WHO/FWC/WSH/16.53

Lead in Drinking-water

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

This document is a revision of document reference number WHO/SDE/WSH/03.04/09/Rev/1, published in 2011. Revisions are indicated with a vertical line in the left margin.

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

Preface

Access to safe drinking-water is essential to health, a basic human right and a component of effective policy for health protection. A major World Health Organization (WHO) function to support access to safe drinking-water is the responsibility "to propose ... regulations, and to make recommendations with respect to international health matters ....", including those related to drinking-water safety and management.

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 third edition of the GDWQ was published in 2004, the first addendum to the third edition was published in 2006 and the second addendum to the third edition was published in 2008. The fourth edition was published in 2011, and the first addendum to the fourth edition was published in 2016.

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 and 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 of potential health concern in drinking-water. In the first and second editions, these constituted Volume 2 of the GDWQ. Since publication of the third edition, they comprise a series of free-standing monographs, including this one.

For each chemical contaminant or substance considered, a background document evaluating the risks for human health from exposure to the particular chemical in drinking-water was prepared. Institutions from Canada, Japan, the United Kingdom and the United States of America (USA) prepared the documents for the fourth edition.

During the preparation of this background document, 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 Meeting 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.

Acknowledgements

The current version of Lead in Drinking-water, Background document for development of WHO *Guidelines for Drinking-water Quality*, is an update of the background document originally prepared for the second edition of the Guidelines.

The work of the following working group coordinators was crucial in the development of this document and others contributing to the fourth edition:

Dr J. Cotruvo, J. Cotruvo & Associates, USA (*Materials and chemicals*)
Professor J.K. Fawell, United Kingdom (*Naturally occurring and industrial contaminants* and *Pesticides*)
Ms M. Giddings, Health Canada (*Disinfectants and disinfection by-products*)
Mr P. Jackson, WRc-NSF, United Kingdom (*Chemicals – practical aspects*)
Professor Y. Magara, Hokkaido University, Japan (*Analytical achievability*)
Dr A.V. Festo Ngowi, Muhimbili University of Health and Allied Sciences, United Republic of Tanzania (*Pesticides*)
Dr E. Ohanian, Environmental Protection Agency, USA (*Disinfectants and disinfection by-products*)

The draft text was discussed at the Expert Consultation for the fourth edition of the GDWQ, held in December 2011. The version for the fourth edition takes into consideration comments from both peer reviewers and the public. Updates made for the first addendum of the fourth edition were prepared by J.K. Fawell. The input of those who provided comments and of participants at the meeting is gratefully acknowledged.

The WHO coordinators were Mr R. Bos and Mr B. Gordon, WHO Headquarters. Ms C. Vickers provided a liaison with the International Programme on Chemical Safety, WHO Headquarters. Mr M. Zaim, Public Health and the Environment Programme, WHO Headquarters, provided input on pesticides added to drinking-water for public health purposes.

Ms P. Ward provided invaluable administrative support throughout the review and publication process. Ms M. Sheffer of Ottawa, Canada, was responsible for the scientific editing of the document.

Many individuals from various countries contributed to the development of the GDWQ. The efforts of all who contributed to the preparation of this document and in particular those who provided peer or public domain review comments are greatly appreciated.

Acronyms and abbreviations used in the text

ALAD	aminolaevulinic acid dehydratase
EP	erythrocyte protoporphyrin
FAO	Food and Agriculture Organization of the United Nations
GCI	General Cognitive Index
IARC	International Agency for Research on Cancer
IQ	intelligence quotient
JECFA	Joint FAO/WHO Expert Committee on Food Additives
MDI	Mental Development Index
MNCV	motor nerve conduction velocity
MSCA	McCarthy Scales of Children's Abilities
NHANES	National Health and Nutrition Examination Survey (USA)
NOAEL	no-observed-adverse-effect level
PDI	Psychomotor Developmental Index
PTWI	provisional tolerable weekly intake
PVC	polyvinyl chloride
USA	United States of America
WHO	World Health Organization

Table of contents

1. GENERAL DESCRIPTION

1.1 Identity

Lead is the commonest of the heavy elements, accounting for 13 mg/kg of 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.

1.2 Physicochemical properties

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

1.3 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 in many countries their use for this purpose has been almost completely phased out. Although lead is occasionally found in source water, the most important source of lead from a drinking-water perspective is lead pipes in older systems with lead service connections (between the water mains and the building) and lead plumbing. Lead solder and lead in alloy fittings can also be important sources of lead in drinking-water (*2*).

2. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

2.1 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 United States of America (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.

2.2 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 tap water to some extent as a result of its dissolution from natural sources, but primarily from household plumbing systems in which the pipes, solder, fittings (including alloy fittings with high lead content) or service connections to homes contain lead. Polyvinyl chloride (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, alkalinity, scale in pipes and standing time of the water, with soft, acidic water being the most plumbosolvent (*11*,*12*). Different types of lead corrosion products (scales) form, depending on water chemistry. The divalent lead scales cerussite, hydrocerussite and lead hydroxide generally determine the lead levels at the tap because of their solubility (*125–127*). However, the formation of insoluble tetravalent lead scales (scrutinyite or plattnerite) results from a low oxidant demand bulk water and the presence of free chlorine (*128, 129*). A disinfectant change from free chlorine (especially at higher doses) to chloramination can result in a lower oxidation-reduction potential (ORP) in the water (*130, 131*). This change in ORP results in the conversion of stable tetravalent to soluble divalent lead scales and increased levels of lead at the tap (*132, 133*). Accordingly, significant changes in the water quality of a supply (e.g. changes in treatment or changes of source) can result in changes in plumbosolvency or solubilization of lead deposits, or both.

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/l) 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*). Lead can also be released from particulate lead carbonate deposits on lead pipe and from iron sediment from old galvanized plumbing that has accumulated lead from sources such as plumbing and service connections, even when the water is no longer plumbosolvent.

In 1988, it was estimated that a lead level of 5 µg/l 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/l (*10*). The median level of lead in drinking-water samples collected in five Canadian cities was 2.0 µg/l (*17*). A recent study in Ontario (Canada) found that the average concentration of lead in water actually consumed over a 1-week sampling period was in the range 1.1–30.7 µg/l, with a median level of 4.8 µg/l (*18*). In the United Kingdom in 1975–1976, there was virtually no lead in the drinking-water in two thirds of households, but levels were above 50 µg/l in 10% of homes in England and 33% in Scotland (*2*). In Glasgow (Scotland), where the water was known to be plumbosolvent, the lead concentration in about 40% of the samples exceeded 100 µg/l (*19*).

If a concentration of 5 µg/l 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.

2.3 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—for example, 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/l has been reported (*25*).

2.4 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 (1983–1985), 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*).

Lead in household dust will vary according to activities in the household, such as sanding old lead-based paint and, in some countries, recycling of industrial materials at a household or occupational level.

2.5 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/l, 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*).

3. 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.

4. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

4.1 Neurological effects

Research on young primates has demonstrated that exposure to lead results in significant behavioural and cognitive deficits, such as 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 there were still significant deficits in both short-term memory and spatial learning at 7–8 years of age (*57*).

4.2 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*).

4.3 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*).

4.4 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 kilogram 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*).

5. EFFECTS ON HUMANS

Lead is a cumulative general poison, with 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.

5.1 Acute and long-term exposure

Overt signs of acute intoxication, including dullness, restlessness, irritability, poor attention span, headaches, muscle tremor, abdominal cramps, kidney damage, hallucinations, loss of memory and encephalopathy, occur 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 United States 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*). No-observed-

adverse-effect levels (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 picomole per litre lead concentrations (an effect similar to that produced by micromole per litre 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*).

5.2 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 4 times higher among women with blood lead levels above 14 µg/dl than in those with 8 µg or less per decilitre (*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*).

5.3 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*).

5.4 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/l) and battery factory workers (mean blood level 62.7 µg/l) 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 non-significant 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*). The International Agency for Research on Cancer (IARC) considers that the overall evidence for carcinogenicity in humans is inadequate for lead (*60*), but that inorganic lead compounds are probably carcinogenic to humans (*124*).

5.5 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*).

5.6 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 intelligence quotient (IQ) scores. Although this study found that a child in the group with "high" dentine lead was 3 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 non-significant 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 the World Health Organization (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.

5.7 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/l (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 that 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 used so far. 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.

5.8 2010 Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluation[1]

There is an extensive body of literature on epidemiological studies of lead. Blood is the tissue used most frequently to estimate exposure to lead, and blood lead levels generally reflect exposure in recent months. However, if the level of exposure is relatively stable, then blood lead level is a good indicator of exposure over the longer term. Longitudinal surveys in some countries have shown substantial reductions in population blood lead levels in recent decades. Programmes such as those that have eliminated the use of leaded petrol are considered to be an important factor, resulting in an average reduction of 39% in mean blood lead level over the 5-year period following implementation. Reductions in population blood lead levels in some countries have also been associated with the discontinued use of lead solder in food cans.

Exposure to lead has been shown to be associated with a wide range of effects, including various neurological and behavioural effects, mortality (mainly due to cardiovascular diseases), impaired renal function, hypertension, impaired fertility and adverse pregnancy outcomes, delayed sexual maturation and impaired dental health. IARC concluded that there is *sufficient evidence* in animals but only *limited evidence* in humans for the carcinogenicity of inorganic lead and that inorganic lead compounds are *probably carcinogenic* to humans (group 2A). More recent studies do not indicate that any revision to the IARC conclusions is required.

For children, the weight of evidence is greatest, and evidence across studies is most consistent, for an association of blood lead levels with impaired neurodevelopment, specifically reduction of IQ. Moreover, this effect has generally been associated with lower blood lead concentrations than those associated with the effects observed in other organ systems. Although the estimated IQ decrease per microgram of lead per decilitre of blood is small when viewed as the impact on an individual child (6.9 points over the range of 2.4–30 µg/dl), the decrement is considered to be important when interpreted as a reduction in population IQ. For example, if the mean IQ were

[1] This text has been extracted from references 122 and 123. The interested reader should refer to reference 123 for additional information and primary references.

reduced by 3 points, from 100 to 97, while the standard deviation and other characteristics of the distribution remained the same, there would be an 8% increase in the number of individuals with a score below 100. Moreover, there would be a 57% increase in the number of individuals with an IQ score below 70 (2 standard deviations below the expected population mean, commonly considered to be the cut-off for identifying individuals with an intellectual disability) and a 40% reduction in the number of individuals with an IQ score greater than 130 (considered to be the cut-off for identifying individuals with a "very superior" IQ). Furthermore, the Committee noted that a lead-associated reduction in IQ may be regarded as a marker for many other neurodevelopmental effects for which the evidence is not as robust but which have been observed in children at approximately the same blood lead levels (e.g. attention deficit hyperactivity disorder, reading deficit, executive dysfunction, fine motor deficit).

For adults, the adverse effect for which the weight of evidence is greatest and most consistent is a lead-associated increase in blood pressure. As with the lead-associated reduction in IQ, the increase is small when viewed as the effect on an individual's blood pressure, but important when viewed as a shift in the distribution of blood pressure within a population. Increased blood pressure is associated with increased risk of cardiovascular mortality. In a meta-analysis of 61 prospective studies involving more than 1 million adults, increased blood pressure was associated with age-specific increased mortality rates for ischaemic heart disease and stroke, and the proportional difference in risk associated with a given absolute difference in blood pressure was similar at all blood pressures above 115 mmHg (15 kPa) systolic or 75 mmHg (10 kPa) diastolic.

6. PRACTICAL CONSIDERATIONS

6.1 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/l 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.

6.2 Prevention and control

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, which requires both time and money. In the interim, all practical measures to reduce total exposure to lead, including corrosion control, should be implemented. In new installations or repairs, lead-free solder and low lead alloy fittings should be used to prevent the introduction of contamination. It is extremely difficult to achieve a concentration below 10 µg/l by central conditioning, such as phosphate dosing.

7. PROVISIONAL 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. Lead has therefore been placed in Group 2B of the IARC classification, namely possible human carcinogen (evidence inadequate in humans, sufficient in animals) (*60*). However, inorganic lead compounds have been placed in Group 2A, namely probable human carcinogen (*124*).

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 kilogram 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*).

In the second and third editions of the Guidelines, a guideline value of 0.01 mg/l was derived on the assumption of a 50% allocation of the PTWI to drinking-water for a 5 kg bottle-fed infant consuming 0.75 litre of drinking-water per day. As infants were considered to be the most sensitive subgroup of the population, this guideline value was thought to also be protective for other age groups.

JECFA re-evaluated lead in 2010 (*122,123*), finding that exposure to lead is associated with a wide range of effects, including various neurodevelopmental effects, mortality (mainly due to cardiovascular diseases), impaired renal function, hypertension, impaired fertility and adverse pregnancy outcomes. Impaired neurodevelopment in children is generally associated with lower blood lead concentrations than the other effects, the weight of evidence is greater for neurodevelopmental effects than for other health effects and the results across studies are more consistent than those for other effects. For adults, the adverse effect associated with lowest blood lead concentrations for which the weight of evidence is greatest and most consistent is a lead-associated increase in systolic blood pressure. JECFA concluded that the effects on neurodevelopment and systolic blood pressure provided the appropriate bases for dose–response analyses (*122,123*).

Based on the dose–response analyses, JECFA estimated that the previously established PTWI of 25 µg/kg of body weight is associated with a decrease of at least 3 IQ points in children and an increase in systolic blood pressure of approximately 3 mmHg (0.4 kPa) in adults. These changes are important when viewed as a shift in the distribution of IQ or blood pressure within a population. JECFA therefore concluded that the PTWI could no longer be considered health protective, and it was withdrawn (*122,123*).

Because the dose–response analyses do not provide any indication of a threshold for the key effects of lead, JECFA concluded that it was not possible to establish a new PTWI that would be considered to be health protective. JECFA reaffirmed that because of the neurodevelopmental effects, fetuses, infants and children are the subgroups that are most sensitive to lead (*122*,*123*).

There remain uncertainties associated with the epidemiology, which relate to very low blood lead levels and end-points that are affected by many factors. Nevertheless, because lead exposure arises from a range of sources, of which water is frequently a minor one, and as it is extremely difficult to achieve a concentration lower than 10 µg/l by central conditioning, such as phosphate dosing, the guideline value is maintained at 10 µg/l but is designated as provisional on the basis of treatment performance and analytical achievability. As this is no longer a health-based guideline value, concentrations should be maintained as low as reasonably practical and should not be allowed to increase up to the provisional guideline value.

The sampling protocol adopted will depend on the objective of taking the samples. First-draw samples typically will have the highest lead concentrations, but this may not be reflected in normal use if the same system provides water for toilet flushing, etc. Flushed samples, in contrast, give the most consistent values, but reflect the minimum exposure of the water to lead. The random daytime samples, although most truly reflecting the water that the consumer drinks, give the most variable levels, and so it is necessary to collect more samples to determine the mean level of exposure. If the objective is to identify the presence of lead in the internal plumbing of a building, then the sample should be from the tap (or representative tap) and reflect a worst case.

It needs to be recognized that 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 lead, which requires much time and money. It is therefore emphasized that all other practical measures to reduce total exposure to lead, including corrosion control, should be implemented. In new installations or repairs, lead-free solder and low lead alloy fittings should be used to prevent the introduction of contamination. In addition, monitoring for lead requires a different approach from that taken for most other contaminants, as lead concentrations vary between properties and at different times, depending on the period of time during which the water has been stagnant in contact with the lead surfaces. Normally, monitoring is designed to identify the incidence of plumbing systems that have high lead concentrations with a view to determining management procedures such as corrosion control or providing advice to owners and tenants. Where there is a need to verify that lead solder and/or high-lead fittings have not been installed in new or repaired systems, the approach used is to take a worst-case sample that reflects an extended period of stagnation to maximize the chance of identifying the presence of lead.

8. REFERENCES

1. *Lead—environmental aspects*. Geneva, World Health Organization, 1989 (Environmental Health Criteria, No. 85).

2. Quinn MJ, Sherlock JC. The correspondence between U.K. ‘action levels’ for lead in blood and in water. *Food Additives and Contaminants*, 1990, 7:387–424.

3. International Organization for Standardization. *Water quality—determination of cobalt, nickel, copper, zinc, cadmium and lead*. Geneva, 1986 (ISO 8288:1986).
4. Environment Canada. *National air pollution surveillance annual summary 1988.* Ottawa, 1989 (Report EPS 7/AP/19).
5. Environmental Protection Service. *Urban air quality trends in Canada, 1970–79.* Ottawa, Environment Canada, 1981 (Report EPS 5-AP-81–14).
6. US Environmental Protection Agency. *Air quality criteria for lead.* Research Triangle Park, NC, 1986 (Report EPA-600/8–83/028F).
7. Tomas X et al. Application of pattern recognition to speciation data of heavy metals in suspended particulates of urban air. *Journal of Chemometrics*, 1988, 3:139.
8. Strehlow CD, Barltrop D. Temporal trends in urban and rural blood lead concentrations. *Environmental Geochemistry and Health*, 1987, 9:74.
9. Pacyna JM, Ottar B. Transport and chemical composition of the summer aerosol in the Norwegian Arctic. *Atmospheric Environment*, 1985, 19:2109.
10. Levin R, Schock MR, Marcus AH. Exposure to lead in U.S. drinking water. In: *Proceedings of the 23rd Annual Conference on Trace Substances in Environmental Health.* Cincinnati, OH, US Environmental Protection Agency, 1989.
11. Schock MR. Understanding lead corrosion control strategies. *Journal of the American Water Works Association*, 1989, 81:88.
12. Schock MR. Causes of temporal variability of lead in domestic plumbing systems. *Environmental Monitoring and Assessment*, 1990, 15:59.
13. Cosgrove E et al. Childhood lead poisoning: case study traces source to drinking water. *Journal of Environmental Health*, 1989, 52:346.
14. Moore MR et al. Maternal lead levels after alterations to water supply. *Lancet*, 1981, 2:203–204.
15. Sherlock JC et al. Reduction in exposure to lead from drinking water and its effect on blood lead concentrations. *Human Toxicology*, 1984, 3:383–392.
16. US Environmental Protection Agency. National primary drinking water regulations for lead and copper. *Federal Register*, 1988, 53:31515–31578.
17. Dabeka RW, McKenzie AD, Lacroix GMA. Dietary intakes of lead, cadmium, arsenic and fluoride by Canadian adults: a 24-hour duplicate diet study. *Food additives and contaminants*, 1987, 4:89–101.
18. Department of National Health and Welfare (Canada). *Guidelines for Canadian drinking water quality: supporting documentation*. *Lead.* Ottawa, 1992.
19. Sherlock JC, Quinn MJ. Relationship between blood lead concentrations and dietary lead intake in infants: the Glasgow Duplicate Diet Study 1979–1980. *Food Additives and Contaminants*, 1986, 3:167–176.
20. Galal-Gorchev H. Dietary intake of pesticide residues, cadmium, mercury and lead. *Food Additives and Contaminants*, 1991, 8(6):793–806.
21. Slorach SA et al. Intake of lead, cadmium and certain other metals via a typical Swedish weekly diet. *Vår Föda*, 1983, 35 (Suppl. 1).
22. Varo P, Kovistoinen P. Mineral element composition of Finnish foods. XII. General discussion and nutritional evaluation. *Acta Agriculturae Scandinavica*, 1980, Suppl. 22:165.
23. Gunderson EL. FDA Total Diet Study, April 1982-April 1984, dietary intakes of pesticides, selected elements, and other chemicals. *Journal of the Association of Official Analytical Chemists*, 1988, 71:1200–1209.
24. Karolinska Institute. *Global Environmental Monitoring System (GEMS) assessment of human exposure to lead: comparison between Belgium, Malta, Mexico and Sweden*. Stockholm, 1985.
25. Elinder C-G et al. Wine—an important source of lead exposure. *Food Additives and Contaminants*, 1988, 5:641–644.
26. Drill S et al. *The environmental lead problem: an assessment of lead in drinking water from a multi-media perspective*. Washington, DC, US Environmental Protection Agency, 1979 (Report EPA-570/9–79–003).
27. Clausing P, Brunekreef B, van Wijnen JH. A method for estimating soil ingestion by children. *International Archives of Occupational and Environmental Health*, 1987, 59:73–82.
28. Centers for Disease Control. *Preventing lead poisoning in young children.* Atlanta, GA, Department of Health and Human Services, 1985:7–19 (Publ. No. 99–2230).
29. Raab GM, Laxen DPH, Fulton M. Lead from dust and water as exposure sources for children. *Environmental Geochemistry and Health*, 1987, 9:80.
30. Davies DJA et al. Lead intake and blood lead in two-year-old U.K. urban children. *Science of the Total Environment*, 1990, 90:13–29.

31. Calabrese E et al. How much soil do young children ingest: an epidemiologic study. *Regulatory Toxicology and Pharmacology*, 1989, 10:123–137.
32. Van Wijnen JH, Clausing P, Brunekreef B. Estimated soil ingestion by children. *Environmental Research*, 1990, 51:147–162.
33. Mushak P, Crocetti AF. Determination of numbers of lead-exposed American children as a function of lead source: integrated summary of a report to the U.S. Congress on childhood lead poisoning. *Environmental Research*, 1989, 50:210–229.
34. Alexander FW. The uptake of lead by children in differing environments. *Environmental Health Perspectives*, 1974, 7:155–159.
35. Ziegler EE et al. Absorption and retention of lead by infants. *Pediatric research*, 1978, 12:29–34.
36. Van Barneveld AA, Van den Hamer CJA. Drinking water hardness, trace elements and cardiovascular diseases: main effects of Ca and Mg on metabolism of Mn, Pb and Cd in mice. *Nutrition Research*, 1985, Suppl. 1:345.
37. Blake KC, Barbezat GO, Mann M. Effect of dietary constituents on the gastrointestinal absorption of ^{203}Pb in man. *Environmental Research*, 1983, 30:182.
38. Blake KC, Mann M. Effect of calcium and phosphorus on the gastrointestinal absorption of ^{203}Pb in man. *Environmental Research*, 1983, 30:188–194.
39. Mahaffey KR. Nutritional factors in lead poisoning. *Nutrition Reviews*, 1981, 39:353.
40. Moore MR. Haematological effects of lead. *Science of the Total Environment*, 1988, 71:419–431.
41. Ong CN, Lee WR. High affinity of lead for foetal haemoglobin. *British Journal of Industrial Medicine*, 1980, 37:292–298.
42. Rabinowitz MB, Wetherill CW, Kopple JD. Kinetic analysis of lead metabolism in healthy humans. *Journal of clinical investigations*, 1976, 58:260–270.
43. Holtzman RB. Application of radiolead to metabolic studies. In: Nriagu JO, ed. *The biogeochemistry of lead in the environment. Part B.* Amsterdam, Elsevier/North Holland Biomedical Press, 1978:37.
44. Alessio L, Foa V. Lead. In: Alessio L et al., eds. *Human biological monitoring of industrial chemicals series*. Luxembourg, Commission of the European Communities, 1983:107.
45. Barry PSI. Distribution and storage of lead in human tissues. In: Nriagu JO, ed. *The Biogeochemistry of Lead in the Environment. Part B.* Amsterdam, Elsevier/North Holland Biomedical Press, 1978:97.
46. Succop PA, O'Flaherty EJ, Bornschein RL. A kinetic model for estimating changes in the concentration of lead in the blood of young children. In: Lindberg SE, Hutchinson TC, eds. *Heavy Metals in the Environment*. Vol. 2. Edinburgh, CEP Consultants, 1987:289.
47. Mushak P et al. Prenatal and postnatal effects of low-level lead exposure: integrated summary of a report to the U.S. Congress on childhood lead poisoning. *Environmental Research*, 1989, 50:11–36.
48. Barltrop D. Transfer of lead to the human foetus. In: Barltrop D, Burland WL, eds. *Mineral Metabolism in Paediatrics*. Oxford, Blackwell Scientific Publications, 1969:135–151.
49. Angell NF, Lavery JP. The relationship of blood lead levels to obstetric outcome. *American Journal of Obstetrics and Gynecology*, 1982, 142:40–46.
50. Moore MR et al. Some studies of maternal and infant lead exposure in Glasgow. *Scottish Medical Journal*, 1982, 27:113–122.
51. Gershanik JJ, Brooks GG, Little JA. Blood lead values in pregnant women and their offspring. *American Journal of Obstetrics and Gynecology*, 1974, 119:508–511.
52. Lacey RF. Lead in water, infant diet and blood: the Glasgow Duplicate Diet Study. *Science of the Total Environment*, 1985, 41:235–257.
53. Syracuse Research Corporation. *Toxicological profile for lead.* Atlanta, GA, Agency for Toxic Substances and Disease Registry (ATSDR), US Public Health Service and US Environmental Protection Agency, 1990.
54. Ryu JE et al. Dietary intake of lead and blood lead concentration in early infancy. *American Journal of Diseases of Children*, 1983, 137:886–891.
55. Rice DC. Primate research: relevance to human learning and development. *Developmental pharmacology and therapeutics*, 1987, 10:314–327.56. Gilbert SG, Rice DC. Low-level lifetime lead exposure produces behavioural toxicity (spatial discrimination reversal) in adult monkeys. *Toxicology and* applied *pharmacology*, 1987, 91:484–490.
57. Rice DC, Karpinski KF. Lifetime low-level lead exposure produces deficits in delayed alternation in adult monkeys. *Neurotoxicology and teratology*, 1988, 10:207–214.
58. Hilderbrand DC et al. Effect of lead acetate on reproduction. *American Journal of Obstetrics and Gynecology*, 1973, 115:1058–1065.

59. Chowdhury AR, Dewan A, Gandhi DN. Toxic effect of lead on the testes of rat. *Biomedica biochimica acta*, 1984, 43:95–100.
60. International Agency for Research on Cancer. *Overall evaluations of carcinogenicity: an updating of IARC monographs volumes 1–42*. Lyon, 1987:230–232 (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Suppl. 7).
61. International Agency for Research on Cancer. *Some metals and metallic compounds*. Lyon, 1980:325 (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 23).
62. Marcus WL. Lead health effects in drinking water. *Toxicology and Industrial Health*, 1986, 2:363–407.
63. Azar A, Trochimowicz HJ, Maxfield ME. Review of lead studies in animals carried out at Haskell Laboratory: two-year feeding study and response to hemorrhage study. In: Barth D et al., eds. *Environmental health aspects of lead. Proceedings of an International Symposium, October 1972, Amsterdam, The Netherlands*. Luxembourg, Commission of the European Communities, 1973:199–210.
64. Campbell BC et al. Renal insufficiency associated with excessive lead exposure. *British Medical Journal*, 1977, 1:482–485.
65. Lilis R et al. Lead effects among secondary lead smelter workers with blood lead below 80 microgram/100 mL. *Archives of Environmental Health*, 1977, 32:256–266.
66. Ritz E, Mann J, Wiecek A. Does lead play a role in the development of renal insufficiency? *Contributions to Nephrology*, 1988, 64:43–48.
67. Pocock SJ et al. Blood lead concentration, blood pressure, and renal function. *British Medical Journal*, 1984, 289:872–874.
68. Harlan WR et al. Blood lead and blood pressure. Relationship in the adolescent and adult US population. *Journal of the American Medical Association*, 1985, 253:530–534.
69. Pirkle JL et al. The relationship between blood lead levels and blood pressure and its cardiovascular risk implications. *American Journal of Epidemiology*, 1985, 121:246–258.
70. Gartside PS. The relationship between blood lead levels and blood pressure and its cardiovascular risk implications. *American Journal of Epidemiology*, 1986, 124:864–867 (letter).
71. Joint FAO/WHO Expert Committee on Food Additives. *Toxicological evaluation of certain food additives and contaminants*. Cambridge, Cambridge University Press, 1987:223–255 (WHO Food Additives Series, No. 21).
72. Granick JL et al. Studies in lead poisoning. II. Correlation between the ratio of activated to inactivated delta-aminolevulinic acid dehydratase of whole blood and the blood lead level. *Biochemical medicine*, 1973, 8:149–159.
73. Piomelli S et al. Threshold for lead damage to heme synthesis in urban children. *Proceedings of the National Academy of Sciences of the United States of America*, 1982, 79:3335–3339.
74. Roels HA et al. Impact of air pollution by lead on the heme biosynthetic pathway in school-age children. *Archives of Environmental Health*, 1976, 31:310–316.
75. Rabinowitz MB, Leviton A, Needleman HL. Occurrence of elevated protoporphyrin levels in relation to lead burden in infants. *Environmental Research*, 1986, 39:253–257.
76. Grandjean P, Lintrup J. Erythrocyte-Zn-protoporphyrin as an indicator of lead exposure. *Scandinavian Journal of Clinical and Laboratory Investigation*, 1978, 38:669–675.
77. Toriumi H, Kawai M. Free erythrocyte protoporphyrin (FEP) in a general population, workers exposed to low-level lead, and organic-solvent workers. *Environmental Research*, 1981, 25:310–316.
78. Zielhuis RL. Dose–response relationships for inorganic lead. *International Archives of Occupational and Environmental Health*, 1975, 35(1):1–18.
79. Angle CR, Kuntzelman DR. Increased erythrocyte protoporphyrins and blood lead—a pilot study of childhood growth patterns. *Journal of Toxicology and Environmental Health*, 1989, 26:149–156.
80. Schwartz J, Angle C, Pitcher H. Relationship between childhood blood lead levels and stature. *Pediatrics*, 1986, 77:281–288.
81. Rosen JF et al. Reduction in 1,25-dihydroxyvitamin D in children with increased lead absorption. *New England journal of medicine*, 1980, 302:1128–1131.
82. Mahaffey KR et al. Association between age, blood lead concentration, and serum 1,25-dihydroxycholecalciferol levels in children. *American Journal of Clinical Nutrition*, 1982, 35:1327–1331.
83. Lester ML, Horst RL, Thatcher RW. Protective effects of zinc and calcium against heavy metal impairment of children's cognitive function. *Nutrition and Behaviour*, 1986, 3:145.
84. Markovac J, Goldstein GW. Picomolar concentrations of lead stimulate brain protein kinase C. *Nature*, 1988, 334:71–73.

85. Otto DA et al. Effects of age and body lead burden on CNS function in young children. I. Slow cortical potentials. *Electroencephalography and Clinical Neurophysiology*, 1981, 52:229–239.
86. Otto DA et al. Effects of low to moderate lead exposure on slow cortical potentials in young children: two-year follow-up study. *Neurobehavioural toxicology and teratology*, 1982, 4:733–737.
87. Schwartz J et al. Threshold effect in lead-induced peripheral neuropathy. *Journal of Pediatrics*, 1988, 112:12–17.
88. Robinson GS et al. Effects of low to moderate lead exposure on brainstem auditory evoked potentials in children. In: *Neurobehavioural methods in occupational and environmental health.* Copenhagen, WHO Regional Office for Europe, 1985:177 (Environmental Health Series No. 3).
89. Schwartz J, Otto D. Blood lead, hearing thresholds, and neurobehavioral development in children and youth. *Archives of Environmental Health*, 1987, 42:153–160.
90. Lancranjan I. Reproductive ability of workmen occupationally exposed to lead. *Archives of Environmental Health*, 1975, 30:396–401.
91. Wildt K, Eliasson R, Berlin M. Effects of occupational exposure to lead on sperm and semen. In: Clarkson TW, Nordberg GF, Sager PR, eds. *Reproductive and developmental toxicity of metals. Proceedings of a joint meeting, May 1982, Rochester, N.Y.* New York, Plenum Press, 1983:279–300.
92. Cullen MR, Kayne RD, Robins JM. Endocrine and reproductive dysfunction in men associated with occupational inorganic lead intoxication. *Archives of Environmental Health*, 1984, 39:431–440.
93. Assennato G et al. Sperm count suppression without endocrine dysfunction in lead-exposed men. *Archives of environmental health*, 1986, 4:387–390.
94. McMichael AJ et al. The Port Pirie cohort study: maternal blood lead and pregnancy outcome. *Journal of Epidemiology and Community Health*, 1986, 40:18–25.
95. Needleman H et al. The relationship between prenatal lead exposure and congenital anomalies. *Journal of the American Medical Association*, 1984, 251:2956–2959.
96. Cooper WC, Gaffey WR. Mortality of lead workers. *Journal of occupational medicine*, 1975, 17:100–107.
97. Kang HK, Infante PR, Carra JS. Occupational lead exposure and cancer. *Science*, 1980, 20(1):935–936 (letter).
98. Cooper WC, Wong O, Kheifets L. Mortality among employees of lead battery plants and lead producing plants, 1947–1980. *Scandinavian Journal of Work, Environment and Health*, 1985, 11:331–345.
99. McMichael AJ, Johnson HM. Long-term mortality profile of heavily-exposed lead smelter workers. *Journal of occupational medicine*, 1982, 24:375–378.
100. Smith M. The effects of low-level lead exposure on children. In: Smith MA, Grant LD, Sors AI, eds. *Lead exposure and child development: an international assessment*. Boston, MA, Kluwer Academic Publishers, 1989:3.
101. Needleman HL et al. Deficits in psychologic and classroom performance of children with elevated dentine lead levels. *New England Journal of Medicine*, 1979, 300:689–695.
102. Smith M et al. The effects of lead exposure on urban children: the Institute of Child Health/Southampton study. *Developmental Medicine and Child Neurology*, 1983, 25 (Suppl. 47):1–54.
103. Winneke G, Hrdina KG, Brockhaus A. Neuropsychological studies in children with elevated tooth-lead concentrations. I. Pilot study. *International Archives of Occupational and Environmental Health*, 1982, 51:169–183.
104. Winneke G, Kraemer U. Neuropsychological effects of lead in children: interactions with social background variables. *Neuropsychobiology*, 1984, 11:195–202.
105. Winneke G et al. Neuropsychological studies in children with elevated tooth-lead concentrations. II. Extended study. *International Archives of Occupational and Environmental Health*, 1983, 51:231–252.
106. Fulton M et al. Influence of blood lead on the ability and attainment of children in Edinburgh. *Lancet*, 1987, 1:1221–1226.
107. Landsdown RG et al. Blood-lead levels, behaviour, and intelligence: a population study. *Lancet*, 1974, i:538–541.
108. Lansdown R et al. The relationship between blood-lead concentrations, intelligence, attainment and behaviour in a school population: the second London study. *International Archives of Occupational and Environmental Health*, 1986, 57:225–235.
109. Harvey PG et al. Blood lead, behaviour, and intelligence test performance in preschool children. *Science of the Total Environment*, 1984, 40:45–60.
110. Yule W, Rutter M. Effect of lead on children's behaviour and cognitive performance: a critical review. In: Mahaffey K, ed. *Dietary and environmental lead: human health effects*. Amsterdam, Elsevier Science Publishers, 1985.

111. Hatzakis A et al. Psychometric intelligence and attentional performance deficits in lead-exposed children. In: Lindberg SE, Hutchinson TC, eds. *Heavy metals in the environment*, Vol. 1. Edinburgh, CEP Consultants, 1987:204–209.
112. Winneke G et al. Results from the European multicenter study on lead neurotoxicity in children: implications for risk assessment. *Neurotoxicology and Teratology*, 1990, 12:553–559.
113. Bellinger D et al. Longitudinal analyses of prenatal and postnatal lead exposure and early cognitive development. *New England Journal of Medicine*, 1987, 316:1037–1043.
114. Bellinger D et al. Low-level lead exposure and child development; assessment at age five of a cohort followed from birth. In: Lindberg SE, Hutchinson TC, eds. *Heavy metals in the environment*, Vol. 1. Edinburgh, CEP Consultants, 1987:49–53.
115. Dietrich KN et al. Low-level fetal lead exposure effect on neurobehavioral development in early infancy. *Pediatrics*, 1987, 80:721–730.
116. Dietrich KN et al. Neurobehavioural effects of foetal lead exposure: the first year of life. In: Smith MA, Grant LD, Sors AI, eds. *Lead exposure and child development, an international assessment*. Dordrecht, Kluwer Academic Publishers, 1989:320.
117. McMichael AJ et al. Port Pirie cohort study: environmental exposure to lead and children's abilities at the age of four years. *New England Journal of Medicine*, 1988, 319:468–475.
118. Ernhart CB, Greene T. Low-level lead exposure in the prenatal and early preschool periods: language development. *Archives of Environmental Health*, 1990, 45:342–354.
119. Cooney GH et al. Low-level exposures to lead: the Sydney lead study. *Developmental Medicine and Child Neurology*, 1989, 31:640–649.
120. Moore MR, Bushnell IWR, Goldberg A. A prospective study of the results of changes in environmental lead exposure in children in Glasgow. In: Smith MA, Grant LD, Sors AI, eds. *Lead exposure and child development, an international assessment*. Dordrecht, Kluwer Academic Publishers, 1989:371.
121. *Evaluation of certain food additives and contaminants: forty-first report of the Joint FAO/WHO Expert Committee on Food Additives.* Geneva, World Health Organization, 1993 (WHO Technical Report Series, No. 837).
122. *Evaluation of certain food additives and contaminants. Seventy-third report of the Joint FAO/WHO Expert Committee on Food Additives*. Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 960).
123. *Safety evaluation of certain food additives and contaminants.* Geneva, World Health Organization, 2011 (WHO Food Additives Series, No. 64).
124. International Agency for Research on Cancer. *Inorganic and organic lead compounds*. Lyon, 2006 (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 87).
125. Schock, M.R. Response of lead solubility to dissolved carbonate in drinking water. *J. Am. Water Works Assoc*., 1980, 72(12): 695–704.
126. Schock, M.R. Internal corrosion and deposition control. In: *AWWA water quality and treatment: a handbook of community water supplies*. McGraw-Hill, Inc., New York, NY (for the American Water Works Association), 1990.
127. Sheiham, I. and Jackson, P.J. Scientific basis for control of lead in drinking water by water treatment. *Journal of the Institution of Water Engineers and Scientists*, 1981, 35(6), pp.491–515.
128. Schock, M.R., Wagner, I. and Oliphant, R.J. Corrosion and solubility of lead in drinking water. In: *Internal corrosion of water distribution systems*. 2nd edition. American Water Works Association Research Foundation and DVGW Technologiezentrum Wasser, Denver, CO. 1996, pp. 131–230.
129. Schock, M.R., Harmon, S.M., Swertfeger, J. and Lohmann, R. Tetravalent lead: a hitherto unrecognized control of tap water lead contamination. In: *Proceedings of the 2001 AWWA Water Quality Technology Conference, Nashville, TN*. American Water Works Association, Denver, CO 2001.
130. Edwards, M. and Dudi, A. Role of chlorine and chloramine in corrosion of lead-bearing plumbing materials. *J. Am. Water Works Assoc*., 2004, 96(10): 69–81.
131. Lytle, D.A. and Schock, M.R. Formation of Pb(IV) oxides in chlorinated water. *J. Am. Water Works Assoc*., 2005, 97(11): 102–114.
132. Schock, M.R. and Giani, R. (2004) Oxidant/disinfectant chemistry and impacts on lead corrosion. In: *Proceedings of the 2004 AWWA Water Quality Technology Conference, San Antonio, TX*, American Water Works Association, Denver, CO, 2004.
133. Switzer, J.A., Rajasekharan, V.V., Boonsalee, S., Kulp, E.A. and Bohannan, E.M.W. Evidence that monochloramine disinfectant could lead to elevated Pb levels in drinking water. *Environ. Sci. Technol.*, 2006, 40(10): 3384–3387.