study, mean blood lead levels in the "high" exposure group (15.1 µg/dl) were lower than the mean of the “low” group (24 µg/dl) in the American study, which may explain why the results lacked statistical significance. The results of studies on children in Germany (*103–105*) were similar to those of the British study, in that the effect of lead on behaviour was only of borderline significance.

In another study (*106*) involving 500 Edinburgh schoolchildren aged 6–9 years, a small (up to 5 points in the British Ability Scales) but significant negative relationship was found between

blood lead levels and intelligence scores, reading skills, and number skills. There was a dose–response relationship in the range 5.6–22.1 µg/dl. The effect of lead was small compared with that of several of the other 33 variables considered. A series of studies (*107–109*) on about 800 children in the United Kingdom with blood lead levels between 4 and 32 µg/dl failed to find any significant associations between lead and indices of intelligence and behaviour after socioeconomic and family characteristics were taken into account. It was suggested that lead might have a noticeable effect only when other factors predisposing to social disadvantage (particularly low socioeconomic status or poor home environment) are present (*108–110*).

In a cross-sectional study in Lavrion (Greece) involving 509 primary schoolchildren living near a lead smelter, blood lead levels between 7.4 and 63.9 µg/dl (mean 23.7 µg/dl) were recorded (*111*). When the IQ was measured by means of the revised Wechsler Intelligence Scale for Children and due account taken of 17 potential confounders, a significant association was found between blood lead levels and IQ, with a threshold at about 25 µg/dl. Attentional performance was also associated with blood lead levels in two different tests, but no threshold level was found. This study was part of a multicentre collaborative international study on schoolchildren sponsored by WHO and the Commission of the European Communities (*112*). A more or less uniform protocol was used, and quality assurance procedures were applied to the exposure analyses. The most consistent associations were for visual-motor integration as measured by the Bender Gestalt test and for reaction performance as measured by the Vienna Reaction Device. The results of many of the remaining tests were inconsistent. The degree of association between lead exposure and outcome was very weak (<0.8%), even in the statistically significant cases.

The cross-sectional studies are, on balance, consistent in demonstrating statistically significant associations between blood lead levels of 30 µg/dl or more and IQ deficits of about 4 points. Although there were associations between lower blood lead levels and IQ deficits of about 2 points, these were only marginally statistically significant, except in the Edinburgh study. It is particularly difficult to determine minimum levels above which significant effects occur.

Longitudinal studies

Longitudinal studies have the advantage as compared with cross-sectional studies that more precise estimates of exposure can be made; in addition, the reversibility of the effects and the temporal sequence of causality can be investigated. However, such studies also have certain disadvantages: for example, repeated psychometric testing may lead to artefactual results, and there may also be problems of bias associated with attrition within the study population.

The possible relationship between low-level lead exposure during the fetal period and in early childhood and later effects on infant and child development has been investigated in at least six prospective studies, in the USA (Boston, Cincinnati, and Cleveland), Australia (Port Pirie, Sydney), and Scotland (Glasgow). Broadly similar methodologies were used in all the studies to facilitate comparisons. The Bayley Scales of Infant Development or subsets of this test were used to evaluate early cognitive development in verbal and performance skills in infants and young children, whereas the McCarthy Scales of Children's Abilities (MSCA) were used in most studies on older children. In all the studies, except that in Glasgow, the average maternal and cord blood lead concentrations were less than 10 µg/dl (range 6.0–9.5 µg/dl).

In the Boston Lead Study, three groups of infants and young children were classified according to umbilical cord blood lead concentrations, the levels in the low-, middle-, and high-lead groups being <3, 6–7, and 10–25 µg/dl (mean 14.6 µg/dl), respectively. Children were tested twice a year from age 6 months to almost 5 years (*113,114*). After controlling for 12 potential confounders, a significant inverse relationship was demonstrated between fetal

exposure, measured as lead levels in cord blood, and mental development at age 2, as measured using the Bayley Mental Development Index (MDI). There was no significant correlation with the children's current blood lead levels, all of which were less than 8.8 µg/dl. However, the results of testing at almost 5 years, using the McCarthy Scales, showed an attenuation of this association. At 57 months, only the association between intelligence scores and blood lead 3 years previously, at age 2, remained significant after controlling for confounding variables (*114*).

In a longitudinal study involving 305 pregnant women in Cincinnati (*115*), an inverse relationship was found between either prenatal or neonatal blood lead levels and performance in terms both of the Bayley Psychomotor Developmental Index (PDI) and the Bayley MDI at the ages of 3 and 6 months for both male infants and infants from the poorest families. The mean blood lead levels for neonates and their mothers were 4.6 and 8.2 µg/dl, respectively, and all blood lead levels were below 30 µg/dl. Multiple regression analysis for boys only showed that, for every increment of 1 µg/dl in the prenatal blood lead level, the covariate-adjusted Bayley MDI at 6 months of age decreased by 0.84 points. The inverse relationship between MDI and prenatal blood lead disappeared at age 1, because it was accounted for, and mediated through, the effect of lead on birth weight; however, the Bayley PDI was still significantly related to maternal blood lead (*116*).

In a prospective study of design similar to that of the Boston study, undertaken at Port Pirie, a lead smelter town in Australia, 537 children were studied from birth to 4 years (*117*). The cohort was divided into four groups on the basis of maternal and umbilical blood lead, which ranged from a geometric mean of 0.21 to 0.72 µmol/litre (4.3–14.9 µg/dl). The mean blood lead level varied from 9.1 µg/dl at mid-pregnancy to 21.3 and 19 µg/dl at 2 and 4 years, respectively. The integrated postnatal average blood lead level was 19.1 µg/dl. At 6, 15, 24, and 36 months, the developmental status of the child was assessed by means of the Bayley MDI; the MSCA were used at 4 years. At each age, a consistent but weak inverse relationship was found between concurrent postnatal blood lead levels and MSCA scores; no allowance was made for possible confounding factors. No such relationship was found for perinatal blood lead. After 18 covariates considered to be potential confounders were incorporated in the multivariate analysis, the integrated blood lead level showed the strongest inverse relation with the General Cognitive Index (GCI) score (a subset of the McCarthy Scales) at age 4 years, which suggests that the detrimental effect of lead on child development is cumulative during early childhood. Repeated analysis restricted to children whose blood lead levels were below 25 µg/dl showed that the inverse relationship with the GCI score was as strong for this group as for the cohort as a whole, thus demonstrating the absence of a clear threshold below which a detrimental effect of lead on child development does not occur.

A number of prospective studies have failed to show any consistent association between mental development and blood lead, either during the perinatal period or in early childhood. In a study carried out on extremely socially disadvantaged mothers and infants in Cleveland, Ohio (USA), no relationship was found between blood lead at any time and language development, MDI, or the results of the Stanford-Binet IQ test at age 3 years, after confounding factors, the most important of which was the care-giving environment, were taken into account. In this cohort, half the mothers had alcohol-related problems, and the average maternal IQ was 79 (*118*). In a second Australian study carried out in Sydney on a relatively prosperous population of 318 mothers and children, no association was found between blood lead in the mother or the child at any age and mental or motor deficits at age 4 years, after account was taken of six covariates, including the HOME score (a measure of the care-giving environment) (*119*). A third negative study was that carried out in Glasgow (Scotland), where the primary exposure was to high lead levels in water which were dramatically reduced by corrosion-control measures shortly after the children were born. The cohort was divided into high, medium, and low groups, on the basis of maternal blood lead, with means of 33.1, 17.7, and 7.0 µg/dl, respectively. Although the expected decrements in

scores in the Bayley MDI and PDI were observed at ages 1 and 2 years as lead exposure increased, they could be better accounted for by birth weight, home environment, and socioeconomic status, as shown by stepwise multiple regression analysis (*120*).

The results of the prospective studies have been somewhat disappointing because of the inconsistency between studies. It appears that prenatal exposure may have early effects on mental development, but that these do not persist up to age 4, at least not as shown by the tests so far used. There are indications that these early effects may be mediated through birth weight or other factors. Several studies indicated that the generally higher exposures of children in the 18–36-month age range may be negatively associated with mental development, but this, too, has not been confirmed by other studies.

GUIDELINE VALUE

The evidence for the carcinogenicity of lead in humans is inconclusive because of the limited number of studies, the small cohort sizes, and the failure to take adequate account of potential confounding variables. However, an association has been demonstrated experimentally between the ingestion of lead salts and renal tumours. Lead and inorganic lead compounds have therefore been placed in Group 2B of the IARC classification, namely possible human carcinogen (evidence inadequate in humans, sufficient in animals) (*60*).

As there is evidence from human studies that adverse effects other than cancer may occur at very low lead levels, and that a guideline thus derived would also be protective for carcinogenic effects, it is considered appropriate to derive the guideline using the TDI approach.

In 1986, JECFA established a provisional tolerable weekly intake (PTWI) of 25 µg of lead per kg of body weight (equivalent to 3.5 µg/kg of body weight per day) for infants and children which took account of the fact that lead is a cumulative poison so that any increase in the body burden of lead should be avoided (*71*). The PTWI was based on metabolic studies in infants (*35,54*) showing that a mean daily intake of 3–4 µg/kg of body weight was not associated with an increase in blood lead levels or in the body burden of lead, whereas an intake of 5 µg/kg of body weight or more resulted in lead retention. This PTWI was reconfirmed by JECFA in 1993 and extended to all age groups (*121*).

On the assumption of a 50% allocation to drinking-water for a 5-kg bottle-fed infant consuming 0.75 litres of drinking-water per day, the guideline value is 0.01 mg/litre. As infants are considered to be the most sensitive subgroup of the population, this guideline value will also be protective for other age groups.

Lead is exceptional in that most lead in drinking-water arises from plumbing in buildings and the remedy consists principally of removing plumbing and fittings containing it. This requires time and money, and it is recognized that not all water will meet the guideline immediately. Meanwhile, all other practical measures to reduce total exposure to lead, including corrosion control, should be implemented.

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