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LEAD (addendum)

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1. EXPLANATION

Lead (Pb) occurs in Earth's crust primarily as the mineral galena (lead(II) sulfide) and, to a lesser extent, as anglesite (lead(II) sulfate) and cerussite (lead carbonate). It occurs in the environment both naturally and, to a greater extent, from anthropogenic activities such as mining and smelting, battery manufacturing and the use of leaded petrol (gasoline). Lead contamination of food arises mainly from the environment or from food processing, food handling and food packaging. Atmospheric lead can contaminate food through deposition on agricultural crops. Water is another source of lead contamination of food. Although lead exists in both organic and inorganic forms, only inorganic lead has been detected in food.

Lead was previously evaluated by the Committee at its sixteenth, twenty-second, thirtieth, forty-first and fifty-third meetings (Annex 1, references *30*, *47*, *73*, *107* and *143*). At the sixteenth meeting, the Committee established a provisional tolerable weekly intake (PTWI) of 3 mg of lead per person, equivalent to 50 µg/kg body weight (bw), stating that this did not apply to infants and children. At its twenty-second meeting, the Committee retained the PTWI for adults, noting that establishing a PTWI for children was not yet possible owing to the lack of relevant scientific data. The health risks associated with exposure of infants and children to lead were evaluated at the thirtieth meeting, and a PTWI of 25 µg/kg bw was established for this population group, based on the information that a mean daily exposure to lead of 3–4 µg/kg bw for infants and children was not associated with an increase in blood lead levels. At the forty-first meeting, the Committee withdrew the previous PTWI of 50 µg/kg bw for adults and extended the PTWI of 25 µg/kg bw to all age groups. In these previous evaluations, it was emphasized that the PTWI applied to lead from all sources. At its fifty-third meeting, the Committee was asked to assess the risk of dietary exposure of infants and children to lead. It concluded that current concentrations of lead in food would have very little impact on the neurobehavioural development of infants and children but stressed that a full risk assessment of lead should take other sources of exposure into account.

At its present meeting, the Committee considered information on lead related to the toxicology, epidemiology, exposure assessment and analytical methodology, in particular for a dose–response analysis below blood lead levels of 10 µg/dl, at the request of the Codex Committee on Contaminants in Food.

The literature relating to lead is extensive, and the present Committee used the recent review of the European Food Safety Authority (EFSA, 2010) as the starting point for its evaluation, together with newer studies that were considered to

be informative. Only brief summaries of toxicological effects are given, but studies of the effects critical for the risk assessment are evaluated in more detail. The main emphasis is on studies in humans.

2. BIOLOGICAL DATA

2.1 Biochemical aspects

2.1.1 Absorption, distribution and elimination

Exposure to lead and lead chemicals can occur through ingestion, inhalation and dermal contact. Gastrointestinal absorption of ingested lead varies depending on physiological factors such as age, fasting, nutritional calcium and iron status, pregnancy and physicochemical characteristics of particles (size, solubility and lead species) (EFSA, 2010).

Several studies have reported that lead absorption from the gastrointestinal tract appears to be higher in children than in adults (Alexander, Clayton & Delves, 1974; Ziegler et al., 1978; Rabinowitz, Kopple & Wetherill, 1980; Heard & Chamberlain, 1982; James, Hilburn & Blair, 1985), although another study suggested that children aged 6–11 years and their mothers absorb a similar percentage of ingested lead (Gulson et al., 1997). Experimental studies with Rhesus monkeys and rats have provided additional evidence for age-dependent differences in gastrointestinal absorption (Forbes & Reina, 1972; Kostial et al., 1978; Pounds, Marlar & Allen, 1978; Aungst, Dolce & Fung, 1981).

Fasting humans absorb much larger fractions of lead than do their fed counterparts. The presence of food in the gastrointestinal tract decreases the absorption of water-soluble lead (Rabinowitz, Kopple & Wetherill, 1980; Heard & Chamberlain, 1982; Blake & Mann, 1983; Blake, Barbezat & Mann, 1983; James, Hilburn & Blair, 1985; Maddaloni et al., 1998). Fasting subjects absorbed approximately 63% of a tracer dose of lead acetate in water, whereas fed subjects absorbed 3% (Heard & Chamberlain, 1982; James, Hilburn & Blair, 1985).

Iron is believed to impair lead uptake in the gut, whereas iron deficiency is associated with increased blood lead concentrations in children (Cheng et al., 1998; Bárány et al., 2005). Studies in rats also showed that iron deficiency increased lead absorption, possibly by enhancing its binding to iron-binding carriers (Barton et al., 1978; Morrison & Quaterman, 1987; Bannon et al., 2003). Diets with low levels of calcium have been shown to increase lead absorption in children (Ziegler et al., 1978; Mahaffey et al., 1982) and in laboratory animals (Mykkänen & Wasserman, 1981, 1982).

Absorption through the respiratory tract is influenced by the particle size distribution and the ventilation rate. In adults, the rate of deposition of airborne lead is approximately 30–50%. This rate is dependent on the size of the particles and the ventilation rate of the individual. Smaller particles (<1 μm) have been shown to have greater deposition and absorption rates than larger particles (USEPA, 1986). Once deposited in the lower respiratory tract, lead appears to be almost completely absorbed (Morrow et al., 1980).

Dermal absorption of lead compounds is substantially lower than absorption by inhalation or oral routes of exposure. Dermal absorption of lead in humans has been estimated to be 0.06% during normal use of lead-containing preparations (Moore et al., 1980).

Inorganic lead is minimally absorbed through the skin, but organic lead, such as tetraethyl lead (as in leaded gasoline), which is still legally allowed to be used in aircraft, watercraft and farm machinery, is well absorbed through the skin (Patrick, 2006).

Once absorbed, 96–99% of circulating lead in blood is bound to erythrocytes. At low blood lead concentrations, whole blood lead levels increase linearly with serum levels. However, at higher blood lead concentrations, owing to saturation of lead-binding sites in the erythrocytes, the relationship between serum lead and blood lead is non-linear. The distribution of lead in the body is route independent; in adults, approximately 90% of the total body burden of lead is in the bones, compared with approximately 70% in children, but its concentration increases with age (EFSA, 2010).

Bone lead can contribute to elevated blood levels long after the exposure ceases (Fleming et al., 1997). Studies have reported that conditions such as ageing (Drasch, Bohm & Baur, 1987), osteoporosis (Gulson, Palmer & Bryce, 2002), pregnancy (Lagerkvist et al., 1996; Maldonado-Vega et al., 1996; Schuhmacher et al., 1996; Franklin et al., 1997; Gulson et al., 1997), lactation (Gulson et al., 2003, 2004), menopause and postmenopause (Hernandez-Avila et al., 2000; Gulson, Palmer & Bryce, 2002; Berkowitz et al., 2004; Nash et al., 2004; Popovic et al., 2005) increase bone resorption and consequently also increase lead levels in blood. Lead can be transferred from the mother to the fetus (Goyer, 1990; Graziano et al., 1990; Carbone et al., 1998) and also from the mother to infants via maternal milk (Gulson et al., 1998b; Ettinger et al., 2006).

The unexcreted fraction of absorbed lead is distributed among blood, soft tissues and bones (Barry, 1975). Half-lives for inorganic lead in blood and bone are approximately 30 days and between 10 and 30 years, respectively (Rabinowitz, 1991).

It has been reported that liver is the largest repository of soft tissue lead, followed by kidney cortex and medulla, pancreas, ovary, spleen, prostate, adrenal gland, brain, fat, testis, heart and skeletal muscle. Despite lead's faster turnover in these tissues, its concentrations are relatively constant (Barry, 1975; Treble & Thompson, 1997). Regardless of the route of exposure, lead is excreted primarily in urine and faeces (Rabinowitz, 1991). Minor routes of excretion include sweat, saliva, hair, nails and breast milk (Hursh & Suomela, 1968; Hursh et al., 1969; Rabinowitz, Wetherill & Kopple, 1976; Kehoe, 1987; Stauber et al., 1994).

2.1.2 Biotransformation

Metabolism of inorganic lead consists primarily of reversible ligand reactions, including the formation of complexes with amino acids and non-protein thiols and binding to various proteins (Goering & Fowler, 1985; Goering, 1993).

Organic lead compounds are metabolized to inorganic lead both in humans and in experimental animals. Organic or alkyl lead, such as tetraethyl and tetramethyl lead, undergo oxidative dealkylation to the highly neurotoxic metabolites triethyl and trimethyl lead, respectively. In the liver, the reaction is catalysed by a cytochrome P450–dependent mono-oxygenase system (IARC, 2006).

2.1.3 Effects on enzymes and other biochemical parameters

The toxicity of lead may be attributed to the affinity of lead for thiol groups (–SH) (Vallee & Ulmer, 1972) and other organic ligands in proteins.

Lead has been known to alter the haematological system by inhibiting the activities of enzymes essential for haem biosynthesis, such as δ-aminolaevulinic acid synthase (ALAS), δ-aminolaevulinic acid dehydratase (ALAD) and ferrochelatase. The enzyme most sensitive to the effect of lead is ALAD (EFSA, 2010).

Inhibition of ALAD by lead results in increased circulating aminolaevulinic acid (ALA), a weak γ-aminobutyric acid (GABA) agonist that decreases GABA release by presynaptic inhibition, which may account for some of the behavioural disorders seen in patients with porphyria and perhaps in lead toxicity. Inhibition of ALAD activity occurs over a wide range of blood lead concentrations beginning at less than 10 µg/dl (ATSDR, 2007).

Simmonds, Luckhurst & Woods (1995) observed a decrease in ALAD activity in erythrocytes in rats given lead acetate at 1000 mg/l in the drinking-water for 6 days. Blood lead concentrations increased to 44 µg/dl after the first day and remained within 10 µg/dl of that value until the end of the exposure period.

It has been reported that lead indirectly stimulates the mitochondrial enzyme ALAS, which catalyses the condensation of glycine and succinyl coenzyme A to form ALA. The activity of ALAS is the rate-limiting step in haem biosynthesis; ALAS is induced by negative feedback from the depression of haem synthesis (EFSA, 2010).

Lead is also known to inhibit the activity of the zinc-containing mitochondrial enzyme ferrochelatase, which catalyses the insertion of iron(II) into the protoporphyrin ring to form haem (USEPA, 1986; Goering, 1993). Lead-related anaemia is known to be a late complication when blood lead levels exceed 50 µg/dl (USEPA, 1986; Goering, 1993).

Other enzymes have also been reported to be inhibited by lead. Lead was shown to inhibit Na^+,K^+-adenosine triphosphatase (ATPase) activity and to increase intracellular Ca^{2+} levels, possibly with activation of protein kinase C (Kramer, Gonick & Lu, 1986; Watts, Chai & Webb, 1995; Hwang et al., 2001), resulting in hypertension (Carmignani et al., 2000; Ni et al., 2004; Vaziri & Sica, 2004) and subsequent depletion of nitric oxide, which is involved in the regulation of blood pressure (Gonick et al., 1997; Vaziri et al., 1997; Vaziri, 2008).

The activity of dihydrobiopterin reductase, an enzyme involved in the synthesis of catecholamines, is reduced by lead in rat brain. The activity of nicotinamide adenine dinucleotide synthetase in erythrocytes may also be inhibited by lead (Annex 1, reference *144*).

Lead also competitively interferes with divalent cations, such as calcium, magnesium and zinc. Subsequent impairment of mitochondrial oxidative phosphorylation and the intracellular messenger system affects endocrine and neuronal function and smooth muscle contraction (ATSDR, 2007).

Lead is reported to compete with calcium for binding sites on cerebellar phosphokinase C, thereby affecting neuronal signalling (Markovac & Goldstein, 1988). Furthermore, high lead exposure in children has been shown to decrease circulating levels of the active form of vitamin D, 1,25-dihydroxyvitamin D, resulting in perturbation of calcium homeostasis (Mahaffey et al., 1982; Rosen & Chesney, 1983).

2.1.4 Physiologically based pharmacokinetic (PBPK) modelling

The relationship between dietary exposure to lead and blood lead levels has been previously evaluated by the Committee (Annex 1, reference *144*). For infants, the evaluation is based on data from a study of a group of Scottish infants exposed to lead from drinking-water (Lacey, Moore & Richards, 1985). In this study, the kinetic relationship between exposure to lead and blood lead levels was analysed. An analysis conducted by the United States Environmental Protection Agency (USEPA) concluded that there is a linear relationship between exposure and blood lead levels, with a linear slope of 0.16 µg/dl per 1 µg/day of dietary exposure (USEPA, 1989). This analysis is the basis for the USEPA's toxicokinetic model used in the EFSA (2010) evaluation. The previous evaluation by the Committee (Annex 1, reference *144*) presented a reanalysis of the same data that included an intercept parameter to account for unquantified sources of exposure other than drinking-water and concluded that a range between 0.05 and 0.10 µg/dl per 1 µg/day of dietary exposure was appropriate for low levels of lead exposure. In the present analysis, the Committee employed a range of 0.05–0.16 µg/dl per 1 µg/day for children.

The Committee (Annex 1, reference *144*) also previously evaluated the relationship between dietary exposure to lead and blood lead levels in adults. Based on a similar study of drinking-water in Scotland (Sherlock et al., 1982), the Committee identified a range of 0.023–0.07 µg/dl per 1 µg/day for adults.

2.2 Toxicological studies

2.2.1 Acute toxicity

Lead has been described as a classic chronic poison. Health effects are generally not observed after a single exposure, and oral median lethal doses (LD_{50} values) for lead salts have been reported to be greater than 2000 mg/kg bw. The lowest observed lethal doses in experimental animals after multiple short-term oral exposures to lead acetate, lead chlorate, lead nitrate, lead oleate, lead oxide or lead sulfate range from 300 to 4000 mg/kg bw (Annex 1, reference *143*).

Acute kidney damage was reported in male rats following intraperitoneal administration of lead acetate (0, 0.05, 0.15 and 0.30 mmol/kg bw as Pb^{2+}) to groups of five male and five female rats. Minimal kidney damage, as shown by increased urinary γ-glutamyl transferase activity, was observed only in males given the highest

dose. It was also observed that in all animals and at all doses, natriuria was significantly decreased on the first day (from 4 h after administration). Such changes evoke mild tubular abnormalities, but glomerular disturbances may also be involved (IARC, 2006).

2.2.2 Short-term studies of toxicity

There are very few short-term studies of the toxicity of lead reported in the literature. In a study of exposure by the inhalation route, Bizarro et al. (2003) observed that CD-1 male mice exposed to a mist containing lead acetate at a concentration of 0.01 mol/l in deionized water intermittently for 4 weeks showed a time-related increase in the fraction of damaged mitochondria in Sertoli cells, which, according to the investigators, could lead to a transformation process that may interfere with spermatogenesis.

Sundström & Karlsson (1987) reported that lead administered to newborn rats postnatally on days 1–15 by daily intraperitoneal injections of lead nitrate at a dose of 10 mg/kg bw was found to cause haemorrhagic encephalopathy in the cerebellum at 15 days.

Sokol (1987) reported that Wistar rats given 0.3% (3000 mg/l) lead acetate in their drinking-water for 30 days manifested a hyper-responsiveness to stimulation with both gonadotropin-releasing hormone and luteinizing hormone, whereas they manifested a blunted response to naloxone, indicating that lead exerts its toxic effects at hypothalamic or supra-hypothalamic sites.

2.2.3 Long-term studies of toxicity and carcinogenicity

The studies on the long-term toxicity of lead in experimental animals are extensive, and most findings are in agreement with the observations in humans (ATSDR, 2007). Chronic oral exposure to inorganic lead has effects on multiple organs, such as kidney and liver, and systems, including cardiovascular, haematological, immune, reproductive and nervous systems. Increased mortality, weight loss and depression of weight gain have also been reported in rats (IARC, 2006).

Studies of the carcinogenicity of lead in experimental animals have been reviewed by the International Agency for Research on Cancer (IARC), and no new studies have been published since the last monograph (IARC, 2006). Inorganic lead salts are the main lead compounds tested via oral exposure, mostly in rats.

A substantial body of literature has demonstrated the association between lead exposure and renal tumours in rats. With an extremely low spontaneous incidence in rodents, renal tumours have been consistently observed in rats exposed to lead acetate or lead subacetate for 1 year or longer. The exposure levels in these studies, however, are considered very high compared with human dietary exposure (EFSA, 2010). A 2-year study in rats found 500 mg/kg in diet to be the highest lead acetate concentration at which no renal tumours occurred and 100 mg/kg in diet to be the concentration at which no renal pathological lesions were observed. Renal tumours have also been found in lead-treated mice, but the results

are not as consistent as those in rats. In one study using hamsters, no tumours developed following lead exposure (IARC, 2006).

Brain gliomas, also rarely spontaneous in rodents, seem to be associated with chronic inorganic lead exposure as well. Lead-induced brain gliomas were reported in three independent studies, each using a different strain of rat (IARC, 2006).

Results of genotoxicity (see section 2.2.4) and mechanistic studies suggest indirect mechanisms, including the inhibition of deoxyribonucleic acid (DNA) repair, interference with cellular redox regulation and induction of oxidative stress, and deregulation of cell proliferation for lead carcinogenicity (Beyersmann & Hartwig, 2008). It is therefore possible that lead can augment the effects of other carcinogens, and lead has been examined together with various organic carcinogens in a number of studies. Oral exposure to lead salts enhanced the incidence of renal tumours induced by *N*-ethyl-*N*-hydroxyethylnitrosamine and *N*-nitrosodimethylamine. However, there is not enough evidence showing that lead increases the incidence of chemical-induced skin tumours and lung tumours (IARC, 2006).

In summary, there is sufficient evidence for the carcinogenicity of inorganic lead compounds in experimental animals (IARC, 2006). Lead induces renal and brain tumours in experimental animals and may also act as a tumour promoter together with other renal carcinogens.

2.2.4 Genotoxicity

(a) In vitro studies

When tested in bacterial and yeast systems, lead compounds usually give negative results. The few positive results might have resulted because of the mutagenic effects of the anions, such as chromium in lead chromate. In cell-free systems, lead acetate causes DNA strand breaks, increases 8-hydroxy-deoxyguanosine and inhibits tubulin assembly (IARC, 2006; EFSA, 2010).

Genotoxic assays using different animal cells and measuring different genotoxic end-points are summarized in Table 93 in the IARC (2006) monograph. Mutagenesis assays have given equivocal results. Among those showing positive results, the type of mutation, the extent of mutagenicity and the effective doses varied with experimental conditions. Several studies revealed an increase in mutation frequency stimulated by lead in combination with other mutagens, such as ultraviolet C (UVC) irradiation. Lead-induced inhibition of DNA repair was also observed in X-ray or UVC-treated cells. As for chromosomal aberrations, results are mostly negative, except for lead chromate, the positive results for which may be due to the action of chromate, but not lead. Equivocal results have been published for DNA strand breaks and sister chromatid exchange. A dose-dependent increase of micronuclei was induced by lead chloride and lead acetate, but not by lead nitrate.

The above evidence indicates that it is not likely that lead interacts directly with DNA. The mechanisms of lead genotoxicity probably involve multiple indirect

effects, such as the production of reactive oxygen species, the generation of protein crosslinks and the inhibition of DNA repair.

(b) In vivo studies in experimental animals

Results from in vivo animal studies have been summarized in Table 92 in the IARC (2006) monograph. Most rat studies have demonstrated DNA damage and micronucleus formation in kidney cells and aneuploidy in bone marrow cells. However, studies with mice and monkeys have not yielded consistent results.

(c) In vivo studies in humans

Genetic effects such as DNA damage, chromosomal aberrations and micronucleus formation have been observed in individuals occupationally exposed to lead, whereas there is no evidence showing similar effects related to non-occupational exposure. A complete list of the human studies can be found in Table 91 in the IARC (2006) monograph. Depending on the genotoxic end-point, the effect is noted when blood lead concentration falls in the range of 15–65 µg/dl (IARC, 2006). A major limitation in these studies is the occupational co-exposure to other genotoxic metals, such as cadmium, and therefore the contribution of lead alone is difficult to evaluate. In addition, many studies did not consider smoking as a potential confounder, making it difficult to derive a dose–response relationship.

2.2.5 Reproductive and developmental toxicity

A number of studies in male rats and other rodent species indicate that blood lead concentrations above 30–40 µg/dl for at least 30 days are associated with reductions in spermatogenesis and serum testosterone levels. Equivocal results have been reported for end-points such as reproductive organ histopathology, spermatozoal end-points and levels of pituitary hormones. It appears that certain animal species and strains are quite resistant to the reproductive toxicity of lead, probably as a result of the physiology-based differences in lead accumulation and distribution in target organs (Apostoli et al., 1998). Increased DNA damage, cytotoxicity and reactive oxygen species have been found in male germ cells, yet it is still not clear whether the reproductive toxicity of lead is caused by its direct interaction with reproductive organs or by the impairment of the pituitary testicular axis, or both.

In female rats chronically exposed to lead, irregular estrous cycles and morphological changes in ovaries have been observed. Ronis et al. (1996) reported that exposure of the dams to lead acetate caused a significant dose-responsive decrease in birth weight of rat litters. In addition, reduced serum testosterone level and dose-dependent pubertal delay were observed in male offspring. Delayed vaginal opening in female offspring and suppression of circulating estradiol were also observed.

Exposure to lead in early development results in several endocrine disruptions, accompanied by delayed puberty, suppression of prepubertal growth and suppression of the male pubertal growth spurt. Studies on hormonal changes

suggest that functions of the hypothalamic–pituitary–gonadal axis can be affected when related structures are undergoing rapid proliferation (IARC, 2006).

2.2.6 Special studies

(a) Neurological and behavioural effects

In rodent and non-human primate models, it has been demonstrated that chronic exposure to low-level lead affects learning abilities and behaviour, particularly in the developing animals. The magnitude of these effects appears to be strongly dependent on the developmental period in which exposure takes place (IARC, 2006). Deficits in reversal or repeated learning have consistently been observed in lead-exposed animals, the magnitude of which varied by species and stimulus dimensions (EFSA, 2010). It has also been suggested that lead is associated with some symptoms of attention deficit hyperactivity disorder (ADHD), particularly impulsivity and inattention (EFSA, 2010).

Effects of lead on visual and hearing functions have also been observed in experimental animals. Outcomes of chronic exposure to lead include the impairment of scotopic visual function (night blindness), decreased amplitudes and prolonged latencies of flash-evoked visual potentials, and reduction of ocular motor function. However, there is not enough evidence for loss of the spatial and temporal contrast sensitivity functions of the visual system (IARC, 2006; EFSA, 2010). The effects of lead on auditory functions have been studied in monkeys, but the association remains unclear. Changes in the auditory brainstem-evoked potentials and pure tone detection were observed in some, but not all, studies. It seems that the results were influenced by the age of the test animals and the level and length of the exposures (IARC, 2006).

Although the exact mechanism or site of action is not clear, effects of lead on motor function and aggressive behaviour have been reported and reviewed by IARC (2006). Results of behavioural tests performed primarily in rats and monkeys have suggested that the impaired performance is the result, at least in part, of a combination of distractibility, inability to inhibit inappropriate responding and perseverance of behaviours that are no longer appropriate (ATSDR, 2007).

(b) Nephrotoxicity

The renal effects of lead in animal models occur as a result of both acute and chronic exposures. Studies on the mechanisms of lead nephrotoxicity suggest the involvement of oxidative stress. Chronic exposure to lead induces the formation of characteristic intranuclear inclusion bodies in the proximal tubular epithelial cells in various animal species. These inclusion bodies may function as an intracellular depot of non-diffusible lead.

In rats, the lowest chronic lead dose related to detectable renal effects is 5 mg/l in drinking-water. At this exposure level, pathological changes in renal proximal tubular cells, formation of intranuclear inclusion bodies, inhibition of renal mitochondrial respiration and swollen mitochondria were seen after 9 months of exposure. At higher doses, various nephropathy symptoms were observed,

including increased glomerular filtration rate (GFR), focal tubular atrophy, interstitial fibrosis, elevated urinary *N*-acetyl-β-D-glucosaminidase and glutathione *S*-transferase. Many symptoms appear only at certain stages of exposure. For example, the hyperfiltration effect is observed only during the first 3 months of lead exposure (EFSA, 2010). A comparative study of prenatal and postnatal exposure suggested that lead exposure during kidney development resulted in more severe damage compared with later lead exposure and that exposure to lead starting at weaning was more nephrotoxic than exposure starting 2 months later (Vyskocil, Cizkova & Tejnorova, 1995).

(c) Cardiovascular effects

The cardiovascular effects of lead in experimental animals have been reviewed by IARC (2006) and EFSA (2010). Low-level (<100 mg/l in drinking-water) chronic lead exposure has consistently been associated with a hypertensive effect in rats. However, the effects of high-level lead on blood pressure are equivocal, making it difficult to derive a dose–response relationship. In some studies, high-level exposure failed to demonstrate increased blood pressure, suggesting a biphasic response (Victery, 1988). In one study, exposure of spontaneously hypertensive rats to low-level lead resulted in an enhanced susceptibility to ischaemia-induced arrhythmias, although this effect was less marked when the exposure level was higher (IARC, 2006). In rats given lead acetate at 100 mg/l in their drinking-water, increased heart rate and heart contraction were seen (Reza et al., 2008). Observations in a large number of experimental animal studies suggest that the cardiovascular effects are secondary to lead-induced nephropathy. However, there is also evidence suggesting that direct actions, such as the alteration in intracellular calcium concentration and the inactivation of nitric oxide synthase, may also play a role (Vaziri, 2008).

(d) Immunotoxicity

Lead reduces resistance to bacterial and viral infections and decreases antibody production in different experimental animals (IPCS, 1995). The immunological effects of lead in experimental animals have been previously reviewed (IARC, 2006). Decreased B-lymphocyte responsiveness, suppressed humoral antibody titres and inhibited mitogenic responses of lymphocytes have been observed in mice. Lead also attenuates the delayed-type hypersensitivity (DTH) response, causes the shift of immune responses away from thymus-dependent T helper 1 (Th1)–associated responses towards Th2-dependent responses and increases serum immunoglobulin E levels (Farrer et al., 2008). Lead nitrate has effects on the proliferative responses of B and T lymphocytes of many animal species (IARC, 2006). The underlying mechanisms for lead-induced immunomodulation have remained elusive. Overall, available data suggest that nitric oxide, produced via the modulation of inducible nitric oxide synthase activity, is a key mediator in lead-induced immunomodulation (Farrer et al., 2008).

In rats exposed to lead in utero, depressed cell-mediated immune function was observed, as shown by a decrease in DTH reactions. Exposure of pregnant females to moderate levels of lead produces chronic immunomodulation in their

offspring. Rat embryos may be more sensitive to lead-induced immunotoxic effects when exposed during late gestation, with the effects on DTH function being more pronounced in females. Dietert et al. (2004) reviewed the recent findings pertaining to the effects of lead on the developing immune system compared with effects on the adult immune system. Several rodent studies have shown that the adult blood lead level required for immunotoxicity appears to be significantly greater than the minimum blood lead level needed for embryonic- or neonatal-associated immune impairment, suggesting that the sensitivity to lead immunotoxicity during embryonic and neonatal periods is much greater than that in the adult.

(e) Effects on haematopoietic system

The effects of lead on the haematopoietic system in experimental animals have been studied and reviewed extensively (IPCS, 1995; IARC, 2006; ATSDR, 2007). Lead is known to be a potent inhibitor of haem synthesis. A reduction in haem-containing enzymes could compromise energy metabolism.

A number of studies have shown that the haem biosynthesis enzyme ALAS is induced by lead as a feedback regulation. Haem oxygenase in liver and kidney is also induced, leading to increased haem degradation. The mechanism of alteration in the haem synthesis pathway is suggested to be lead-induced oxidative stress (Gautam & Flora, 2010).

2.3 Observations in humans

2.3.1 Biomarkers of exposure

Blood is the tissue used most frequently to estimate exposure to lead and its association with health outcomes. This is largely because blood is easily sampled and the methods for measuring blood lead concentration are well developed. The elimination half-life of lead in blood is approximately 30–40 days in adults, however, so the blood lead level provides information primarily about an individual's exposure in recent months. The exposure averaging time will vary among individuals, depending on the extent to which endogenous pools of lead, representing past exposure, are contributing to blood lead. Under conditions of steady-state exposure, only a small percentage of total body burden of lead is in blood (~5%), and nearly all of this is bound to erythrocytes (96–99%), with the balance in plasma. The ratio of erythrocyte to plasma lead decreases as lead levels increase owing to saturation of binding sites on erythrocytes. Typically, whole blood lead concentration is measured. Although the fraction in plasma is thought to be more relevant than whole blood lead to lead's toxicity, it has rarely been used as the exposure biomarker owing to the analytical challenges and the cost of measuring such low concentrations accurately.

Because 90% of the body lead burden in adults, and 70% in children, is in bone, methods based on X-ray fluorescence (primarily K-line) have been developed for measuring the concentration of lead in bone, expressed as grams of lead per gram of bone mineral (Hu et al., 2007). The half-life of lead in bone varies depending on bone type, being longer in cortical bone (approximately 30 years) than in

trabecular bone (5–10 years). The bones in which measurements are most frequently made are tibia, patella and calcaneus. The technology required to make these measurements is limited to only a small number of laboratories, however. Moreover, the correlation between bone lead level and a concurrent blood lead level is often poor because of the very different exposure averaging times that these two biomarkers capture. For instance, in one study of 50- to 70-year-olds with primarily only environmental exposures to lead, the correlation between bone and blood lead levels was 0.12 (Martin et al., 2006). The correlation can be much higher in individuals who, in the past, had substantial occupational exposures to lead, for whom bone stores contributed to blood lead in later life (i.e. after occupational exposure ended) (Morrow et al., 2007). These considerations make it difficult to base risk assessments, particularly for food, on the dose–response relationships derived from studies that relied on bone lead level as the exposure biomarker in cohorts with only environmental exposures to lead.

The X-ray fluorescence methods currently available have been used almost exclusively with adults, as they are not sufficiently sensitive for measuring bone lead in children, presumably because of the rapid remodelling of bones that occurs during a child's growth. Some epidemiological studies have measured the lead concentration in shed deciduous teeth as an alternative assay of mineralized tissue. Efforts have been made to reconstruct temporal features of a child's exposure history from the spatial distribution of stable lead isotopes in a tooth (Gulson & Wilson, 1994).

Lead is excreted in urine, but urinary lead levels have not been widely used in health outcome studies. Lead diuresis in response to a chelating agent challenge is used clinically, however, to determine the need for therapeutic chelation and to monitor treatment efficacy. The relationship between blood lead and urinary lead levels under other conditions is weak (Gulson et al., 1998a).

Because of the possibility of external contamination by ambient lead, the concentration of lead in hair is not viewed as an acceptable biomarker.

(a) Blood lead level during pregnancy

Lead crosses the placenta by passive diffusion, and blood lead levels in newborns are generally 80–90% of the maternal venous level at delivery. The kinetics of lead during pregnancy are complex. The blood lead level during pregnancy changes as a result of a variety of factors, even if external exposures remain stable. These factors include changes in plasma volume, red cell mass and the redistribution of lead among the different body pools caused by pregnancy-related physiological changes. During the first half of pregnancy, blood lead level declines by approximately 15%, most likely due to haemodilution, organ growth and increased GFR or increased lead excretion (Rothenberg et al., 1994). After the 20th week of pregnancy, however, an increase of 14–40% in blood lead level, in both whole blood and plasma, has been observed in numerous cohorts (Hertz-Picciotto et al., 2000; Tellez-Rojo et al., 2004). Considerable evidence now supports the hypothesis that this is the result, at least in part, of increased influx of lead into the blood by means of the mobilization of bone lead stores. The timing of this increase coincides with the increased requirement for calcium to support fetal ossification.

Other studies suggest that bone lead is mobilized at rates that are consistent with the pattern of bone loss in menopausal women (Symanski & Hertz-Picciotto, 1995; Nash et al., 2004). In pregnant women, plasma lead level was highest in women who had both a high bone lead level and greater bone resorption activity (Tellez-Rojo et al., 2004). Studies evaluating changes in the ratios of stable lead isotopes over the course of pregnancy provide compelling evidence that lead stored in deep pools, such as bone, is, indeed, redistributed to the blood compartment during pregnancy (Gulson et al., 2003; Manton et al., 2003). There are several case reports of women who were lead poisoned in early life and, when they became pregnant, again developed symptoms of lead toxicity (e.g. Riess & Halm, 2007). Some epidemiological evidence (Hertz-Picciotto et al., 2000; Gulson et al., 2004) and one randomized trial conducted during lactation, when calcium needs exceed those during pregnancy (Hernandez-Avila et al., 2003), suggest that increased calcium intake can reduce the amount of mobilization of bone lead.

(b) Estimates of blood lead levels by region

For the World Health Organization's (WHO) Global Burden of Disease 2005 project, an updating of the estimates of the global burden of disease for the period 1990–2005, A. Pruss-Ustun (unpublished data, 2010) derived estimates of the distribution of blood lead levels for the 21 regions being considered in the project (Table 1). Where possible, separate estimates are provided by age (child versus adult), sex and area of residence (urban versus rural). Clearly, the average level of exposure varies considerably across regions, with the means for some subgroups exceeding 10 µg/dl. In an analysis to estimate the global burden of lead-related disease, Fewtrell, Kaufmann & Pruss-Ustun (2003) noted that, worldwide, 40% of children had a blood lead level greater than 5 µg/dl, 20% had a level greater than 10 µg/dl and less than 10% of children had a blood lead level greater than 20 µg/dl. However, 99% of the children with a level above 20 µg/dl lived in developing countries, demonstrating the regional disparities in exposure that exist.

(c) Sources of exposure

Lead is a "multimedia" contaminant, with sources or pathways that include air, water, soil, dust, food, paint and consumer products. This complexity can make source attribution very challenging. Airborne lead is largely attributable to industrial emissions. The reduction in the use of lead as a petrol additive, which began around 1980 worldwide, had a substantial impact on the blood lead distribution. WHO estimated that, in the years following phase-down of lead in petrol, the mean blood lead level in a country declined by an average of 7.8% per year (Fewtrell, Kaufmann & Pruss-Ustun, 2003). This value varies depending on the relative importance of the different sources or pathways in a particular population, however. Studies from several regions suggest that exposures can continue to be elevated for a large percentage of children even after the removal of lead from gasoline. For example, after the phase-out of leaded petrol in India, the percentage of children less than 12 years of age in Mumbai who had a blood lead level above 10 µg/dl fell to half the percentage measured in 1997, but one third (33.2%) of children still had a level above this value, and the geometric mean blood lead level was 8.4 µg/dl

Table 1. Estimated blood lead levels worldwide,[a] 1990 and 2005

	Blood lead level (µg/dl)																	
	AsiaC	AsiaE	AsiaPhi	AsiaS	AsiaSE	Aus	Car	EurC	EurE	EurW	LAA	LAC	LAS	LAT	NAHI	NAME	OC	SSAfrica
1990																		
Children, urban mean	10.7	8.5	3.8	12.0	6.8	6.3	8.4	6.2	7.0	6.8	12.7	13.9	10.9	11.1	2.7	11.4	4.7	9.7
Children, rural mean	2.9	7.5	1.9	8.2	5.2	2.4	2.2	4.2	4.7	3.3	8.5	8.5	4.6	4.6	2.7	7.3	4.7	1.9
Adults, urban mean	10.7	9.1	3.6	13.9	5.5	6.3	8.8	6.2	7.0	6.9	12.7	12.7	10.9	11.1	2.2	11.4	2.2	9.4
Adults, rural mean	2.9	8.1	1.9	8.2	5.2	2.4	2.2	4.2	4.7	3.3	10.3	10.3	4.6	4.6	2.2	7.3	2.2	1.9
Urban GSD	1.6	1.7	1.8	1.6	1.5	1.6	2.1	2.0	1.5	1.4	1.4	1.4	1.5	1.3	NA	1.7	1.9	1.6
Rural GSD	2.0	1.7	1.8	1.7	1.7	2.0	2.2	2.7	1.6	1.8	1.9	1.9	1.8	1.8	NA	2.0	1.9	2.8
Children GSD	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	2.2	NA	NA	NA
Adults GSD	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	2.1	NA	NA	NA
2005																		
Children, urban mean	3.7	4.6	2.1	9.0	5.4	2.1	9.7	3.4	3.0	1.6	3.2	5.4	3.8	4.5	1.9	6.5	2.6	6.8
Children, rural mean	2.4	4.1	1.9	8.2	5.3	2.4	2.2	2.9	3.0	1.6	3.6	3.6	2.2	2.2	1.9	6.5	2.6	1.9
Adults, urban mean	3.7	4.2	3.2	10.2	4.6	2.1	9.7	3.8	3.0	2.9	3.2	6.0	3.8	4.5	1.5	6.5	0.6	6.6
Adults, rural mean	2.4	3.8	1.9	8.2	5.3	2.4	2.2	2.9	3.0	2.9	3.6	3.6	2.2	2.2	1.5	6.5	0.6	1.9
Urban GSD	2.4	1.9	1.8	1.6	1.7	2.4	1.8	1.5	1.5	NA	2.1	1.6	1.9	1.6	NA	1.8	2.4	1.9
Rural GSD	1.6	1.9	1.8	1.7	1.7	2.0	2.2	1.5	1.5	NA	1.8	1.8	2.2	2.2	NA	1.8	2.4	2.6
Children GSD	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.9	NA	NA	NA	NA	2.17	NA	NA	NA
Adults GSD	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.6	NA	NA	NA	NA	2.18	NA	NA	NA

Table 1 (contd)

GSD, geometric standard deviation; mean, geometric mean; NA, not available or applicable

[a] The country groupings used in the table are as follows:

AsiaC: Asia, Central
Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Mongolia, Tajikistan, Turkmenistan, Uzbekistan

AsiaE: Asia, East
China, Democratic People's Republic of Korea

AsiaPHI: Asia Pacific, High Income
Brunei, Japan, Republic of Korea, Singapore

AsiaS: Asia, South
Afghanistan, Bangladesh, Bhutan, India, Nepal, Pakistan

AsiaSE: Asia, Southeast
Cambodia, Indonesia, Lao People's Democratic Republic, Malaysia, Maldives, Mauritius, Mayotte, Myanmar, Philippines, Seychelles, Sri Lanka, Thailand, Timore Leste, Viet Nam

Aus: Australasia
Australia, New Zealand

Car: Caribbean
Anguilla, Antigua and Barbuda, Aruba, Bahamas, Barbados, Belize, Bermuda, British Virgin Islands, Cayman Islands, Cuba, Dominica, Dominican Republic, French Guiana, Grenada, Guadaloupe, Guyana, Haiti, Jamaica, Martinique, Montserrat, Netherlands Antilles, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, Turks and Caicos Islands

EurC: Europe, Central
Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Hungary, Montenegro, Poland, Romania, Serbia, Slovakia, Slovenia, The former Yugoslav Republic of Macedonia

EurE: Europe, Eastern
Belarus, Estonia, Latvia, Lithuania, Republic of Moldova, Russian Federation, Ukraine

EurW: Europe, Western
Andorra, Austria, Belgium, Channel Islands, Cyprus, Denmark, Faeroe Islands, Finland, France, Germany, Gibraltar, Greece, Greenland, Holy See, Iceland, Ireland, Isle of Man, Israel, Italy, Liechtenstein, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, Saint Pierre et Miquelon, San Marino, Spain, Sweden, Switzerland, United Kingdom

Table 1 (contd)

LAA: Latin America, Andean
Ecuador, Peru, Plurinational State of Bolivia
LAC: Latin America, Central
Colombia, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Venezuela (Bolivarian Republic of)
LAS: Latin America, Southern
Argentina, Chile, Falkland Islands (Malvinas), Uruguay
LAT: Latin America, Tropical
Brazil, Paraguay
NAHI: North America, High Income
Canada, United States of America
NAME: North Africa / Middle East
Algeria, Bahrain, Egypt, Iran (Islamic Republic of), Iraq, Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Morocco, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, Turkey, United Arab Emirates, West Bank and Gaza Strip, Western Sahara, Yemen
OC: Oceania
American Samoa, Cook Islands, Fiji, French Polynesia, Guam, Kiribati, Marshall Islands, Micronesia (Federated States of), Nauru, New Caledonia, Niue, Northern Mariana Islands, Palau, Papua New Guinea, Pitcairn, Samoa, Solomon Islands, Tokelau, Tonga, Tuvalu, Vanuatu, Wallis and Futuna Islands
SSAC: Sub-Saharan Africa, Central
Angola, Central African Republic, Congo, Democratic Republic of the Congo, Equatorial Guinea, Gabon
SSAE: Sub-Saharan Africa, East
Burundi, Comoros, Djibouti, Eritrea, Ethiopia, Kenya, Madagascar, Malawi, Mozambique, Rwanda, Somalia, Sudan, Uganda, United Republic of Tanzania, Zambia
SSAS: Sub-Saharan Africa, Southern
Botswana, Lesotho, Namibia, South Africa, Swaziland, Zimbabwe
SSAW: Sub-Saharan Africa, West
Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Côte d'Ivoire, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Mauritania, Niger, Nigeria, Saint Helena, Sao Tome and Principe, Senegal, Sierra Leone, Togo
NB: For the purpose of lead exposure estimates, all sub-Saharan regions have been pooled into one (SSAfrica) because of a lack of data.

(Nichani et al., 2006). After the phase-out in Uganda, 20% of 4- to 8-year-old children still had a blood lead level greater than 10 µg/dl (Graber et al., 2010). In a pooled analysis of studies of Chinese children, the mean blood lead level after the phase-out was 8.1 µg/dl, with 24% of children having a level greater than 10 µg/dl (He, Wang & Zhang, 2009).

Some sources of lead exposure are specific to particular regions or cultures. Some traditional medicines (e.g. Ayervedic preparations) and spices from Asia have been reported to have high lead content and to have caused lead toxicity (Kales & Saper, 2009; Shamshirsaz et al., 2009; Lin et al., 2010), as have some cosmetics used primarily in the Middle East and South Asia (e.g. surma) (Rahbar et al., 2002). In Mexico, the preparation of food in lead-glazed ceramics that were not fired at sufficiently high temperatures has been identified as a major risk factor for elevated lead exposure (Villalobos et al., 2009). With the large-scale migration across national boundaries and international transport of foods, this problem has contributed to increased exposure in Hispanic subpopulations elsewhere (Handley et al., 2007; Lynch, Elledge & Peters, 2008). Electronic wastes sent to developing countries for recycling of materials have been reported to be associated with greater lead exposure to children in proximity to the recovery facilities (Albalak et al., 2003; Huo et al., 2007).

2.3.2 Biomarkers of effect

A variety of biomarkers of effect have been used in studies on the health effects of exposure to lead. Because lead inhibits the activity of certain enzymes in the haem pathway, such as ALAD and ferrochelatase, the accumulation products ALA and free erythrocyte protoporphyrin (or zinc protoporphyrin) have been used. For studies in which renal function was the end-point of interest, biomarkers of function such as GFR, serum creatinine level and serum uric acid concentration have been used. Studies of cardiovascular health have relied on biomarkers such as blood pressure, heart rate variability and pulse pressure. Studies of nervous system toxicity have employed biomarkers such as nerve conduction velocity, postural balance, tremor and intelligence quotient (IQ). Typically, these biomarkers have been considered both as continuously distributed variables and as categorical variables, with category boundaries specified according to judgements about clinical significance.

2.3.3 Clinical observations

High-dose exposure is associated with toxic effects on several organ systems, affecting haematopoiesis, renal function and, most prominently, particularly in children, the central nervous system. The haematological effects include anaemia, which is attributable to the inhibition of the enzymes ALAD and ferrochelatase. Effects on the kidney include an acute renal nephropathy involving proximal tubule dysfunction due to impairment of mitochondrial respiration and a more chronic nephropathy that is associated with reductions in GFR and atrophy of proximal and distal tubules. The neurological effects include encephalopathy characterized by brain oedema and haemorrhage due to microvascular damage.

Clinical signs and symptoms at presentation are variable and occur at blood lead levels that differ widely across individuals. In some people, blood lead levels of several hundred micrograms per decilitre have been reported to be asymptomatic, whereas others with a blood lead level of 100 µg/dl might present with an encephalopathy. Many of the symptoms and signs are nonspecific and might include abdominal colic, nausea, vomiting, constipation, anorexia, changes in consciousness, lethargy, irritability, paraesthesias and other signs of peripheral neuropathy, and pallor.

2.3.4 Epidemiological studies

(a) Mortality

Recent prospective cohort studies provide reasonably consistent evidence, in both men and women, that higher lead levels are associated with higher all-cause mortality and that deaths from cardiovascular diseases are largely responsible for the associations.

In the first of several studies in the USA that relied on data from the National Health and Nutrition Examination Survey (NHANES) to evaluate this association, Lustberg & Silbergeld (2002) followed up, in 1992, individuals who participated in NHANES II (1976–1980) (n = 4292, 30–74 years of age). A baseline blood lead level of 20–29 µg/dl was associated with an adjusted hazard ratio (HR) for all-cause mortality of 1.46 (95% confidence interval [CI] 1.14–1.86), using individuals with a baseline blood lead level below 10 µg/dl as the reference group. The HRs were also significant for circulatory mortality (1.39, 95% CI 1.01–1.91) and cancer (1.68, 95% CI 1.02–2.78). The HRs for individuals with baseline blood lead levels of 10–19 µg/dl were increased, but not significantly.

Menke et al. (2006) used NHANES III data (1988–1994) to consider the association between blood lead level and all-cause and cause-specific mortality in the adult population in the USA. The follow-up interval was 12 years in the 13 946 individuals with a blood lead level less than 10 µg/dl (mean 2.6 µg/dl). The causes of death considered in the analyses were cardiovascular disease, myocardial infarction, stroke, cancer and lung cancer. Cox proportional hazard regression was used to estimate HRs for individuals in baseline blood lead tertiles, adjusting for age, race, sex, diabetes mellitus, body mass index, smoking, alcohol consumption, physical activity, income, C-reactive protein, total cholesterol, education, urban residence, postmenopausal status, hypertension and kidney function (GFR <60 ml/min per 1.73 m^3). Comparing individuals in the highest versus the lowest tertile, the adjusted HR for all-cause mortality was 1.25 (95% CI 1.0–1.5, P for trend = 0.002). The associations with baseline blood lead level were also significant for cardiovascular deaths (HR 1.6, 95% CI 1.1–2.2), myocardial infarction (HR 1.9, 95% CI 1.0–3.4) and stroke (HR 2.5, 95% CI 1.2–5.3). Spline regressions, used to describe the shapes of the relationships, suggested that the increase in mortality was evident at blood lead levels greater than 2 µg/dl.

Schober et al. (2006) also evaluated mortality among participants in the NHANES III survey (n = 9757). Compared with the group with a baseline blood lead

level below 5 µg/dl, individuals with a baseline blood lead level of 5–9 µg/dl had a significantly increased adjusted risk of all-cause mortality (HR 1.24, 95% CI 1.05–1.48), as did individuals with a baseline blood lead level of 10 µg/dl or higher (HR 1.59, 95% CI 1.28–1.98). The HRs were similar in these two exposure strata for deaths from cardiovascular disease or cancer.

The associations between lead biomarkers and total and cause-specific mortality were evaluated in approximately 868 men enrolled in the United States Veterans Administration Normative Aging Study (Weisskopf et al., 2009). The mean age at baseline was 67.3 years (standard deviation [SD] 7.3 years), and a mean length of follow-up was 8.9 (SD 3.9) years. Blood lead level at baseline, which averaged 5.6 (SD 3.4) µg/dl, was not associated with mortality. Adjusting for age, smoking and education, lead concentration in patella was significantly associated with all-cause, cardiovascular (HR 5.6, 95% CI 1.7–18.3) and ischaemic heart disease deaths. For example, the HR for men in the highest tertile of patella lead, compared with men in the lowest tertile, was 2.5 (95% CI 1.2–5.4). Adjustment for hypertension, race, alcohol use, physical activity, body mass index, high-density lipoprotein, cholesterol and diabetes mellitus did not affect the results appreciably. Exploration of the functional forms of the associations suggested linear dose–response relationships. The HRs associated with tibia lead concentration were greater than 1 for these three end-points, but the 95% CIs included 1.

Khalil et al. (2009b) followed up 533 women, aged 65–87 at baseline, for a mean of 12 (SD 3) years. The mean blood lead level was 5.3 (SD 2.3) µg/dl (range 1–21 µg/dl). For the purposes of analyses, the mortality among women with a baseline blood lead level less than 8 µg/dl was compared with the mortality of women with a level of 8 µg/dl or greater. For all-cause mortality, the HR for women with a blood lead level of 8 µg/dl or greater was 1.6 (95% CI 1.0–2.5, $P = 0.04$). For deaths from cardiovascular diseases, the HR was 3.1 (95% CI 1.2–7.7, $P = 0.02$). Blood lead level was not significantly associated with stroke, cancer or non-cardiovascular deaths.

(b) Cancer

IARC (2006) recently reviewed studies of the carcinogenicity of inorganic lead. These included studies of both occupational and environmental (i.e. general population) exposures. The following section summarizes IARC's conclusions about the evidence.

(i) Occupational exposures

In one study conducted on primary smelter workers in Sweden, a 2-fold excess in the number of lung cancer cases was observed. However, these workers were also exposed to arsenic, a known risk factor for lung cancer. In a Finnish study of workers from a variety of industries, blood lead level, measured as part of surveillance programmes, showed a modest, but non-significant, dose–response relationship between blood lead level and incidence of lung cancer. In five other studies, involving battery and smelter workers in the USA, the United Kingdom and Italy, no consistent increase in risk was found as exposures increased. Data on smoking were not available for some of these cohorts.

In five of the cohorts considered with regard to lung cancer, the association between blood lead level and stomach cancer was also evaluated. Compared with the reference populations, the numbers of stomach cancer cases were 30–50% higher in the workers than in the reference populations, but data necessary to conduct dose–response analyses were not available. In addition, it was not possible to consider the possible contributions of other risk factors for stomach cancer, such as ethnicity, diet, socioeconomic status or *Helicobacter pylori* infection.

In one of five cohort studies, a 2-fold excess of kidney cancers was reported, but in the other four studies, the rates were close to the expected values. It was noted that the numbers of cases in these cohorts were small.

In four cohort studies that evaluated tumours of the brain and nervous system, no excess risk was observed among the exposed workers, compared with the reference population. A nested case–control study of Finnish workers reported a significant association between blood lead level and risk for glioma. As with kidney cancers, however, the numbers of cases on which these conclusions are based were small.

(ii) Environmental exposures

One study analysed data for a subgroup of participants in NHANES II, which was conducted between 1976 and 1980 (Jemal et al., 2002). The mean blood lead level was 7.3 µg/dl in the lowest quartile and 19.7 µg/dl in the highest quartile. Adjusting for a variety of baseline variables (age, poverty, alcohol and tobacco use, region and year of examination), risk of cancer mortality across blood lead quartiles was not significant for men or women, nor were site-specific cancer risks. The numbers of cases observed for some specific cancers were small, however.

Lustberg & Silbergeld (2002) analysed a somewhat different subgroup of NHANES II participants, including non-Caucasians but excluding participants whose blood lead level was 30 µg/dl or higher. In analyses that adjusted for baseline values of age, sex, race, education, income, smoking, body mass index, exercise and region, a positive association was found between blood lead level and risk of cancer. Using individuals with a blood lead level below 10 µg/dl as the referent group, the relative risk observed among individuals with a blood lead level of 10–19 µg/dl was 1.46 (95% CI 0.87–2.48). The relative risk among individuals with a blood lead level of 20–29 µg/dl was 1.68 (95% CI 1.02–2.78). The relative risks for lung cancer in these two blood lead groups were 1.70 (95% CI 0.60–4.81) and 2.20 (95% CI 0.80–6.06), respectively. The IARC working group expressed concern about possible residual confounding resulting from the investigators' failure to adjust for duration of smoking.

Based on its evaluation, IARC concluded that although the evidence for carcinogenicity is sufficient in animals, there is *limited evidence* in humans for the carcinogenicity of inorganic lead and that inorganic lead compounds are *probably carcinogenic* to humans (group 2A).

Since the completion of the IARC evaluation, additional studies have been published in which the association between lead exposure and mortality from cancer has been evaluated, but the results do not indicate that any revision to the IARC

conclusions is required. In a study using the data on 13 946 participants in NHANES III, conducted between 1988 and 1994, Menke et al. (2006) evaluated the association between blood lead level (mean of 2.6 µg/dl) and overall cancer mortality and mortality from lung cancer. In analyses adjusting for age, race/ethnicity, sex, diabetes mellitus, body mass index, smoking, alcohol consumption, physical activity, income, C-reactive protein, total cholesterol, education, residence, postmenopausal status, hypertension and kidney function, the HR for individuals in tertile 2 of blood lead level (≥1.94–3.62 µg/dl) was 0.72 (95% CI 0.46–1.12). The HR for individuals in tertile 3 of blood lead level (3.63 µg/dl) was 1.10 (95% CI 0.82–1.47). The *P* for trend was 0.10. The HRs for lung cancer in tertiles 2 and 3 were 0.70 (95% CI 0.34–1.42) and 0.79 (95% CI 0.40–1.58), respectively.

Among 868 men participating in the United States Veterans Administration Normative Aging Study, Weisskopf et al. (2009) found that neither baseline blood lead level nor patella lead level, measured using K-line X-ray fluorescence, was significantly associated with cancer mortality. For baseline blood lead level, adjusting for age, smoking and education, the HR for individuals in tertile 2 (4–6 µg/dl) was 1.03 (95% CI 0.42–2.55), and the HR for individuals in tertile 3 (>6 µg/dl) was 0.53 (95% CI 0.20–1.39) (*P* for trend = 0.15). For patella lead level, the HR for individuals in tertile 2 (22–35 µg/g bone) was 0.82 (95% CI 0.26–2.59), and the HR for individuals in tertile 3 (>35 µg/g bone) was 0.32 (95% CI 0.08–1.35) (*P* for trend = 0.14).

In a case–control study of primary smelter workers, arsenic exposure, but not lead exposure, was a risk factor for lung cancer in 141 cases and age-matched controls (Lundstrom et al., 2006).

Alatise & Schrauzer (2010) reported that women newly diagnosed with infiltrating ductal carcinoma of the breast had higher levels of blood and hair lead and that hair lead level correlated significantly with tumour volume.

In a study of 362 patients with brain tumours (glioma or meningioma) and 494 controls, gene–environment interactions were found. Specifically, cumulative lead exposure as a main effect, estimated on the basis of job history, was not associated with glioblastoma multiforme and meningioma, but polymorphisms in the *RAC2* and *GPX1* genes (for glioblastoma multiforme) and the *GPX1* and *XDH* genes (for meningioma) were observed to modify the association (Bhatti et al., 2009).

(c) Renal function

In a sample of 769 adolescents (12–20 years old) in NHANES III, Fadrowski et al. (2010) evaluated the association between blood lead level and GFR, estimated on the basis of both serum cystatin C level and serum creatinine level. The former is considered preferable to the latter as a marker of kidney function, as it appears to be less dependent than creatinine-based estimates on age, sex, height and muscle mass. The median blood lead level was 1.5 µg/dl (interquartile range 0.7–2.9 µg/dl). Models were adjusted for age, sex, race/ethnicity, urban/rural, tobacco smoke exposure, annual household income and educational level of family reference person. Participants with a blood lead level in the highest quartile (≥3 µg/dl) had a 6.6 ml/min per 1.73 m^3 lower cystatin C–estimated GFR (95% CI of −0.7 to −12.6 ml/min per 1.73 m^3) compared with those in the first quartile

(<1 μg/dl), with a significant trend ($P = 0.009$). Restricted quadratic spline analyses showed no departures from linearity and no threshold. The associations were qualitatively similar but weaker using creatinine to estimate GFR, suggesting that previous studies that depended on creatinine-based estimates of kidney function might have underestimated the association between GFR and blood lead level. Many of the previous studies had been conducted in adults with chronic kidney disease or hypertension. This study extends the association to the general population of adolescents in the USA in whom significant co-morbidities were absent. A limitation of this study is its cross-sectional design, leaving open the possibility of reverse causation (i.e. kidney disease causes decreased excretion of lead). This appears unlikely, however, as at least some prospective studies have shown that baseline blood lead level is associated with subsequent decline in kidney function (Kim et al., 1996), particularly among participants with diabetes or hypertension (Tsaih et al., 2004).

Using adult (≥20 years old) participants in NHANES III ($n = 15\,211$), Muntner et al. (2003) evaluated the associations between blood lead level and two indices of renal dysfunction: serum creatinine (cut-points representing the 99th percentiles for race/sex) and chronic kidney disease (GFR <60 ml/min per 1.73 m^3). Models were adjusted for age, sex, systolic blood pressure, diabetes mellitus, current smoking, history of cardiovascular disease, body mass index, alcohol consumption, household income, marital status and health insurance. Significant associations between blood lead level and kidney dysfunction were found among individuals with hypertension ($n = 4813$), but not among those without hypertension ($n = 10\,398$). Among those with hypertension, the adjusted odds ratio (OR) for elevated serum creatinine level for individuals in the highest quartile of blood lead level (6.0–56.0 μg/dl) was 2.4 (95% CI 1.5–4.0), and the adjusted OR for chronic kidney disease for the same individuals was 2.6 (95% CI 1.5–4.5). For both outcomes, the adjusted ORs were also significant for individuals in quartiles 2 (2.5–3.8 μg/dl) and 3 (3.9–5.9 μg/dl), with the trend across quartiles significant ($P < 0.001$). Muntner et al. (2005) subsequently reported similar associations using data from NHANES 1999–2002 ($n = 9961$). Adjusting for the same set of covariates plus race/ethnicity, they found that individuals in the highest quartile of blood lead level (2.47 μg/dl) were 2.7 (95% CI 1.5–5.0) times more likely than individuals in quartile 1 of blood lead level (<1.1 μg/dl) to have chronic kidney disease (defined as a GFR <60 ml/min per 1.73 m^3).

In a sample of adults from Taiwan, China ($n = 1565$), Lai et al. (2008) evaluated the associations between blood lead level and two indices of renal dysfunction: serum creatinine level (levels above 1.2 mg/dl considered abnormal) and serum uric acid level (levels above 7 mg/dl in males and 6 mg/dl in females considered abnormal). Adjusting for age, sex, occupation, education, marital status, smoking, alcohol, betel nut chewing, hypertension and lipid levels, they found that the ORs for individuals with blood lead levels in the highest tertile (>7.5 μg/dl; 0.8% of individuals had blood lead levels above 10 μg/dl) were 1.9 (95% CI 1.2–3.1) for elevated serum creatinine level and 2.7 (95% CI 1.6–4.5) for hyperuricaemia (both $P < 0.01$).

Lin and colleagues reported a series of studies on patients with chronic kidney disease, evaluating whether the rate of decline in kidney function over time differs depending on lead burden. Some studies have been observational. For example, Yu, Lin & Lin-Tan (2004) followed 121 patients for 4 years, classifying their baseline ethylenediaminetetraacetic acid (EDTA)-chelatable lead as "low" (urinary lead level below 80 µg/72 h urine collection following a provocative chelation dose) or "high" (urinary lead level between 80 and 600 µg/72 h). Significantly more patients with high compared with low baseline lead burdens experienced a doubling of serum creatinine level or required haemodialysis ($P = 0.001$). Each microgram per decilitre increase in baseline blood lead level, which was 4.9 µg/dl in the high-chelatable lead group and 3.4 µg/dl in the low-chelatable lead group, was associated with a reduction of 4.0 ml/min per 1.73 m^3 in GFR over the period of observation. Other studies by this group involved random assignment of patients with chronic kidney disease to receive therapeutic chelation, with decline in kidney function as the primary end-point. For instance, in one study involving 64 patients, whose baseline chelatable lead levels ranged from 80 to 600 µg/72 h, the patients randomized to active treatment received EDTA for up to 3 months, with additional rounds of treatment if indicated. The mean baseline blood lead levels of the chelation and placebo groups were 6.1 and 5.9 µg/dl, respectively. At the end of 2 years, the mean estimated GFR had increased by 2.1 ml/min per 1.73 m^3 in the chelated group and declined by 6.0 ml/min per 1.73 m^3 in the placebo group ($P < 0.01$) (Lin et al., 2003). In a subsequent study involving 108 patients with chronic kidney disease with chelatable lead levels between 20 and 80 µg/72 h and baseline blood lead levels of 1.2–4.6 µg/dl, the mean change in GFR was 6.6 ml/min per 1.73 m^3 in the chelated group and −4.6 ml/min per 1.73 m^3 in the placebo group ($P < 0.001$) (Lin et al., 2006a). This group conducted a study similar in design on 87 patients with type II diabetes and diabetic nephropathy, baseline chelatable lead levels between 30 and 373 µg/72 h and a mean blood lead level of 6.5 µg/dl (range 1.6–19.1 µg/dl) (Lin et al., 2006b). In the 12-month observation period following random assignment of patients to chelation or placebo, the rate of decline in GFR was 5.0 (SD 5.7) ml/min per 1.73 m^3 in the chelation group and 11.8 (SD 7.0) ml/min per 1.73 m^3 in the placebo group. Baseline blood and chelatable lead levels were both significant predictors of progressive nephropathy in patients with diabetes.

A case–control study compared the blood and tibia lead levels of 55 African Americans with end-stage renal disease (patients receiving chronic haemodialysis treatment) with those of 53 age- and sex-matched controls (Muntner et al., 2007). The cause of end-stage renal disease was hypertension for 40% of the cases, diabetes for 36%, glomerulosclerosis for 6% and unknown for 18%. The mean blood lead level was significantly higher among cases (6 versus 3 µg/dl, $P < 0.001$), with 67% of cases (compared with 6% of controls) having a level of 5–9 µg/dl and 15% (compared with no controls) having a level of 10 µg/dl or greater. The tibia lead levels of cases were somewhat higher than those of controls, but the difference was not significant. The authors suggested that this finding, along with the fact that blood and tibia lead levels were more highly correlated for cases than for controls, might indicate greater bone turnover in the cases, resulting in higher blood lead levels.

The association between lead exposure and renal function in children has not been studied extensively. The few data available suggest that higher blood lead levels are associated with increased GFR (as estimated by serum creatinine or cystatin C levels), suggesting a paradoxical effect, perhaps a hyperfiltration phenomenon (Staessen et al., 2001; de Burbure et al., 2006).

Several factors have been found to modify the association between blood lead level and kidney function, although the evidence is inconsistent. Among these are certain genetic polymorphisms, including ALAD, the vitamin D receptor and nitric oxide synthase (Weaver et al., 2003, 2006; Wu et al., 2003). Among adults who participated in NHANES 1999–2006 (n = 14 778), Navas-Acien et al. (2009) found that higher cadmium exposure resulted in more striking positive associations between blood lead level and renal dysfunction. Adjusting for survey year, age, sex, race/ethnicity, body mass index, education, smoking, cotinine, alcohol consumption, hypertension, diabetes mellitus and menopausal status, individuals with blood lead and blood cadmium levels that placed them in the highest quartile for both metals had ORs of 2.3 (95% CI 1.7–3.2) for albuminuria and 2.0 (95% CI 1.3–3.1) for reduced GFR (estimated based on serum creatinine). The same ORs calculated without taking blood cadmium level into account were much smaller: 1.2 (95% CI 1.0–1.5) and 1.6 (95% CI 1.2–2.1), respectively. For individuals in the highest quartiles of both metals, the OR associated with having both indicators of kidney dysfunction was 4.1 (95% CI 1.6–10.7).

(d) Cardiovascular system

Increased blood pressure/hypertension have long been recognized as a consequence of occupational exposure to lead, raising the question of whether a similar, but more modest, association between lead burden and other cardiovascular outcomes is evident as well at the lower lead exposures experienced by the general population. A variety of reviews (e.g. Navas-Acien et al., 2007) have evaluated the evidence with regard to blood pressure, generally finding that it supports the presence of a positive relationship, with the magnitude of the increase in blood pressure per microgram per decilitre being modest, approximately 1 mmHg (0.13 kPa). The CIs of the estimates derived from consideration of the integrated evidence are mostly positive values but usually include 0 as well (e.g. in the USEPA [2006] integrative analysis, the 95% CI was −3.9 to 11 for systolic pressure and −1.3 to 7.3 for diastolic pressure).

Some analyses suggest that the association between lead exposure and blood pressure varies across sociodemographic strata. Limiting analyses of NHANES III data to women aged 40–59 years (n = 2165), Nash et al. (2003) reported that, compared with women with blood lead levels in the lowest quartile (0.5–1.6 µg/dl), women in the highest quartile (4–31 µg/dl) had an adjusted OR of 3.4 (95% CI 1.3–8.7) for diastolic hypertension (>90 mmHg [12 kPa]) and an adjusted OR of 1.5 (95% CI 0.7–3.2) for systolic hypertension (>140 mmHg [19 kPa]). The associations were strongest for postmenopausal women. In analyses of NHANES III data stratifying by race, Vupputuri et al. (2003) found significant adjusted associations between blood lead level and blood pressure in black males and females: each 3.3 µg/dl increase was associated with a 0.82 mmHg (0.11 kPa)

increase in systolic blood pressure in black males (95% CI 0.19–1.44 mmHg [0.025–0.19 kPa]) and a 1.55 mmHg (0.21 kPa) increase in systolic pressure in black females (95% CI 0.47–2.64 mmHg [0.063–0.35 kPa]). No associations were found in white males or females.

Glenn et al. (2003, 2006) conducted two longitudinal studies, in occupationally exposed cohorts, of the association between changes in blood lead level and changes in systolic blood pressure. In a cohort of 496 current and former workers followed for 4 years, the baseline blood lead level was 4.6 ± 2.6 µg/dl. Adjusting for covariates, systolic blood pressure increased 0.64 mmHg (0.085 kPa) (standard error [SE]: 0.25 mmHg [0.033 kPa]), 0.73 mmHg (0.097 kPa) (SE: 0.26 mmHg [0.035 kPa]) and 0.61 mmHg (0.081 kPa) (SE: 0.27 mmHg [0.036 kPa]) for each standard deviation increase in blood lead level at baseline, tibia lead at year 3 or peak past tibia lead levels, respectively (Glenn et al., 2003). In a cohort of 575 Korean workers also followed for 4 years, the baseline blood lead level was 31.4 ± 14.2 µg/dl. Adjusting for covariates, systolic blood pressure increased 0.9 mmHg (0.12 kPa) (95% CI 0.1–0.6 mmHg [0.013–0.08 kPa]) for each 10 µg/dl increase in blood lead per year (Glenn et al., 2006).

Park et al. (2009) used a prediction model, developed using data from the United States Veterans Administration Normative Aging Study, for predicting bone lead level from blood lead level to reanalyse the association between lead and hypertension in NHANES III. The association was stronger using estimated bone lead level compared with using blood lead level, suggesting that use of a biomarker of shorter-term exposure to lead might result in an underestimate of the association. Among the potential mechanisms proposed to underlie this association are lead-related impairments in renal function, oxidative stress, effects on the renin–angiotensin system and suppression of nitric oxide. Another potential mechanism is suggested by the finding, in a random sample of 1140 50- to 70-year-olds in the Baltimore Memory Study, that blood lead level is significantly correlated with homocysteine levels after adjustment for age, sex, race/ethnicity, education, tobacco use, alcohol consumption and body mass index (Schafer et al., 2005). The same finding was reported in a smaller cross-sectional study in occupationally exposed workers (Chia et al., 2007a).

Published studies used by WHO in estimating the global burden of disease attributable to lead indicate that relative risks of ischaemic heart disease and cerebrovascular stroke associated with small increases in blood pressure (0.4–3.7 mmHg [0.053–0.49 kPa] systolic blood pressure) have been estimated to be in the range of 1.01–1.4, with higher relative risks at younger ages. A large meta-analysis that included 61 prospective studies showed that increases in blood pressure, even among individuals who are clinically normotensive, are associated with increased vascular mortality (Prospective Studies Collaboration, 2002). This analysis included 12.7 million person-years of follow-up for 958 000 adults who were free of known vascular disease at baseline. Blood pressure was significantly associated with age-specific mortality rates for stroke, ischaemic heart disease and other vascular causes, with the relationships apparent throughout the blood pressure range, extending down to 115 mmHg (15 kPa) systolic blood pressure and 75 mmHg (10 kPa) diastolic blood pressure. The association was log-linear, such

that the proportional difference in risk associated with a given increase in blood pressure was similar across the entire range. For example, among those of middle age, reducing systolic blood pressure by 2 mmHg (0.3 kPa) would be estimated to produce a 10% reduction in stroke mortality and a 7% decrease in mortality from ischaemic heart disease.

As noted previously, studies relating lead exposure to overall mortality have tended to find that deaths from cardiovascular disease are largely responsible for the association (Lustberg & Silbergeld, 2002; Schober et al., 2006). The evidence regarding lead and clinical cardiovascular end-points is mixed, however, with most of the studies focusing on individuals with occupational exposure. In cross-sectional analyses of NHANES 1999–2002, an association was reported between concurrent blood lead level and the risk of peripheral artery disease (Navas-Acien et al., 2004; Muntner et al., 2005). Other studies have shown a non-significant elevation in risk of stroke. In a study of non-occupational exposure and heart rate variability in a sample of people from the Republic of Korea (n = 331, comparing blood lead levels below 1.39 µg/dl with those above 3.45 µg/dl), Jhun, Kim & Paek (2005) reported inverse associations between low-frequency, high-frequency and total power spectrum, but these associations were not significant in adjusted analyses. In community-exposed adult men (n = 413) in the United States Veterans Administration Normative Aging Study, Park et al. (2006) also did not find significant adjusted associations between higher tibia or patella lead levels and indices of heart rate variability, although they did find significant associations between patella lead level and heart rate variability (higher low-frequency power and the ratio of low- to high-frequency power) among men with metabolic syndrome. No such associations were found for tibia lead level, however. The authors interpreted these findings as evidence that oxidative stress induced by lead exposure in these men was responsible for autonomic dysfunction in the cardiovascular system. In analyses of the same cohort (n = 593), Perlstein et al. (2007) found a significant association between tibia lead level and pulse pressure (the difference between systolic and diastolic pressures), an index of arterial stiffening, but not between blood lead level and pulse pressure. One mechanism of arterial stiffening is thought to be vascular oxidative stress. Men with tibia lead levels greater than the median value (19.0 µg/g) had pulse pressures that were 4.2 mmHg (0.56 kPa) higher (95% CI 1.9–6.5 mmHg [0.25–0.87 kPa]), compared with men with tibia lead levels below the median, adjusting for age, race, diabetes, family history of hypertension, education, waist circumference, alcohol intake, smoking, height, heart rate, fasting glucose and ratio of total cholesterol to high-density lipoprotein cholesterol. Patella lead levels were also measured, but results were not reported.

Limited data are available on the association between lead exposure and blood pressure in children. Among the children participating in the Kosovo prospective lead study (Factor-Litvak et al., 1996), in whom blood lead levels were substantially elevated (mean of 37 µg/dl in children in the exposed town, 8.7 µg/dl in children in the unexposed town), an increase in blood lead level of 10 µg/dl was associated with a very small increase in systolic blood pressure (0.5 mmHg [0.07 kPa], 95% CI −0.2 to 1.3 mmHg [−0.027 to 0.17 kPa]) and diastolic blood pressure (0.4 mmHg [0.05 kPa], 95% CI −0.1 to 0.9 mmHg [−0.013 to 0.12 kPa]). In contrast,

Gerr et al. (2002) reported significant adjusted associations between higher tibia lead levels and higher systolic and diastolic blood pressures in young adults, half of whom had grown up in the vicinity of a lead smelter. Subjects in the highest quartile of tibia lead level (>10 µg/g) had systolic pressures that were 4.3 mmHg (0.57 kPa) higher than those in the lowest quartile (<1 µg/g) and diastolic pressures that were 2.8 mmHg (0.37 kPa) higher. Although the current blood lead levels were low for subjects in all tibia lead quartiles and were unrelated to either systolic or diastolic blood pressure, the subjects with tibia lead levels in the highest quartile were estimated to have had a mean childhood blood lead level of 65 µg/dl. No association between blood lead level and blood pressure was found in children 12–33 months of age (n = 780) who participated in the Treatment of Lead-Exposed Children (Chen et al., 2006), a randomized clinical trial in which oral succimer was administered to children with baseline blood lead levels of 20–44 µg/dl. Children were followed up for 5 years post-chelation.

A series of studies in 9-year-old children (n = 108) suggest that early lead exposure (blood lead level measured at a mean of 2.6 years: mean 4.0 µg/dl, range 1.5–13.0 µg/dl) mediates the association between lower family socioeconomic status and greater salivary cortisol response to acute stress (Gump et al., 2005, 2007, 2008, 2009).

(e) Reproduction

A recent review (Bellinger, 2005) on lead and pregnancy concluded that fertility is reduced in couples during periods in which the male has a blood lead level greater than 40 µg/dl or a blood lead level greater than 25 µg/dl for several years. The reduced fertility is manifested as fewer live births, reduced likelihood of conception or increased time to pregnancy. Although the evidence regarding lead and spontaneous abortion is limited, in one well-designed study of 668 women in Mexico (Borja-Aburto et al., 1999), the risk was doubled (OR 2.3) at maternal blood lead levels of 5–9 µg/dl and was 5-fold higher (OR 5.4) at maternal blood lead levels of 10–14 µg/dl.

High-dose lead exposure has long been recognized as a risk factor for eclampsia (Troesken, 2006), and a case–control study conducted in the Islamic Republic of Iran of women and newborns suggested that risk of pre-eclampsia is increased among women with blood lead levels largely below 20 µg/dl (Vigeh et al., 2006). Hypertension is a clinical feature of pre-eclampsia, so several studies have investigated the link between blood pressure during pregnancy and lead. Two case–control studies suggest that the risk of pregnancy hypertension is increased at blood lead levels below 10 µg/dl (Sowers et al., 2002; Magri, Sammut & Savona-Ventura, 2003). A prospective cohort study (Rothenberg et al., 2002) found that lead concentration in the calcaneus, but not lead concentration in the tibia or blood lead level, was significantly associated with third-trimester hypertension. In a study conducted in Kosovo (Factor-Litvak et al., 1993), the OR for proteinuria was 4.5 (95% CI 1.5–13.6) for women in the highest decile of pregnancy blood lead level (>40 µg/dl), although the OR rose above 1 for women with a blood lead level greater than 5.8 µg/dl.

Increased paternal or maternal lead exposure has been linked to the risk of a congenital malformation in offspring, although the evidence is somewhat inconsistent across studies. In some studies demonstrating such an association, exposure status was based solely on job title rather than on a lead biomarker. An increased risk of neural tube defects has been reported in offspring of women residing in an area with high lead levels in water (Bound et al., 1997). A study conducted using data from a regional birth defect surveillance programme in the USA found that men who were presumed (on the basis of self-report, an industrial hygiene assessment or job exposure matrix) to have been exposed to lead in the 3-month period prior to conception through the first trimester had an OR of 1.83 (95% CI 1.00–3.42) of delivering a child with total anomalous pulmonary venous return (Jackson et al., 2004). For maternal exposure during this interval, the OR was 1.57 (95% CI 0.64–3.47).

Evidence continues to mount that higher prenatal exposure to lead impairs fetal growth. In a cohort of Mexican women in whom bone lead level was measured 1 month postpartum, higher tibia lead levels were significantly associated with shorter birth length (infants in the highest quintile of maternal tibia lead level had an OR of 1.79 [95% CI 1.10–3.22]) (Hernandez-Avila et al., 2002). In the same cohort, infants of mothers with higher patella lead levels, measured 1 month postpartum, had a significantly smaller head circumference (Hernandez-Avila et al., 2002) as well as lower weight at 1 month of age and less weight gain between birth and 1 month (Sanin et al., 2001). Similar relationships between cord blood lead level (mean 3.9 [SD 3.6] µg/dl) and birth weight and length have been reported in a study conducted in Brazil (Zentner et al., 2006). In a study of 262 pregnancies in California (Jellife-Pawlowski et al., 2006), women with a blood lead level greater than 10 µg/dl during pregnancy were at increased risk of delivering an infant that was preterm (OR 3.2, 95% CI 1.2–7.4) or small for gestational age (OR 4.2, 95% CI 1.3–13.9). Second-trimester blood lead level was a particularly strong predictor of length of gestation (−1.0 days for each microgram per decilitre above 10 µg/dl).

(f) Nervous system

(i) Nerve conduction velocity

A recent meta-analysis was conducted investigating the association between blood lead level and peripheral nerve conduction velocities, latencies and amplitudes in adults (Krieg, Chrislip & Brightwell, 2008). Forty-nine studies, which included 2825 individuals exposed to lead, primarily as a result of occupation, and 1629 controls, were included in the analysis. The nerves measured in these studies included the median, ulnar and radial nerves in the arm and the deep and superficial peroneal, posterior tibial, aural and fibular nerves in the leg. Mixed models were used to estimate the slopes of the dose–effect relationships. The slopes of the relationships were generally negative for velocities, positive for latencies and flat for amplitudes. The lowest blood lead levels at which relationships were found ranged from 33.0 µg/dl (conduction velocity of the median sensory nerve) to 64.0 µg/dl (distal motor latency of the median nerve). The authors noted that these should not be interpreted as estimates of a biological threshold but merely as estimates of the

blood lead levels at which the exposure-related changes in nerve function reached statistical significance. Increasing the number or the precision of the nerve conduction measurements or increasing the number of subjects with lower blood lead levels might have produced lower estimates.

(ii) Postural balance

The association between blood lead level and postural sway, measured using the Neuromotor Test System (CATSYS), was evaluated in a cohort of 181 Japanese workers (121 lead-exposed, 60 controls) (Iawata et al., 2005). Analyses were adjusted for age, height, smoking and alcohol use. Most postural sway measures were significantly greater in the lead-exposed workers and significantly related, in multiple regression analyses, to blood lead level. Benchmark dose (BMD) modelling produced lower bounds on the BMD (BMDLs) in the range of 12–17 µg/dl for the different indices of sway.

(iii) Essential tremor

In a case–control study, the mean blood lead level of 100 patients with essential tremor (3.3 [SD 2.4] µg/dl) was significantly higher than the mean blood lead level of 143 controls (2.6 [SD 1.6] µg/dl) (Louis et al., 2003). In a logistic regression analysis adjusting for age and current cigarette smoking, the OR was 1.19 (95% CI 1.03–1.57, $P = 0.02$). The adjusted OR was somewhat greater when patients with a family history of essential tremor were excluded (OR 1.38, 95% CI 1.15–1.64, $P = 0.001$). This association was also found in a subsequent study of 105 essential tremor cases and 105 controls (Dogu et al., 2007). In this study, the mean blood lead level of cases was 3.2 (SD 1.9) µg/dl, compared with a mean blood lead level of 1.6 (SD 0.8) µg/dl in the controls. Adjusting for age, sex, education, cigarette smoking, cigarette pack-years and alcohol use, the OR was 4.19 (95% CI 2.59–6.78, $P < 0.001$). In addition, the correlation between tremor severity and blood lead level was 0.48 ($P < 0.001$), although this relationship was not found when the analysis was restricted to essential tremor cases.

Neither of these studies involved incident cases of essential tremor, and the cross-sectional design used in each study makes it uncertain whether the higher blood lead levels measured in the cases preceded or followed the diagnosis of essential tremor. More importantly, as the authors noted, even if elevated lead exposure preceded the diagnosis and the role of lead can be considered causal, these studies cannot be used to identify the critical blood lead level. If a blood lead level as low as 3 µg/dl were sufficient to cause essential tremor, the observed prevalence in the population would be much higher than it is (1–6%). Given that the mean age of the participants was greater than 50 years in the Louis et al. (2003) study and greater than 66 years in the Dogu et al. (2007) study, it is possible that their blood lead levels had been considerably higher in the past.

(iv) Amyotrophic lateral sclerosis

Past lead exposure has been associated with the risk of amyotrophic lateral sclerosis (ALS) in case–control studies (Kamel et al., 2002, 2008; Fang et al., 2010)

and one case report (Oh et al., 2007). Information on lead exposure was obtained for 109 cases recruited from two hospitals in Boston, Massachusetts, USA, and from 256 community controls frequency matched on age, sex and residence (Kamel et al., 2002). Bone and blood lead levels were measured in most cases (n = 107) and a subset (n = 41) of controls. Self-reported occupational exposure to lead was associated with an OR of 1.9 (95% CI 1.1–3.3). The risk of ALS increased, as well, with increasing patella lead level (OR 3.6, 95% CI 0.6–20.6, for each 1 μg/g increase), increasing tibia lead level (OR 2.3, 95% CI 0.4–14.5, for each 1 μg/g increase) and increasing blood lead level (OR 1.9, 95% CI 1.4–2.6, for each 1 μg/dl increase). A follow-up study using Cox proportional hazard analysis found a weak association between longer survival and high baseline blood lead level (HR 0.9, 95% CI 0.8–1.0), baseline patella lead level (HR 0.5, 95% CI 0.2–1.0) and baseline tibia lead level (HR 0.3, 95% CI 0.1–0.7) (Kamel et al., 2008). In an additional study involving 184 cases and 194 controls, a doubling of blood lead level was associated with a 1.9-fold (95% CI 1.3–2.7) increase in risk of ALS, adjusting for age and an index of bone resorption (C-terminal telopeptides of type 1 collagen) (Fang et al., 2010). Additional adjustment for an index of bone formation (procollagen type 1 amino-terminal peptide) did not affect the results.

(v) Adult cognitive function

Seeber, Meyer-Baron & Schaper (2002) reviewed two meta-analyses involving data from 24 studies of neurobehavioural performance of workers occupationally exposed to lead. They concluded that although the evidence is not entirely consistent across studies, deficits in different domains are present at blood lead levels between 37 and 52 μg/dl. Several recent studies have reported on the associations between measurements of bone lead levels and cognitive function, both in occupationally exposed adults and in the general adult population. Khalil et al. (2009a) administered a battery of neuropsychological tests to 83 lead battery plant workers and 51 controls who had previously been part of a cohort of 469 individuals administered the same battery 22 years earlier. Current mean blood lead levels were 12 μg/dl for the workers and 3 μg/dl for the controls. Tibia lead level was associated with lower scores, both cross-sectionally and longitudinally, in that it predicted declines in performance over the follow-up interval in the workers, but not in the controls, adjusting for baseline scores, age, education, years of employment and lifestyle factors. The domains most strongly related to cumulative lead exposure were spatial ability, executive functions and learning/memory. Other studies of occupationally exposed workers have also reported that bone lead levels predict decline in test scores over time (Schwartz et al., 2005).

Similar findings have also been reported in cohorts drawn from the general population. Using the Baltimore Memory Study, a longitudinal cohort study of urban adults of diverse ethnicity, Bandeen-Roche et al. (2009) evaluated the association between tibia lead levels and performance on a battery of neuropsychological tests (n = 943–1140 for the baseline and two follow-up assessments). Previous cross-sectional analyses of these data had revealed relationships between tibia lead levels and test scores (Shih et al., 2006). In adjusted longitudinal analyses, higher tibia lead levels were significantly associated with greater decline in eye–hand

coordination over time. Tibia lead level–associated deficits were also found in multiple other skills, including executive functioning, verbal memory and learning. Weisskopf et al. (2004, 2007) reported similar findings in the United States Veterans Administration Normative Aging Study, with the domains of response speed, visuospatial and visuomotor being most strongly associated with bone lead level measured 3.5 years earlier, but not with concurrent blood or bone lead levels.

Most studies of lead and adult cognitive function have been conducted in males. Weuve et al. (2009) assessed biomarkers of lead exposure (tibia, patella, blood) in 587 women 47–74 years of age drawn from the Nurses' Health Study cohort in the USA. Five years later, their cognitive function was assessed. Mean blood lead level at baseline was 2.9 (SD 1.9) µg/dl. All three biomarkers were inversely associated with women's test scores.

Several types of variables have been investigated as potential effect modifiers of the association between increased lead exposure and adult cognition. In a study of workers, Bleecker et al. (2007b) found that among pairs of workers matched in terms of lifetime weighted blood lead level, the inverse association between lead and test scores was more pronounced, at least in certain domains (not motor function), among the members of the pairs that had low "cognitive reserve", operationalized as poorer reading achievement. They suggested that greater cognitive reserve is protective against lead's adverse effects. Analyses of both the Baltimore Memory Study (Glass et al., 2009) and the Veterans Administration Normative Aging Study suggest that greater levels of stress, either self-reported (Peters et al., 2010) or operationalized as the level of psychosocial hazards in the neighbourhood of residence, render an individual more vulnerable to the adverse effects of lead. Finally, several genetic polymorphisms have been investigated as potential effect modifiers. Stewart et al. (2002) reported that the slope of the inverse association between tibia lead level and cognitive test score was steeper among workers carrying at least one *ε4* allele of the apolipoprotein E gene than among workers not carrying one. Analysing NHANES III data, Krieg et al. (2009, 2010) reported that effect modifications of the association between lead and cognition by both vitamin D receptor genotypes and ALAD genotypes were complex and differed as a function of age (e.g. 12–16 years, 20–59 years, >60 years). Other studies have investigated the role of ALAD polymorphisms. Chia et al. (2004, 2007b) suggested that workers carrying the *ALAD2* allele are, to some extent, protected against lead neurotoxicity. In contrast, among men in the Veterans Administration Normative Aging Study, those with the *ALAD2* allele showed a stronger inverse association between blood lead level and performance on the Mini-Mental Status Examination (Weuve et al., 2006) and poorer scores on a spatial copying test (Rajan et al., 2008). In the same cohort, however, carriers of the *ALAD1* allele were at greater risk of lead-associated changes in mood (Rajan et al., 2007).

(vi) Brain imaging

Several studies suggest that white matter is particularly vulnerable to injury as a result of lead exposure. Stewart et al. (2006) found that increasing tibia lead levels were significantly associated with grade of white matter lesion in 536 former

organolead workers (for a 1 µg/g increase in lead concentration, adjusted OR associated with having a lesion of grade 5+ was 1.04, 95% CI 1.02–1.06, $P = 0.004$). Because the workers were all at least 15 years removed from occupational exposure, these changes likely represent progressive or persistent structural lesions.

T.J. Hsieh et al. (2009) used diffusion-tensor imaging to compare the integrity of white matter in workers occupationally exposed to lead (n = 19) in Taiwan, China, with that of age- and sex-matched community controls (n = 18). The mean blood lead level of the workers was 11.5 (SD 1.5) µg/dl, compared with 3.2 (SD 1.2) µg/dl in the controls ($P < 0.001$). Tibia and patella lead levels were also measured. The fractional anisotropy values of the workers and controls differed significantly bilaterally in parietal, occipital and temporal white matter (all $P < 0.05$). Moreover, significant correlations were found between fractional anisotropy values in these regions and the three lead exposure indices. Fractional anisotropy values for the genu and splenium of the corpus callosum did not differ, nor did mean diffusion values in any of the regions measured. These findings suggest that white matter is injured, as reduced fractional anisotropy is widely interpreted as an indication of axonal damage (fibre orientation and organization) and demyelination. This hypothesis is supported by the results of a study of workers at a primary lead smelter, with blood lead levels that averaged 29 µg/dl (range 16–42 µg/dl), conducted by Bleecker et al. (2007a). Damage to white matter, presenting as hyperintensities on T2-weighted magnetic resonance imaging, mediated, to some extent, the inverse association between lead exposure and motor performance.

There is also evidence that grey matter volume in the adult brain is associated with past lead exposure. In the study of occupational lead exposures conducted by Stewart et al. (2006), significant associations were found between higher tibia lead levels and reduced total brain volume, total grey matter and volumes in several specific regions, including frontal, the cingulate gyrus and the insula. These analyses were adjusted for age, education, height and apolipoprotein ε4 status. Cecil et al. (2008) and Brubaker et al. (2010) reported on structural and volumetric imaging studies in young adulthood (mean age 21 [SD 1.5] years) of individuals enrolled prior to birth in the Cincinnati Prospective Lead Study. Significant inverse linear associations were found between annual mean blood lead level measured in the interval from 3 to 6 years of age and grey matter volume, with the magnitude of volume loss increasing with age. The associations were most striking in the frontal regions, particularly the anterior cingulate cortex and ventrolateral prefrontal cortex. Associations were more striking for males than for females. In diffusion-tensor imaging studies of 91 subjects in this cohort, Brubaker et al. (2009) found diverse changes in white matter that were significantly associated with childhood blood lead levels. Specifically, reduced fractional anisotropy and axial diffusivity were found throughout the white matter, as well as changes in the genu, body and splenium of the corpus callosum. Together, these changes suggest lead-related alterations in myelination and in axonal integrity. Finally, using functional magnetic resonance imaging in members of this study cohort (n = 42), Yuan et al. (2006) reported that significant lead-associated changes in activation patterns in the left frontal cortex and left middle temporal gyrus were found as subjects completed a verb generation task.

As found with respect to white matter changes, there is some evidence that the lead-associated changes in brain volume might mediate the lead-associated changes observed in adults' cognitive function. In their cohort of former organolead workers, Schwartz et al. (2007) found that larger volumes of different brain regions were associated with better scores on tests of visuoconstruction, processing speed, visual memory, executive functioning and eye–hand coordination. Furthermore, for the three domains for which test scores were significantly associated with peak tibia lead level (visuoconstruction, eye–hand coordination, executive functioning), volumetric mediation was found. Specifically, the magnitudes of the associations were reduced when volumes of the regions of interest were included as covariates in regression models relating tibia lead level to test scores (Caffo et al., 2007).

(vii) Child IQ and neuropsychological function

To enable a more powerful exploration of the quantitative characteristics of the dose–response relationship between children's blood lead levels and their IQ scores, particularly at blood lead levels below 10 μg/dl, the data from seven prospective cohort studies were pooled (Lanphear et al., 2005). The studies were conducted in the USA (Boston, Rochester, Cincinnati, Cleveland), Mexico City, Kosovo and Port Pirie, South Australia. The analyses included a total of 1333 children, followed from infancy to 5–10 years of age, for whom serial assessments of blood lead level were available. Four indices of lead exposure history were compared in terms of their relationship to IQ: concurrent (the blood lead level measured closest in time to the IQ test), maximum blood lead level measured prior to the IQ test, average lifetime blood lead level (mean blood lead level between 6 months of age and the measurement of IQ) and early childhood blood lead level (mean blood lead level from 6 to 24 months of age). Adjustments were made for 10 covariates measured in each study: HOME Inventory (a measure of the home environment and parental practices and attitudes), sex, birth weight, birth order, maternal education, maternal IQ, maternal age, marital status, prenatal smoking and prenatal alcohol use. A variety of functional forms relating blood lead indices to IQ were evaluated in terms of their relative fit to the data. Of the four blood lead variables, concurrent blood lead level provided the best fit to the data and was selected as the primary exposure metric. A restricted cubic spline model indicated that a log-linear model provided the best fit and suggested that a decline of 6.9 (95% CI 4.2–9.4) IQ points occurred over the blood lead level range of 2.4–30 μg/dl (the upper and lower 5th percentiles of the blood lead distribution). Moreover, a restricted spline model, which does not impose any assumptions about the shape of the dose–response relationship, suggested that the steepest declines in IQ were apparent at blood lead levels below 10 μg/dl. An IQ decrement of 3.9 (95% CI 2.4–5.3) points was associated with an increase in blood lead level from 2.4 to 10 μg/dl; a decrement of 1.9 (95% CI 1.2–2.6) points was associated with an increase in blood lead level from 10 to 20 μg/dl; and a decrement of 1.1 (95% CI 0.7–1.5) points was associated with an increase in blood lead level from 20 to 30 μg/dl. Piecewise linear models were also fit to specific ranges of blood lead levels, defined a priori. Among children for whom the maximum blood lead level measured was below 7.5 μg/dl (n = 103), the regression coefficient for concurrent blood lead level was −2.94 (95% CI −5.16 to −0.71), compared with a regression

coefficient of −0.16 (95% CI −2.4 to −0.08) for children with a maximum blood lead level greater than or equal to 7.5 µg/dl ($P = 0.015$). Sensitivity analyses indicated that the results did not depend unduly on the data from any one study, as the coefficient for concurrent blood lead level changed only by −2.6% to +8.6% when the data from any one of the seven studies were excluded.

The importance of a lead-associated shift of a relatively small number of points in mean IQ can best be appreciated by examining the impact on the population IQ distribution (Bellinger, 2004). Consider the example of a downward shift of 3 points from the expected value of 100 to 97. A reduction of this size would be of uncertain importance to an individual child. However, if all other characteristics of the IQ distribution remain the same (i.e. its dispersion), the shift in the mean would result in an increase of 8% in the number of children with an IQ below 100 and a 57% increase in the number of children with an IQ below 70, the criterion often used to identify those with an intellectual disability. It would also result in a 40% reduction in the number of children with a score of 130 or higher. A downward shift of 5 points in the mean IQ would result in a doubling of the number of children with a score below 70. Using data from a study of low-level lead exposure, Needleman et al. (1982) demonstrated these phenomena empirically. Rose & Day (1990) provided similar demonstrations for changes in mean body mass and the prevalence of obesity, as well as changes in systolic blood pressure and the prevalence of hypertension. A mean reduction of 5 mmHg (0.7 kPa) in systolic blood pressure would result in a reduction of 50% in the prevalence of hypertension, for example.

Although no explanation has been found for a supralinear relationship between blood lead level and child IQ, the same relationship has been reported in several independent studies since the publication of the international pooled analyses (e.g. Kordas et al., 2006; Tellez-Rojo et al., 2006). Tellez-Rojo et al. (2006) evaluated blood lead levels and neurodevelopmental outcome data at 12 and 24 months from 294 children participating in a prospective study conducted in Mexico City, Mexico (note: this is not the Mexico City study that was included in the international pooled analysis). Analyses were restricted to children whose blood lead levels were less than 10 µg/dl at both 12 and 24 months. Adjusting for covariates, blood lead level at 24 months was significantly associated, inversely, with both mental and motor development scores at 24 months, whereas blood lead level at 12 months was inversely associated with the motor development score at 24 months of age, but not with concurrent mental or motor development. The results were stable when adjustment was made for prenatal (cord) blood lead level. For both mental and motor development scores at 24 months, the coefficients that were associated with concurrent blood lead level were significantly larger among children with blood lead levels less than 10 µg/dl than among children with blood level levels greater than or equal to 10 µg/dl.

Numerous other studies have reported adverse neurodevelopmental outcomes in children at blood lead levels below 10 µg/dl. In cross-sectional analyses of 534 6- to 10-year-old children, Surkan et al. (2007) found, using children with blood lead levels of 1–2 µg/dl as the reference group and adjusting for age, race, socioeconomic status and caregiver IQ, that children with blood lead levels of 5–10 µg/dl had a 5-point deficit in IQ ($P = 0.03$), a 7.8-point deficit in reading, a 6.9-point deficit in mathematics as well as deficits in specific neuropsychological domains, such as spatial attention and executive functions.

In a cohort of 246 7.5-year-old African American children (mean blood lead level of 5.4 µg/dl, range 1–25 µg/dl), Chiodo, Jacobson & Jacobson (2004) found significant covariate-adjusted inverse associations between blood lead level and performance on a variety of neuropsychological tests. The domains for which significant associations were observed included intelligence, reaction time, visuomotor integration, fine motor skills and executive functions. Non-parametric regression analyses failed to identify non-linearities for 12 of 15 end-points. For the remaining three end-points, the deviation from linearity was a steeper slope at the lowest blood lead levels. On the basis of analyses exploring the significance of different cut-point values, the authors concluded that a threshold is not readily apparent, with most associations apparent at blood lead levels as low as 3–5 µg/dl.

Chandramouli et al. (2009) investigated the associations between blood lead level at 30 months of age and academic performance and behaviour of 488 7- to 8-year-old children participating in the Avon Longitudinal Study of Parents and Children. The mean blood lead level was 4.2 µg/dl, with 21% of children having a level of 5–10 µg/dl and 6% having a level exceeding 10 µg/dl. Adjusting for covariates, which included sex, child IQ, maternal education, home ownership, maternal smoking, home facilities, paternal socioeconomic status, Family Adversity Index and parenting attitudes, blood lead level was inversely related to reading, writing, spelling and mathematics scores (*P*-values of 0.004, 0.001, 004 and 0.053, respectively). The results of analyses in which blood lead level was categorized (2–5, 5–10, >10 µg/dl) indicated that the associations became significant when the blood lead level exceeded 5 µg/dl.

Solon et al. (2008) reported a cross-sectional study of 877 children, ages 6 months to 5 years, from the Philippines. This was a population-based stratified random sample of children, in whom the mean blood lead level was 7.1 µg/dl. In age-stratified analyses (0.5–3 years, 3–5 years) and adjusting for covariates, each 1 µg/dl increase in blood lead level was associated with a 3.3-point decline in neurodevelopmental score in the younger age group and a 2.5-point decline in the older age group. Nutritional factors, notably folate status and haemoglobin levels, appear to be effect modifiers, with deficiency states exacerbating the inverse associations between lead and neurodevelopment.

In a cohort of 261 8- to 11-year-old children from the Republic of Korea, with a mean blood lead level of 1.7 µg/dl (range 0.42–4.91 µg/dl), blood lead level was inversely associated with IQ score (coefficient −0.18, $P = 0.003$), adjusting for age, sex, maternal education, paternal education, income, maternal smoking during pregnancy, exposure to second-hand smoke after birth, birth weight, maternal age at birth and blood manganese level (Kim et al., 2009). In addition, an additive interaction was observed between blood lead and blood manganese levels, such that the inverse associations between blood lead level and IQ scores were more strongly inverse among children with blood manganese levels greater than the median value (14 µg/l) compared with children with blood manganese levels below the median value.

Miranda and colleagues have linked existing state-wide databases in North Carolina, USA, including blood lead surveillance data and children's scores on an

end-of-grade (Grade 4) reading test. In a study involving 8603 children, they reported that children with a higher blood lead level were at significantly increased risk of failing the reading test, with the association evident at blood lead levels as low as 2 µg/dl (Miranda et al., 2007). In a subsequent study of blood lead screening results at ages 9–36 months and end-of-grade (again Grade 4) reading score, data were available on 57 678 children from all 100 counties in North Carolina. Using children with a blood lead level of 1 µg/dl as the referent group and creating dummy variables for groups of children with each integer unit increase in blood lead level, Miranda et al. (2009) found significant inverse coefficients for all blood lead categories. For instance, for children with a blood lead level of 2 µg/dl, the linear regression coefficient was −0.30 (95% CI −0.58 to −0.01); for children with a blood lead level of 5 µg/dl, the coefficient was −0.80 (95% CI −1.08 to −0.51); and for children with a blood lead level greater than 10 µg/dl, the coefficient was −1.75 (95% CI −2.09 to −1.41). Quantile regression analyses revealed a significant difference in the association between blood lead level and reading score depending on location in the reading score distribution. Specifically, the difference between the reading scores of children with high versus low blood lead levels was greater among children who were performing in the lower tail of the reading distribution. In other words, higher blood lead levels had a disproportionately greater impact on children who, for reasons other than lead, were at risk of reading difficulties. This implies an effect modification, such that the impact of a given level of lead exposure can vary depending on a child's circumstances, specifically the presence or absence of other risk factors for the outcome of interest.

The initial reports of an apparently steeper slope of the relationship between blood lead level and IQ at blood lead levels below 10 µg/dl compared with above 10 µg/dl generated concern that this reflects only a statistical artefact. Bowers & Beck (2006) argued, for instance, that "the dose–response curve between an environmental measure that is lognormally distributed and any cognitive score that is normally distributed will by necessity have a non-linear slope" (p. 523). This contention was dismissed by several respondents to this paper (e.g. Hornung, Lanphear & Dietrich, 2006; Jusko et al., 2006; Bergdahl, 2006, 2007; Svensgaard et al., 2007), all of whom argued that it was based on inappropriate assumptions. Bowers & Beck (2007) responded to the technical issues raised, but, in an important respect, the issue is moot. In the analyses of the pooled international studies, piecewise linear models were fit to different ranges of the blood lead distribution (e.g. <7.5 µg/dl, <10 µg/dl), with the results showing that the linear slopes were significantly steeper in the lower than in the higher ranges and that the linear fits were adequate within these more restricted ranges. Moreover, it was found that for each of the studies included in the pooled analysis, a linear model provided the best fit across the blood lead range in the individual studies. As had been noted more than a decade before (Schwartz, 1994), the inverse slopes of the studies in which participants tended to have lower blood lead levels appeared to be greater than the slopes in studies involving children with higher blood lead levels. From this observation, it follows, then, that when the individual studies were combined in a pooled analysis, the functional form that would provide the best fit over the more extended blood lead range covered by the studies, in aggregate, is one that is non-linear. This was the result that was obtained when relative fits of different models were compared.

(viii) Attention deficit hyperactivity disorder (ADHD)

Older studies in children consistently identified dose-related increases in behavioural outcomes such as inattention, distractibility and hyperactivity (Needleman et al., 1979; Yule et al., 1984; Thomson et al., 1989; Bellinger et al., 1994). The exposures of the children who participated in these studies were considerably higher than the exposures of contemporary children, and the outcomes were based on teacher or parent reports instead of formal diagnostic evaluations. Recent studies have addressed at least some of these limitations.

In NHANES 1999–2002, parents were asked whether they had ever been told by a health professional that their 6- to 16-year-old child met criteria for ADHD and whether the child was taking a stimulant medication. Braun et al. (2006) found that the OR for children in the fifth quintile in terms of blood lead level (>2 µg/dl), compared with children in the first quintile (<0.8 µg/dl), was 4.1 (95% CI 1.2–14.0). The increase in risk was dose dependent, as the ORs associated with the intermediate three quintiles were 1.1 (95% CI 0.4–3.4), 2.1 (95% CI 0.7–6.8) and 2.7 (95% CI 0.9–8.4), respectively. In these analyses, adjustments were made for age, sex, prenatal and postnatal exposure to environmental tobacco smoke, preschool or child-care attendance, health insurance coverage and serum ferritin level.

The same group analysed data (n = 2588) from NHANES 2001–2004, in which the diagnosis of ADHD in 8- to 15-year-old children was based on the Diagnostic Interview Schedule for Children, a structured interview based on the fourth edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) (Froehlich et al., 2009). Children with a blood lead level that placed them in the upper tertile had an adjusted OR for ADHD of 2.3 (95% CI 1.5–3.8). Children with both prenatal exposure to tobacco and a current blood lead level in the upper tertile were at particularly increased risk (adjusted OR 8.1, 95% CI 3.5–18.7).

In a study of 1778 school-age children in the Republic of Korea, for whom blood lead levels ranged from 0.1 to 10.1 µg/dl (geometric mean 1.8 µg/dl), parents completed the Connors' scale for ADHD, a screening tool (Ha et al., 2009). Adjusting for age, sex, income, place of residence, parental history of neuropsychiatric disease (but not specifically ADHD) and blood mercury level, the risk of ADHD, defined as a score exceeding a cut-off derived for children from the Republic of Korea, increased linearly with increasing blood lead level. Compared with children with a blood lead level below 1 µg/dl, the OR associated with a blood lead level above 3.5 µg/dl was 1.96 (95% CI 0.76–5.11). The P for trend across blood lead categories was 0.07. A child's blood lead level was significantly and positively correlated with the number of ADHD symptoms a parent endorsed ($P < 0.001$), although it appeared from a scatterplot that this association was largely attributable to the small number of children with a blood lead level greater than 5 µg/dl.

In a case–control study conducted among Chinese children aged 4–12 years, 630 children who met diagnostic criteria established by the DSM-IV (revised edition) were matched to 630 controls on age, sex and socioeconomic status (Wang et al., 2008). In a conditional logistic regression analysis in which children with a

blood lead level below 5 μg/dl was the referent group and adjusting for household composition, birth weight, family history of ADHD, pregnancy, labour and delivery complications, medical history, maternal and paternal age, maternal and paternal education, and use of alcohol and cigarettes during pregnancy, risk of ADHD was 5.19 ($P < 0.01$) among children with a blood lead level of 5–10 μg/dl and 7.15 ($P < 0.01$) among children with a blood lead level above 10 μg/dl.

Nigg et al. (2008) implemented a multistage screening and verification process to confirm a diagnosis of ADHD using DSM-IV criteria and to rule out co-morbidities in a sample of 150 8- to 17-year-old children (97 cases and 53 controls). Blood lead levels ranged from 0.40 to 3.47 μg/dl (mean 1.03 μg/dl). Blood lead level was significantly related to the ADHD symptom count for total symptoms and for hyperactivity-impulsivity counts ($P < 0.05$). Adjusting for income and sex, children with ADHD combined subtype had a significantly higher blood lead level than did controls ($P < 0.04$). This group did an additional study of 236 6- to 17-year-olds, 108 of whom met diagnostic criteria for ADHD (Nigg et al., 2010). With adjustment for confounders (e.g. IQ, parental smoking), blood lead level (mean 0.73 μg/dl, maximum 2.2 μg/dl) was associated with risk of ADHD combined subtype, but not the inattentive subtype.

(ix) Adult psychiatric status

Two studies followed up in adulthood children in the Childhood Health and Development Study (Oakland, California, USA) and the New England cohort of the National Collaborative Perinatal Project (Opler et al., 2004, 2008). Cases of schizophrenia spectrum disorder were identified in each cohort, and archived serum samples from pregnancy were analysed for ALA, which accumulates when ALAD is inhibited by lead. Based on the relationship between ALA and blood lead level, cases and controls were stratified into groups with a fetal blood lead level estimated to be greater than or equal to 15 μg/dl or less than 15 μg/dl. In analyses that pooled the data in the two cohorts and adjusted for maternal age at delivery and maternal education, the OR for schizophrenia associated with an estimated blood lead level of 15 μg/dl or higher was 1.92 (95% CI 1.05–3.87).

In NHANES 1999–2004, 1987 20- to 39-year-olds were administered a DSM-IV-based Composite International Diagnostic Interview. Individuals with a current blood lead level in the highest quintile (>2.11 μg/dl; 13 individuals had levels above 10 μg/dl), compared with those in the lowest quintile (<0.7 μg/dl), had 2.3 (95% CI 1.1–4.8) times the odds of meeting criteria for a major depressive disorder and 4.9 (95% CI 1.3–18.5) times the odds of meeting criteria for panic disorder, adjusting for sex, age, race/ethnicity, education and poverty to income ratio (Bouchard et al., 2009). Blood lead level was not significantly associated with generalized anxiety disorder.

(x) Violence and aggression

Lead has long been known to impair behaviour in myriad ways, with an important early case series report (Byers & Lord, 1943) noting that lead-poisoned children exhibited explosive tempers and poor impulse control. Denno (1993)

assembled retrospective evidence that childhood lead poisoning is a risk factor for juvenile crime. Studies exploring the association between lower levels of lead exposure and aggression began with Needleman et al. (1996), who found that children with higher bone lead levels were more likely to receive parent and teacher ratings categorizing their behaviours in the range of clinical concern. Needleman et al. (2002) followed this study up with a case–control study of 216 adjudicated delinquents in Pittsburgh, Pennsylvania, USA. Compared with controls, and adjusting for race, parent education, parent occupation, family size, presence of two biological parents and presence of two parental figures in the home, the OR associated with having an elevated bone lead level was 2.0 (95% CI 1.1–31.0) among the delinquent boys and 7.8 (95% CI 1.7–35.0) among the delinquent girls.

Several studies using ecological designs have reported significant associations between air lead concentrations and homicide rate (Stretesky & Lynch, 2001) and property and violent crime rates (Stretesky & Lynch, 2004) and between lead production and murder rate (Nevin, 2000, 2007). Using aggregated data from Australia, Canada, Finland, France, Germany, Great Britain, Italy, New Zealand and the USA, Nevin (2007) examined the association between preschool blood lead level and different types of crime. Relative fits were compared for models incorporating lags of various durations between measurement of blood lead level and outcome measurement. The lags identified in this way coincided well with the known peak offending ages for various offences (e.g. burglary versus homicide). The ability to adjust for potential confounders in studies of ecological design is limited, however, making inferences about causality tenuous.

Braun et al. (2008) used data for 2619 children 8–15 years of age who participated in NHANES 1999–2002 to evaluate the association between concurrent blood lead level and the diagnosis of conduct disorder. A total of 68 children met DSM-IV criteria, established by parental interview. Adjusting for age, maternal age, sex, race, prenatal tobacco exposure and serum cotinine level and using children in the lowest quartile of blood lead as the referent group (0.8–1.0 µg/dl), significant ORs were found for children in quartile 3 (1.1–1.4 µg/dl) (12.4, 95% CI 2.4–64.6) and quartile 4 (1.5–10 µg/dl) (8.6, 95% CI 1.9–40.0).

In a cross-sectional study of 173 14- to 18-year-olds from Brazil, surface dental enamel lead level was associated, adjusting for familial and sociodemographic confounders, with clinically significant elevation of children's rule-breaking behaviour (by parent report) on the Child Behavior Check List (OR 3.72, 95% CI 0.99–14.04) (Olympio et al., 2010). Enamel lead level was not significantly associated with children's self-report of delinquent behaviours, however.

Three prospective studies of environmental lead exposure in children and later criminal activities have been reported. In the Christchurch Health and Development Study, a birth cohort of 1265 children in New Zealand, dentine lead levels in deciduous teeth, measured at 6–9 years of age, were related, in a dose-dependent manner, to the number of violent/property convictions and self-reported violent/property offences between the ages of 14 and 21 (Fergusson, Boden & Horwood, 2008). The effect sizes for both outcomes were reduced by adjustment for sociodemographic variables and aspects of family functioning, but remained

significant ($P < 0.005$ for convictions and 0.047 for self-reported offences). Additional analyses suggested that educational underachievement (leaving school without qualifications, low grade point average) might mediate the association between increased early lead exposure and criminal behaviour.

Among 488 children in the Avon Longitudinal Study of Parents and Children cohort (Avon, England), a higher blood lead level at 30 months of age was significantly associated with greater antisocial behaviours at age 7–8, as reported by an adult (Chandramouli et al., 2009). Although the association was present when blood lead level was treated as a continuous variable, the increase in these behaviours was most apparent among children whose earlier blood lead levels had exceeded 10 µg/dl.

County records of arrests were collected for 250 19- to 24-year-olds enrolled in a prospective study in Cincinnati, Ohio, USA (Wright et al., 2008). Prenatal blood lead levels and childhood blood lead levels had been measured frequently, providing an unusually detailed blood lead history for the participants up to the age of 6.5 years. The median prenatal blood lead level (first or second trimester) was 7.8 µg/dl (range 2.9–16.0 µg/dl); the median early childhood average blood lead level was 12.3 µg/dl (range 6.0–26.3 µg/dl); and the median blood lead level at 6.5 years was 6.8 µg/dl (range 3.4–18.3 µg/dl). A previous analysis of this cohort had found that adolescents who had had higher blood lead levels in early childhood self-reported more delinquent acts. In analyses of total arrests after age 18, adjusting for maternal IQ, sex, socioeconomic status and maternal education, the rate ratios associated with each 5 µg/dl increase were significant for prenatal blood lead level (1.4, 95% CI 1.1–1.9) and 6-year blood lead level (1.3, 95% CI 1.0–1.6). In analyses of arrests for violent offences, the adjusted rate ratios were significant for average childhood blood lead level (1.3, 95% CI 1.0–1.6) and for 6-year blood lead level (1.5, 95% CI 1.1–1.9). Among the strengths of this study are the prospective collection of data on exposure and potential confounding variables, as well as reliance on administrative records rather than self-report as the basis for assessment of the outcomes (Dietrich et al., 2001).

The biological plausibility of the hypothesis that elevated lead exposure is causally associated with aggression is supported by studies in experimental models, such as cats (Li et al., 2003), primates (Moore et al., 2008) and hamsters (Cervantes et al., 2005).

(f) Sexual maturation

Several cross-sectional studies have reported that higher blood lead levels in children are associated with delayed sexual maturation. Selevan et al. (2003) evaluated the relationship between blood lead level and age at menarche and Tanner stage for pubic hair and breast development in 2186 girls 8–18 years old who participated in NHANES II. Both breast and pubic hair development as well as age at menarche were significantly delayed in African American and Mexican American girls with a blood lead level greater than 3 µg/dl, compared with girls with a blood lead level of 1 µg/dl. Each 1 µg/dl increase in blood lead level was associated with a delay of 2.1–6.0 months in progressing from one Tanner stage to the next in

breast and pubic hair development. The delay in age at menarche among girls with a blood lead level greater than 3 µg/dl was 3.6 months. These indices of maturation were also delayed in white females, but not significantly.

In another set of analyses using NHANES III data, Wu, Buck & Mendola (2003) studied girls 10–16 years of age. Data on age at menarche were available for 1235 girls, and physician-determined data on Tanner stage 2 pubic hair and breast development were available for 1706 girls. Blood lead level was categorized as 0.7–2.0 µg/dl, 2.1–4.9 µg/dl and 5.0–21.7 µg/dl. Blood lead level was inversely related to both pubic hair development and age at menarche, but not breast development, adjusting for race/ethnicity, age, family size, residence in a metropolitan area, poverty-to-income ratio and body mass index. In the three blood lead groups, for example, 60.0%, 51.2% and 44.4% of 10-year-olds, respectively, had reached Tanner stage 2 for pubic hair, and 68.0%, 44.3% and 38.5% of 12-year-olds, respectively, had reached menarche.

In a study of 138 10- to 17-year-old girls from the Akwesasne Mohawk Nation in the USA, Denham et al. (2005) found that, among those with a blood lead level above the median value of 1.2 µg/dl, menarche was reached 10.5 months later than it was among girls with a blood lead level below the median, adjusting for age, socioeconomic status and other pollutants (dichlorodiphenyldichloroethylene, hexachlorobenzene, mirex, mercury).

One cohort study has investigated sexual maturation in boys in relation to lead exposure. Hauser et al. (2008) studied 489 8- to 9-year-old boys in Chapaevsk, Russian Federation. The end-points assessed were physician-assessed testicular volume and genitalia stage. The median blood lead level was 3 µg/dl (interquartile range 2–5 µg/dl). In cross-sectional analyses, adjusting for birth weight, gestational age and age at examination, boys with a blood lead level of 5 µg/dl or greater had reduced odds of having reached genitalia stage 2 (OR 0.6, 95% CI 0.3–0.95, P = 0.03). This cohort was followed up (n = 481) several years later (Williams et al., 2010), when more boys had entered puberty, with similar findings. After adjusting for baseline body mass index and height, boys with a baseline blood lead level greater than or equal to 5 µg/dl had a reduced risk of pubertal onset based on testicular volume (HR 0.73, 95% CI 0.55–0.97), genitalia staging (HR 0.76, 95% CI 0.59–0.98) and pubic hair staging (HR 0.69, 95% CI 0.44–1.07). The effect sizes corresponded to delays of 6–8 months in the onset of puberty.

(g) Dental health

Lead has been reported to be a risk factor for dental caries among children with blood lead levels less than 10 µg/dl, but the evidence is mixed and lacks consistency across studies in terms of the patterns of associations. Among 24 901 participants ages 2 years and older in NHANES III, blood lead level was evaluated in relation to the number of decayed, filled and missing surfaces (Moss, Lanphear & Auinger, 1999). In all age strata, higher blood lead level was significantly associated with the number of affected surfaces in both deciduous and permanent teeth, adjusting for age, race, poverty-to-income ratio, cigarette exposure, sex, region, parent education, carbohydrate intake, dietary calcium intake and dental

care. For instance, using dental caries as the outcome, among 5- to 17-year-old children, the OR associated with a 5 µg/dl increase in blood lead level was 1.8 (95% CI 1.3–2.5). Among children with blood lead levels in the upper tertile of the distribution (greater than approximately 3 µg/dl), the OR was 1.66 (95% CI 1.1–2.5).

The association between blood lead level and caries was examined in secondary analyses of 543 6- to 10-year-old children participating in the New England Children's Amalgam Trial (Gemmel et al., 2002). The mean blood lead level was 2.3 (SD 1.7) µg/dl. No association between blood lead level and the number of carious surfaces was observed among children from a rural area. An association was observed, however, in the half of the cohort recruited from an urban area (P = 0.005), adjusting for age, sex, family income, ethnicity, maternal education, maternal smoking, dental hygiene habits (frequency of brushing, firmness of brush) and gum chewing. This association was somewhat stronger in deciduous than in permanent teeth. The ranges of both blood lead levels and the numbers of carious tooth surfaces were greater in the urban than in the rural subgroup, which might have made it easier to detect an association. Alternatively, the possibility of residual confounding or the influence of effect modifying factors whose distributions differed across regions cannot be dismissed.

In another set of secondary analyses of 507 8- to 12-year-old children from Lisbon, Portugal, participating in a study of dental amalgam, Martin et al. (2007) reported that blood lead level (mean 4.6 [SD 2.4] µg/dl) was significantly associated with number of carious surfaces, but only among males, and only in primary teeth (adjusting for age, race, IQ and scores on tests of attention, memory and visuomotor function). In contrast, in a study of 292 6- to 11-year-old children in Thailand whose mean blood lead level was 7.2 (SD 1.5) µg/dl, a significant adjusted OR was observed for the number of decayed/filled surfaces (2.4, 95% CI 1.4–4.2), but only in deciduous teeth, not primary teeth (Youravong et al., 2006). Finally, in a retrospective cohort study evaluating blood lead level and the number of decayed, filled and missing surfaces in second and fifth graders, Campbell, Moss & Raubertas (2000) found that children with a mean blood lead level greater than 10 µg/dl in the interval of 18–37 months of age were not at increased risk.

In adults, greater lead exposure has been associated with risk of tooth loss (Arora et al., 2009). In the United States Veterans Administration Normative Aging Study cohort, men in the highest tertile of tibia lead level had an OR of 3.0 (95% CI 1.6–5.8) for having more than nine missing teeth, whereas men in the highest tertile of patella lead level had an OR of 2.4 (95% CI 1.3–4.5) (Arora et al., 2009). Among 4899 men and women 20–56 years of age included in NHANES III (1988–1994), the adjusted prevalence of periodontitis (presence of more than 20% of mesial sites with greater than or equal to 4 mm of attachment loss) was significantly greater among men and women with a blood lead level greater than 7 µg/dl (men: prevalence ratio 1.7, 95% CI 1.0–2.9; women: prevalence ratio 3.8, 95% CI 1.7–8.7) than among men and women with a blood lead level less than 3 µg/dl (Saraiva et al., 2007). Similar findings were reported in smaller studies (Yetkin-Ay et al., 2007; El-Said et al., 2008).

3. ANALYTICAL METHODS

3.1 Determination of lead in food

The analytical methods for the determination of lead are well established. The most common detection techniques are flame atomic absorption spectrometry (FAAS), electrothermal atomic absorption spectrometry (ETAAS), hydride generation atomic fluorescence spectrometry (HG-AFS), inductively coupled plasma optical emission spectrometry (ICP-OES) and, more recently, inductively coupled plasma mass spectrometry (ICP-MS).

The method for the determination of lead by FAAS has been widely used in the past. The method is selective and practically free from interferences. Some common interferences caused by aluminium and iron can be overcome by the addition of ascorbic acid, citric acid or EDTA. The threshold of sensitivity of this technique is around 10 ng/ml. For trace lead quantification in food matrices, preconcentration steps before quantification are usually required. The sensitivity of FAAS is limited by several factors, such as low atomization efficiency and inefficiency of the nebulization process. To overcome this limitation and improve the process of sample introduction, methods such as thermospray flame furnace atomic absorption spectrometry (TS-FF-AAS) were developed (Da-Col, Domene & Pereira-Filho, 2009). By using this procedure, total sample introduction, long residence time and good sensitivity can be achieved (Pereira-Filho, Berndt & Arruda, 2002).

ETAAS is a good alternative to FAAS and is widely employed for the determination of the trace elements in biological samples. Preconcentration and separation steps are often employed with this technique before quantification of lead in food. However, several constraints have limited its performance, because the response is often perturbed by multiple physical or chemical reactions in the atomizer, and the limits of detection (LODs) are not always adequate for trace analysis (Sardans, Montes & Peñuelas, 2010). In general, the technique requires the use of a modifier to stabilize lead, allowing its quantification without matrix effect. Various modifiers are used for the determination of lead, among them palladium(II) nitrate/palladium (Daftsis & Zachariadis, 2007), palladium(II) chloride/palladium plus ascorbic acid (Licata et al., 2004), palladium(II) nitrate/palladium plus magnesium nitrate (Tüzen & Soylak, 2005) and ammonium phosphate, Triton X-100 plus monoammonium dihydrogen phosphate (Viñas, Pardo-Martínez & Hernández-Córdoba, 2000). Many improvements have enhanced the use of ETAAS for the determination of traces of lead in biological samples, including advances in atomizer designs, background correction systems, the development of in situ trapping methods, appropriate modifiers and improvements in the light source and detector. Significant enhancement of the technique has been achieved using transversally heated atomizers with platforms, which allow the reduction of LODs. In recent years, the high-resolution continuum source electrothermal atomic absorption spectrometer (HR-CS-ETAAS) has allowed the direct analysis of lead in solid materials with low LODs.

ICP-OES has been widely employed to determine lead in various types of samples. Owing to several spectral interferences, this technique is more useful for

measuring high levels of lead contamination. When lower levels of lead are present, preconcentration steps are necessary. This technique also suffers from interferences and was replaced in the last decade by the use of ICP-MS.

The use of ICP-MS has become more common in food laboratory analysis because of its capability for multielement measurements coupled to low LODs (in the order of nanograms per gram). Additionally, compared with ICP-OES, the technique provides simpler spectral interpretation and isotopic information (Nardi et al., 2009). However, polyatomic interferences resulting from the combination of matrix ions with argon may interfere in this technique; to ensure correct results, some of the interferences must be eliminated or controlled by microwave digestion at high temperatures, whereas others have to be controlled using a mathematical approach (Rocha et al., 2009). The recent use of the dynamic reaction cell technology combined with ICP-MS (DRC-ICP-MS) has allowed the removal of the interferences with a minimum loss of sensitivity. This technology may be considered as a valid alternative to the above-mentioned spectrometric techniques, because it offers various possibilities for the element's determination in different matrices (D'Llio et al., 2008).

Alternative methods, such as stripping voltammetry, have been sporadically employed for the determination of lead in food at the nanogram per gram level (Melucci, Torsi & Locatelli, 2007; Jannat, et al., 2009).

The analytical performances of some techniques for the determination of lead in food are presented in Table 2.

3.1.1 Quality assurance

Certified reference materials (CRMs) have been widely employed in new methods reported in the literature for the determination of lead in food to demonstrate analytical quality assurance.

Julshamn et al. (2007) reported on an interlaboratory method performance (collaborative) study for the determination of lead by ICP-MS after pressure digestion including microwave heating. Thirteen laboratories participated, and the method was tested on a total of seven foodstuffs: carrot purée, fish muscle, mushroom, graham flour, simulated diet, scampi and mussel powder. The elemental concentration of lead (dry matter) ranged from 0.01 to 2.4 mg/kg. The repeatability relative standard deviation and reproducibility relative standard deviation for lead ranged from 3% to 27% and from 8% to 50%, respectively. The study showed that the ICP-MS method is satisfactory as a standard method for the determination of elemental lead in foodstuffs.

A proficiency testing programme for determining lead in seawater shrimp for 97 laboratories worldwide under the auspices of the Asia-Pacific Laboratory Accreditation Cooperation is discussed by Kong, Chan & Wong (2008). Pooled data for lead were normally distributed, with interlaboratory variations of about 35%.

Table 2. Analytical methods for the determination of lead in food

Commodity	*n*	Country (year)	Sample preparation (EF)	Technique	LOD	*n* <LOD	Mean concentration (range)	Reference
Seaweed: *Porphyra*, *Laminaria*	4	France, Japan, Republic of Korea, Spain (2004)	Microwave-assisted digestion (HNO_3 + H_2O_2)	ICP-MS	1.74 ng/g	0	(312–848 ng/g)	Rocha et al. (2009)
Rice, bean, egg, meat, fish, bread, sugar, vegetables, cheese, milk powder, butter, wheat, pear, Brazil nut, coffee, chocolate, biscuit, pasta	18	Brazil	Microwave-assisted digestion (HNO_3 + H_2O_2)	ICP-MS	4 ng/g	2	(ND–104.4 ng/g)	Nardi et al. (2009)
Milk and infant formula	8	Italy	Microwave-assisted digestion (HNO_3 + H_2O_2)	DRC-ICP-MS	0.5 ng/g	0	(3.1–19.2 ng/g)	D'Llio et al. (2008)
Semolina	3	—	Microwave-assisted digestion (HNO_3 + H_2O_2)	ICP-MS	16 ng/l	0	(1.9–12.8 ng/g)	Cubadda & Raggi (2005)
Milk	42	Brazil (2004)	Acid digestion (HNO_3 + HCl)	ETAAS	0.41 ng/ml (LOQ)	4	230 ng/ml (62–476 ng/ml)	Soares et al. (2010)

Table 2 (contd)

Commodity	*n*	Country (year)	Sample preparation (EF)	Technique	LOD	*n* <LOD	Mean concentration (range)	Reference
Non-fat milk powder (CRM), water (CRM)	2	—	Ionic liquid-based single drop microextraction (76)	ETAAS	0.017 ng/ml	—	—	Manzoori, Amjadi & Abdulhassani (2009)
Tomato, pepper, onion	9	Mediterranean countries	Microwave-assisted digestion (HNO_3 + H_2O_2)	ETAAS	0.81 ng/g	0	(12.2–70.6 ng/g)	Bakkali et al. (2009)
Anchovy, spinach, cabbage, onion, dill, parsley, lettuce, tea, rice, salami, chicken	23	Turkey	Coprecipitation with MBT	ETAAS	1.38 ng/g	0	(0.58–73.8 ng/g)	Oymak et al. (2009)
Vegetables (100 varieties)	416	China	Acid digestion (HNO_3 + $HClO_4$ + H_2SO_4)	ETAAS	1 ng/g	—	46 ng/g (<1–655 ng/g)	Song et al. (2009)
Milk	97	Islamic Republic of Iran (2004)	Protein precipitation + acid digestion (HNO_3)	ETAAS	—	—	7.9 ng/ml (1–46 ng/ml)	Tajkarimia et al. (2008)
Konjac flour	7	China	Enzymatic hydrolysis and slurry preparation	ETAAS	27.8 ng/g	0	(96.76–859.91 ng/g)	Chen et al. (2008)
Milk	54	Turkey (2003–2004)	Filtration + centrifugation + microwave-assisted digestion (HNO_3 + H_2O_2)	ETAAS	0.62 ng/ml	0	31.4 ng/g (2.5–313 ng/g)	Sarica & Turker (2007)

Table 2 (contd)

Commodity	*n*	Country (year)	Sample preparation (EF)	Technique	LOD	*n* <LOD	Mean concentration (range)	Reference
Raisins	46	Turkey (2005)	Acid digestion (HNO_3 + $HClO_4$ + H_2SO_4)	ETAAS	6.2 ng/g	—	0.056 µg/g (0.012–0.359 µg/g)	Calisir & Akamn (2007)
Cabbage, wheat, potato, egg, baby food formula, baby food, instant milk, gilthead bream, anchovy, golden grey mullet, trout	14	Slovenia	Microwave-assisted digestion (HNO_3 + HF)	ETAAS	0.2 mg/kg	13	<LOD	Milacic & Kralj (2003)
Mussels							0.85 mg/kg	
Spinach, palmito, crab, shrimps, mussel, sardine, squid	7	Brazil	Cryogenic grinding + slurry preparation	ETAAS	75 ng/g	2	(228–574 ng/g)	Santos et al. (2002)
Infant formula powders	152 (38 brands)	—	Dry ashing	ETAAS	6.4 ng/g	0	(25.7–45.5 ng/g)	Moreno-Rojas et al. (2002)
Wheat flour, corn flour	3	Turkey	Wet digestion (HNO_3 + H_2O_2 and membrane filtration of the PAN–Pb complex) (20)	FAAS	3.5 µg/l (blank sample)	0	(4.1–54.7 µg/g)	Soylak et al. (2010)

Table 2 (contd)

Commodity	*n*	Country (year)	Sample preparation (EF)	Technique	LOD	*n* <LOD	Mean concentration (range)	Reference
Tomato, apple, mustard	2	Islamic Republic of Iran	Wet digestion (HNO_3 + H_2O_2; $HClO_4$) and SPE on sodium dodecyl sulfate–coated alumina (63)	FAAS	1.6–2.8 µg/l (blank sample)	0	(0.054–11.6 ng/mg)	Ghaedi et al. (2009)
Coffee, fish, black tea, green tea	4	—	Coprecipitation with zirconium(IV) hydroxide (25)	FAAS	2.5 ng/ml	4	—	Citak, Tuzen & Soylak (2009)
Black tea, black pepper, plant, cocoa powder	4	India	Wet digestion (HNO_3 + $HClO_4$) SPE-C18 membrane disc impregnated with Cyanex 302 (400)	FAAS	1 ng/ml	0	(12.85–49.3 ng/mg)	Karve & Rajgor (2007)
Food supplement	—	Brazil	Microwave-assisted digestion (HNO_3 + H_2O_2)	TS-FF-AAS	6 ng/ml	—	—	Da-Col, Domene & Pereira-Filho (2009)
Seafood (CRM)	—	—	Solid sampling	SS-ZAAS	0.008 ng	—	—	Detcheva & Grobecker (2006)
Guaraná, cabbage	2	Brazil	Acid digestion + SPE (minicolumn of Amberlite XAD-4 modified with DHB) (53)	ICP-OES	0.54 ng/ml	0	(2.7–3.3 ng/mg)	Bezerra et al. (2007)

Table 2 (contd)

Commodity	*n*	Country (year)	Sample preparation (EF)	Technique	LOD	*n* <LOD	Mean concentration (range)	Reference
Whole meal, maize meal, cereal plant meals, cereal plants	5	—	Wet digestion ($HCl + HNO_3 + H_2SO_4$)	SWASV	0.15–0.103 µg/g	0	(0.349–3.71 µg/g)	Melucci, Torsi & Locatelli (2007)
Infant formula	1	Islamic Republic of Iran	Acid digestion (HNO_3) + dry ashing	DPASV	5 ng/g	0	0.384 mg/kg	Jannat et al. (2009)

CRM, certified reference material; DHB, dihydroxybenzoic acid; DPASV, differential pulse anodic stripping voltammetry; EF, enrichment factor; *n*, number of samples analysed; MBT, 2-mercaptobenzothiazole; ND, not detected; PAN, 1-(2-pyridylazo)-2-naphthol; SPE, solid-phase extraction; SS-ZAAS, solid sampling Zeeman atomic spectrometry; SWASV, square wave anodic stripping voltammetry

3.1.2 Sample preparation

Food samples in general require mineralization and dissolution prior to lead quantification. Sample preparation for food and biological matrices depends on the quantification method and usually begins with matrix pretreatment (acid digestion, slurry, leaching or ashing). Acid digestion with strong acids and oxidants (nitric acid and hydrogen peroxide) is the most employed sample treatment in analysis of food for the determination of lead. Microwave-assisted acid digestion has been extensively employed for this purpose, as it allows the use of large sample masses (1–2 g) under controlled temperature and pressure of the system, which reduces contamination and limits losses of the element during mineralization.

Slurry sampling techniques are also employed, to a lesser extent, but may offer some advantages over microwave-assisted acid digestion, such as time, safety and economy. This technique requires the optimization of particle size, slurry concentration and homogeneity.

Ashing and leaching have been used in only a few studies. Calcination at temperatures above 400 °C may induce losses of lead. In general, ashing methods provide lower analyte recovery when compared with acid digestion methods.

Owing to the very low lead levels in food matrices, insufficient detectability of some techniques and matrix effects, the direct determination of trace amounts of lead is not always reliable, and preliminary preconcentration steps are often required. For this purpose, techniques such as coprecipitation, liquid–liquid extraction, solid-phase extraction, cloud point extraction and on-line coprecipitation using a knotted reactor have been widely employed for lead determination in biological matrices. More recently, in order to reduce amounts of toxic organic solvents, liquid-phase microextraction, single drop microextraction, room temperature ionic liquids and membrane filtration have been proposed (Manzoori, Amjadi & Abdulhassani, 2009; Soylak et al., 2010).

Coprecipitation is one of the most efficient separation techniques for trace heavy metal ions, based on the separation of the collector from the matrix solution. For this purpose, inorganic (aluminium, cerium(IV), erbium, iron(III), magnesium, gallium, samarium and zirconium hydroxides and manganese dioxide) and organic coprecipitants (bismuth diethyldithiocarbamate, ammonium pyrrolidine dithiocarbamate, cobalt tris(pyrrolidine dithioate), sodium diethyldithiocarbamate) have been used as efficient collectors of trace elements (Korn et al., 2006). Coprecipitation has mainly been applied to water analyses.

Separation and concentration procedures using liquid–liquid extraction usually result in high enrichment factors and have been carried out in batch mode and in flow injection or sequential injection systems. The last two have the advantage that all manipulations are carried out automatically, minimizing the risk of sample contamination. To allow the extraction of the lead from an aqueous solution, lead needs to be complexed in a previous step. For this purpose, dithizone and ammonium pyrrolidine dithiocarbamate have been widely employed.

Solid-phase extraction enables the selective removal of trace amounts of metal ions from solutions containing complex matrices with minimal usage of

organic solvents. Several procedures for lead have been reported using various solid supports, such as activated carbon, silica gel, cellulose, Amberlite XAD series resins, Chromosorb resin, Ambersorb resin, polyurethane foam and sodium dodecyl sulfate–coated alumina (Karve & Rajgor, 2007; Ghaedi et al., 2009). Many reagents have been used to load these supports and to retain lead by complexation, among them 2-(2′-thiazolylazo)-*p*-cresol, 2-propylpiperidine-1-carbodithioate, 2-(2-benzothiazolylazo)-2-*p*-cresol, pyrogallol red, 1-(2-pyridylazo)-2-naphthol, dithizone and 2-(5-bromo-2-pyridilazol)-5-diethyl-aminophenol (Korn et al., 2006).

The cloud point extraction procedure offers advantages over conventional liquid–liquid extraction, such as high extraction and preconcentration factors, operational safety due to low surfactant flammability and lower toxicity for the analyst and the environment. The cloud point phenomenon occurs when a non-ionic or amphoteric surfactant above its critical micellar concentration causes the separation of the original solution into two phases when heated at a characteristic temperature called the cloud point temperature. Triton X-114 and PONPE 7.5 have been used as surfactants (Korn et al., 2006).

3.2 Determination of lead in blood

The determination of lead in biological materials, such as blood, urine and tissues, poses several problems, mainly due to the low concentration and the complexity of the sample matrix. In general, the techniques employed for the determination of lead in blood are the same as those described previously for the analysis of lead in food.

Electrothermal absorption spectrometry has been widely employed for blood and clinical analyses. Ashing and atomizing the sample in the presence of a chemical modifier and Zeeman effect background correction are essential for precise direct determination of trace elements in blood fractions. A simultaneous atomic absorption spectrometric (SIMAAS) method for the determination of lead and cadmium was proposed by Kummrow et al. (2008). The method requires a sample volume of 200 µl and presents an LOD of 0.65 ng/ml for lead.

More recently, ICP-MS has proven to be an good alternative method to other analytical techniques that have frequently been applied for this purpose, such as ETAAS, due to its low LODs, wide dynamic range, capability for rapid multielement determination and simple sample pretreatment. Whole blood samples can be analysed directly after simple dilution or decomposition of the organic matrix by ICP-MS. LODs in the picograms per millilitre range can be achieved (Heitland & Köster, 2006).

However, the direct analysis of whole blood after dilution can cause clogging of the sample introduction devices and signal instability in the ICP-MS. Several digestion procedures have been reported, including high-pressure ashing in quartz ampoules and microwave-assisted acid digestion in open or closed vessels. The latter is more frequently used for efficient mineralization and reduced contamination risk.

The volume of the sample for analysis is an important aspect that needs to be considered. It is difficult to acquire blood samples from children through invasive paediatric venipuncture. Furthermore, blood samples must be conserved properly immediately after sampling and stored at low temperatures. To overcome these limitations, the preparation of dried blood spots on filter paper has been proposed as an alternative. H.-F. Hsieh et al. (2009) proposed a method for lead determination in whole blood by laser ablation coupled with ICP-MS, requiring a sample volume of 0.5 µl and with a reported LOD of 0.1–2 ng/ml.

The analytical performance of some methods for the determination of lead in blood is shown in Table 3.

3.2.1 Quality assurance

CRMs have been extensively employed in new methods reported in the literature for the determination of lead in blood to demonstrate analytical quality assurance.

The network of external quality assessment scheme organizers in the field of occupational and environmental laboratory medicine sets standards of performance for laboratories. It aims to develop procedures that permit equivalence of assessment among schemes, so that performance of laboratories taking part in different external quality assessment schemes can be directly compared. The use of a *z*-score clearly demonstrates when a laboratory achieves results that are fit for purpose and allows for comparison of performance among schemes. The network organized a study in 2005, with 420 participants, for the determination of lead in blood. The analytical techniques employed were ETAAS, ICP-MS and others, representing 85%, 13% and 2%, respectively. For a target concentration of 2 µmol/l (416 ng/ml) blood lead, a typical between-laboratory precision (coefficient of variation) in the range of 10–16% was established. The quality specification that was proposed based on the desirable total allowable error for lead in blood was ±40 µg/l or ±10%, whichever is the greater value (Taylor et al., 2006).

4. SAMPLING PROTOCOLS

In recent years, considerable attention has been directed towards improving and ensuring the quality of analytical data on contaminants in foods. Whether the data are used for assessing risk from exposure (food surveillance), for food control (regulatory monitoring) or for monitoring standards for trading purposes, it is critical that contaminants be identified correctly and that quantitative data be reliable. Sampling should be based on the use of appropriate sampling techniques, sampling plans and testing methodology. Data collected should be sufficient for the statistical analyses required. Information on appropriate sampling procedures should be supplied.

Sampling plans to be implemented either by food control authorities or by commercial entities (self-inspection performed by producers and/or traders) are described in the general guidelines for sampling for food, provided in the Codex Alimentarius Commission guidelines CAC/GL 50-2004 (FAO/WHO, 2004a).

Table 3. Analytical methods for the determination of lead in blood

Country (year)	*n*	Sample amount	Sample preparation (EF)	Technique	LOD (ng/ml)	Mean concentration (range)	Reference
Brazil (2007)	92 (mothers)	100 µl	Acid digestion (HNO_3)	ICP-MS	0.2	2.7 ng/ml (median) (1.0–5.5 ng/ml)	Koyashiki et al. (2010)
—	CRM	0.5 µl	Sample is loaded onto the surface of a hydrophobic filter membrane	LA-ICP-MS	0.1–2	—	H.-F. Hsieh et al. (2009)
South Africa (1995)	Schoolchildren (8–10 years)	1 ml	Wet digestion (HNO_3 + H_2O_2)	ICP-MS	0.72	56.4 ng/ml	Bazzi, Nriagu & Linder (2008)
Belgium (2003)	1679 adolescents	500 µl	Wet digestion (HNO_3 + H_2O_2)	HR-ICP-MS	2	21.7 ng/ml[a] (9.9–45.4 ng/ml) ($P <$ 0.0001)	Schroijen et al. (2008)
Germany (2005)	130	500 µl	Dilution (Triton X-100 + NH_4OH)	DRC-ICP-MS	0.008	22 ng/ml (5–83 ng/ml)	Heitland & Köster (2006)
USA	934 (African American communities)	16 µl	Dilution with HNO_3	ICP-MS	15	27 ng/ml (<15–200 ng/ml)	Nriagu et al. (2006)
—	—	—	Microwave-assisted acid digestion	SF-ICP-MS	0.32	—	Bocca et al. (2005)
Sweden	31	1 ml	Microwave digestion	ICP-SMS	0.085	17 ng/ml (4–43 ng/ml)	Rodushkin, Ödman & Branth (1999)

Table 3 (contd)

Country (year)	*n*	Sample amount	Sample preparation (EF)	Technique	LOD (ng/ml)	Mean concentration (range)	Reference
—	—	—	Microwave digestion (2.71)	ETAAS	0.83	—	Olmedo et al. (2010)
Sweden	5	30 µl	Drop-to-drop microextraction assisted with ultrasonication	ETAAS	0.08	35.6 ng/ml (15.5–50.5 ng/ml)	Shrivas & Patel (2010)
Brazil (2007)	40	200 µl	Protein precipitation and dilution	ETAAS	0.65	25.1 ng/ml (9.3–56.7 ng/ml)	Kummrow et al. (2008)
—	CRM	50–100 µl	Direct sampling of the punched blood filter paper	ETAAS	2.5	—	Resano et al. (2007)
—	—	5 ml	Wet digestion (HNO_3)	ETAAS	16–19 ng/g pellet 45–152 ng/g supernatant	—	Daftsis & Zachariadis (2007)
—	CRM	2 ml	Microwave-assisted digestion	ETAAS (colloidal Pd modifier)	1.2	—	Viitak & Volynsky (2006)
Germany (2000)	238 (children) 213 (mothers)	—	—	ETAAS	1.3	Children 31.5 ng/ml (6–86 ng/ml) Mothers 26.6 ng/ml (2–91 ng/ml)	Wilhelm et al. (2005)
Egypt	93 (28–40 years)	1 ml	Oxidation with $KMnO_4$	ETAAS	0.95	124 ng/ml (65–175 ng/ml)	Mortada et al. (2002)

Table 3 (contd)

Country (year)	*n*	Sample amount	Sample preparation (EF)	Technique	LOD (ng/ml)	Mean concentration (range)	Reference
Germany (2002–2003)	430 (children, aged about 10 years)	—	—	FAAS	12.5 (LOQ)	22.2 ng/ml (42 samples <LOQ)	Link et al. (2007)
Italy (2004)	110	—	Wet digestion (HNO_3)	ICP-OES	0.32	39.5 ng/ml	Alimonti et al. (2005)
—	CRM	50 µl	Wet digestion and then online resin column preconcentration	HG-AFS	0.004	—	Wan, Xu & Wang (2006)
China	5	3 ml	Wet digestion (HNO_3)	CL	5	21.1 ng/ml (5.3–44.3 ng/ml)	Qu et al. (2008)

CL, chemiluminescence; CRM, certified reference material; EF, enrichment factor; HR-ICP-MS, high-resolution inductively coupled plasma mass spectrometry; ICP-SMS, double focusing sector field inductively coupled plasma mass spectrometry; LA-ICP-MS, laser ablation coupled with inductively coupled plasma mass spectrometry; LOQ, limit of quantification; *n*, number of samples analysed; SF-ICP-MS, sector field inductively coupled plasma mass spectrometry

[a] Geometric mean.

5. PREVENTION AND CONTROL

Lead contamination of food arises mainly from the environment (air and soil) and from food processing (lead paint and lead-containing equipment), food handling and food packaging (lead-soldered cans, coloured plastic bags and wrapping papers, lead-glazed ceramic, lead-containing metal vessels). Atmospheric lead from industrial pollution or leaded gasoline can contaminate food through deposition on agricultural crop plants. Water is also a source of lead contamination of food.

There have been worldwide efforts to reduce lead exposure from food, focusing on implementing standards for allowable lead levels in food and food additives; ending the use of lead-soldered cans; controlling lead levels in water; reducing leaching from lead-containing vessels or restricting their use for decorative purposes; and identifying and reacting to additional sources of lead contamination in foods or dietary supplements. Although not targeted specifically at food, efforts to reduce environmental sources of lead, including restrictions on industrial emissions and restricted use of leaded gasoline, have also contributed to declining lead levels in food (FAO/WHO, 2004b).

For the prevention and control of lead in food, good agricultural and manufacturing practices should be followed. The main source of lead in vegetables arises from atmospheric lead deposition. During processing, maximum removal of surface lead from plants should be practised, for example, by thoroughly washing vegetables, particularly leafy vegetables; removing the outer leaves of leafy vegetables; and peeling root vegetables, where appropriate. The transfer of lead from soil to crop tissues is generally low; the bioconcentration factor is in the range of 0.001–0.5, depending on plant species, environmental conditions and experimental setup (Chamberlain, 1983).

Food processors should ensure that the water supply for food processing complies with maximum limits for lead established by national or local authorities. Food processors should choose foods and food ingredients, including ingredients used for dietary supplements, that have the lowest lead levels possible.

6. LEVELS AND PATTERNS OF CONTAMINATION IN FOOD COMMODITIES

The Committee, at its present meeting, reviewed data on lead occurrence in different food commodities received from seven countries—namely, Australia, Brazil, China, France, Germany, Singapore and the USA—and from the European Food Safety Authority (EFSA), covering data from Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Great Britain, Ireland, Norway, Poland, Romania, Spain, Sweden and three commercial operators (EFSA, 2010). The Committee conducted a literature search and identified published literature for five additional countries: Egypt, India, Lebanon, New Zealand and Nigeria.

The data submitted by France and Germany were included in the assessment report of EFSA (2010). In order to avoid duplicating the data in this analysis, the individual data submitted from both countries were not separately considered in the assessment of the current meeting.

The total number of analytical results (single or composite samples) was 110 899, with 84.9% coming from Europe, 7.6% from the USA, 1.9% from Latin

America, 3.1% from Asia and 2.5% from the Pacific region. No data were received from Africa.

The Committee noted that the occurrence data reported by the countries were, in general, obtained using validated analytical methods.

The data submitted for each country are summarized below. The occurrence data obtained by the Committee from the published literature are summarized in section 7.

6.1 Australia

Food Standards Australia New Zealand (FSANZ) submitted lead data collected in the 23rd Australian Total Diet Study (TDS) conducted in 2008–2009. The data submitted were not in the Global Environment Monitoring System – Food Contaminant Monitoring and Assessment Programme (GEMS/Food) format. The analytical method used for the determination of lead was ICP-MS, and the LOD and limit of quantification (LOQ) were reported as the same value, varying in the range of 0.0001–0.005 mg/kg, according to the food commodity. Lead concentrations in different food commodities (570 individual samples) were reported (Table 4). The highest lead value of 0.248 mg/kg was determined in a food in the baked goods category (a "fancy bread"). Sixteen per cent of the samples analysed presented a lead concentration below the LOD of the method.

Data from the 20th and 19th Australian TDSs were also submitted (FSANZ, 2001, 2003). For these data, the analytical methods used were not reported. The weighted mean lead levels for the food commodities are presented in Tables 5 and 6 for the 20th and 19th Australian TDSs, respectively.

6.2 Brazil

Brazil submitted data on lead levels in three meat categories: meat muscles (beef and pork), poultry muscles (chicken and turkey) and kidneys (beef, chicken and turkey). The data were provided from industry, and the samples were collected during the 2002–2009 period. The results were aggregated and reported in 38 groups. No information was provided about the analytical method used for the quantification of lead. The LOD and LOQ were reported as 0.005 mg/kg and 0.010 mg/kg, respectively. In total, 2163 samples were analysed (616 pork and beef muscles; 1368 poultry muscles; 179 kidneys); the lead concentrations were below the LOQ of the method in 91% of these samples. The maximum weighted mean lead concentrations were in meat muscles, poultry muscles and kidney, at 0.345 mg/kg, 0.270 mg/kg and 0.140 mg/kg, respectively.

6.3 China

Data from two different sources were provided by China. Results from China's 2007 TDS (China, 2010) included lead levels in 12 food composites from 12 provinces. The mean lead levels were as follows: cereals, 0.015 mg/kg; legumes, 0.060 mg/kg; potatoes, 0.064 mg/kg; meat, 0.038 mg/kg; eggs, 0.039 mg/kg; aquatic foods, 0.075 mg/kg; milk, 0.003 mg/kg; vegetables, 0.037 mg/kg; fruits, 0.033 mg/kg; sugar, 0.004 mg/kg; beverages and water, 0.001 mg/kg; and alcoholic beverages, 0.002 mg/kg.

Table 4. Lead concentration in different food commodities from Australia (23rd Australian TDS)

Food category	*n*	*n* <LOD	Mean lead concentration (mg/kg)	Maximum lead concentration (mg/kg)
Cereals/grains not included elsewhere and mixed grains	24	2	0.008	0.022
Wheat (including breads)	16	1	0.009	0.020
Rice	4	1	0.003	0.007
Baked goods including fancy bread	20	0	0.027	0.248
Oats	4	0	0.003	0.003
Roots and tubers	12	0	0.004	0.011
Pulses + legumes	4	0	0.005	0.007
Fruits	80	20	0.003	0.031
Dried fruit	12	0	0.016	0.030
Fruit juices	12	0	0.013	0.032
Vegetables including juices	118	21	0.013	0.072
Meat muscle	36	0	0.010	0.057
Poultry muscle	20	0	0.005	0.017
Poultry liver	4	0	0.007	0.008
Eggs	10	3	0.002	0.039
Finfish	18	0	0.005	0.010
Shellfish	8	0	0.010	0.019
Dairy products	42	13	0.004	0.056
Nuts and oilseeds	8	1	0.004	0.007
Animal fats	4	2	0.002	0.008
Vegetable oils and fats	8	7	0.0001	0.001
Stimulants	12	1	0.015	0.101
Sugar and honey	8	4	0.026	0.095
Spices	8	0	0.002	0.005
Alcoholic beverages	20	3	0.007	0.018
Miscellanous	50	15	0.009	0.143
Total samples	570	94	—	—

Table 5. Lead concentration in different food commodities from Australia (20th Australian TDS)

Food category	*n*	*n* <LOD	Weighted mean (maximum) lead concentration (mg/kg)
Cereals/grains not included elsewhere and mixed grains	48	33	0.006 (0.05)
Wheat (including most breads)	46	31	0.009 (0.06)
Rice	9	9	<LOD
Baked goods (including fancy breads)	30	22	0.004 (0.02)
Oats	9	9	<LOD
Roots and tubers	28	26	0.001 (0.01)
Pulses + legumes	9	9	<LOD
Fruits	144	142	0.0003 (0.01)
Dried fruit	9	0	0.038 (0.06)
Fruit juices	28	28	<LOD
Vegetables including juices	202	177	0.002 (0.05)
Meat muscle	133	113	0.004 (0.17)
Poultry muscle	21	20	0.001 (0.01)
Poultry liver	21	19	0.002 (0.04)
Eggs	28	26	0.001 (0.01)
Finfish	51	48	0.001 (0.02)
Shellfish	21	13	0.189 (0.05)
Dairy products	67	58	0.003 (0.04)
Nuts and oilseeds	18	18	<LOD
Vegetable oils and fats	28	28	<LOD
Stimulants	9	9	<LOD
Sugar and honey	9	9	<LOD
Spices	21	21	<LOD
Alcoholic beverages	21	0	0.018 (0.06)
Total samples	1010	868	—

Table 6. Lead concentration in different food commodities from Australia (19th Australian TDS)

Food category	*n*	Weighted mean lead concentration (mg/kg)	Maximum lead concentration (mg/kg)
Cereals/grains not included elsewhere and mixed grains	45	0.0142	0.290
Wheat (including breads)	48	0.010	0.010
Rice	18	0.005	0.019
Baked goods	27	0.007	0.050
Oats	9	0.003	0.007
Roots and tubers	27	0.001	0.022
Pulses + legumes	27	0.012	0.050
Fruits	168	0.004	0.040
Dried fruit	9	0.020	0.050
Fruit juices	27	<LOD	0.006
Vegetables including juices	198	0.003	0.030
Organ meats	48	0.106	0.630
Meat muscle	8331	0.002	0.037
Minced meats	69	0.003	0.078
Eggs	27	<LOD	0.007
Finfish	30	0.003	0.007
Shellfish	30	0.147	1.100
Dairy products	84	0.008	0.050
Nuts and oilseeds	18	0.003	0.014
Vegetable oils and fats	18	<LOD	<LOD
Stimulants	9	0.003	0.010
Sugar and honey	9	0.079	0.110
Spices	21	<LOD	<LOD
Alcoholic beverages	21	<LOD	<LOD
Miscellaneous	27	0.004	0.020
Total samples	9345	—	—

Table 7. Lead concentration in different food commodities from China

Food category	*n*	*n* <LOD	Mean lead concentration (mg/kg)	Maximum lead concentration (mg/kg)
Fruits	1929	643	0.075	3.73
Leeks and onions	326	64	0.104	2.72
Total	2255	707	—	—

Individual results were also submitted by China from its monitoring programme using the GEMS/Food format and comprising the 2000–2006 period. In total, 2255 samples of fruits and vegetables were analysed; 707 of the samples presented a quantifiable result (above the LOQ of the method). The analytical method used was not reported. The LOQs of the method were in the range of 0.0005–0.05 mg/kg. The LOD was reported as the same value as the LOQ. The highest lead concentration (3.73 mg/kg) was reported for a sample of pome fruit collected in 2000. The mean and maximum lead concentrations and number of samples analysed are reported in Table 7.

6.4 Europe

EFSA carried out an assessment on lead in food, including the risks to humans from dietary exposure to lead (EFSA, 2010). The work was conducted by the Scientific Panel on Contaminants in the Food Chain at the request of the European Commission.

The Committee at the present meeting decided that the summary results from the EFSA report would be used in the current assessment.

EFSA received a total of 139 423 results from food testing, of which 97.9% were from 14 member states (Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Great Britain, Ireland, Poland, Romania, Spain and Sweden) and Norway and 2.1% from three commercial operators.

Approximately 94 000 results covered the period from 2003 to 2009 and were suitable for calculating lead concentrations in 15 major food categories (Table 8). Germany was the major contributor, providing 44% of the concentration data, followed by France (15%), the Czech Republic (9.7%) and Romania (9.6%).

The analytical methods used to perform the determination of lead were graphite furnace atomic absorption spectrometry (GFAAS) (24.3% of the analyses), followed by ICP-MS (9.8% of the analyses). For 52.5% of the samples analysed, no information was provided on the analytical method used, apart from detection and quantification limits. The median LODs for non-specified atomic absorption spectrometry, GFAAS and ICP-MS were 0.006 mg/kg, 0.01 mg/kg and 0.003 mg/kg, respectively.

Table 8. Lead concentration in different food commodities from Europe

Food category	*n*	% of samples <LOD	Mean lead concentration (mg/kg)	Maximum lead concentration (mg/kg)
All cereal and cereal products	4 774	56.6	0.0286	7.120
Sugar and sugar products including chocolate	1 794	63.6	0.0339	4.100
Fat	518	76.7	0.0387	7.300
All vegetables, nuts and pulses	11 011	52.3	0.0733	16.20
Starchy root and potatoes	1 059	47.8	0.0223	1.321
Fruits	3 915	61.4	0.0137	3.700
Juices, soft drinks and bottled water	3 565	69.7	0.0047	0.660
Coffee, tea, cocoa	655	36.2	0.222	6.210
Alcoholic beverages	2 228	36.2	0.0216	5.800
All meat and meat products and offal	40 301	52.3	0.2534	867.0
All fish and seafood	11 453	68.7	0.0543	4.060
Eggs	615	88.6	0.0052	0.205
Milk and dairy products	3 210	80.6	0.0089	4.550
Miscellaneous/ special dietary products	4 923	42.8	0.3652	155.0
Tap water	4 087	38.2	0.0052	1.950
Total	94 108	—	—	—

6.5 Singapore

In total, 1009 samples were collected during 2008. Lead was determined in 437 samples. The analytical method used for the quantification of lead was not reported. The LOD and LOQ were 0.09 mg/kg and 0.3 mg/kg, respectively. Fifty-seven per cent of the samples presented a lead content lower than the LOD. The highest lead levels were reported for three cocoa powder samples (45.4, 35.4 and 25.3 mg/kg). Lead concentrations in different food commodities are presented in Table 9 (Singapore, 2010).

Table 9. Lead levels in different food commodities from Singapore

Food category	*n*	*n* <LOD	Mean lead concentration (mg/kg)	Maximum lead concentration (mg/kg)
Cereals/grains not included elsewhere and mixed grains	5	5	<LOD	<LOD
Baked goods	8	7	0.018	0.14
Fruit juices	5	4	0.032	0.16
Vegetables including juices	66	20	0.402	1.97
Mushrooms/fungus	113	28	0.616	10.1
Molluscs	8	4	0.074	0.19
Finfish	9	0	0.224	0.45
Shellfish	2	0	0.125	0.14
Seaweed	101	38	0.180	1.44
Cocoa products except for cocoa butter	206	44	0.692	45.4
Cocoa butter	34	34	<LOD	<LOD
Nuts and oilseeds	3	3	<LOD	<LOD
Animal fats	59	59	<LOD	<LOD
Vegetable oils and fats	197	196	0.001	0.1
Stimulants	40	0	1.029	3.9
Sugar and honey	66	61	0.019	0.72
Spices	27	11	0.107	0.44
Alcoholic beverages	2	2	<LOD	<LOD
Miscellaneous	58	55	0.004	0.16
Total	1009	572	—	—

6.6 United States of America

The USA published data on selected food items in its TDS comprising the period from 1999 to 2008. In total, 4841 samples were analysed using GFAAS. The LOD and the LOQ of the method were in the range of 0.004–0.02 mg/kg and 0.01–0.06 mg/kg, respectively. Eighty-three per cent of the samples presented a lead content lower than the LOD of the method. The highest lead content of 0.18 mg/kg was reported for a shrimp sample collected in 2006.

Lead levels in different food commodities from the TDS (1999–2008) are presented in Table 10 (USFDA, 2010).

Table 10. Lead levels in different food commodities from the USA (TDS 1999–2008)

Food category	*n*	*n* <LOD	Mean lead concentration (mg/kg)	Maximum lead concentration (mg/kg)
Cereals/grains not included elsewhere and mixed grains	93	90	0.0004	0.017
Wheat (including breads)	366	311	0.002	0.026
Rice	39	39	<LOD	<LOD
Baked goods	39	28	0.004	0.019
Oats	39	38	0.0004	0.014
Roots and tubers	117	104	0.001	0.019
Pulses + legumes	156	146	0.001	0.013
Fruits	769	565	0.003	0.046
Dried fruit	54	34	0.006	0.032
Fruit juices	361	223	0.003	0.029
Vegetables including juices	1302	1055	0.003	0.136
Meat muscle	483	465	0.001	0.054
Organ meats	39	18	0.013	0.049
Poultry muscle	102	99	0.0004	0.014
Eggs	93	93	<LOD	<LOD
Finfish	102	96	0.001	0.013
Shellfish	39	23	0.012	0.180
Dairy products	288	269	0.001	0.033
Nuts and oilseeds	117	114	0.001	0.033
Animal fats	39	38	0.001	0.029
Vegetable oils and fats	63	61	0.001	0.021
Stimulants	39	36	0.0004	0.007
Sugar and honey	39	39	<LOD	<LOD
Miscellaneous	63	51	0.002	0.021
Total	4841	4035	—	—

The USA also provided non-TDS monitoring/surveillance data from the period 1999–2006 (Table 11) (USFDA, 2010). In total, 3633 samples were analysed using four different analytical methods: FAAS, GFAAS, ICP-OES and ICP-MS. The highest lead content of 74 mg/kg was reported for a fruit juice sample collected in 2000. Fifty-six per cent of all samples analysed presented a lead concentration lower than the LOD of the method.

Table 11. Lead levels in different food commodities from the USA (non-TDS 1999–2006)

Food category	*n*	*n* <LOD	Mean lead concentration (mg/kg)	Maximum lead concentration (mg/kg)
Cereals/grains not included elsewhere and mixed grains	35	27	0.013	0.123
Rice	15	11	0.004	0.021
Baked goods	79	49	0.232	16.50
Oats	2	2	<LOD	<LOD
Pulses + legumes	24	16	0.006	0.063
Fruits	425	238	0.130	28.86
Dried fruit	198	90	0.046	1.336
Fruit juices	428	220	0.352	74
Vegetables including juices	277	158	0.300	27.56
Mushrooms and other fungi	18	9	0.224	3.670
Seaweed	1	0	0.100	0.1
Dairy products	130	113	0.013	0.290
Nuts and oilseeds	20	15	0.024	0.299
Sugar and honey including candy	25	10	0.082	0.750
Meat muscle	319	285	0.013	1.359
Organ meats	319	124	0.047	1.237
Poultry muscle	200	152	0.003	0.075
Mollusc	3	0	0.065	0.102
Finfish	446	288	0.009	0.233
Shellfish	665	211	0.075	11.80
Miscellaneous	4	3	0.012	0.046
Total	3633	2021	—	—

7. FOOD CONSUMPTION AND DIETARY EXPOSURE ESTIMATES

7.1 Introduction

Human exposure to lead can occur via food, water, air, soil and dust. Lead is found in all categories of food, including meat, milk, fruits and vegetables, cocoa and cocoa products and processed foods. Water can also contain lead, depending upon the source and the water system characteristics. Although non-dietary sources are potentially important sources of exposure, the Committee generally did not have data to estimate exposure via non-dietary routes and thus did not evaluate the relative contributions of non-dietary sources of exposure.

7.2 Considerations in determining dietary exposure to lead

The sources of lead in food may include soil remaining in or on the food, atmospheric deposition, water, contact with lead-containing processing equipment and packaging. Therefore, it is important to estimate lead levels in food that is as close as possible to the form of the food that is consumed. Levels in raw agricultural commodities do not necessarily reflect levels in foods as they are consumed.

The guidelines for conducting exposure assessments for contaminants in foods (http://www.who.int/ipcs/food/principles/en/index1.html) recommend that regional dietary exposure estimates should be calculated using regional average contaminant concentration data and the GEMS/Food consumption cluster diets (http://www.who.int/foodsafety/chem/gems/en/index1.html). The Committee considered estimates from the TDS or similar studies to be the most relevant in the case of lead, as lead may be introduced during cooking and processing. In contrast, the WHO GEMS/Food consumption cluster diets cannot distinguish the form of the food that is consumed. Therefore, the Committee focused on exposure assessments in which the data were collected on foods as they are consumed and did not use the GEMS/Food data to calculate exposure to lead for this evaluation.

Lead occurrence data were submitted by seven countries. All but one of those countries provided a national exposure assessment using the submitted data in combination with national food consumption data. Most of the exposure assessments were conducted using TDS data that took into consideration the effects of processing/cooking. EFSA provided data for 14 countries and used those data to estimate exposures for 19 countries. Cooking and processing were considered where possible. In addition to the submitted studies, the Committee conducted a literature search and identified several additional national exposure assessments that also took into account cooking and processing.

The Committee included estimates of children's exposure wherever possible. Most of the submitted TDSs estimated children's exposure. The GEMS/Food consumption cluster diets do not include estimates of children's consumption. For those countries that did not report children's exposure, the Committee assumed that children's exposure would be 2–3 times that of the entire population and included those values in this report.

7.3 Assessment of dietary exposure to lead

Dietary exposure estimates were available to the Committee for 29 countries. Each region/country made its own decisions as to the appropriate matching of food lead levels to food consumption data as well as the treatment of samples without detectable lead levels. Estimates of dietary exposure for individual countries are presented below. EFSA conducted assessments for 19 European countries, and those are presented together. In addition, results from the United Kingdom and France TDSs are presented as part of the Committee's evaluation of trends in dietary exposure to lead.

Exposure assessments for each country are presented below.

7.3.1 Australia

FSANZ conducted exposure assessments for Australian[1] consumers using the 19th and 20th Australian TDSs and provided those assessments to the Committee. Although there are more recent Australian TDSs, exposure assessments are not yet available for lead. Therefore, the Committee relied on the 19th and 20th TDSs for evaluating exposures. The 19th Australian TDS was published in 2001 (FSANZ, 2001), with samples collected and analysed in 1998–1999. The 20th Australian TDS was published in 2003 (FSANZ, 2003), with samples collected and analysed in 2000–2001. FSANZ reported a range of exposures based on mean food consumption and either the lower- or upper-bound median concentrations of lead in the analysed foods. The lower end of the range of reported exposures in the Australian TDSs assumed that results less than the limit of reporting (LOR) are equal to zero (lower-bound approach), and the upper end of the range assumed that results less than the LOR are the same as the LOR (upper-bound approach). The LOQ of the method was reported to be 0.0005–0.001 mg/kg food. The food consumption data used in estimating exposures for both the 19th and 20th Australian TDSs were from the 1995 National Nutrition Survey. For infants, estimated dietary exposures are based on a constructed infant diet. The resulting Australian dietary exposures to lead are summarized in Table 12.

The highest estimated exposures (per unit body weight) were for toddlers (2 years), whose mean exposures were 1.19–1.92 µg/kg bw per day in the 19th Australian TDS and 0.03–0.93 µg/kg bw per day in the 20th Australian TDS.

7.3.2 Brazil

Brazil provided lead levels for meat only. Lead levels in beef and poultry muscle meat and kidney from beef and poultry were provided. The Committee decided that it would be misleading to estimate dietary exposure from a single food category; thus, no estimate was undertaken.

[1] New Zealand also conducts a TDS, which is published separately and is summarized under New Zealand.

Table 12. Australian dietary exposures to lead (based on the 19th and 20th Australian TDSs and the 1995 National Nutrition Survey)

Population group	Dietary exposure (µg/kg bw per day)		Average body weight (kg)
	19th Australian TDS	20th Australian TDS	
Adult males 25–34 years	0.42–0.73	0.06–0.40	82
Adult females 25–34 years	0.27–0.56	0.02–0.35	66
Boys 12 years	0.70–1.01	0.02–0.43	49
Girls 12 years	0.59–0.84	0.01–0.34	52
Toddlers 2 years	1.19–1.92	0.03–0.93	14
Infants 9 months	0.57–1.50	0.01–1.2	9.2

7.3.3 Canada

Health Canada has repeated its TDS over six separate periods since 1969. The most recent TDS was started in 2005 (Canadian TDS, 1993–2010). The data were available to the Committee from the Canadian TDS web site (Health Canada, 2010).

Each TDS is conducted in several major Canadian cities over the span of the survey period, normally one city each year. For each city, each individual food item tested (there are about 210 individual food items for the current Canadian TDS) is purchased from three to four different supermarkets. Food samples are prepared and processed as they "would be consumed" in the average household kitchen (i.e. raw meats are cooked; fresh vegetables are cooked or properly peeled, trimmed or otherwise cleaned for serving, if not cooked). These processed foods are then mixed according to each category to make composites (there are over 140 different food composites in the current study). All food composites are analysed for the presence of toxic and nutritionally important chemicals. These concentrations are then combined with food intake information (estimates of how much Canadians consume of each food group) to provide estimates of the dietary exposures to these chemicals for Canadians for 16 different age/sex groups.

The results for the 2002 and 1993–1996 surveys are presented in Table 13.

In 2002, mean lead exposures for the total population were 0.11 µg/kg bw per day. Children 1–4 years of age were the subgroup with the highest mean lead exposure, 0.27 µg/kg bw per day.

In previous TDSs, lead exposure was higher. In 1993–1996, lead exposure for the total population was 0.19 µg/kg bw per day. Between 1993–1996 and 2002, exposure declined about 40% from 0.19 µg/kg bw per day (Table 13).

Table 13. Average dietary exposures of lead for Canadians in different age/sex groups for TDSs in 2002 (Vancouver) and in 1993–1996 (Montreal)

Population subgroup	Dietary exposure (µg/kg bw per day)	
	2002 (Vancouver)	1993–1996 (Montreal)
0–1 month, male + female	0.20	0.45
2–3 months, male + female	0.26	0.54
4–6 months, male + female	0.19	0.42
7–9 months, male + female	0.22	0.45
10–12 months, male + female	0.24	0.50
1–4 years, male + female	0.27	0.49
5–11 years, male + female	0.21	0.36
12–19 years, male	0.15	0.25
12–19 years, female	0.12	0.19
20–39 years, male	0.13	0.22
20–39 years, female	0.11	0.18
40–64 years, male	0.12	0.20
40–64 years, female	0.10	0.17
65+ years, male	0.09	0.16
65+ years, female	0.08	0.14
All ages, male + female	0.11	0.19

7.3.4 Chile

No data on Chilean lead exposures were submitted to the Committee, but a published study was available (Muñoz et al., 2005). In that study, dietary exposure to lead by the population of Santiago, Chile, was determined using the Chilean TDS. The most frequently consumed food products were included in the basket. Prior to analysis, the foods were prepared according to typical Chilean procedures and then grouped into 17 food categories according to their chemical characteristics and analysed. The LOD for lead was 50 µg/kg dry weight for solid samples and 1.6 µg/l for liquid samples. The estimated dietary exposure to lead was 210 µg/day (3 µg/kg bw per day for a 63 kg individual). The authors acknowledged that these exposures were quite high and that they were due to high lead levels in foods rather than from high amounts of food consumption. Milk and milk products, fruits, breads and sugars contributed most to the dietary exposure.

Children's exposures were not reported. The Committee assumed that children would have 2–3 times the exposure of adults per unit body weight and that the range of Chilean children's exposures would be 6–9 µg/kg bw per day.

Table 14. Chinese consumer lead exposures by food category (2007 Chinese TDS)

Food category	Mean exposure (µg/day)	SD	Mean exposure (µg/kg bw per day)[a]	% of total
Cereals	16.44	20.87	0.26	34
Legumes	4.11	5.72	0.07	9
Potatoes	5.7	12.74	0.09	8
Meat	3.32	8.26	0.05	7
Eggs	1.74	3.03	0.03	2
Aquatic foods	3.06	5.51	0.05	9
Milk	0.08	0.07	0.00	0
Vegetables	16.85	34.36	0.27	21
Fruits	2.57	5.94	0.04	8
Sugar	0.01	0.02	0.00	0
Beverages and water	0.58	0.41	0.01	2
Alcoholic beverages	0.02	0.02	0.00	0
Total	54.48	62.61	0.86	100

[a] Assuming a body weight of 63 kg.

7.3.5 China

China submitted two exposure assessments based on the results of the 2007 and the 2000 Chinese TDSs (Wang et al., 2009).

The 2007 Chinese TDS estimated exposure for the total population. The overall exposure to lead for Chinese consumers was estimated to be 55 µg/day (0.87 µg/kg bw day, assuming a mean body weight of 63 kg). The food categories making the largest contributions were cereals (34%) and vegetables (21%). The contributions to exposure from these and other food categories are presented in Table 14.

In the 2000 Chinese TDS (Wang, 2009), the exposures for various age groups were determined. The results are presented in Table 15. When exposures are presented on a microgram per day basis, adults have the highest exposures. If data are adjusted by body weight, children 2–7 years of age have estimated exposures of 3.1 µg/kg bw per day (mean) and 8.2 µg/kg bw per day (upper 97.5th percentile).

Table 15. Lead dietary exposures of different age/sex population groups in China (2000 Chinese TDS)

Age/sex	Body weight (kg)	Mean exposure ± SD (µg/day)	97.5th percentile exposure (µg/day)	Mean exposure (µg/kg bw per day)
2–7 years, male + female	17.9	54.9 ± 37.5	146.8	3.1
8–12 years, male + female	33.1	78.0 ± 54.0	207.9	2.4
13–19 years, male	56.4	99.0 ± 59.2	250.5	1.8
13–19 years, female	50	92.1 ± 56.7	230	1.8
20–50 years, male	63	112.7 ± 83.5	308.3	1.8
20–50 years, female	56	101.2 ± 68.9	279.7	1.8
51–65 years, male	65	102.9 ± 56.5	228.4	1.6
51–65 years, female	58	92.8 ± 51.8	253.3	1.6
>65 years, male	59.5	102.0 ± 65.2	250.9	1.7
>65 years, female	52	79.4 ± 49.8	202.8	1.5

7.3.6 Egypt

No data were submitted to the Committee for Egypt. The Committee obtained a published report of a market basket survey that contained levels of lead in various fruits and vegetables sold in Egyptian markets. Atomic absorption spectrometry was used to estimate and evaluate the levels of lead (Radwan & Salama, 2006). The authors reported dietary exposures of 21 µg/day from fruits, 30 µg/day from vegetables and 1 µg/day from potatoes. Total exposure was not estimated. Assuming a body weight of 68 kg, total exposure from these categories would be 0.74 µg/kg bw per day.

7.3.7 Europe

EFSA released an assessment of lead exposure on 18 March 2010. Some European countries also conduct exposure assessments using their own TDSs. For example, the United Kingdom has conducted exposure assessments using the United Kingdom TDS since 1980.

(a) EFSA

The Committee reviewed the EFSA report and included the results in the present evaluation of European consumer exposures to lead.

EFSA conducted a detailed evaluation of the submitted data and created a single database of occurrences of lead in foods, which was then used to estimate lead exposure in 19 countries. Some data were determined by the study authors to be outliers and were excluded. The foods were grouped into categories. The number of test results for each food in a category was not proportional to the food's relative contribution to the diet. Therefore, sampling adjustment factors were developed to allow the determination of a weighted lead level for each food category.

For the purposes of exposure assessment, EFSA assumed that the lead levels were the same in all countries and that only the diet varied. EFSA combined the occurrence data with consumption information obtained from the EFSA Concise European Food Consumption Database. According to the EFSA report, individual food consumption data that were available in the Concise European Food Consumption Database were used for the lead exposure analysis. This provides a more accurate estimate, in that individual body weights are used for the calculations. Only aggregated food consumption statistics for this database are presented on the EFSA web site (http://www.efsa.europa.eu/en/datex/datexfooddb.htm). The individual data were not available to the Committee.

EFSA divided the food consumption data into 15 broad food groups and some subgroups, giving a total of 28 separate groups. Individual data on sex, age and body weight were included.

EFSA determined lead dietary exposure for average adult consumers in 19 European countries—Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Great Britain, Hungary, Iceland, Ireland, Italy, the Netherlands, Norway, Poland, Slovakia and Sweden—by combining the lead levels in the analysed foods with information on consumption from the EFSA Concise European Food Consumption Database.

EFSA recognized the variation in the methods used to collect and analyse the data as well as the need to consider the impact of assumptions regarding censored data. Thus, EFSA estimated exposures using several different assumptions and methods. For example, mean exposures were estimated with two different assumptions regarding residue levels in samples without detectable lead (lower-bound estimates assumed a zero concentration for samples without detectable lead, and upper-bound estimates assumed that lead was present at the limits of the analytical method). Two different exposure assessment methods were also used: 1) a deterministic approach and 2) a probabilistic approach. The probabilistic assessment was conducted twice, using lower-bound and upper-bound values for the non-quantifiable samples. EFSA concluded that estimates of exposure were similar for assessments that used probabilistic and deterministic methods. Therefore, only the results of the deterministic approach were reported by EFSA (upper- and lower-bound deterministic estimates). The Committee reviewed the estimates of dietary exposure to identify the most useful information to include in

this analysis. In order to facilitate cross-country comparisons, the Committee selected the results of analyses that were as similar as possible to those that were available for other countries (e.g. lower-bound estimates).

The Committee selected the ranges that estimate the lower bound for the country with the lowest average exposure and the upper bound for the country with the highest average exposure. The range was 0.36–1.24 µg/kg bw per day for consumers with mean dietary exposures and 0.73–2.43 µg/kg bw per day for consumers with high dietary exposures, respectively.

EFSA estimated mean and 95th percentile lead dietary exposures for each country using the standardized European-wide distribution of lead occurrence in foods in combination with national estimates of food consumption. Mean and 95th percentile lead dietary exposures were determined for each country's whole population and subgroups of the population. In a separate analysis, EFSA estimated exposures for children and infants by combining the results of multiple surveys of exposure.

EFSA estimated children's exposures based on a compilation of several different surveys of children's exposure to lead. Mean exposures for children aged 1–3 years ranged from 1.10 to 3.10 µg/kg bw per day based on lower-bound and upper-bound assumptions, respectively. Estimates for children aged 1–3 years with high dietary exposure ranged from 1.71 to 5.51 µg/kg bw per day. The corresponding exposures for children aged 4–7 years are 0.80–2.61 µg/kg bw per day based on lower-bound and upper-bound assumptions, respectively, for the mean and 1.30–4.4 µg/kg bw per day for children with high dietary exposure.

EFSA also concluded that "the available evidence for women of child-bearing age and vegetarians does not indicate a dietary exposure that is different from that of the general adult population".

EFSA estimated exposures for breastfed infants to be 0.21 µg/kg bw per day on average and 0.32 µg/kg bw per day for consumers with high dietary exposure. EFSA noted that the lead levels in breast milk were very variable.

EFSA also estimated exposures for infants fed infant formula and reported average exposures from 0.27 to 0.63 µg/kg bw per day, based on lower-bound and upper-bound assumptions, respectively. For infants with high dietary exposure, lead exposures ranged from 0.40 to 0.94 µg/kg bw per day.

Lead exposures for vegetarians from the adult population were reported to be similar to those of other consumers. EFSA estimated exposures to be 1.98–2.44 µg/kg bw per day for consumers of game and 0.81–1.27 µg/kg bw per day for consumers of offal.

EFSA evaluated the contribution of different food categories to exposure and noted that it varied widely between countries. EFSA reported that

> the largest contributors to the calculated overall lead exposure are vegetables, nuts and pulses contributing 19 % to the lower bound and 14 % to the upper bound estimates. Cereals and cereal products contributed 13 % to the lower bound and 14 % to the upper bound. For the lower bound miscellaneous products and food for special uses

contributed 12 %, starchy roots and potatoes 8%, meat and meat products 8 %, alcoholic beverages 7 % and milk and dairy products 6 %. For the upper bound the contributions were: juices, soft drinks and bottled water (11 %), alcoholic beverages (9%) meat and meat products including offal (9 %), milk and dairy products (8 %), miscellaneous products and food for special uses (7 %) and starchy roots and potatoes (6 %).

Additional detail is available in the EFSA study report (EFSA, 2010).

(b) European TDSs

France and the United Kingdom submitted TDS data to the Committee.

(i) France

In addition to the results presented by EFSA, the Committee reviewed the results of a lead exposure assessment conducted by France based on the French TDS (Leblanc et al., 2005), which provided information about trends in dietary exposure to lead. The estimated average daily dietary exposure of the French population to lead was 18 µg for adults aged 15 years or more (0.26 µg/kg bw per day for a 70 kg person) and 13 µg for children aged 3–14 (0.43 µg/kg bw per day for a 30 kg child).

The 97.5th percentile exposure for adults was 3.6 µg/kg bw per week (0.51 µg/kg bw per day), and for children, 6.4 µg/kg bw per week (0.91 µg/kg bw per day).

The food groups contributing most to exposure of the population were bread, rusk, soups, vegetables, fruits, drinking-water, non-alcoholic beverages, alcoholic beverages, and sugars and confectionery.

The study authors noted that “compared to existing French data, the Pb exposures have declined by a factor of 2 to 4”. No information was available as to the time frame for these declines.

(ii) United Kingdom

The Committee also reviewed the United Kingdom exposure assessments based on its TDS since 1980. The United Kingdom TDS allowed the Committee to evaluate trends in lead levels in the diet over time. Based on the 2006 TDS, the population dietary exposure to lead was 0.006 mg/day. In the 2006 TDS, the major contributors to the population dietary exposure were the beverages, bread and other vegetables groups. Dietary exposures of the general United Kingdom population in the 1980 TDS were estimated to be 0.12 mg/day. Lead exposure declined by 95% from 1980 to 2006.

7.3.8 India

No occurrence data were submitted for India. The Committee obtained a published study of lead exposures that was conducted from a TDS-like market basket study in Mumbai, India, in 1991–1994 (Tripathi et al., 1997). Lead levels were estimated in air particulates, water and food samples collected from different suburbs in Mumbai. The data were used to estimate exposure via inhalation and ingestion. In the study, food samples were purchased from different grocery stores

situated in different suburbs. The foods were selected to represent the food and liquids consumed during a 24 h period by the adult population. The samples were divided into seven groups: cereals (rice, wheat and Jowar); pulses (red gram, black gram and green gram); vegetables (potato, tomato, carrot, brinjal, cauliflower, beans, cabbage and ladies finger); leafy vegetables (amaranth, spinach and fenugreek); milk; meat; and fruits. The concentrations of lead and cadmium in all these samples were estimated by the differential pulse anodic stripping voltammetric (DPASV) technique using PARC Model 174 A Polarographic Analyser. Approximately 1000 ml drinking-water samples were collected from 13 houses located in different suburbs of Mumbai.

The concentration of lead in water varied between 0.6 and 2.6 µg/l, with a geometric mean of 1.2 µg/l and a geometric standard deviation of 1.73 µg/l (Table 16).

The total dietary lead exposure was reported to be 25.1 µg/day (Table 17).

Table 16. Mean concentrations of lead in food in India

Food	No. of samples	Geometric mean lead concentration (µg/kg)
Cereal	15	18.2
Pulses	13	253.3
Leafy vegetables	11	100.4
Other vegetables	32	4.1
Milk and milk products	4	1.6
Meat	6	57.0
Fruits	7	7.4
Water	13	1.2

Table 17. Food consumption and dietary lead exposure of Mumbai adults

Name of food	Food consumption (g/day)	Dietary lead exposure (µg/day)
Cereal	445	8.1
Pulses	5.5	13.9
Leafy vegetables	17	1.7
Other vegetables	88	0.4
Milk and milk products	113	0.2
Meat	14	0.8
Fruits	18	0.02
Total	—	25.1

The study also measured levels of lead in air and estimated uptake by humans. The total intake of lead through air, water and food was reported to be 30 µg/day. The diet was reported to account for about 60% of total exposure to lead.

7.3.9 Lebanon

No occurrence data were submitted for Lebanon. The Committee obtained a published study of lead exposures in adult urban populations of Lebanon (Nasreddine et al., 2006). According to the report, the exposure assessment was performed using the TDS approach, as recommended by WHO. Five "total diets" were collected during 2003–2004. The concentrations in food were expressed in milligrams of lead per kilogram fresh matter, and lead exposures were expressed in milligrams per day per person. For foods containing levels of lead below the LOQ, a value equal to half the LOQ was assigned and used for calculation purposes. The LOD for lead was 2 µg/kg. Average and maximal consumer exposures to lead were calculated. Using these data in conjunction with a TDS, the mean and maximal daily dietary exposures per person per day from "total diet" food groups were determined. The mean exposure was estimated to be 18.5 µg/day, and the maximum exposure was 29.6 µg/day. Water contributed the most to exposure. The foods contributing most to exposure were bread and toast, fruits, pizza and pies, and vegetables (raw and cooked).

The study did not estimate exposure for children or other subgroups of the population. The Committee estimated exposure for children by assuming that children's exposures would be 2–3 times the adult exposures (37–55.5 µg/day).

7.3.10 New Zealand

No occurrence data were submitted for New Zealand. The Committee obtained the New Zealand TDS for 2003–2004 (NZFSA, 2005; Vannoort & Thomson, 2005), which provided dietary exposure estimates for lead. In that study, the New Zealand TDS sampled 121 different foods, 110 of which represented at least 70% of the most commonly consumed food items for the majority of New Zealanders. The foods were analysed for lead. Fourteen-day simulated typical diets using these 121 foods were derived mainly from food frequency and 24 h diet recall data from the 1997 National Nutrition Study for adults 15+ years of age and the 2002 Children's Nutrition Study for 5- to 14-year-olds (both commissioned by the New Zealand Ministry of Health). Data from recent studies were used to simulate typical diets for children younger than 5 years of age. The simulated typical diets were established for the following eight age/sex groups: 25+ years, male; 25+ years, female; 19–24 years, young male; 11–14 years, boy; 11–14 years, girl; 5–6 years, child; 1–3 years, toddler; and 6–12 months, infant.

Approximately 4440 different food samples that were intended to be typical of what was available at the point of sale were obtained. All foods were bought at two different times of the year to provide a measure of seasonal variation. Most of these were composited to provide a total of 968 different food samples for elemental analyses. The foods in the 2003–2004 New Zealand TDS were prepared ready for consumption, prior to analysis.

The estimates of dietary exposure were calculated by using the mean concentration of lead in the food samples and the model diets. The estimated exposures were 0.13 µg/kg bw per day (0.91 µg/kg bw per week) for a young male and 0.34 µg/kg bw per day (2.4 µg/kg bw per week) for an infant.

Most food groups contributed to dietary lead exposure for all age/sex groups. Grains contributed 24–27% of dietary lead for adults and 36–39% for children. Chicken, eggs, fish and meat contributed 12–16%, and takeaways contributed 9–24%, of adult dietary lead; the corresponding percentages for children were 7–12% and 10–15%. The main food groups contributing to weekly dietary exposure to lead for infants are grain (18%), chicken, eggs, fish and meat (4%), takeaways (6%), fruit (18%) and infant formula and weaning foods (38%).

7.3.11 Nigeria

No occurrence data were submitted for Nigeria. The Committee obtained a published study (Maduabuchi et al., 2006) that estimated the levels of lead in some foods (canned and non-canned beverages, paediatric syrups, fish, spinach, fluted pumpkin, root crop [type not specified] and cocoa yam). Only very limited information is available about the study. There is no information about the analytical methods used, LODs or numbers of samples. The authors reported lead concentrations of 2–7.3 µg/l in canned beverages and 1–92 µg/l in non-canned beverages. No further details were presented about the types of beverages, either canned or non-canned. Several paediatric syrups were also analysed. One syrup was reported to contain lead at 90 µg/l. One fish (*Ethmaliosa timbriata*) was reported to contain lead at a concentration of 2400 µg/kg. No further details are available about the study.

No dietary exposure assessment was provided. Given the limited information about the data and the limited numbers of foods, the Committee could not conduct an assessment.

7.3.12 Singapore

No exposure assessment was provided by Singapore. The Committee decided that it would not be reliable to use the GEMS/Food consumption cluster diets to estimate exposure, as many of the sampled foods do not have consumption estimates in the consumption cluster diets; conversely, many foods that are commonly eaten were not analysed for lead in the Singapore study (see section 6.5 above).

7.3.13 United States of America

Estimates of dietary exposure to lead were provided based on the analytical results of the USA TDS samples collected from 2004 through 2008 and food consumption data collected in the 2003–2006 NHANES. The TDS is an ongoing monitoring programme in which about 280 foods and beverages representing all major components of the average American diet are collected and analysed for various contaminants and nutrients. TDS samples are collected 4 times each year. Samples are collected from grocery stores and fast food restaurants in three

different cities. The foods are prepared table-ready (i.e. as they would be consumed), and the three samples of each TDS food are then composited before analysis.

Consumption data from the NHANES 2003–2006 Dietary Interview were used to calculate daily dietary exposures to lead. During the 2003–2006 NHANES, consumption records were collected on 2 non-consecutive days for approximately 16 800 individuals. Survey participants reported detailed information about the types and amounts of foods consumed on those days; in all, approximately 6000 different foods and beverages were reported in the survey.

For calculating dietary exposures, lead analytical results for TDS foods were linked to the 2003–2006 NHANES consumption data by mapping TDS foods to NHANES food codes that were most similar in composition. As an example, the TDS food "white bread" was linked to all NHANES codes for yeast breads and rolls made from white flour. As another example, the TDS food "applesauce" was linked to NHANES codes for applesauce as well as other cooked apple products. This approach assumes that, based on the similarity of their ingredients, the analytical result for a TDS food would be an acceptable surrogate for the NHANES foods to which it is mapped. Exposure to lead was estimated via Monte Carlo simulations. For each instance of food consumption as reported by a survey participant, a value for lead was randomly selected from the distribution of analytical results for TDS samples collected from 2004 to 2008. Total daily exposures were calculated for each of 14 age/sex subgroups and the total population of the USA; self-reported body weights of survey participants were used to convert exposure estimates to a per kilogram of body weight basis.

Table 18 summarizes the results for the mean and 90th percentile exposures to lead for consumers in the USA.

7.3.14 Comparisons between countries

The Committee selected a representative dietary exposure value for each country in order to allow comparisons across countries and across regions for the total and/or adult population (Table 19) and for children (Table 20). Unfortunately, estimates of exposure for the same population were not always available for every country. In order to improve comparability, the Committee adjusted some data by standard body weight assumptions if the study reported only dietary exposure per day. For the total/adult population, mean exposures ranged from 0.02 to 3 µg/kg bw per day, depending on the country and also on the assumptions made in conducting the assessments. Children's exposures ranged from 0.03 to 9 µg/kg bw per day, again depending on the country, age of the children and assumptions made in conducting the assessments.

Lead is widely distributed in food. Lead was reported in all but one of the food categories for which data were submitted for this evaluation. The relative contribution of a food category to dietary exposure to lead depends upon the level in the food (both the quantities and the frequency of occurrence) and the amount of the food that is consumed. Among the data submitted, foods with the highest frequency of detection were shellfish (especially bivalves), cocoa products, organ

Table 18. Consumer dietary exposure to lead in the USA (USA 2004–2008 TDSs)

Population group	Dietary lead exposure (µg/kg bw per day)	
	Mean	90th percentile
6–11 months, male + female	0.13	0.30
2 years, male + female	0.11	0.23
6 years, male + female	0.06	0.13
10 years, male + female	0.04	0.09
14–16 years, female	0.02	0.05
14–16 years, male	0.02	0.05
25–30 years, female	0.03	0.06
25–30 years, male	0.02	0.06
40–45 years, female	0.03	0.06
40–45 years, male	0.03	0.06
60–65 years, female	0.02	0.05
60–65 years, male	0.02	0.06
70+ years, female	0.03	0.06
70+ years, male	0.02	0.05
Total, male + female	0.03	0.08

meats, tea, roots and tubers, seaweed and mushrooms/fungi. Foods with the highest amounts of residues were found within every category. No single food or food category always had high or low levels of lead. Levels greater than 1 mg/kg were reported by some countries in wild game, some meat and meat products (especially organ meats and offal), cereals and cereal products, fruits and vegetables. Some countries identified water as having low but frequently detected concentrations of lead. Food consumption, a third determinant of exposure, also varied widely and was considered in all of the assessments. The assignment of values to samples without detectable lead has important effects. The most important contributors to overall dietary exposure were reported by some countries. Foods contributing most to exposure are noted for each country in the sections above.

7.4 Relative contribution of diet to total lead exposure

The relative contribution of diet to total lead exposure is not well known but will probably vary depending upon locale and the contribution from non-dietary sources. Estimates from EFSA suggest that at least half of children's exposure may be due to non-dietary sources of exposure and that soil and dust are major contributors to the non-dietary exposures. The diet was reported to contribute 60% of lead exposure for adults in Mumbai, India.

Table 19. National lead dietary exposure estimates for total/adult population

Country/region	Population group	Exposure (µg/kg bw per day)	
		Mean	High
Australia	Adult males 25–34 years	0.06–0.40[a]	—
	Adult females 25–34 years	0.02–0.35[a]	—
Canada	All (2002 study)	0.11[b]	—
Chile	Adults in Santiago	3[c]	—
China	Adults	0.9[d]	1.8 (97.5th percentile)
Egypt	All (exposures measured for selected crops only)	0.74	—
Europe	Adults (individual estimates by country)	0.36–1.24[e]	0.73–2.43 (95th percentile)
India	Adults in Mumbai	0.44[c]	—
Lebanon	All	0.27[f]	0.43
New Zealand	Adult males	0.13[g]	—
USA	All	0.03[h]	0.08 (90th percentile)

[a] The lower end of the range of reported exposures assumed that results less than the LOR are equal to zero, and the upper end of the range assumed that results less than the LOR are the same as the LOR (data from the 20th TDS).
[b] LOD/LOQ not provided; mean values were specified for all but a few foods.
[c] Assuming a body weight of 68 kg.
[d] From the 2007 study and assuming a body weight of 63 kg.
[e] Range between country with lowest mean exposure and country with highest mean exposure. For lowest mean exposure values, results less than the LOQ were set to zero; for highest mean exposure values, results less than the LOQ were set equal to the LOQ.
[f] Assuming a body weight of 68 kg; foods with concentrations less than the LOQ were assigned a concentration of ½ LOQ.
[g] Samples with concentrations less than the LOD were assigned a concentration of ½ LOD.
[h] Samples with concentrations less than the LOQ were assigned a concentration of zero.

7.5 Temporal changes in lead exposures

Lead levels in foods have declined over time. The estimated values depend upon the population, the time frame and, to some extent, the methods for lead analysis. The Committee had access to data from five countries (Canada, France, New Zealand, the United Kingdom and the USA) that allowed the trends in lead exposure to be estimated.

Table 20. National lead dietary exposure estimates for children

Country/region	Age	Exposure (µg/kg bw per day)	
		Mean	High
Australia	2 years	0.03–0.93[a]	
Canada	4 years	0.19[b]	
	2–3 years	0.26[b]	
Chile	Children	6–9[c]	
China	2–7 years	3.1	8.2 (97.5th percentile)
Europe	1–3 years	1.10–3.10[d]	1 year: 2.1–5.5 (95th percentile)[e] 3 years: 1.7–5.2 (95th percentile)
	4–7 years	0.80–2.61[d]	4 years: 1.5–4.4 (95th percentile) 7 years: 1.4–4.4 (95th percentile)
India	Children	0.9–1.3[c]	
New Zealand	Infants	0.34[f]	
	1–3 years	0.31[f]	
USA	6–11 months	0.13[g]	0.3 (90th percentile)
	2 years	0.11[g]	0.2 (90th percentile)

[a] The lower end of the range of reported exposures assumed that results less than the LOR are equal to zero, and the upper end of the range assumed that results less than the LOR are the same as the LOR.

[b] LOD/LOQ not provided; mean values were specified for all but a few foods.

[c] Assuming that children have 2–3 times the adult exposure per unit body weight, respectively.

[d] Means for the country with the lowest exposure and the country with the highest exposure. Lowest mean exposure (lower bound) calculated with results less than the LOQ assigned zero; highest mean exposure (upper bound) calculated with results less than the LOQ set at the LOQ.

[e] Children's estimates for consumers with high exposure are based on EFSA's combination of estimates from multiple surveys (depending upon the age group, 8–13 surveys were combined).

[f] Samples with concentrations less than the LOD were assigned a concentration of ½ LOD.

[g] Samples with concentrations less than the LOQ were assigned a concentration of zero.

New Zealand summarized changes in dietary exposure to lead since 1982 in its 2003–2004 TDS report. Lead exposures for 19- to 24-year-old males were 3.6 µg/kg bw per day in 1982 and 0.13 µg/kg bw per day in 2003–2004. This represents a decline of approximately 75%.

Dietary exposures for the general population in the United Kingdom have declined approximately 95% between 1980 and 2006. Exposures were estimated to be 0.12 mg/day in the 1980 TDS and 0.006 mg/day in the 2006 TDS.

Canada and France have reported a 50% decline in exposure to lead over the past 10–15 years.

The USA reported declines in lead exposure for all age groups (M. Bolger, personal communication, 2010). Teenage males (14–16 years) showed the greatest decline, from 70 µg/day in 1976 to 3.45 µg/day in 2000.

8. DOSE–RESPONSE ANALYSIS

8.1 Identification of key data for risk assessment

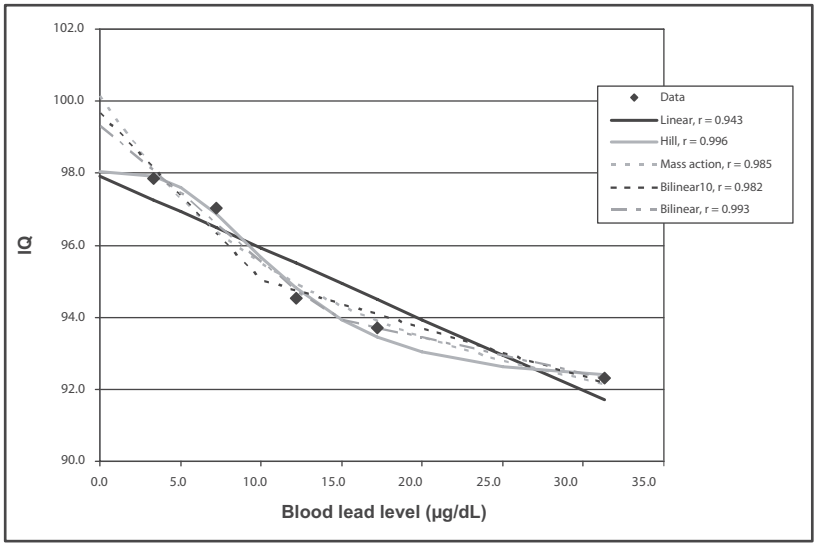
8.1.1 Pivotal data from biochemical and toxicological studies

The data from biochemical and toxicological studies in experimental animals provide support for the plausibility of associations reported in epidemiological studies. However, in view of the large numbers of studies providing quantitative data on dose–response relationships in humans, the studies in experimental animals are not considered to be pivotal for the dose–response analysis.

8.1.2 Pivotal data from human clinical/epidemiological studies

Exposure to lead has been shown to be associated with a wide range of effects, including various neurological effects, mortality (mainly due to cardiovascular diseases), impaired renal function, hypertension, impaired fertility and adverse pregnancy outcomes, reduced sexual maturation and effects on dental health. EFSA (2010) identified three effects as providing pivotal data for its risk assessment: 1) developmental neurotoxicity in young children, as measured by decreased IQ score; 2) cardiovascular effects in adults, measured by increased systolic blood pressure; and 3) increased prevalence of chronic kidney disease in adults, as measured by a decrease in GFR. For each of these end-points, EFSA calculated a BMD and its lower 95th percentile confidence limit (BMDL). The lowest BMD and BMDL were for a decrease in cognitive ability by 1 IQ point, which could be adverse at the population level. The Committee agreed that the neurodevelopmental effects of lead occurred at lower blood lead concentrations than the other effects and therefore considered these to be the pivotal data in its assessment for children. For adults, the Committee concluded that the pivotal data were for the lead-associated increase in systolic blood pressure, as this was associated with the lowest blood lead concentrations and with the greatest and most consistent weight of evidence.

Figure 1. Five models fit to central estimates from Lanphear et al. (2005)



8.2 General modelling considerations

8.2.1 Selection of data

As it is the most recent and most comprehensive meta-analysis available, the results of Lanphear et al. (2005) were used as the basis for a dose–response model. This meta-analysis is based on the same studies used in the EFSA (2010) analysis. Although four different measures of dose were examined as part of the meta-analysis, concurrent blood lead level as the measure of exposure was used for dose–response modelling because it showed the highest correlation with changes in IQ. The mean values for each of the five dose groups are shown in Figure 1.

8.2.2 Selection of mathematical model

Six different models were initially considered. The first four have a linear form, whereas the last two are sigmoidal:

1) *Linear*: The change in IQ from the zero intercept is proportional to dose. This model has two adjustable parameters: intercept and slope. The linear model is equivalent to the hockey stick model with a threshold of zero.
2) *Hockey stick*: The change in IQ above a threshold is proportional to the dose above the threshold. This model has three adjustable parameters: intercept, threshold and slope. The hockey stick model is equivalent to a bilinear model with a low-dose slope of 0.
3) *Bilinear10*: High- and low-dose slopes, with an inflection point at a lead concentration of 10 µg/dl. Although 10 µg/dl has traditionally been used as a

cut-off level to distinguish between high and low exposures to lead, there is no empirical support for the use of this value as an inflection point. This model was included because it is one of the models used in the EFSA analysis (i.e. the piecewise linear model). The bilinear10 has three adjustable parameters: intercept, low-dose slope and high-dose slope.

4) *Bilinear*: High- and low-dose slopes, with an inflection point as an additional parameter. This model has four adjustable parameters: intercept, low-dose slope, high-dose slope and the inflection point.
5) *Mass action*: A simple sigmoidal model that is theoretically based on reversible ligand–receptor interaction. This model has three adjustable parameters: intercept, maximum effect (amplitude) and median effective dose (ED_{50}). Mass action is equivalent to the Hill model with the power parameter equal to one.
6) *Hill*: This model is a more complex sigmoidal model that is theoretically based on reversible ligand interaction with multiple binding sites. From a curve-fitting point of view, the inclusion of an additional power parameter makes the slope of the model more flexible. This model has four adjustable parameters: intercept, maximum effect (amplitude), ED_{50} and power.

8.3 Dose–response modelling

8.3.1 Blood lead and IQ in children

All six models were fit to the central estimates using least-squares regression. The results for five of the models are shown in Figure 1 above. The hockey stick model provided the same fit with the same slope parameter as the linear model. CIs were estimated with a 1000-iteration bootstrap analysis, in which each model was successively fit to a set of dose–response pairs generated by random sampling from the CIs from the Lanphear et al. (2005) meta-analysis.

Table 21 compares the blood lead levels associated with a change of 1 IQ point for each model with estimates from the previous evaluation by the Committee and the EFSA evaluation. It may be noted that while the central (median) estimates from the present analysis are quite similar to those presented by EFSA (Budtz-Jørgensen, 2010), the CIs are wider. This difference is attributable to the wider CIs present in the estimates from the Lanphear et al. (2005) meta-analysis. Similarly, the estimates from the 2000 evaluation by the Committee (Annex 1, reference *144*) do not have CIs, as they are based on a meta-analysis (Schwartz, 1993) that had no representation of uncertainty. The slight differences in central estimates are presumably attributable to the fact that the Schwartz (1993) meta-analysis does not include some of the newer studies used by Lanphear et al. (2005) and Budtz-Jørgensen (2010).

8.3.2 Dietary lead exposure and IQ

The relationship between dietary lead exposure and blood lead level was assumed to be linear with a slope somewhere between 0.052 and 0.16 µg/dl per 1 µg/day of lead exposure. The high end of this range comes from a USEPA (1986) analysis of infants consuming lead-contaminated drinking-water in Scotland. This estimate underlies the USEPA lead model used by EFSA (2010). The low end of the range comes from the 2000 reanalysis by the Committee (Annex 1, reference

Table 21. Blood lead levels associated with a decrease of 1 IQ point in children

Model	Blood lead level (µg/dl) associated with a decrease of 1 IQ point		
	FAO/WHO (2000)[a]	EFSA (2010): BMD (BMDL)	Present analysis: Central estimate (CI)
Linear	2.6	5.6 (4.1)[b]	5.1 (2.8–25)
Hockey stick	7.6	—	5.1 (2.8–25)
Mass action	—	—	1.4 (0.1–9)
Hill	6.9	—	8.5 (0.7–27)
Bilinear10	—	1.8 (1.2)	2.3 (0.9–19)
Bilinear	—	—	2.1 (0.8–17)

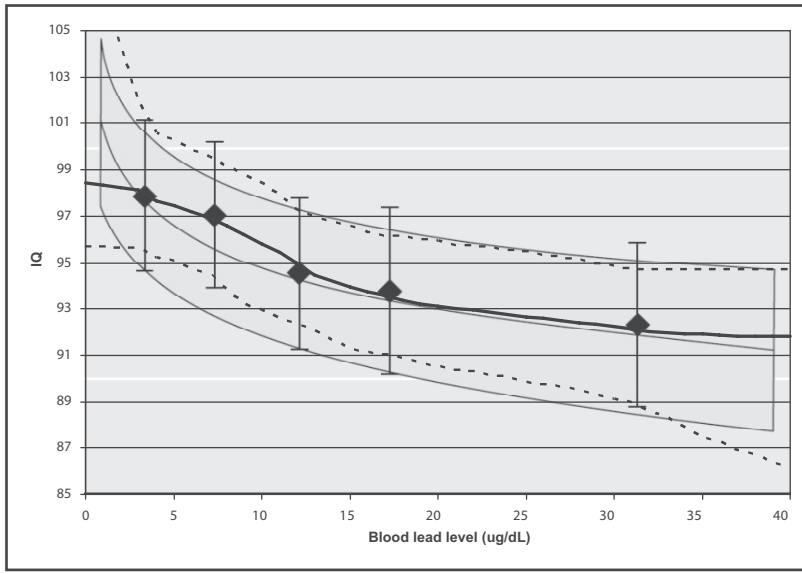
[a] Annex 1, reference *144*.
[b] From Budtz-Jørgensen (2010).

144) of the same data with an intercept parameter included that presumably accounts for other sources of lead exposure.

Since the Hill and bilinear models provided the best fit and have the characteristics of the other models, they were chosen for characterization of the dose–response relationship. Each of these two models is superimposed over the Lanphear et al. (2005) meta-analysis results in Figures 2 and 3, respectively. In order to integrate model uncertainty with the uncertainty inherent in the meta-analysis, a dose–response function was also developed with combined output from both the Hill and bilinear models, with each model considered to be equiprobable (i.e. the outputs from the 1000-iteration bootstrap analysis for each model were combined to produce a set of 2000 estimates). This function is shown in Figure 4. It may be noted that the uncertainty associated with this function is greater at low doses. This is attributable to the contribution of model uncertainty in addition to the uncertainty from the meta-analysis. In particular, the bilinear model tends to yield higher estimated impacts on IQ at low doses compared with the Hill model. Dietary exposures associated with specific decreases in IQ are presented in Table 22.

However, it should be noted that these estimates presume that there are no other exposures to lead. As dietary exposure is less than exposure from air, water, soil and paint for many people in the world, this assumption is often not correct. This is particularly important for the Hill model, where impacts on IQ are greatest when lead exposure is close to the ED_{50}. So, although a few micrograms per day may have a negligible impact on IQ without other exposures, such a dietary exposure may be a concern when other lead exposures push total exposure to the steeper part of the curve. As the bilinear model is linear at low doses, the impact of a given dietary exposure will be about the same regardless of what the other exposures are. Because the bilinear model may provide a better estimate when other exposures are unknown or highly variable, estimates using the bilinear model only are presented in Table 23.

Figure 2. Hill model bootstrap analysis, superimposed over Lanphear et al. (2005)



Note: The data points and associated CIs are derived from the the Lanphear et al. (2005) meta-analysis. The thin line and shaded area represent a log-linear model and associated CIs, which are also from the Lanphear et al. (2005) meta-analysis. The thicker line plots the Hill model from the current analysis, with associated CIs given by the dotted lines.

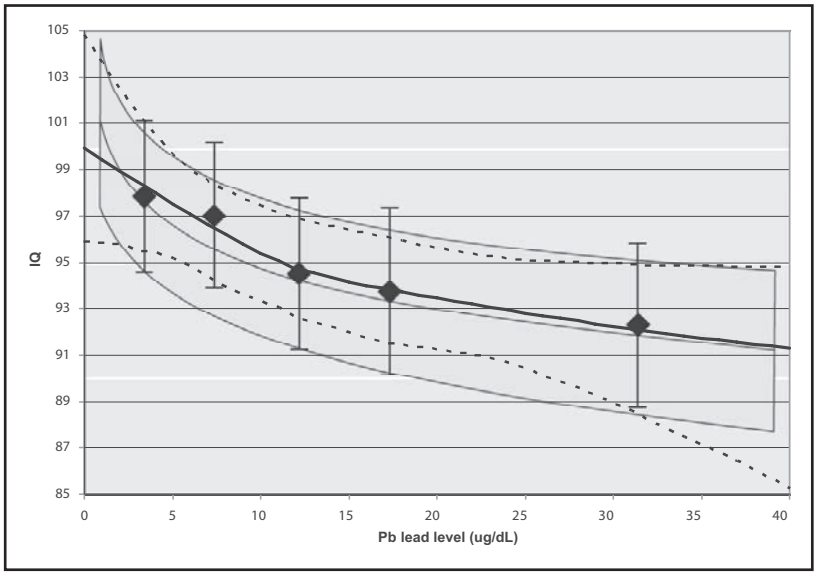
8.3.3 Blood lead and blood pressure in adults

For adults, increased systolic blood pressure was selected as the most sensitive end-point. A linear slope relating increases in systolic blood pressure as a function of blood lead level was derived by averaging the estimates from four different studies (Table 24). This resulted in a median of 0.28 mmHg (0.037 kPa) per 1 µg/dl, with an SD of 0.15 mmHg (0.02 kPa) per 1 µg/dl (5th to 95th percentiles 0.03–0.53 mmHg [0.004–0.071 kPa] per 1 µg/dl).

8.3.4 Dietary lead exposure and blood pressure in adults

Blood lead levels were converted to dietary exposures using the range of values previously used by the Committee for adults (blood lead level of 0.023–0.07 µg/dl per 1 µg/day of dietary lead exposure). Dietary exposure corresponding to an increase in systolic blood pressure of 1 mmHg (0.1333 kPa) was estimated to be 80 (5th to 95th percentiles 34–1700) µg/day, or about 1.3 (5th to 95th percentiles 0.6–28) µg/kg bw per day, assuming a body weight of 60 kg. As the relationship is linear, the changes in blood pressure associated with other dietary exposures are proportional.

Figure 3. Bilinear model bootstrap analysis, superimposed over Lanphear et al. (2005)



Note: The data points and associated CIs are derived from the Lanphear et al. (2005) meta-analysis. The thin line and shaded area represent a log-linear model and associated CIs, which are also from the Lanphear et al. (2005) meta-analysis. The thicker line plots the bilinear model from the current analysis, with associated CIs given by the dotted lines.

9. COMMENTS

9.1 Absorption, distribution, metabolism and excretion

Absorption of lead from the gastrointestinal tract is influenced by physiological factors (e.g. age, fasting, calcium and iron status, pregnancy) and the physicochemical characteristics of the ingested material. Absorption is higher in children than in adults and is lower in the presence of food. Absorbed lead is transferred to soft tissues, including liver and kidney, and to bone tissue, where it accumulates with age. Under certain conditions, such as pregnancy and osteoporosis, bone resorption can result in increased concentrations of lead in blood. Lead readily crosses the placenta and is transferred into breast milk. In humans, the half-life of lead is approximately 30 days in blood and 10–30 years in bone. Urine and faeces are the major routes of excretion. Lead binds to thiol groups and other ligands in proteins. Its toxicity has been attributed to inhibition of enzymes (e.g. those involved in haem synthesis) and to interference with calcium, magnesium and zinc homeostasis.

Figure 4. Dose–response function from pooled bilinear and Hill models

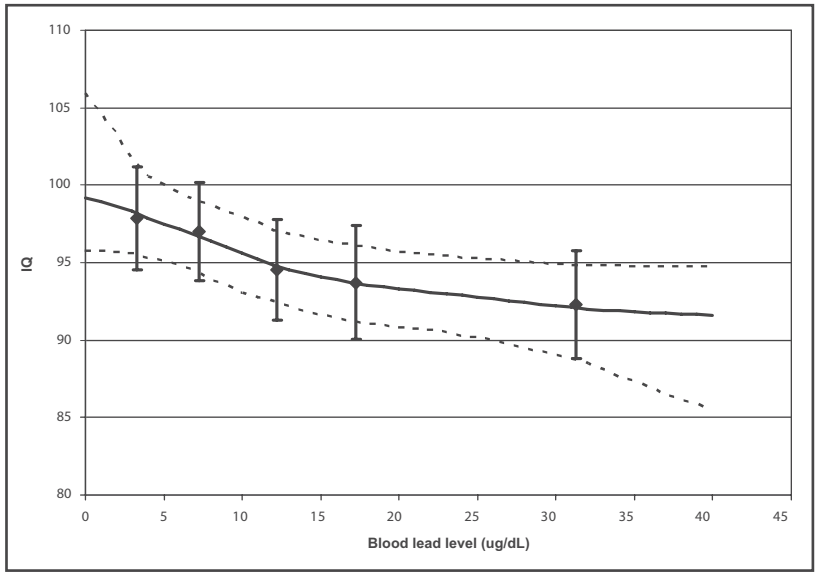


Table 22. Estimated dietary lead exposures associated with decreases in IQ in children using the combined outputs of the bilinear and Hill models

IQ decrease in children	Dietary exposure (µg/day)[a]	Dietary exposure for 20 kg child (µg/kg bw per day)[a]
0.5	17 (2–194)	0.8 (0.1–9.7)
1	30 (4–208)	1.5 (0.2–10.4)
1.5	40 (5–224)	2.0 (0.3–11.2)
2	48 (7–241)	2.4 (0.4–12.0)
2.5	55 (9–261)	2.8 (0.4–13.1)
3	63 (11–296)	3.1 (0.5–14.8)

[a] Median estimate with 5th to 95th percentile CI in parentheses.

9.2 Toxicological data

The acute toxicity of lead is low. Chronic oral exposure of experimental animals to inorganic lead has effects on multiple organs, including kidney and liver, and systems, including the cardiovascular, haematological, immune, reproductive and nervous systems. IARC has concluded that there is sufficient evidence for the carcinogenicity of inorganic lead compounds in experimental animals, causing renal and brain tumours, and that the evidence for the carcinogenicity of organic lead

Table 23. Estimated dietary exposures associated with IQ impacts using the bilinear model only[a]

IQ decrease in children	Dietary exposure (µg/day)[a]	Dietary exposure for 20 kg child (µg/kg bw per day)[a]
0.5	6 (2–124)	0.3 (0.1–6.2)
1	12 (4–145)	0.6 (0.2–7.2)
1.5	19 (6–170)	0.9 (0.3–8.5)
2	25 (8–193)	1.3 (0.4–9.7)
2.5	31 (9–217)	1.6 (0.5–10.9)
3	38 (11–237)	1.9 (0.6–11.8)

[a] Median estimate with 5th to 95th percentile CI in parentheses.

Table 24. Slope estimates relating blood lead level to systolic blood pressure

Reference	Slope estimate (mmHg[a] per 1 µg/dl)	
	Median estimate	Standard deviation
Glenn et al. (2003)	0.25	0.12
Vupputuri et al. (2003)	0.47	0.20
Nash et al. (2003)	0.32	0.19
Glenn et al. (2006)	0.09	0.05
Average	0.28	0.15

[a] 1 mmHg = 0.1333 kPa.

compounds is inadequate. The results of genotoxicity studies and the inhibition of DNA repair suggest a non-DNA-reactive mode of action for the carcinogenicity of lead.

9.3 Observations in humans

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 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. ADHD, 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.

9.4 Analytical methods for the determination of lead in food and blood

The analytical methods for the determination of lead in food are well established. The techniques of choice are ETAAS and ICP-MS. To a minor extent, FAAS and ICP-OES are used. In the last decade, many technical improvements have been made to ETAAS, such as the design of the atomizer, background correction systems and improvement in the light source and detector. These have allowed the determination of lead in food at the low microgram per kilogram level. ICP-MS is increasingly used in food laboratories owing to its capability to perform multi-element measurements in a wide variety of food matrices. In addition, the use of DRC-ICP-MS has allowed the removal of interferences with a minimum loss of sensitivity, while lowering the LOQs for lead, to allow the determination of lead in food at levels lower than 0.1 µg/kg.

The determination of lead in blood has been carried out using mainly ETAAS or ICP-MS. The methods are well established, and the LODs at the 0.1 ng/ml level are adequate to quantify lead in blood. Sample preparation is simple, but advances can be made in reducing the volume of sample required for analyses. One novel technique is the use of laser ablation coupled with ICP-MS, which requires a sample volume of less than 1 µl of whole blood for the quantification of lead.

The sample preparation procedure used most frequently for the determination of lead in food is acid digestion in the presence of strong oxidants in open or closed vessels. Microwave-assisted acid digestion has been extensively employed, which allows the use of large sample masses (1–2 g) under controlled temperature and pressure of the system, reducing contamination and avoiding losses of the element during mineralization.

Lead data for different food commodities submitted and evaluated at this meeting were almost all obtained by validated analytical methods or generated by accredited laboratories. The LODs and LOQs depend on the food matrix and the analytical technique employed. Analytical methods with poor LODs (>0.01 mg/kg) may erroneously lead to the conclusion that there is no lead present in the food.

As an example, Australia used a more sensitive analytical method for its 23rd TDS than previously used in its 19th and 20th TDSs. This resulted in a significant increase in the percentage of samples with detectable lead. However, more sensitive methods require greater resources and may limit the numbers of samples that can be analysed. Therefore, an appropriate balance in number of samples that can be analysed and the sensitivity of the method will be required in the planning of surveillance programmes.

9.5 Sampling protocols

General guidance for sampling for foods is described in the Codex Alimentarius Commission guidelines CAC/GL 50-2004 (FAO/WHO, 2004a).

9.6 Prevention and control

There have been widespread efforts to reduce lead exposure from food, focusing on implementing standards for lead levels in food, water and food additives;

ending the use of lead-soldered cans; regulating the use of lead in paint and petrol; controlling lead levels in water; reducing leaching from lead-containing vessels; and identifying and reacting to additional sources of lead contamination in foods or dietary supplements. Dust on foods should be removed before processing and/or consumption. For the prevention and control of lead in foods, good agricultural and manufacturing practices should be followed.

9.7 Levels and patterns of contamination in food commodities

At its present meeting, the Committee reviewed data on lead occurrence in different food commodities received from seven countries—Australia, Brazil, China, France, Germany, Singapore and the USA. In addition, EFSA submitted data from Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Great Britain, Ireland, Norway, Poland, Romania, Spain and Sweden and three commercial operators. The data from France and Germany were included in the assessment report of EFSA. In order to avoid duplicating the data in this analysis, the individual data submitted from both countries were not separately considered in the assessment of the current meeting.

The total number of analytical results (single or composite samples) was 110 899, with 84.9% coming from Europe, 7.6% from the USA, 1.9% from Latin America, 3.1% from Asia and 2.5% from the Pacific region. No data were received from Africa.

A summary of the available occurrence data submitted for this meeting by food category is presented in Table 25. The weighted mean is provided for each food category and for the range of means across countries. The means were weighted to adjust for different numbers of samples for foods within a category from different countries. All but one food category contained at least some foods with detectable lead levels. Maximum lead concentrations were determined for each category. However, some data sets, such as the Chinese TDS, provided mean lead concentrations only, so it was not possible to determine maximum concentrations for every data set. Thus, data contributing high concentrations to the country mean could not be included in the evaluation of the maximum concentrations. Each category contains a number of foods with similar characteristics (e.g. baked goods, muscle meats). The miscellaneous category includes beverages, food supplements, infant formula, tap and bottled water and other foods for special dietary purposes, as well as foods that did not fit in other categories. Within the miscellaneous category, generally the highest reported concentrations were for foods for special dietary uses and not for beverages. Infant formula essentially contained no detectable lead. EFSA reported that breast milk contained highly variable levels of lead. Sugar and sugar products and animal and vegetable fats rarely contained detectable levels of lead. Food categories with the highest frequency of detectable lead include meat, especially offal, organ meats and wild game, shellfish (particularly bivalves), cocoa, tea, cereal grains and cereal products, and vegetables.

Table 25. Summary of lead occurrence data submitted for this meeting

Food category	*n*	Weighted mean lead concentration (mg/kg)[a]	Range of national mean concentrations (mg/kg)[b]	Maximum lead concentration (mg/kg)
Cereals/grains not included elsewhere and mixed grains	5 027	0.009	<LOD–0.029	7.12
Wheat (including breads)	506	0.005	<LOD–0.009	0.040
Rice	85	0.002	<LOD–0.004	0.021
Baked goods including "fancy breads"	203	0.047	0.001–0.23	16.5
Oats	63	0.001	<LOD–0.003	0.050
Roots and tubers	1 255	0.007	0.001–0.065	1.32
Pulses + legumes	326	0.004	<LOD–0.060	0.063
Fruits	7 480	0.030	<LOD–0.13	28.9
Dried fruit	282	0.086	0.006-0.34	1.34
Fruit juices	4 426	0.058	<LOD–0.35	74
Vegetables including juices	13 402	0.101	<LOD–0.40	27.6
Eggs	785	0.008	<LOD–0.039	0.21
All seafood (EFSA only)	11 453	0.054	—	4.06
Snails	11	0.069	0.065–0.074	0.19
Finfish	656	0.040	<LOD–0.22	0.45
Shellfish	765	0.070	0.010–0.19	11.80
Aquatic animals (China only)	12	0.015	—	—
Dairy foods	3 833	0.006	0.001–0.013	4.55
Nuts and oilseeds	184	0.005	<LOD–0.024	0.30
Animal fats	102	0.001	<LOD–0.002	0.029
Vegetable oils and fats	832	0.007	<LOD–0.039	7.30
Stimulants (coffee, tea, cocoas)[c]	764	0.211	<LOD–1.03	6.21

Table 25 (contd)

Food category	*n*	Weighted mean lead concentration (mg/kg)[a]	Range of national mean concentrations (mg/kg)[b]	Maximum lead concentration (mg/kg)
Sugar and honey	1 962	0.032	<LOD–0.082	4.10
Spices	86	0.027	<LOD–0.11	0.44
Alcoholic beverages	2 304	0.070	<LOD–0.38	5.80
Cocoa & chocolate & products[c]	206	0.692	<LOD–0.69	45.4
Cocoa butter	34	<LOD	<LOD	<LOD
Muscle meat excluding poultry	1 817	0.047	0.0001–0.013	1.36
Meat not included elsewhere	131	0.420	0.22–0.25	10.10
Organ meats except kidney	102	0.140	0.10–0.18	1.44
Muscle meat and poultry combined	40 313	0.134	0.004–0.25	867
Muscle minced	69	0.001	0.001	0.078
Kidney	537	0.067	0.013–0.14	1.24
Muscle poultry	1 589	0.098	0.003–0.021	0.075
Offal	73	0.018	0.006–0.042	0.008
Miscellaneous	9 224	0.035	<LOD–0.20	155
Total	110 899	—	—	—

[a] The means were weighted to adjust for different numbers of samples for foods within a category.

[b] Range includes means from the 2007 Chinese TDS and the 20th Australian TDS; maximum lead values were not available from the Chinese TDS and the 20th Australian TDS.

[c] In some cases, cocoas were included in a stimulants category, and in others, they were separately categorized.

9.8 Food consumption and dietary exposure assessment

The Committee obtained estimates of exposure to lead based on TDSs for nine countries (Australia, Canada, Chile, China, France, Lebanon, New Zealand, the United Kingdom and the USA) or from other evaluations that had considered levels in foods as consumed (Egypt, India and EFSA). EFSA conducted assessments for 19 European countries, and those are presented together.

The guidelines for conducting exposure assessments for contaminants in foods recommend that dietary exposure estimates should be calculated using regional average contaminant concentration data and the GEMS/Food consumption cluster diets. The WHO GEMS/Food consumption cluster diets contain limited information on the forms of the foods that are considered. Dietary exposure estimates were available to the Committee for 28 countries, mostly based on food as consumed. Lead is taken up from soil into food crops, and the sources of lead in food may also include soil remaining in or on the food, atmospheric deposition, water, contact with lead-containing processing equipment and packaging. It is important to estimate lead levels in food that is as close as possible to the form of the food that is consumed, as levels in raw agricultural commodities do not necessarily reflect levels in foods as they are consumed. The Committee concluded that the submitted data reflected lead exposures in foods as consumed and were more appropriate than the GEMS/Food consumption cluster diets for use in lead assessments. Limited information was available describing lead levels in foods or estimating dietary exposures in developing countries.

The Committee included estimates of children's exposure wherever possible. The GEMS/Food consumption cluster diets do not include estimates of children's consumption. Estimates of children's exposure were available for 19 European countries (in the EFSA assessment) and for Australia, Canada, China, New Zealand and the USA. Where exposure assessments were available for the adult population but not for children, the Committee assumed that children's exposure would be 2–3 times that of the general population on a body weight basis, based on the general observation that children consume 2–3 times more food than adults relative to their body weight, and included those values in this report.

Estimates of dietary exposure for individual countries are presented below. Each region/country made its own decisions as to the appropriate matching of food lead levels to food consumption data and also in the treatment of samples without detectable lead levels.

The Committee selected a representative dietary exposure value for each country in order to allow comparisons across countries and across regions for the total/adult population (see Table 19 in section 7.3.14 above) and for children (see Table 20 in section 7.3.14 above). Unfortunately, estimates for the same population subgroup were not always available. In particular, estimates were provided for different age groups by different countries. The Committee selected subgroups that were as similar as possible for comparison purposes. In order to improve comparability, the Committee adjusted some data by standard body weight assumptions. For the total/adult population, mean exposures ranged from 0.02 to 3 µg/kg bw per day (see Table 19). Some of the countries also provided estimates of high exposure for consumers. The definition of a consumer with high exposure ranged from the 90th to 97.5th percentile for the population, depending on the country. The estimated high exposures ranged from 0.06 to 2.43 µg/kg bw per day (see Table 19). Children's mean exposures ranged from 0.03 to 9 µg/kg bw per day (see Table 20). Some countries also provided estimates of high exposures for children. The definition of a consumer with high exposure ranged from the 90th to 97.5th percentile exposures for children. The estimated exposures for children who

were defined by the country as consumers with high exposure ranged from 0.2 to 8.2 µg/kg bw per day (see Table 20).

9.8.1 Food category contributions to exposure

The most important contributors to overall dietary exposure were reported by some countries. EFSA evaluated the categories of foods contributing most to exposure and reported large differences between countries. EFSA reported that

> the largest contributors to the calculated overall lead exposure are vegetables, nuts and pulses contributing 19 % to the lower bound and 14 % to the upper bound estimates. Cereals and cereal products contributed 13 % to the lower bound and 14 % to the upper bound. For the lower bound miscellaneous products and food for special uses contributed 12 %, starchy roots and potatoes 8%, meat and meat products 8 %, alcoholic beverages 7 % and milk and dairy products 6 %. For the upper bound the contributions were: juices, soft drinks and bottled water (11 %), alcoholic beverages (9%) meat and meat products including offal (9 %), milk and dairy products (8 %), miscellaneous products and food for special uses (7 %) and starchy roots and potatoes (6 %).

Milk and milk products, fruits, breads and sugars contributed most to the dietary exposure in a published Chilean TDS. In the 2007 Chinese TDS, the food categories making the largest contributions were cereals (34%) and vegetables (21%). The Lebanese TDS included water and food, water contributing the most to exposure. The foods contributing most to Lebanese exposure were bread and toast, fruits, pizza and pies, and vegetables (raw and cooked). In the New Zealand TDS, grains contributed 24–27% of dietary lead for adults and 36–39% for children. Chicken, eggs, fish and meat contributed 12–16% of adult dietary lead, and takeaways contributed 9–24%; for children, the corresponding contributions were 7–12% and 10–15%. New Zealand also identified the main food groups contributing to weekly dietary exposure to lead for infants: grains (18%), chicken, eggs, fish and meat (4%), takeaways (6%), fruit (18%) and infant formula and weaning foods (38%).

The relative contribution of diet to total lead exposure is not well known but will probably vary depending upon locale and the contribution from non-dietary sources. Estimates from EFSA suggest that at least half of children's exposure may be due to non-dietary sources of exposure and that soil and dust are major contributors to the non-dietary exposures.

9.8.2 Temporal changes in estimates of dietary exposure to lead since the 1980s

Lead levels in foods have declined over time in many developed countries. The Committee had access to data from five countries (Canada, France, New Zealand, the United Kingdom and the USA) that allowed the trends in lead exposure to be estimated. New Zealand reported changes in dietary exposure to lead since 1982 in its 2003–2004 TDS report. Lead exposure estimates for 19- to 24-year-old males were 3.6 µg/kg bw per day in 1982 and 0.13 µg/kg bw per day in 2003–2004. This represents an apparent decline in exposure to lead of approximately 75%. Dietary exposure estimates for the general population in the United Kingdom declined by approximately 95% between 1980 and 2006, from 0.12 mg/day

estimated in the 1980 TDS to 0.006 mg/day in the 2006 TDS. Canada and France have also reported a 50% decline in exposure to lead over the past 10–15 years. The USA reported declines in lead exposure for all age groups, with the greatest decline in teenage males (from 70 µg/day in 1976 to 3.45 µg/day in 2000). During the time periods reported by these countries, there were changes in the food supply that likely contributed to actual declines in dietary exposures. However, some of the apparent decline in exposure may actually be due to improved sensitivity of the analytical methods and the corresponding selection of less conservative values for those samples without detectable levels of lead.

9.9 Dose–response analysis

The dose–response modelling for blood lead levels and children's IQ is based on estimates in the Lanphear et al. (2005) pooled analysis, which includes several newer studies that were not included in the meta-analysis used by the Committee at its fifty-third meeting (Annex 1, reference *143*). The Lanphear et al. (2005) analysis included 1333 children enrolled in seven longitudinal cohort studies conducted in the USA, Mexico, Kosovo and Australia, who were followed from birth or early infancy to 5–10 years of age. In this analysis, use of a log-linear model produced an estimated IQ decline of 6.9 points in concurrent blood lead level over a range of 2.4–30 µg/dl. The slope of the inverse association between IQ and concurrent blood lead level was steeper among children with a maximum observed (at any time point) blood lead level below 7.5 µg/dl than it was among children with a maximum blood lead level of 7.5 µg/dl or higher. After initial consideration of six different dose–response models, the bilinear and Hill models were selected for use in characterizing the dose–response relationship between blood lead level and IQ because they provided the best fit.

The relationship between blood lead levels and dietary exposure to lead was estimated to be between 0.052 and 0.16 µg/dl of lead in blood per 1 µg/day of dietary lead exposure. This range was based on toxicokinetic analyses of data on Scottish infants exposed to lead in drinking-water. These analyses were used by the Committee previously.

Dietary exposures associated with a range of decreases in IQ (i.e. 0.5–3 IQ points) were calculated by combining the dose–response models with the toxicokinetic data, using a Monte Carlo simulation. The resulting CIs reflect the uncertainties in both the dose–response modelling of blood lead levels and the extrapolation to dietary exposure. When the outputs from the Monte Carlo simulation of the alternative bilinear and Hill models were combined, the chronic dietary exposure corresponding to a decrease of 1 IQ point was estimated to be 30 µg of lead per day, with a 5th to 95th percentile CI ranging from 4 to 208 µg/day (see Table 22 in section 8.3.2 above). This is equivalent to 1.5 µg/kg bw per day (5th to 95th percentiles 0.2–10.4 µg/kg bw per day) for a 20 kg child.

Although the combined outputs of the bilinear and Hill models provide a more complete accounting of the uncertainties associated with the dose–response relationship of lead and IQ, the bilinear model may be more useful in circumstances where other, non-dietary exposures are highly variable or unknown, because the

incremental effect of any given lead source/exposure is theoretically independent of other exposures (i.e. the impact of a given dietary exposure will be about the same, regardless of other exposures). Using the bilinear model alone, the chronic dietary exposure corresponding to a decrease of 1 IQ point was estimated to be 12 µg/day, with a 5th to 95th percentile CI ranging from 4 to 145 µg/day (see Table 23 in section 8.3.2 above). This is equivalent to 0.6 µg/kg bw per day (5th to 95th percentiles 0.2–7.2 µg/kg bw per day) for a 20 kg child. The Committee decided to use the results of the bilinear model in its evaluation because it represents a more conservative approach at low doses and allows non-dietary sources of exposure to be considered independently. However, application of the results of the combined model outputs might be more appropriate in situations where non-dietary exposure is minimal.

For adults, increased systolic blood pressure was selected as the most sensitive end-point. A linear slope relating increases in systolic blood pressure as a function of blood lead level was derived by averaging the estimates from four different studies: 0.28 mmHg (0.037 kPa) per 1 µg/dl (5th to 95th percentiles 0.03–0.53 mmHg [0.004–0.071 kPa] per µg/dl). Blood lead levels were converted to dietary exposures using the range of values previously used by the Committee for adults (blood lead level 0.023–0.07 µg/dl per 1 µg/day of dietary lead exposure). Dietary exposure corresponding to an increase in systolic blood pressure of 1 mmHg (0.1333 kPa) was estimated to be 80 (5th to 95th percentiles 34–1700) µg/day, or about 1.3 (5th to 95th percentiles 0.6–28) µg/kg bw per day. As the relationship is linear, the increases in blood pressure associated with other dietary exposures are proportional. Published studies used by WHO in estimating the global burden of disease attributable to lead indicate that relative risks of ischaemic heart disease and cerebrovascular stroke associated with small increases in blood pressure (0.4–3.7 mmHg [0.053–0.49 kPa] systolic blood pressure) have been estimated to be in the range of 1.01–1.4, with higher relative risks at younger ages.

10. EVALUATION

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. Therefore, the Committee concluded that the effects on neurodevelopment and systolic blood pressure provided the appropriate bases for dose–response analyses.

Based on the dose–response analyses, the Committee estimated that the previously established PTWI of 25 µg/kg bw 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. The Committee therefore concluded that the PTWI could no longer be considered health protective, and it was withdrawn.

Because the dose–response analyses do not provide any indication of a threshold for the key effects of lead, the Committee concluded that it was not possible to establish a new PTWI that would be considered to be health protective. The dose–response analyses conducted by the Committee should be used to identify the magnitude of effect associated with identified levels of dietary lead exposure in different populations.

The Committee reaffirmed that because of the neurodevelopmental effects, fetuses, infants and children are the subgroups that are most sensitive to lead. The mean dietary exposure estimates for children aged about 1–4 years range from 0.03 to 9 µg/kg bw per day. The health impact at the lower end of this range is considered negligible by the Committee, because it is below the exposure level of 0.3 µg/kg bw per day calculated to be associated with a population decrease of 0.5 IQ point. The higher end of the exposure range is higher than the level of 1.9 µg/kg bw per day calculated to be associated with a population decrease of 3 IQ points, which is deemed by the Committee to be a concern. For adults, the mean dietary lead exposure estimates range from 0.02 to 3 µg/kg bw per day. The lower end of this range (0.02 µg/kg bw per day) is considerably below the exposure level of 1.2 µg/kg bw per day calculated by the Committee to be associated with a population increase in systolic blood pressure of 1 mmHg (0.1333 kPa). The Committee considered that any health risk that would be expected to occur at this exposure level is negligible. At the higher end of the range (3 µg/kg bw per day), a population increase of approximately 2 mmHg (0.3 kPa) in systolic blood pressure would be expected to occur. An increase of this magnitude has been associated, in a large meta-analysis, with modest increases in the risks of ischaemic heart disease and cerebrovascular stroke.

The Committee considered this to be of some concern, but less than that for the neurodevelopmental effects observed in children.

The Committee stressed that these estimates are based on dietary exposure (mainly food) and that other sources of exposure to lead also need to be considered. The Committee concluded that, in populations with prolonged dietary exposures to lead that are at the higher end of the ranges identified above, measures should be taken to identify major contributing sources and foods and, if appropriate, to identify methods of reducing dietary exposure that are commensurate with the level of risk reduction.

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