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Cadmium
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CADMIUM (addendum)

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1. EXPLANATION

The presence of cadmium (Cd) in food results from contamination of soil and water both from natural sources and from anthropogenic activities. Crops differ with respect to absorption of cadmium, and cadmium is known to accumulate in the tissues (particularly the liver and kidney) of terrestrial animals and in aquatic animals (particularly detritus feeders, such as molluscs).

Cadmium was evaluated by the Committee at its sixteenth, thirty-third, forty-first, fifty-fifth, sixty-first and sixty-fourth meetings (Annex 1, references *30*, *83*, *107*, *149*, *166* and *176*). At the thirty-third meeting, a provisional tolerable weekly intake (PTWI) of 400–500 µg or 7 µg/kg body weight (bw) (assuming a body weight of 60 kg) was derived from a critical concentration of cadmium in the kidneys (200 mg/kg tissue), which caused an increase in β_2-microglobulin (β2MG) concentration in urine, and a toxicokinetic model that related cadmium bioaccumulation in the kidneys to dietary exposure. In 1992, Environmental Health Criteria 134 (IPCS, 1992a) provided a detailed description of the model on which the PTWI was based and its various assumptions. At the forty-first meeting, the Committee concluded that the model estimates used to derive the PTWI were conservative, but it did not include a safety factor and reiterated that there was only a small margin of safety between exposure via the diet and the exposure that would result in deleterious effects.

At its fifty-fifth meeting, the Committee concluded that the prevalences of renal tubular dysfunction that correspond to various dietary exposures to cadmium were still appropriate for risk assessment and that the risk of renal tubular dysfunction in the general population would be negligible below a urinary cadmium excretion of 2.5 µg/g creatinine. The estimate of 2.5 µg/g creatinine was based on occupational data and involved a number of assumptions about creatinine excretion, cadmium absorption and bioavailability and the ratio of dietary exposure to cadmium to excreted cadmium.

At the sixty-first meeting, the Committee considered studies including epidemiological investigations of environmental exposure to cadmium, such as the CadmiBel studies from Belgium and a series of Japanese reports. The Committee reaffirmed that renal tubular dysfunction remained the critical health outcome with regard to the toxicity of cadmium and that an excess prevalence of renal tubular dysfunction would not be expected to occur if the urinary cadmium concentration did not exceed 2.5 µg/g creatinine. The Committee concluded that the new data did not provide a sufficient basis for revising the PTWI and therefore maintained the PTWI of 7 µg/kg bw.

At its sixty-fourth meeting, the Committee evaluated the impact of different maximum levels (MLs) for cadmium in commodities that contribute to dietary exposure. The dietary assessment took into account the potential impact of different MLs on the distribution of concentrations of cadmium in each commodity and the dietary exposures to cadmium from each individual commodity. The Committee concluded that a change in the proposed Codex Alimentarius Commission MLs would result in a change of only 1–6% in the dietary exposure to cadmium and therefore was of no significance in terms of risk to human health, considering that the total dietary exposure to cadmium was only 40–60% of the PTWI of 7 µg/kg bw.

At the request of the Codex Committee on Contaminants in Food, the Committee considered new information that had become available since cadmium was last evaluated, together with the data it had previously reviewed. The Committee also considered new information on cadmium levels in food and dietary exposure. As it is now acknowledged that renal dysfunction is the most sensitive toxicological end-point arising from cadmium exposure, most of the new data involved the use of urinary biomarkers to estimate risk based on statistical modelling. The Committee considered whether these recent modelled risk estimates for cadmium would support the current PTWI.

2. BIOLOGICAL DATA

A number of detailed evaluations have reviewed data on the kinetics and toxicity of cadmium (IPCS, 1992a; ATSDR, 2008; EFSA, 2009a). Overall, the absorption or bioavailability of cadmium from the gastrointestinal tract is generally considered to be slightly lower (0.5–3.0%) in experimental animals (mice, rats and monkeys) than in humans (1–10%). Previous reviews have described how the composition of the diet, including fibre, protein (sunflower seeds) and carbohydrates (rice), can also affect the bioavailability of cadmium (Annex 1, references *149* and *166*). Following absorption, cadmium binds to metallothionein, but this binding can be overloaded at relatively moderate doses. In adult experimental animals, cadmium concentrations in liver and kidneys are comparable after short-term exposure, but the kidney concentration generally exceeds the liver concentration following prolonged exposure, except at very high exposures. Cadmium is virtually absent at birth but accumulates with time, especially in the liver and kidneys; renal concentration occurs mainly during the early years of life, and 50–75% of the total body burden is found in these two organs at autopsy. An additional 20% is found in muscle, whereas the quantity of cadmium in bone is small. In human cadavers, no statistically significant relationship has been observed linking bone cadmium content with demineralization (Knuuttila et al., 1982).

2.1 Biochemical aspects

2.1.1 Absorption

Groups of 12 male ICR mice were fed a diet with sufficient iron (120 mg/kg) or insufficient iron (2–6 mg/kg) for 4 weeks. Tissue iron concentrations were analysed in half the animals at the end of the study, whereas tissue cadmium

concentrations were analysed in the remaining mice 24 h after a single oral dose of $^{109}CdCl_2$ at 100 µg/kg bw. The expression of divalent metal transporter 1 (*DMT1*) and metal transporter protein 1 (*MTP1*) genes was also analysed in various tissues. Iron stores were shown to be depleted in mice on the iron-deficient diet. The majority of the tissues analysed from the iron-deficient mice contained significantly higher ($P < 0.05$) concentrations of cadmium compared with the tissues from the iron-sufficient mice. In particular, the duodenums of the iron-deficient mice contained approximately 3-fold more cadmium than those of the iron-sufficient mice. The body burden of cadmium was also approximately 3-fold higher in iron-deficient than in iron-sufficient mice. The *DMT1* and *MTP1* genes were expressed in all of the tissues analysed in both groups of mice. However, in the iron-deficient mice, there was a 65- and 8-fold upregulation of the *DMT1* and *MTP1* genes, respectively, in the duodenum. These results indicate that iron deficiency increases the uptake of cadmium from the digestive tract, which appears to be associated with the increased expression of *DMT1* and *MTP1* in the duodenum (Kim et al., 2007).

Reeves & Chaney (2008) reviewed the effect of marginal deficiencies of zinc, iron and calcium on the gastrointestinal absorption of cadmium in rats. Absorption and retention of cadmium (present at 0.25–0.45 mg/kg) from diets containing suboptimal concentrations of zinc, iron and calcium were increased up to 10-fold following repeated dosing.

2.1.2 Elimination

From previously evaluated reports, the retention of cadmium in various tissues is variable, and its release appears to be multiphasic. The apparent half-life estimates range between 200 and 700 days for mice and rats and up to 2 years in the squirrel monkey. In humans, the reported half-life of cadmium in kidneys ranges from 10 to 33 years, and in liver, from 4 to 19 years.

Recently, Amzal et al. (2009) estimated the apparent half-life of kidney cadmium in 680 Swedish women aged between 56 and 70 years who had never smoked to be lognormally distributed, with a mean of 11.6 years (95% confidence interval [CI] 10.1–14.7) and a standard deviation of 3.0 years. The half-life of cadmium in kidneys was calculated using toxicokinetic modelling based on a one-compartment model (IPCS, 1992a). By assuming that cadmium concentration in urine was proportional to the cadmium concentration in the kidney cortex, that gastrointestinal absorption among females ranged between 1% and 10% and that approximately one third of the absorbed fraction was transported to the kidney, the model accurately predicted the observed level of cadmium in the urine except at the lowest concentrations (<0.1 µg/g creatinine).

The Amzal et al. (2009) study was the first to investigate, on a population level, variability in cadmium kinetics using paired individual data on dietary intake and urinary excretion. A determination of intervariability in a population is considered important in risk assessment because it overcomes the need to use uncertainty or safety factors to protect a portion of the population. Of particular value in this study was the availability of data matching dietary exposure with urinary cadmium levels on three separate occasions over a 20-year period (i.e. 1987, 1997

and 2007). The overall average daily dietary exposure from the three measurements was 14 µg (0.2 µg/kg bw; range 0.1–0.4 µg/kg bw) after an adjustment for a total daily energy intake of 1700 kcal. The mean urinary cadmium level was 0.34 µg/g creatinine (median 0.31 µg/g; range 0.09–1.23 µg/g).

2.2 Toxicological studies

2.2.1 Acute toxicity

Oral median lethal doses (LD_{50} values) for experimental animals (mainly rodents) range from approximately 100 to 300 mg/kg bw and are dependent on the form of cadmium administered (Annex 1, reference *166*).

2.2.2 Long-term studies of toxicity and carcinogenicity

The kidney is the critical organ in humans and other mammals exposed for long periods to the relatively small amounts of cadmium that might occur in foods and feed, respectively. Many studies in experimental animals have demonstrated an association between morphological and/or functional changes in the kidney and the renal concentration of cadmium. In most of these studies, cadmium was given parenterally rather than in food or water. The many studies of this type performed before 1990 were reported in detail and tabulated by IPCS (1992a) and are only summarized here. Although a variety of toxicological end-points have been observed in experimental animals (reproductive toxicity, neurotoxicity, carcinogenicity), those of relevance to humans are the renal effects that manifest after low-level, long-term exposure to cadmium and accumulation of cadmium to a critical concentration in the kidney (Annex 1, reference *166*).

(a) Renal effects

Long-term exposure to cadmium eventually results in a variety of renal changes involving damage to proximal tubule epithelial cells, degeneration and apoptosis. Morphological changes observed include atrophy, interstitial fibrosis, glomerular sclerosis and focal necrosis. Earlier indications usually associated with renal damage include low molecular weight proteinuria, glucosuria and aminoaciduria. The results of relevant experimental studies are summarized in Table 1. In general, although some variability exists, renal effects in laboratory animals are associated with kidney concentrations of cadmium of between 200 and 300 µg/g, resulting from long-term exposures of, on average, between 1 and 10 mg/kg bw per day.

(b) Carcinogenicity

Studies in experimental animals treated by injection or inhalation have provided considerable evidence that cadmium is carcinogenic. In rats, cadmium causes a variety of tumours, including malignant tumours at the site of injection and in the lungs after inhalation. Oral intake is associated with proliferative lesions of the ventral lobe of the prostate gland in rats fed diets that are adequate in zinc, whereas deficiency in zinc in the diet appears to inhibit the tumorigenic effect of

Table 1. NOAELs and LOAELs for renal effects of cadmium chloride administered in drinking-water

Species	Strain	Sex	Effect	NOAEL (mg/kg bw per day)	LOAEL (mg/kg bw per day)
Rabbit	New Zealand/ Flemish Giant	Male	Tubular necrosis Interstitial necrosis at 200 days	ND	15
Rat	Sprague-Dawley	Male and female	Cloudy swelling of tubular epithelium at 92 weeks (males) and 84 weeks (females)	0.8	1.5
	Wistar	Male	Increased urinary metallothionein; no tubular dysfunction	2.6	ND
	Sprague-Dawley	Female	Albuminuria	ND	13
Monkey	Rhesus	Male	Tubular dysfunction	0.4	4.0

LOAEL, lowest-observed-adverse-effect level; ND, not determined; NOAEL, no-observed-adverse-effect level
Source: Adapted from Annex 1, reference *150*

cadmium. The relevance of these studies to carcinogenesis in the human prostate gland is questionable because of anatomical differences between the prostate gland in humans and that in rodents.

2.2.3 Developmental toxicity

Groups of 7–9 pregnant Wistar rats were given drinking-water containing cadmium chloride (10 mg/l) from day 0 to day 21 of gestation. A control group received deionized water. At the end of the dosing period, concentrations of cadmium and lead were measured in placenta, fetal brain, fetal blood and maternal blood. Metallothionein was analysed in placenta and fetal brain. The average fetal weight of the cadmium-treated group was approximately 20% lower than that of the control group ($P < 0.05$). The average dam weight of the cadmium-treated group was approximately 14% lower than that of the control group, whereas the number of fetuses per dam was slightly lower (10 versus 13, respectively); neither difference was statistically significant. Fetal brain weight and placenta weight were similar between control and treated groups. Significantly elevated ($P < 0.05$) concentrations of cadmium were detected in dam blood, fetal blood, placenta and fetal brain (approximately 13-, 2.5-, 17- and 3-fold higher than the controls, respectively). Metallothionein concentrations in placenta, but not in brain, in the cadmium-treated group were significantly higher ($P < 0.05$) than those of the controls (4.39 µg/g versus 2.96 µg/g, respectively). Statistical analysis indicated a significant ($P = 0.017$) linear relationship between metallothionein and cadmium concentrations in

the placenta. Immunohistochemistry indicated a normal appearance of the placenta in the cadmium-treated group (Benitez et al., 2009).

2.2.4 Genotoxicity

Although cadmium is not a redox-active metal and therefore cannot bind directly to deoxyribonucleic acid (DNA), it has been shown to indirectly induce oxidative stress and thereby compromise the integrity of the genome. In addition to indirect DNA damage, cadmium also inhibits the mechanism necessary for DNA repair, although its precise mode of action has not been elucidated (reviewed in Giaginis, Gatzidou & Theocharis, 2006). Through this inhibition process, cadmium is able to enhance the mutagenicity induced by other DNA-damaging agents.

(a) In vitro

The excision repair of bulky DNA adducts induced by benzo(*a*)pyrene diolepoxide and of ultraviolet C–induced photolesions in two human cell lines was inhibited by non-cytotoxic concentrations of cadmium chloride or particulate cadmium oxide. Inhibition was associated with the dose-dependent uptake of Cd^{2+} into the nucleus. The mechanism of inhibition appeared to be via the disruption of the assembly and disassembly of nucleotide excision repair proteins (Schwerdtle et al., 2010).

(b) In vivo

In a micronucleus assay, cadmium chloride (15 mg/kg bw) in distilled water was administered to male Wistar rats (four per group) as a single dose or a daily gavage dose for 60 days. Negative and positive control groups received isotonic saline and mitomycin C at 2 mg/kg bw, respectively. Bone marrow and peripheral blood were sampled from the single- and repeated-dose groups, respectively, the day after the last dose. In the repeated-dose group, there was a significant increase in micronuclei in peripheral blood (5.5 versus 2.5 per 2000 polychromatic erythrocytes in the negative control; $P < 0.01$). A similar magnitude of increase occurred in bone marrow from the single-dose group (4.25 versus 2.25 per 2000 polychromatic erythrocytes in the negative control; $P < 0.001$), concomitant with cytotoxicity. These increases were approximately 4- to 5-fold lower than those of the positive control group. Blood cadmium levels were significantly higher ($P < 0.001$) in the treated groups relative to the control (approximately 2-fold higher) (Çelik et al., 2009).

2.3 Observations in humans

2.3.1 Absorption

Based on studies reviewed previously by the Committee, the gastrointestinal absorption of cadmium is influenced by diet and nutritional status, with iron status being particularly important. On average, a few per cent of the total oral exposure to cadmium is absorbed, but individual values range from less than 1% up to 5% in males and 10% in females. For women with a low iron status, gastrointestinal absorption estimates of up to 10% seem to be in concordance with toxicokinetic modelling of long-term dietary exposures and observed urinary cadmium levels

(Amzal et al., 2009). A recent study by Kippler et al. (2007) appears to confirm the important influence of iron status on cadmium absorption in women. They found that among 890 pregnant Bangladeshi women, urinary cadmium levels were higher for those with low serum ferritin and adequate plasma zinc than for those with adequate iron and zinc status ($P = 0.03$).

The cadmium content in the kidneys of 109 living donors (aged 24–70 years; median 51 years) in Sweden was determined from kidney biopsies. The average kidney cadmium concentration was 15 µg/g wet weight (median 12.9 µg/g wet weight). The concentrations of cadmium in the kidneys of non-smokers were similar to those observed in the 1970s, suggesting that exposure via the diet had changed little over the previous 40 years. Multiple linear regression analysis revealed that the kidney cadmium concentration increased by 3.9 µg/g ($P < 0.001$) for each 10-year increase in age and by 3.7 µg/g ($P < 0.001$) for each 10 pack-years of smoking. The cadmium concentrations increased by 4.5 µg/g ($P = 0.03$) for women with low iron stores (serum ferritin below 30 µg/l) and by 1.3 µg/g ($P = 0.03$) for a 10 kg reduction in body weight, suggesting that a low iron status is at least as important as 10 pack-years of smoking or a 10-year increase in age and much more important than a 10 kg reduction in body weight for cadmium accumulation in the kidney (Barregård et al., 2010).

2.3.2 Renal effects

Although there is good evidence to indicate a relationship between the urinary excretion of cadmium following renal damage and various renal biomarkers (e.g. β2MG, retinol binding protein [RBP], α_1-microglobulin [α1MG] and *N*-acetyl-β-D-glucosaminidase), especially from occupational exposure, the health significance of these nonspecific biomarkers in relation to renal damage in the general population remains uncertain. Assuming that the associations between the excretion of renal biomarkers and cadmium exposure observed in population-based studies reflect a causal relationship, then these associations imply potentially adverse effects, rendering the kidneys more susceptible to other stressors. However, these effects might also reflect only an early renal response to cadmium, which may be purely adaptive or reversible in nature. Another explanation is that the observed association between low molecular weight proteins and cadmium in urine might simply be a result of a co-excretion of markers of exposure and effect.

Several studies monitoring populations following a reduction in cadmium exposure have attempted to address the question of the reversibility of early renal changes. A modest increase in urinary excretion of β2MG or RBP (Table 2) in the range of 300–1000 µg/g creatinine, as found at the early stage, is unlikely to compromise renal function. Such a small increase is usually reversible after industrial cadmium exposure has ceased. Low molecular weight proteinuria in itself does not appear to give rise to any subjective symptoms or objective disease and is, in its early stage, not accompanied by any histological changes. By contrast, when the urinary excretion of these proteins is increased by more than an order of magnitude (10 000 µg/g creatinine), tubular dysfunction caused by cadmium becomes irreversible and may be associated with a lower glomerular filtration rate (GFR) and an accelerated decline of the GFR with ageing.

Table 2. Interpretation of elevated urinary β2MG and RBP concentrations induced by occupational or environmental exposure to cadmium

β2MG or RBP concentration in urine (µg/g creatinine)	Significance
<300	Normal value
300–1000	Incipient cadmium tubulopathy (possibility of some reversal after removal of exposure if urinary cadmium is not too high, i.e. below 20 µg/g creatinine)
>1000–10 000	Irreversible tubular proteinuria that may accelerate the decline of GFR with age. At this stage, GFR is normal or slightly impaired.
>10 000	Overt cadmium nephropathy usually associated with a decreased GFR.

Source: Adapted from Bernard (2008)

In a large cross-sectional study representative of adults in the USA (National Health and Nutrition Examination Survey [NHANES], *n* = 14 778), both cadmium and lead concentrations in blood were assessed in relation to chronic kidney disease (i.e. urinary albumin excretion and an estimate of GFR). Increased blood cadmium and lead levels were strong independent risk factors for the prevalence of albuminuria, reduced GFR and both outcomes together. The geometric mean cadmium and lead concentrations in blood were 0.41 µg/l and 16 µg/l, respectively. After adjustment for survey year, sociodemographic factors, chronic kidney disease risk factors and blood lead concentration, the odds ratios (ORs) for albuminuria (≥30 mg/g creatinine), reduced GFR (<60 ml/min per 1.73 m^2) and both albuminuria and reduced GFR were 1.92 (95% CI 1.53–2.43), 1.32 (95% CI 1.04–1.68) and 2.91 (95% CI 1.76–4.81), respectively, comparing the highest with the lowest blood cadmium quartiles. The ORs comparing participants in the highest with the lowest quartiles of both cadmium and lead concentrations were 2.34 (95% CI 1.72–3.18) for albuminuria, 1.98 (95% CI 1.27–3.10) for reduced GFR and 4.10 (95% CI 1.58–10.65) for both outcomes. Among the subgroup of persons who reported never having smoked, the OR for albuminuria was 1.43 (95% CI 1.12–1.84), comparing the 75th percentile with the 25th percentile, but was not significant for reduced GFR. The major advantages with the present study were that the kidney effects represent clinically defined end-points and that for albuminuria, the exposure and effects markers were not assessed in the same medium (i.e. cadmium in blood versus albumin in urine). Thus, a possible co-excretion of cadmium and proteins is of no concern. The main limitation with the study is its cross-sectional design. As the effect markers used in the present study are related to glomerular damage only, the results may be of greater concern. According to the authors, their analysis may underestimate the consequences of the exposure due to the known limitations of albuminuria and creatinine-based GFR as markers of kidney damage, and the OR observed in models with both outcomes may reflect, in part, improved specificity in outcome assessment (Navas-Acien et al., 2009).

2.3.3 Osteoporosis and fractures

It has been established that prolonged exposure to cadmium affects the metabolism of calcium, leading to osteomalacia subsequent to proximal tubular dysfunction in the damaged kidneys; in the most severe cases, patients develop itai-itai disease, with osteomalacia as well as osteoporosis. A possible link between osteoporosis and exposure to cadmium at concentrations considerably lower than those found in itai-itai disease has been evaluated starting in 1999.

Except for fracture incidence, considered the most adverse end-point with regard to bone, reduced bone mineral density is frequently used as a biomarker of an adverse effect on bone. Osteoporosis is defined as a *t*-score below 2.5 (i.e. 2.5 standard deviations below the mean bone mineral density for young adults) (WHO, 1994). A *z*-score below –1 is sometimes used to define low bone mineral density (i.e. 1 standard deviation below a sex- and age-standardized mean bone mineral density) (Kanis et al., 1997). Based on a meta-analysis, a 1 standard deviation reduction in bone mineral density was reported to result in a relative risk (RR) of 1.5 (95% CI 1.4–1.6) for a fracture at any site. However, a 1 standard deviation reduction in spinal bone density was reported to result in an RR of 2.3 (95% CI 1.9–2.8) for vertebral fractures, and for hip bone density, another measurement for predicting vertebral fractures, the RR was 2.6 (95% CI 2.0–3.5) (Marshall, Johnell & Wedel, 1996).

Several epidemiological studies have reported on the association between cadmium and bone mineral density. So far, two studies have considered fracture incidence, whereas the other studies have included markers of bone metabolism.

In the OSCAR (**Os**teoporosis—**Ca**dmium as a **R**isk Factor) study, both bone mineral density and risk of fractures were assessed in relation to urinary and blood cadmium levels. The OSCAR study involved all people aged 16–80 years who had lived for at least 5 years during the period 1910–1992 in the proximity of a nickel–cadmium battery plant in southern Sweden. An additional group of age- and sex-matched people was randomly selected from a general medical practice register in a nearby area and was included in this “environmentally exposed” group. A group of workers at the battery plant was also enrolled. The overall participation rate was 60%, resulting in a total sample size of 1021. The mean (10th–90th percentiles) urinary concentration of cadmium was 0.82 (0.18–1.8) mg/g creatinine in men and 0.66 (0.21–1.3) mg/g creatinine in women. Bone mineral density was measured at a distal site on an individual’s non-dominant forearm while in the supine position. The degree of osteoporosis was expressed as an individual’s *z*-score. The risk of the *z*-score being less than −1 was assessed in relation to both urinary cadmium and blood cadmium concentrations. Inverse relationships were found between cadmium and both tubular proteinuria and bone mineral density. It was particularly apparent in people over 60 years of age. There was also a dose–response relationship between urinary cadmium concentration and *z*-score being less than −1. The ORs for men were 2.2 (95% CI 1.0–4.8) for the group having a urinary cadmium concentration of 0.5–3 nmol/mmol creatinine and 5.3 (2.0–14) for the group with the highest urinary cadmium concentrations (≥3 nmol/mmol creatinine) compared with the group with the lowest urinary cadmium concentrations

(<0.5 nmol/mmol creatinine). For women, the OR was 1.8 (95% CI 0.65–5.3) in the group with urinary cadmium concentrations of 0.5–3 nmol/mmol creatinine (Alfvén et al., 2000). For the analysis with blood cadmium levels, in a multiple linear regression, there was a negative association between blood cadmium concentration and bone mineral density for both men and women in the older age group (>60 years of age)—significant for women and close to significant for men. In the whole group (all ages), no significant correlations could be found among blood cadmium concentration, blood lead concentration and bone mineral density. Smoking did not appear to affect the outcome. The dose–response relationships in relation to low bone mineral density (*z*-score less than 1) showed ORs for three blood cadmium groups for people over 60 years of age, adjusted for weight and smoking (*z*-score already includes adjustment for age and sex). Compared with the group with blood cadmium concentrations below 5 nmol/l, ORs were 2.0 (95% CI 1.1–3.9) for the group with blood cadmium concentrations greater than or equal to 5 nmol/l and less than 10 nmol/l (mean 7.2 nmol/l) and 2.0 (95% CI 1.4–5.8) for the group with blood cadmium concentrations greater than or equal to 10 nmol/l (mean 21 nmol/l) (Alfvén, Järup & Elinder, 2002).

Fracture incidence was also assessed retrospectively in the Swedish OSCAR study. For fractures occurring after the age of 50 years ($n = 558$, 32 forearm fractures), the fracture hazard ratio, adjusted for sex and other relevant covariates, increased by 18% (95% CI 1.0–38%) per unit urinary cadmium (1 nmol/mmol creatinine). When subjects were grouped in exposure categories, the hazard ratio reached 3.5 (90% CI 1.1–11) in the group of subjects with urinary cadmium concentrations between 2 and 4 nmol/mmol creatinine and 8.8 (90% CI 2.6–30) in the group of subjects with urinary cadmium concentrations greater than or equal to 4 nmol/mmol creatinine. Associations between cadmium and fracture risk were absent before the age of 50 (Alfvén et al., 2004).

In Belgium, the exposure to cadmium in relation to fracture incidence was assessed in populations living close to zinc smelters and in control areas (Staessen et al., 1999). Urinary cadmium excretion in the 225 residents of the six districts near the smelters (mean 9.7 nmol/day; 10th–90th percentiles 6.9–24.1 nmol/day) was 22.8% higher ($P = 0.001$) than in the 281 inhabitants of the four low-exposure districts (mean 7.9 nmol/day; 10th–90th percentiles 3.4–16.3 nmol/day). These levels correspond to approximately 0.58 and 0.83 µg/g creatinine in men and women, respectively. The approximate 90th percentile urinary cadmium excretion corresponds to 2 µg/g creatinine. In their prospective cohort, including 506 subjects, Staessen et al. (1999) observed RRs associated with doubled urinary cadmium concentrations of 1.73 (95% CI 1.16–2.57; $P = 0.007$) for fractures in women and 1.60 (95% CI 0.94–2.72; $P = 0.08$) for height loss in men. Similar risk estimates were observed if cadmium concentrations in soil, leek and celery sampled in the relevant district of residence were used as a proxy of cadmium exposure instead of urinary cadmium concentration.

More recent Swedish and Belgian data confirmed the adverse effects of low-level cadmium exposure on bone mineral density. The median urinary cadmium concentration was 0.67 (5th–95th percentiles 0.31–1.6) µg/g creatinine in the Swedish study, and the median blood cadmium concentration was 0.38 (5th–95th percentiles 0.16–1.8) µg/l (Åkesson et al., 2006); the median blood cadmium concentration was 8 nmol/l (0.90 µg/l) in the Belgian study (Schutte et al., 2008a). Both studies suggest direct effects of cadmium on bone resorption, which seemed to be intensified after menopause. Even in the absence of cadmium-induced renal tubular dysfunction, low-level environmental exposure to cadmium seems to mobilize bone minerals from the skeletal tissue, indicated by increased calciuria and reactive changes in calciotropic hormones. Because cadmium was associated with lower levels of parathyroid hormone in both studies, the cadmium-associated calciuria was most likely a result of increased bone resorption, rather than decreased tubular reabsorption. If the calciuria was due to kidney damage, an increase in parathyroid hormone levels would then be a more likely scenario. An assessment of the benchmark dose (BMD) of cadmium in relation to bone mineral density was recently performed in the study on Swedish women mentioned above (Åkesson et al., 2006).

A large study in the USA using NHANES data reported an increased risk of osteoporosis in the hip in 3207 women aged 50 years and older; the ORs were 1.43 (95% CI 1.03–2.0) at urinary cadmium levels between 0.50 and 1.0 µg/g creatinine and 1.40 (95% CI 0.97–2.03) for urinary cadmium concentrations greater than 1.0 µg/g creatinine compared with the reference (<0.50 µg/g creatinine) (Gallagher et al., 2008). Only 15% of the women had urinary cadmium concentrations above 1.0 µg/g creatinine. Osteoporosis was defined according to *t*-score less than −2.5 (in this case, <0.56 g/cm^2), and this study was the first to assess bone mineral density at a site on the skeleton with high relevance to a fracture with great public health concern (i.e. hip fracture). This multivariate-adjusted model included adjustment for age, race, income, ever-smoking and underweight. Dose–response relationships were reported between the risk of osteoporosis and urinary cadmium as a continuous variable expressed in microgram per gram creatinine (OR 1.15; 95% CI 1.00–1.33).

In a recent publication, an association between urinary cadmium levels and bone mineral density was confirmed in occupationally exposed individuals (Nawrot et al., 2010). In 83 male (ex-)workers (mean age 45 years; range 24–64 years) of a radiator factory using cadmium-containing solder, bone mineral density in distal forearm, hip and lumbar spine (by dual-energy photon absorptiometry) and urinary calcium excretion were assessed. The geometric mean urinary cadmium concentration was 1.02 µg/g creatinine (5th–95th percentiles 0.17–5.51 µg/g creatinine). Bone mineral density was negatively correlated with urinary excretion of cadmium: the partial correlation coefficients (r) adjusted for age, body mass index (BMI) and current smoking were −0.30 (P = 0.008) for bone mineral density in the forearm, −0.27 (P = 0.017) in the hip and −0.17 (P = 0.15) in the spine. Urinary calcium levels correlated positively (r = 0.23; P = 0.044) with the urinary cadmium excretion. Adjusted for the same covariates, the risk of osteoporosis (defined as a *t*-score below −2.5 in at least one measured bone site) increased dose dependently.

Compared with the lowest tertile of urinary cadmium concentration, the risks were 4.8- and 9.9-fold higher in the middle and highest tertiles, respectively. Only four (5%) men had evidence of renal tubular dysfunction (β2MG concentration above 300 µg/g creatinine). It was concluded that even in the absence of renal tubular dysfunction, occupational exposure of men to cadmium is associated with lower bone mineral density, a higher risk of osteoporosis and higher urinary calcium excretion, suggesting a direct osteotoxic effect of cadmium (Nawrot et al., 2010).

The long-term effects of cadmium on forearm bone mineral density after the cessation of the ingestion of cadmium-polluted rice were investigated in 458 persons (294 women, 164 men) from three cadmium exposure areas (low, moderate and heavy) in China. Those living in the moderate and heavy exposure areas ceased ingesting cadmium-polluted rice (0.51 mg/kg and 3.7 mg/kg, respectively) in 1996 (10 years prior to the present analysis). The bone mineral density was measured by dual-energy X-ray absorptiometry at the proximal radius and ulna. The cadmium concentrations in urine and blood in 1998 were used as cadmium exposure markers. The values of the absolute decrease and per cent decrease in bone mineral density from 1998 to 2006 increased with increasing urinary and blood cadmium levels and were significant at urinary cadmium concentrations above 5 µg/g creatinine and at blood cadmium concentrations above 10 µg/l compared with the low exposure groups (urinary cadmium <2 µg/g creatinine and blood cadmium <2 µg/l) in all subjects (after stratification by sex, these differences were significant in the women only; $P < 0.001$). Analysis of the *z*-score revealed that the prevalence of osteoporosis in 2006 was higher than that in 1998 and increased along with the level of urinary and blood cadmium in both men and women, especially for those women with higher blood cadmium (blood cadmium >5 µg/l, OR = 3.45 [0.95–13.6]; blood cadmium >10 µg/l, OR = 4.51 [1.57–13.54]) and urinary cadmium (urinary cadmium >10 µg/g creatinine, OR = 4.74 [1.82–12.81]). The authors concluded that decreasing dietary cadmium exposure at the population level is not associated with bone recovery at the individual level (Chen et al., 2009).

Two other studies have failed to establish any association between urinary cadmium levels and bone mineral density. In 196 men and 184 women (Swedish fishermen and their wives), there was no significant association between urinary cadmium concentration and forearm bone mineral density (Wallin et al., 2005). In a study comprising 170 women and 100 men, urinary and blood cadmium concentrations and the markers of renal tubular dysfunction and forearm bone mineral density were measured. The results of the multivariate analysis did not indicate an association between exposure to cadmium and a reduction in bone density. The authors concluded that the excretion of low molecular weight proteins occurred at a lower level of cadmium exposure than that associated with potential loss of bone mass (Trzcinka-Ochocka et al., 2010).

A third study included 908 Swedish women with data on single photon absorptiometry in the non-dominant forearm. Cadmium level in blood was negatively associated with bone mineral density and parathyroid hormone level and positively associated with the biochemical marker of bone resorption (serum crosslinked C-telopeptide of type I collagen, or CTX). However, this association disappeared after adjustment for smoking, and it was concluded that no convincing

associations were observed between cadmium concentration in blood and bone mineral density (Rignell-Hydbom et al., 2009).

2.3.4 Cardiovascular disease

A cross-sectional analysis of data from the NHANES in the USA found an association between urinary cadmium concentration and myocardial infarction (Everett & Frithsen, 2008) and between blood cadmium concentration and risk of reported stroke and heart failure (Peters et al., 2010). In subjects with environmental cadmium exposure in Belgium, the urinary cadmium excretion was correlated with changes in some physiological indicators of cardiovascular function: pulse wave velocity, arterial pulse pressures and arterial compliance and distensibility (Schutte et al., 2008b). The pathogenesis of these cadmium-associated abnormalities is unclear at present. In a study conducted in the Republic of Korea, blood cadmium level was associated with increased risk of hypertension (Eum, Lee & Paek, 2008), and cadmium levels in blood, but not in urine, were associated with a modest elevation in blood pressure levels in the NHANES data (Tellez-Plaza et al., 2008).

2.3.5 Cancer

Cadmium is classified as a cancer-causing agent in humans based on an elevated incidence of lung cancer and mortality data derived from occupational groups with evidence of elevated exposure to cadmium. Occupational exposures have historically been through inhalation (IARC, 1993). The available evidence was considered sufficient for lung cancer, but limited for kidney, liver and prostate cancer.

The previous evidence with respect to prostate cancer has not been regarded as convincing (Verougstraete, Lison & Hotz, 2003; Sahmoun et al., 2005), but the available human studies have limited ability to detect an effect (Huff et al., 2007). A recent case–control study (40 cases and 58 hospital-based controls from two provinces in southern and northern Italy), which compared newly diagnosed cases of prostate cancer with the cadmium levels in their toenails, showed an apparent relationship for an increased prostate cancer risk. An excess prostate cancer risk in subjects in the third and fourth (highest) quartiles of toenail cadmium concentration (ORs of 1.3 and 4.7, respectively), compared with subjects in the bottom quartile, was observed. Results were basically unchanged when limiting the analysis to each province or entering toenail cadmium concentrations as continuous values in the regression model ($P = 0.004$). Despite the limited statistical stability of the point estimates, these findings appear to support the hypothesis that cadmium exposure increases prostate cancer risk (Vinceti et al., 2007).

A prospective cohort study from Belgium assessed the association between environmental exposure to cadmium and cancer incidence. This study was a prolongation of the Flemish part of the CadmiBel study, including six districts with high cadmium exposure close to zinc smelters and four districts with low exposure. In total, 994 subjects were included at baseline. Occupationally exposed people were not excluded, but a sensitivity analysis was performed based on environmentally exposed people alone. The population-attributable risk of lung cancer was

67% (95% CI 33–101) in a high exposure area, compared with 73% (95% CI 38–108) for smoking. For lung cancer (n = 19, of which 18 occurred in the high exposure area), the adjusted hazard ratio was 1.70 (95% CI 1.13–2.57; P = 0.011) for a doubling of the 24 h urinary cadmium excretion, 4.17 (95% CI 1.21–14.4; P = 0.024) for residence in the high exposure area compared with the low exposure area and 1.57 (95% CI 1.11– 2.24; P = 0.012) for a doubling of cadmium concentration in soil (Nawrot et al., 2006). Overall cancer incidence (n = 70) was also increased in the high exposure group, but a clear excess was seen only with regard to lung. The median urinary cadmium excretion in this study was 0.8 µg/g creatinine, and the 25th–75th percentile range was about 0.5–1.4 µg/g creatinine (EFSA, 2009a). The exact relevance to dietary cadmium exposure is not clear.

A Belgian case–control study of bladder cancer (172 cases and 359 population controls) showed an OR of 5.7 (95% CI 3.3–9.9) for bladder cancer, comparing the highest tertile of blood cadmium with the lowest after adjustments for sex, age, smoking status (current/non-current), number of cigarettes smoked per day, number of years of smoking and occupational exposure to polycyclic aromatic hydrocarbons or aromatic amines (Kellen et al., 2007).

More recently, a case–control study (246 cases and 254 controls) in the USA showed that women in the highest quartile of creatinine-adjusted urinary cadmium levels had twice the breast cancer risk of those in the lowest quartile after adjustment for established risk factors, and there was a statistically significant increase in risk with increasing cadmium level (McElroy et al., 2006).

The significance of the estrogen-mimicking effects, such as the well-characterized estrogenic responses of the endometrial lining (hypertrophy and hyperplasia), observed in experimental animals exposed to environmentally relevant doses of cadmium (Johnson et al., 2003) was further explored in humans. In a large population-based prospective cohort among Swedish postmenopausal women (n = 32 210), the association between dietary cadmium exposure and endometrial cancer incidence was assessed (Åkesson, Julin & Wolk, 2008). This is the first study exploring health effects in relation to dietary cadmium exposure, in contrast to smaller studies in which cadmium concentration has been monitored in urine. Thus, based on the construction of a food cadmium database in the cohort, a large study population was utilized, and the incidence was assessed prospectively. This design, on one hand, reduces the selection bias that often occurs in case–control studies, but it is, on the other hand, dependent on the assumption that estimated dietary cadmium exposure is a valid reflection of the internal dose of cadmium. The average estimated dietary cadmium exposure was 15 µg/day (1.5 µg/kg bw per week). During 16 years of follow-up, 378 cases of endometrial adenocarcinoma were ascertained through computerized linkage to the Swedish Cancer Registry, with virtually no loss to follow-up. The highest versus lowest tertile of cadmium exposure was associated with risk of endometrial cancer (RR 1.39, 95% CI 1.04–1.85; P for trend = 0.02). To reduce the influence of endogenous estrogen exposure, analyses were stratified by BMI and by postmenopausal hormone use. Analyses were also stratified by smoking status, because an anti-estrogenic effect of cigarette smoking on circulating estrogen concentrations has been shown as a result of increased metabolic clearance, a reduction in relative

body weight and an earlier age at menopause (Terry et al., 2002). Among never-smoking, non-overweight women, the RR was 1.86 (95% CI 1.13–3.08; *P* for trend = 0.009). A 2.9-fold increased risk (95% CI 1.05–7.79) was observed with long-term cadmium exposure consistently above the median exposure in 1987 and in 1997 in never-smoking women with low available estrogen (non-overweight and non-users of postmenopausal hormones). Although the data support the hypothesis that cadmium may exert estrogenic effects and possibly increase the risk of hormone-related cancers, this needs to be confirmed by other studies.

The association between cancer mortality and cadmium of dietary origin was assessed in Japanese cohorts. In the Kakehashi cohort with high baseline urinary cadmium concentrations (median urinary cadmium concentrations for men and women were 7.0 and 12.1 µg/g creatinine, respectively), a 2.5-fold increase in cancer mortality was observed among women with permanent tubular impairment (Nishijo et al., 2006). Similarly, Arisawa et al. (2007a) observed a 2.58-fold concurrent increased risk of cancer mortality among those with tubular impairment in the Nagasaki cohort I.

2.3.6 Reproductive toxicity

Maternal blood cadmium concentration is not highly correlated with blood cadmium concentration in the newborn, but it is correlated with cord blood cadmium concentration, with correlation coefficients of 0.5–0.6 (Galicia-Garcia et al., 1997; Salpietro et al., 2002). Limited evidence suggests that neonatal outcomes, such as reduced birth weight (Galicia-Garcia et al., 1997; Nishijo et al., 2002; Salpietro et al., 2002) and reduced length of gestation (Nishijo et al., 2002), are related to indices of prenatal exposure to cadmium (maternal urinary cadmium level, maternal blood cadmium level). The fact that, in the study by Nishijo et al. (2002), urinary cadmium concentration was not significantly associated with infant height and weight after adjustment was made for gestational age suggested that fetuses with higher prenatal exposures to cadmium were of appropriate gestational age for date, but tended to be born earlier. In this study, conducted among women living in the Jinzu River basin in Toyama, the area in which itai-itai disease was most common, most adverse fetal outcomes were no longer significantly associated with urinary cadmium concentration after adjustment was made for maternal age. Because the study area was known to have been contaminated with cadmium over a long period, maternal age is likely to have been a marker for duration of exposure and thus for body burden of cadmium. Thus, controlling for maternal age might represent overcontrol, and alternative analytical approaches, such as stratification, might have been preferable.

Concentrations of cadmium were measured in the placenta, cord blood and urine of 44 non-smoking, rural Bangladeshi women. The concentrations of magnesium, calcium, manganese, copper, zinc, arsenic and selenium in the placenta and cord blood and the level of metallothionein in the placenta were also measured. Concentrations of cadmium in urine, placenta and cord blood were variable, with means (range) of 1.4 µg/l (0.29–10 µg/l), 130 mg/kg (40–492 mg/kg) and 0.16 µg/kg (0.074–0.32 µg/kg), respectively. The concentration of cadmium in the placenta was positively associated with that in cord blood ($r_s = 0.62$; $P < 0.001$),

but negatively associated with zinc concentration in cord blood ($r_s = -0.30$; $P = 0.05$). Placenta metallothionein protein expression was positively associated with cadmium ($P < 0.01$) and arsenic ($P = 0.04$) concentrations in placenta, but not with zinc or copper concentration in placenta. The authors concluded that the cadmium concentrations in placenta were clearly elevated, which seemed to impair zinc transfer to the fetus. Induction of metallothionein explained the placental accumulation of cadmium, but not the impairment of zinc transport (Kippler et al., 2010).

2.3.7 Mortality

(a) Japanese data

Recent studies from Japan found that the mortality risk was significantly increased among subjects with a urinary cadmium concentration of more than 3 µg/g creatinine in proportion to the increases in the urinary cadmium concentration after adjustment for age, especially in women (Nakagawa et al., 2006). In a recent study on mortality of targeted participants in the 1974–1975 health impact survey in the Kakehashi River basin, Japan, standardized mortality ratios were assessed instead of proportional mortality ratios. An increased mortality risk from cerebral infarction in men was found in the category with a urinary β2MG concentration of 300–1000 µg/g creatinine during observation for 15 years. Therefore, the increase in mortality from cerebral infarction may contribute to the increase in mortality for men exposed to cadmium. Whereas the increase in mortality from cerebral infarction did not reach significance in women with urinary β2MG concentrations of 300–1000 µg/g creatinine (hazard ratio 1.88, 95% CI 0.82–4.29), the mortality from heart failure was significantly increased in this subgroup of women (hazard ratio 1.94, 95% CI 1.08–3.48) (Nishijo et al., 2006).

In 1992, Iwata et al. reported that individuals who resided in the cadmium-polluted areas of Nagasaki and Akita prefectures in Japan and had renal tubular dysfunction and glomerular dysfunction had a reduced life expectancy. In a follow-up study 23 years later, Arisawa et al. (2007b) compared the same cohort (cohort I) with a second younger cohort of adults (≥40 years) from the same area. The daily cadmium exposure from food had decreased from over 200 µg/day in 1967 to less than 100 µg/day after 1980–1983 due to the restoration of cadmium-polluted paddy fields. In the older cohort I, the mortality rate among those with urinary β2MG concentration greater than or equal to 1000 µg/g creatinine was 1.41 (95% CI 1.07–1.83) times higher than the regional reference rate. After adjusting for age and other variables, urinary *N*-acetyl-β-D-glucosaminidase activity in men and serum creatinine level, β2MG clearance and urinary β2MG concentration in women were significantly associated with increased mortality. However, in cohort II, urinary β2MG or total protein level was not significantly associated with survival. The authors concluded that these findings indicated that cadmium-induced renal dysfunction was a significant predictor of mortality, but that such an association is disappearing, probably because of the selective loss of advanced cases and reduced exposure and body burden.

(b) Data from Europe and the USA

A recent European prospective cohort study (n = 1107 subjects at baseline, of the original 1419 subjects invited to participate between 1985 and 1989) assessed the long-term changes in body burden of cadmium and the incidence of mortality simultaneously. The study was a prolongation of the Flemish part of the CadmiBel study, including six districts with high cadmium exposure close to zinc smelters (cadmium concentrations above 3 mg/kg soil) and four districts with low exposure more than 10 km away from the smelters (cadmium concentrations below 1 mg/kg soil). The median urinary cadmium concentrations at baseline were 1.03 µg/g creatinine and 0.74 µg/g creatinine in high and low exposure areas, respectively. Individuals reporting possible exposure to cadmium at work were excluded from the baseline population of 1107 subjects, and some subjects did not provide blood or urine samples, leaving 956 persons to be followed up (50% from each of low and high exposure areas). Except for blood cadmium level and 24 h urinary cadmium excretion, blood pressure, serum creatinine level, high-density lipoprotein concentration, total cholesterol level, serum γ-glutamyltransferase activity (as index of alcohol intake), urinary creatinine concentration and RBP level were assessed. Among the group with data on urinary cadmium concentration, 208 deaths occurred during an average 20.3 years of follow-up. Multivariate-adjusted hazard ratios (adjusted for age, sex, BMI, smoking, serum γ-glutamyltransferase activity and socioeconomic status) for all-cause and non-cardiovascular mortality and the risk of death from all cancers and lung cancer increased with high urinary cadmium excretion. The risks ($P \leq 0.04$) associated with a doubling of baseline urinary cadmium concentration were 20% (95% CI 4–39%), 44% (95% CI 16–79%) and 43% (95% CI 8–89%) for total mortality, non-cardiovascular mortality and total cancer mortality, and those associated with a doubling of blood cadmium concentration were 25% (95% CI 4–50%) for total mortality and 33% (95% CI 1–75%) for non-cardiovascular mortality. The increase in risk corresponds to a difference in urinary cadmium concentration between 0.68 µg/g creatinine (the mean in the analysed population) and 1.36 µg/g creatinine. The authors concluded that the increased mortality was directly related to the toxic effects of cadmium, but not directly related to renal dysfunction, as measured by urinary RBP level and serum creatinine level; and that even if zinc smelters close, historical environmental contamination remains a persistent source of exposure, and this exposure increases mortality in a continuous fashion (Nawrot et al., 2008). This study provides the strong advantage of being a prospective cohort with longitudinal exposure assessment. The relevance to dietary cadmium exposure alone cannot be estimated.

Mortality was also assessed in a prospective cohort based on the NHANES (baseline 1988–1994) data, including 13 956 people followed through December 2000. Multivariate models included adjustments for age, race/ethnicity, menopausal status, urban/rural residence, cigarette smoking, alcohol consumption, education, physical activity, income, serum C-reactive protein, total cholesterol, diabetes, blood pressure, use of antihypertensive drugs and GFR. The hazard ratios (95% CI) for all-cause mortality, cancer mortality, cardiovascular disease mortality and coronary heart disease mortality associated with a 2-fold higher creatinine-

corrected urinary cadmium concentration were 1.28 (1.15–1.43), 1.55 (1.21–1.98), 1.21 (1.07–1.36) and 1.36 (1.11–1.66), respectively, for men and 1.06 (0.96–1.16), 1.07 (0.85–1.35), 0.93 (0.84–1.04) and 0.82 (0.76–0.89), respectively, for women. A 2-fold increase in urinary cadmium corresponds approximately to the difference between the median (0.32 µg/g creatinine) and the 75th percentile (0.61 µg/g creatinine). Thus, environmental cadmium exposure was associated with an increased risk of all-cause, cancer, cardiovascular disease and coronary heart disease mortality among men, but not among women (Menke et al., 2009).

A recent study that monitored glomerular dysfunction in 50 subjects who had ingested household rice for 10 years after cadmium-polluted soil in rice paddies was replaced revealed very little improvement based on measured urinary biomarkers (β2MG, RBP, total protein, amino acid nitrogen and glucose levels), with the exception of urinary amino acid nitrogen level in men. The urinary concentration of these biomarkers continued to increase in both sexes over time, with statistically significant differences in RBP and total protein levels in both sexes and glucose level in men. Therefore, although cadmium concentrations in rice and urine were shown to be less after soil replacement, cadmium-induced renal tubular injury (i.e. where β2MG concentration is greater than or equal to 1000 µg/g creatinine) seemed to be irreversible (Kobayashi et al., 2008).

In a study reported in 2009 that investigated the effects of environmental co-exposure to arsenic and cadmium in 290 adults (86 males, 204 females) in the Republic of Korea, biomarkers of kidney toxicity (the concentrations of *N*-acetyl-β-D-glucosaminidase and β2MG in urine) and biomarkers of oxidative stress (urinary malondialdehyde and 8-hydroxy-2′-deoxyguanosine) were determined. The concentrations of these biomarkers were matched to the urinary concentrations of arsenic and cadmium. Oxidative stress biomarkers, such as urinary malondialdehyde and 8-hydroxy-2′-deoxyguanosine, were positively correlated with both cadmium and arsenic levels in urine. However, the correlation was more pronounced with co-exposure than with each metal separately. The urinary concentration of *N*-acetyl-β-D-glucosaminidase but not β2MG was positively correlated with urinary levels of cadmium and arsenic and indices of oxidative stress. The authors concluded that these data indicated that tubular damage in the kidneys was probably related to oxidative stress and that the effect of co-exposure to arsenic and cadmium was more pronounced than exposure to each individual metal (Huang et al., 2009).

3. ANALYTICAL METHODS

3.1 Chemistry

Cadmium is a soft, ductile and silvery-white heavy metal with the atomic number 48, atomic weight 112.411 and density 8.65 g/cm^3 (at 25 °C). It occurs mostly in the valence state of +2. Cadmium forms a number of inorganic salts, and the salts exhibit properties similar to those of the corresponding zinc compounds. The halides and the nitrate of Cd^{2+} are very soluble in water, whereas the hydroxide is insoluble. Cadmium oxide and cadmium carbonate might, however, be soluble at gastric pH.

Cadmium occurs naturally in Earth's crust as part of cadmium-rich geological materials, such as greenockite (cadmium sulfide). Cadmium is also found in ores containing other elements, mainly associated with zinc, and is recovered as a by-product of zinc mining. Approximately 3 kg of cadmium is produced for each tonne of zinc. Cadmium is primarily used for metal plating and coating operations, including transportation equipment, machinery and baking enamels, photography and television phosphors. It is also used in nickel–cadmium and solar batteries and in pigments.

Cadmium occurs in the environment in its inorganic form as a result of volcanic emissions and exfoliation of rocks and minerals (Pacyna & Pacyna, 2001). It is released into the environment via the smelting of other metals, burning of fossil fuels, incineration of waste materials and use of phosphate and sewage sludge fertilizers. An increase in cadmium levels in soil results in an increase in the uptake of cadmium by plants. Although cadmium may bind to proteins and other organic molecules and form salts with organic acids, these compounds are regarded as inorganic with respect to cadmium (IPCS, 1992a). Organic cadmium compounds (compounds in which cadmium binds covalently to carbon) are normally not identified in nature (IPCS, 1992b). Although studies in marine polar regions indicate microbial formation of monomethyl cadmium ($CdCH_3^+$), the significance of these findings is currently not known (Pongratz & Heumann, 1999; Fairbrother et al., 2007). In the aquatic environment at low salinity, cadmium is present as the free Cd^{2+} ion with cadmium hydroxide and organic complexes at levels dependent on pH and amounts of soluble organic material. As salinity increases, the degree of complexation with chloride increases; in 100% seawater, the cadmium exists almost solely as cadmium chloride and $CdCl^+$ complexes (Simpson, 1981). Cadmium is most readily absorbed by aquatic organisms in its free form, Cd^{2+}, and increased salinity has been found to reduce its bioaccumulation (IPCS, 1992a). Shellfish, crustaceans and fungi are natural accumulators of cadmium.

3.2 Description of analytical methods

Analytical methods for the determination of cadmium in foods, water and biological materials are well established. The detection techniques include flame atomic absorption spectrometry (FAAS), electrothermal (graphite furnace and Zeeman furnace) atomic absorption spectrometry (ETAAS), beam injection flame furnace atomic absorption spectrometry (BIFF-AAS), thermospray flame furnace atomic absorption spectrometry (TS-FF-AAS), hydride generation atomic fluorescence spectrometry (HG-AFS), inductively coupled plasma optical emission spectrometry (ICP-OES) and inductively coupled plasma mass spectrometry (ICP-MS).

The sensitivity of FAAS can be improved by increasing the efficiency of aerosol generation/transport and the residence time of free atoms in the absorption volume. In the TS-FF-AAS technique, a nickel tube is placed above an air/acetylene flame, and the sample is directly introduced through a ceramic capillary connected to the nickel tube positioned on the burner of the atomic absorption spectrometer (Da-Col, Domene & Pereira-Filho, 2009). This procedure, unlike FAAS, allows

introduction of total sample and long residence time of gaseous atoms in the spectral zone, which offers good sensitivity (Pereira-Filho, Berndt & Arruda, 2002).

Owing to the high sensitivity (limit of detection [LOD] approximately 100 times lower than that of FAAS) and selectivity, ETAAS has been widely used for the determination of cadmium. However, the response of ETAAS is often perturbed by multiple physical or chemical reactions in the atomizer, and the LODs are not always adequate for trace analysis (Sardans, Montes & Peñuelas, 2010). This technique requires the use of modifiers to stabilize cadmium, allowing its quantification without matrix effect. Various modifiers used include palladium(II) nitrate/palladium (Daftsis & Zachariadis, 2007), palladium(II) chloride/palladium and ascorbic acid (Licata et al., 2004) and ammonium phosphate, Triton X-100 and monoammonium dihydrogen phosphate (Viñas, Pardo-Martínez & Hernández-Córdoba, 2000). Many improvements have enhanced the performance of ETAAS, including background correction systems, especially the Zeeman background correction; advances in atomizer designs; development of in situ trapping methods; improvements in the light source and detector; and use of appropriate modifiers. Use of transversally heated atomizers with platforms further improved the sensitivity. In recent years, the high-resolution continuum source electrothermal atomic absorption spectrometer (HR-CS-ETAAS) allows the direct analysis of solids with low LODs.

ICP-OES and ICP-MS methods offer simultaneous determination of several elements and are used for the determination of cadmium in foods, water and biological samples. ICP-OES instruments are available in two configurations: radial and axial. The benefit of the axial design is that more photons are seen by the detector; as a result, it offers 5–10 times lower LODs compared with the radial configuration. The fundamental difference between ICP-OES and ICP-MS is that the plasma is used in the latter not to generate photons of light, but to generate ions. The ions produced in the plasma are transported and separated according to their atomic mass to charge ratio by means of a mass spectrometer. The generation of large numbers of positively charged ions allows ICP-MS to achieve LODs better than those attainable using ETAAS. Additionally, ICP-MS offers high specificity through spectral interpretation and isotopic information (Nardi et al., 2009). However, polyatomic interferences resulting from the combination of matrix ions with argon may affect this technique. Some of the interferences can be controlled or eliminated by using different sample preparation techniques, such as ashing or microwave digestion prior to determination, 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 an interesting 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 (Melucci, Torsi & Locatelli, 2007; Jannat, et al., 2009), have limitations for the determination of cadmium.

3.2.1 Determination of cadmium in foods

ETAAS and ICP-MS have been largely used for the determination of cadmium in foods and water. FAAS has been used to a lesser extent, owing to its low sensitivity. ICP-MS has been the method of choice, as it offers lower LODs and wide dynamic range and allows simultaneous determination of several elements. Additionally, ICP-MS offers high specificity through spectral interpretation and isotopic information.

Sample preparation for the analysis of cadmium depends on the type of food matrix as well as the quantification method. The two most common techniques used are wet digestion using acids and dry ashing following leaching. The wet digestion technique, which uses a combination of highly pure acids (nitric, hydrochloric, sulfuric) along with oxidants such as hydrogen peroxide to assist digestion, has been most commonly employed in sample preparation. Microwave-assisted acid digestion has been extensively used. This technique allows the use of large sample masses (1–2 g) under controlled temperature and pressure, reducing contamination and avoiding losses of the element during mineralization. The dry ashing and leaching technique has been used to a limited extent, as calcinations at temperatures above 400 °C may induce losses of cadmium. Another technique, which is less commonly used, is the slurry sampling technique. It has some advantages over the microwave-assisted acid digestion technique, such as low sample preparation time, safety and cost. However, this technique requires the optimization of particle size, slurry concentration and homogeneity. This technique may be used in combination with ETAAS, as the ashing step is carried out in the graphite furnace itself.

The performances of some analytical methods for the determination of cadmium contamination levels in different foods are presented in Table 3.

(a) Quality assurance for the determination of cadmium in foods

In general, most countries used validated analytical methods and followed good quality assurance programmes to demonstrate the accuracy and reliability of the data. Certified standards and certified reference materials (CRMs) available from institutions such as the Institute for Reference Materials and Measurements (European Commission), the National Institute of Standards and Technology (USA), the Federal Institute for Materials Research and Testing (Germany) and the LGC (formerly the Laboratory of the Government Chemist; United Kingdom) have been used during method validation and accuracy studies. Many laboratories have also participated in the proficiency testing programmes and achieved good *z*-scores in different participation rounds. Samples from proficiency testing programmes have also been used in method validation as well as internal quality control.

Table 3. Analytical methods for the determination of cadmium in foods

Commodity	*n*	Country (year)	Sample preparation method	Determination method	LOD/LOQ	*n* <LOD or <LOQ	Mean concentration (range)	Reference
Milk	42	Brazil (2004)	Acid digestion (HNO_3 + HCl)	ETAAS	0.13 ng/ml (LOQ)	42	<LOQ	Soares et al. (2010)
Tomato, pepper, onion	9	Mediterranean countries	Microwave-assisted digestion (HNO_3 + H_2O_2)	ETAAS	0.05/0.15 ng/g	0	(10.7–19.9 ng/g)	Bakkali et al. (2009)
Anchovy, spinach, cabbage, onion, dill, parsley, lettuce, tea, rice, salami, chicken	23	Turkey	Coprecipitation with MBT	ETAAS	0.02 ng/g (LOD)	2	(2.67–510 ng/g)	Oymak et al. (2009)
Vegetables (100 varieties)	416	China	Acid digestion (HNO_3 + $HClO_4$ + H_2SO_4)	ETAAS	1 ng/g (LOD)	—	10 ng/g (ND–101 ng/g)	Song et al. (2009)
Konjac flour	7	China	Enzymatic hydrolysis and slurry preparation	ETAAS	3 ng/g (LOD)	0	(52.6–130.7 ng/g)	Chen et al. (2008)
Cabbage, wheat, potato, eggs, instant milk, mussels, marine fish, river fish, baby milk formula, baby foods	14	Slovenia	Microwave-assisted digestion (HNO_3 + HF)	ETAAS	0.03 µg/g (LOD)	13	(<0.03–0.57 µg/g)	Milacic & Kralj (2003)

Table 3 (contd)

Commodity	*n*	Country (year)	Sample preparation method	Determination method	LOD/LOQ	*n* <LOD or <LOQ	Mean concentration (range)	Reference
Spinach, palmito, crab, shrimps, mussel, sardine, squid	7	Brazil	Cryogenic grinding + slurry preparation	ETAAS	3.3 ng/g (LOD)	1	(ND–22.3 ng/g)	Santos et al. (2002)
Seafood (CRM)	0	—	Solid sampling	SS-ZAAS	0.0013 ng/g (LOD)	—	—	Detcheva & Grobecker (2006)
Seaweed: *Porphyra*, *Laminaria*	4	France, Japan, Republic of Korea and Spain (2004)	Microwave-assisted digestion (HNO_3 + H_2O_2)	ICP-MS	0.28 ng/g (LOD)	0	(0.31–3.18 ng/g)	Rocha et al. (2009)
Rice, wheat, beans, egg, meat, fish, bread, sugar, cheese, milk powder, butter, vegetables, pear, Brazil nut, coffee, chocolate, biscuits, pasta	18	Brazil	Microwave-assisted digestion (HNO_3 + H_2O_2)	ICP-MS	0.2 ng/g (LOD)	1	(ND–9.1 ng/g)	Nardi et al. (2009)
Semolina	3	Italy	Microwave-assisted digestion (HNO_3 + H_2O_2)	ICP-MS	6.1 ng/l (LOD)	0	(15.9–26.4 ng/g)	Cubadda & Raggi (2005)
Milk and infant formula	8	Italy	Microwave-assisted digestion (HNO_3 + H_2O_2)	DRC-ICP-MS	0.08/0.24 ng/g	9	(ND–3.7 ng/g)	D'Llio et al. (2008)

Table 3 (contd)

Commodity	*n*	Country (year)	Sample preparation method	Determination method	LOD/LOQ	*n* <LOD or <LOQ	Mean concentration (range)	Reference
Guaraná, cabbage	2	Brazil	Acid digestion + solid-phase extraction (minicolumn of Amberlite XAD-4 modified with DHB)	ICP-OES	0.02/0.07 ng/ml	0	(0.1–0.25 µg/g)	Bezerra et al. (2007)
Coffee, fish, black tea, green tea	4	Turkey	Coprecipitation with zirconium(IV) hydroxide	FAAS	0.27 ng/ml (LOD)	4	ND	Citak, Tuzen & Soylak (2009)
Food supplement	1	Brazil	Microwave-assisted digestion (HNO_3 + H_2O_2)	TS-FF-AAS	0.6/2.0 ng/ml	—	—	Da-Col, Domene & Pereira-Filho (2009)
Infant formula	1	Islamic Republic of Iran	Acid digestion (HNO_3) + dry ashing	DPASV	5 ng/g (LOD)	0	0.359 mg/kg	Jannat et al. (2009)

CRM, certified reference material; DHB, dihydroxybenzoic acid; DPASV, differential pulse anodic stripping voltammetry; LOQ, limit of quantification; MBT, 2-mercaptobenzothiazole; *n*, number of samples analysed; ND, not detected; SS-ZAAS, solid sampling Zeeman atomic absorption spectrometry

A proficiency testing programme for determining cadmium in seawater shrimp under the auspices of the Asia-Pacific Laboratory Accreditation Cooperation was discussed by Kong, Chan & Wong (2008). The performance of an interlaboratory collaborative study for the determination of cadmium by ICP-MS after pressure digestion including microwave heating was reported. Thirteen laboratories participated, and the method was tested on a total of seven foodstuffs: carrot purée, fish muscle, mushroom, wheat flour, simulated diet, scampi and mussel powder. The elemental concentration of cadmium (dry matter) ranged from 0.28 to 1.70 mg/kg. The study indicated that the ICP-MS method is satisfactory for the determination of cadmium in foods (Julshamn et al., 2007).

3.2.2 Determination of cadmium in blood and biological materials

Determination of cadmium in biological materials such as blood, urine and tissues poses problems, mainly due to its presence in low concentrations as well as the complexity of the sample matrix. ETAAS has been widely used for the determination of cadmium in blood and clinical analyses. Ashing and atomization of the sample in the presence of chemical modifiers and use of Zeeman background correction were studied (Sardans, Montes & Peñuelas, 2010). A simultaneous atomic absorption spectrometry (SIMAAS) method for the determination of cadmium was proposed by Kummrow et al. (2008). The method requires a sample volume of 200 µl and presented an LOD of 0.026 ng/ml for cadmium.

ICP-MS has proven to be a superior and attractive alternative method to ETAAS, owing to its low LODs and its simple sample pretreatment. Whole blood samples could be analysed directly after dilution or decomposition of the organic matrix by ICP-MS (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.

The performances of some analytical methods for the determination of cadmium in blood and other biological materials are presented in Table 4.

Cadmium exposure in children and their mothers living in the vicinity of industrial sources (city of Duisburg and a rural area of North Rhine Westphalia, Germany) was assessed by a cross-sectional study performed in 2000. In total, 238 children (mean age 6.4 years, range 5.5–7.7 years; 49% males, 51% females) and 213 mothers (mean age 36 years, range 23–48 years) were included in the study. Mean cadmium levels (children/mothers) in the blood from the industrialized area were higher (0.21/0.61 ng/ml) than those from the rural area (0.19/0.44 ng/ml). Mean cadmium levels (children/mothers) in the urine from the industrialized area were higher (0.13/0.43 ng/ml) than those from the rural area (0.11/0.30 ng/ml) (Wilhelm et al., 2005).

The Centre for Environment and Health in Flanders, in the northern part of Belgium, started a biomonitoring programme on adolescents in 2003. In total, 1679 adolescents from nine areas with different patterns of pollution were selected to participate in this study. Possible confounding effects of lifestyle and personal characteristics were taken into account. A median blood cadmium level of 0.39 ng/ml was reported (Schroijen et al., 2008).

Table 4. Analytical methods for the determination of cadmium in blood and urine

Country (year)	*n*	Analytical sample size	Sample preparation	Technique	LOD/LOQ	Mean concentration (range)	*n* <LOQ or <LOQ	Reference
Spain (2010)	0 (method validation only, no samples analysed)	—	Microwave digestion	ETAAS	0.03/0.09 ng/ml	—	—	Olmedo et al. (2010)
Brazil (2007)	40	200 µl	Protein precipitation and dilution	ETAAS	0.026 ng/ml (LOD)	0.32 ng/ml (0.13–0.71 ng/ml)	—	Kummrow et al. (2008)
—	—	5 ml	Wet digestion (HNO_3)	ETAAS	1–11 ng/g (LOD) for different fractions	(ND–4 ng/g)	—	Daftsis & Zachariadis (2007)
Germany (2002–2003)	430 (children, age about 10 years)	5 ml	—	ZF-AAS	0.15 ng/ml (LOQ)	0.29 ng/ml (<0.15–3.1 ng/ml)	43	Link et al. (2007)
—	CRM	2 ml	Microwave-assisted digestion	ETAAS with Pd modifier	0.021/0.057 ng/ml	—	—	Viitak & Volynsky (2006)
Germany (2000)	Children/mothers Blood: 238/213 Urine: 149/129	—	—	ETAAS	0.03 ng/ml (LOQ) for blood and urine	Children/mothers Blood 0.21/0.57 ng/ml Urine 0.12/0.39 ng/ml	Children/mothers Blood 57/6 Urine 13/0	Wilhelm et al. (2005)

Table 4 (contd)

Country (year)	*n*	Analytical sample size	Sample preparation	Technique	LOD/LOQ	Mean concentration (range)	*n* <LOQ or <LOQ	Reference
Egypt	Blood and urine: 93 Hair: 93 Nails: 68	1 ml (blood and urine) 500 mg (hair and nail)	Oxidation with $KMnO_4$	ETAAS	Blood 0.23/0.59 ng/ml Urine 0.32/0.68 ng/ml Hair 0.015/0.031 µg/g Nails 0.018/0.037 µg/g	Blood 2.07 ng/ml Urine 1.93 ng/ml Hair 0.35 µg/g Nails 1.35 µg/g	—	Mortada et al. (2002)
Italy (2004)	110	10 ml	Wet digestion (HNO_3)	ICP-MS	—	0.99 ng/ml	—	Alimonti et al. (2005)
Sweden	31	1 ml	Microwave digestion	ICP-MS	0.03 ng/ml (LOD)	0.116 ng/ml (<0.03–0.317 ng/ml)	6	Rodushkin, Ödman & Branth (1999)
Belgium (2003)	1679 adolescents	500 µl	Wet digestion (HNO_3 + H_2O_2)	HR-ICP-MS	0.09 ng/ml (LOD)	Median 0.39 (0.045–1.26 ng/ml)	—	Schroijen et al. (2008)
Germany (2005)	130	500 µl	Dilution (Triton X-100 + NH_4OH)	DRC-ICP-MS	0.1 ng/ml (LOQ)	0.57 ng/ml (0.1–4.1 ng/ml)	—	Heitland & Köster (2006)
—	—	1 ml	Microwave-assisted acid digestion	SF-ICP-MS	Blood: 0.03 ng/ml (LOD) Urine: 0.007 ng/ml (LOD)	—	—	Bocca et al. (2005)

HR-ICP-MS, high-resolution inductively coupled plasma mass spectrometry; LOQ, limit of quantification; *n*, number of samples analysed; ND, not detected; SF-ICP-MS, sector field inductively coupled plasma mass spectrometry; ZF-AAS, Zeeman furnace atomic absorption spectrometry

Heitland & Köster (2006) evaluated 37 trace metals, including cadmium, in blood of 130 people (ranging in age from 18 to 70 years) living in northern Germany who were assumed to be unexposed to cadmium from environmental sources. Samples were collected in 2005, and trace metals in blood were determined by DRC-ICP-MS. External quality assurance was performed by participation in three national and international quality assessment schemes to ensure the accuracy and reliability of the data. The mean cadmium level in blood was found to be 0.57 ng/ml.

4. SAMPLING PROTOCOLS

Guidelines on sampling of various foods are described in the Codex Alimentarius Commission guidelines CAC/GL 50-2004 (FAO/WHO, 2004).

5. PREVENTION AND CONTROL

Cadmium contamination of food arises mainly from the uptake of cadmium from soil by plants and grass, resulting in increased cadmium levels in food and feeds (UNEP, 2006). Background cadmium levels in surface soils range from 0.01 to 2.7 mg/kg (Kabata-Pendias, 2001). Cadmium levels in soil are given in the reports of the United Nations Environment Programme (e.g. UNEP, 2006, 2008). However, cadmium is much less mobile in soils than in air and water. The major factors governing cadmium mobility in soils are speciation, pH, soluble organic matter content, hydrous metal oxide content, clay content and type, presence of organic and inorganic ligands, and competition from other metal ions. Cadmium in soil tends to be more available when the soil pH is low (OECD, 1994). Elevated concentrations of cadmium in soils (compared with background values) have also been reported following the application of sewage sludge and farmyard manure, which contain variable and occasionally excessive cadmium concentrations (Steineck et al., 1999; Eriksson, 2000; Bergkvist et al., 2003). Fertilizers also play a role in the cadmium content of plants. The European Union suggested a cadmium limit of 46 mg/kg phosphorus in phosphate fertilizers (European Commission, 2001).

Analyses showed that cadmium levels in fruits and vegetables could be up to 9-fold higher than, and in meat and offal twice as high as, in non-contaminated areas. Cadmium levels appear to be higher in samples produced conventionally than in the corresponding organic products. The observed differences varied from 17% in green beans to 90% in lettuce. This observation could be explained by the cadmium impurities in phosphate fertilizers used in conventional production systems (EFSA, 2009a).

Washing of fruits and vegetables and peeling of roots and tubers can reduce cadmium contamination to some extent. There have been worldwide efforts to reduce cadmium exposure, including implementation of MLs for cadmium in foods, food additives and water. Other prevention and control measures include controlling cadmium levels in fertilizers and feeds and following good agricultural and manufacturing practices.

6. LEVELS AND PATTERNS OF CONTAMINATION IN FOOD COMMODITIES

6.1 National and regional occurrence data

The Committee reviewed new cadmium occurrence data submitted by the European Food Safety Authority (EFSA) covering 19 European countries (Austria, Belgium, Bulgaria, Cyprus, Estonia, France, Germany, Greece, Iceland, Ireland, Italy, the Netherlands, Poland, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom); France also submitted data independently of EFSA. Occurrence data were submitted by 10 other countries (Australia, Brazil, Canada, Chile, China, Ghana, Japan, Singapore, the USA and Viet Nam). The food industry submitted data on cadmium levels in products that are distributed and used worldwide.

The majority of data submitted were individual analytical results for a wide range of foods. Aggregated data were also submitted, with the mean and maximum values reported. Most countries analysed samples using validated analytical methods and followed good internal and external quality control programmes to ensure the accuracy and reliability of the data.

As the Committee last conducted a complete assessment on cadmium in 2003, only data from 2003 to the present were included in the present assessment. In addition, data for certain foods that could not be linked to a specific commodity (e.g. multi-ingredient foods, infant formula, dietary supplements) were excluded from the assessment.

The total number of samples represented by the data submissions was 155 496, with 84.4% coming from Europe, 5.2% from North America, 1.5% from Asia, 1.4% from Latin America, 0.3% from the Pacific region and 0.1% from Africa (Table 5). The data submitted by industry accounted for 7.0% of the data.

In order to summarize and compare all submitted data, it was necessary to group the data by food category. As there were no common food codings or food descriptors used among all data sets, the following food categories were used to summarize the data and have been used throughout this section when presenting and discussing the data:

- Wheat (including breads)
- Rice
- Oats
- Baked goods
- Cereals/grains, other
- Roots & tubers
- Pulses & legumes
- Fruits
- Dried fruit
- Fruit juices
- Vegetables

Table 5. Distribution of new cadmium occurrence data by region

Region	Country	Total no. of samples	Samples with no detectable levels of cadmium (ND)[a]		% of samples by region
			No. of samples	% of total	
Asia	China	1 491	569	38.2	1.5
	Japan	67	0	0.0	
	Singapore	482	208	43.2	
	Viet Nam	317	0	0.0	
	Subtotal	*2 357*	*777*	*33.0*	
Europe	Combined data from 19 European countries[b]	131 167	44 133	33.6	84.4
Latin America	Brazil	2 241	2 067	92.2	1.4
	Chile	9	0	0.0	
	Subtotal	*2 250*	*2 067*	*91.9*	
North America	Canada	706	0	0.0	5.2
	USA	7 411	3 064	41.3	
	Subtotal	*8 117*	*3 064*	*37.7*	
Pacific region	Australia	532	190	35.7	0.3
Africa	Ghana	144	132	91.7	0.1
Food industry	—	10 929	4 418	40.4	7.0
	Total	*155 496*	*54 781*	*35.2*	*100*

ND, non-detects
[a] Samples with results below the LOD, LOQ or level of reporting (LOR).
[b] Submitted by EFSA.

- Vegetables, dried
- Meat & poultry muscle, not further specified (NFS)
- Meat & poultry offal, NFS
- Meat muscle
- Meat kidney
- Meat liver
- Meat offal, NFS
- Poultry muscle
- Poultry liver
- Poultry kidney
- Poultry offal, NFS
- Eggs

- Fish & seafood, NFS
- Finfish
- Shellfish/molluscs
- Dairy products
- Nuts & oilseeds
- Vegetable oils & fats
- Animal fats
- Coffee, tea & cocoa
- Sugar, honey & sweets
- Spices
- Alcoholic beverages
- Drinking-water (bottled & tap)

It was not always possible to determine the form (e.g. fresh versus dried) of the foods that were analysed, so in some cases both fresh and dried products may have been included in the same food category. Additionally, specific foods within a food category are known to contain higher levels of cadmium than most other foods in the category (e.g. horse meat compared with other meat muscle). Both cases could account for an unusually high maximum concentration of cadmium reported within a food category when compared with the mean concentration.

The data from each country or region that were included in the assessment are described below and are summarized in Table 6. Unless otherwise specified, mean values were calculated, assuming a value of zero for samples with results below the LOD, level of quantification (LOQ) or level of reporting (LOR) (i.e. non-detects or ND). In the case of aggregated data, weighted means were calculated based on sample size.

6.1.1 Australia

Food Standards Australia New Zealand submitted data collected in the 23rd Australian Total Diet Study (TDS) conducted in 2008–2009. Individual analytical results for a total of 532 samples covering all food categories were used in the assessment. The LOR for Australian TDS samples was 0.005 mg/kg. The highest mean cadmium levels were found in roots and tubers (0.033 mg/kg) and nuts and oilseeds (0.019 mg/kg).

6.1.2 Brazil

Brazil provided data on cadmium levels in kidney and muscle of meat and poultry samples collected from 2003 to 2009. Aggregated results representing 2241 samples were provided for meat muscle, meat kidney, poultry muscle and poultry kidney; weighted means were calculated for each of the four categories. The LOD was 0.005 mg/kg, and the LOQ was 0.01 mg/kg. Mean cadmium concentrations were higher in kidney (0.012–0.025 mg/kg) than in muscle (0.003 mg/kg), although the maximum cadmium level (0.286 mg/kg) was found in one sample of meat muscle.

Table 6. Cadmium occurrence data by data source

Data source	Food category	No. of samples	No. of non-detects	Mean concentration (mg/kg) (ND = 0)[a]	Maximum concentration (mg/kg)
Australia					
	Wheat (including breads)	16	2	0.009	0.025
	Rice	4	2	0.004	0.009
	Oats	4	0	0.004	0.005
	Baked goods	20	3	0.012	0.032
	Cereals/grains, other	24	1	0.013	0.044
	Roots & tubers	12	0	0.033	0.087
	Pulses & legumes	4	0	0.004	0.006
	Fruits	80	48	0.006	0.051
	Dried fruit	12	1	0.009	0.030
	Fruit juices	12	2	0.001	0.002
	Vegetables	118	12	0.006	0.046
	Meat muscle	44	19	0.002	0.010
	Poultry muscle	20	18	0.000 2	0.003
	Poultry liver	4	0	0.006	0.010
	Eggs	10	8	0.000 3	0.002
	Finfish	18	1	0.006	0.015
	Shellfish/molluscs	8	0	0.014	0.070
	Dairy products	42	30	0.004	0.105
	Nuts & oilseeds	8	1	0.019	0.037
	Animal fats	4	4	ND	ND
	Vegetable oils & fats	8	8	ND	ND
	Coffee, tea & cocoa	12	10	0.000 1	0.001
	Sugar, honey & sweets	8	7	0.000 1	0.001
	Spices	8	0	0.006	0.009
	Alcoholic beverages	20	5	0.002	0.007
	Drinking-water (bottled & tap)	12	8	0.000 09	0.000 5
	Total number	532	190		

Table 6 (contd)

Data source	Food category	No. of samples	No. of non-detects	Mean concentration (mg/kg) (ND = 0)[a]	Maximum concentration (mg/kg)
Brazil					
	Meat muscle	476	438	0.003	0.286
	Meat kidney	118	85	0.025	0.271
	Poultry muscle	1 503	1 418	0.003	0.228
	Poultry kidney	144	126	0.012	0.285
	Total number	2 241	2 067		
Canada					
	Shellfish/ molluscs	706	0	4.820	94.65
Chile					
	Shellfish/ molluscs	9	0	0.949	1.364
China (TDS)					
	Cereals/grains	12	0	0.010	0.068
	Roots & tubers	12	0	0.006	0.024
	Pulses & legumes	12	0	0.016	0.100
	Fruits	12	1	0.001	0.007
	Vegetables	12	0	0.010	0.033
	Meat & poultry, NFS	12	0	0.042	0.249
	Eggs	12	0	0.002	0.011
	Fish & seafood, NFS	12	1	0.077	0.414
	Dairy products	12	12	ND	ND
	Sugar	12	12	ND	ND
	Alcoholic beverages	12	10	0.000 4	0.000 2
	Beverages & water	12	12	ND	ND
	Total number	144	48		

Table 6 (contd)

Data source	Food category	No. of samples	No. of non-detects	Mean concentration (mg/kg) (ND = 0)[a]	Maximum concentration (mg/kg)
China (monitoring data)					
	Fruits	1 109	485	0.006	0.270
	Vegetables	223	36	0.019	0.210
	Molluscs	15 mean values	NA	0.599 (average of means)	NA
	Total number	1 347	521		
EFSA (covering 19 European countries)[a]					
	Cereals and cereal products	12 179	1 705	0.023	0.220
	Starchy roots or potatoes	2 135	320	0.021	0.142
	Vegetables, nuts and pulses	16 335	3 430	0.067	2.709
	Fruits	4 300	2 408	0.004	0.050
	Fruit & vegetable juices, fruit juice drinks (excluding bottled water)	2 920	1 531	0.003	0.090
	Meat and meat products and substitutes (including poultry)	20 142	11 280	0.017	8.746
	Edible offal & offal products (meat and poultry)	16 049	1 765	0.206	34.50
	Eggs	667	320	0.003	0.018
	Seafood & seafood products	5 780	1 040	0.215	4.525
	Fish & fish products	10 172	4 781	0.023	0.660
	Milk- & dairy-based products	7 305	3 433	0.005	0.097
	Fats (vegetable & animal)	1 064	149	0.006	0.104
	Coffee, tea & cocoa	2 115	254	0.074	2.075
	Sugar & sugar products including chocolate	3 810	1 410	0.031	0.470
	Spices	1 336	214	0.062	0.612
	Alcoholic beverages	3 410	1 944	0.002	0.250
	Water, tap	19 000	6 460	0.000 4	0.010
	Bottled water	2 448	1 689	0.000 4	0.003 0
	Total number	131 167	44 133		

Table 6 (contd)

Data source	Food category	No. of samples	No. of non-detects	Mean concentration (mg/kg) (ND = 0)[a]	Maximum concentration (mg/kg)
France					
	Wheat (including breads)	36	2	0.051	0.170
	Rice	30	18	0.010	0.043
	Cereals/grains, other	62	10	0.085	1.260
	Roots & tubers	74	10	0.029	0.560
	Pulses & legumes	28	23	0.008	0.115
	Fruits	1 178	1 047	0.005	3.000
	Dried fruit	27	16	0.003	0.019
	Fruit juices	8	8	ND	ND
	Vegetables	1 279	181	0.203	6.130
	Vegetables, dried	5	0	1.952	7.500
	Meat muscle	6 875	5 245	0.061	40.02
	Meat liver	2 960	328	0.099	40.02
	Meat offal, NFS	1 324	1 035	1.086	47.66
	Poultry muscle	1 149	122	0.005	2.620
	Poultry offal	1 070	255	0.069	10.13
	Finfish	834	681	0.010	1.655
	Shellfish	61	14	0.390	12.27
	Molluscs	357	15	0.467	6.480
	Dairy products	3	3	ND	ND
	Nuts & oilseeds	168	57	0.083	0.740
	Vegetable oils & fats	16	13	0.007	0.055
	Coffee, tea & cocoa	107	6	0.492	5.239
	Sugar, honey & sweets	3	2	0.002	0.005
	Spices	141	18	0.046	0.500
	Alcoholic beverages	104	76	0.0002	0.002
	Drinking-water (bottled & tap)	40	40	ND	ND
	Total number	17 939	9 225		
Ghana					
	Finfish	144	132	0.000 02	0.000 2

Table 6 (contd)

Data source	Food category	No. of samples	No. of non-detects	Mean concentration (mg/kg) (ND = 0)[a]	Maximum concentration (mg/kg)
Japan					
	Shellfish/molluscs	67	0	0.346	1.400
Singapore					
	Baked goods	8	8	ND	ND
	Cereals/grains, other	2	2	ND	ND
	Fruit juices	2	2	ND	ND
	Vegetables	28	24	0.015	0.130
	Vegetables, dried	228	35	0.986	14.87
	Shellfish/molluscs	17	1	0.288	0.790
	Finfish	1	1	ND	ND
	Nuts & oilseeds	9	2	0.086	0.430
	Vegetable oils & fats	27	27	ND	ND
	Coffee, tea & cocoa	74	30	0.149	0.490
	Sugar, honey & sweets	58	58	ND	ND
	Spices	27	17	0.024	0.130
	Alcoholic beverages	1	1	ND	ND
	Total number	482	208		
USA (USFDA TDS)					
	Wheat (including breads)	160	1	0.021	0.047
	Rice	20	0	0.007	0.014
	Oats	20	1	0.003	0.004
	Cereals/grains, other	40	20	0.008	0.029
	Roots & tubers	100	2	0.015	0.058
	Pulses & legumes	60	4	0.003	0.010
	Fruits	360	167	0.003	0.054
	Dried fruit	20	16	0.001	0.006
	Fruit juices	166	106	0.001	0.008
	Vegetables	640	69	0.018	0.420
	Meat muscle	200	183	0.000 3	0.011
	Meat liver	20	0	0.060	0.171

Table 6 (contd)

Data source	Food category	No. of samples	No. of non-detects	Mean concentration (mg/kg) (ND = 0)[a]	Maximum concentration (mg/kg)
	Poultry muscle	60	52	0.000 4	0.006
	Eggs	40	38	0.000 1	0.003
	Finfish	60	32	0.005	0.029
	Shellfish/molluscs	20	6	0.005	0.026
	Dairy products	140	134	0.000 2	0.005
	Nuts & oilseeds	80	12	0.131	0.874
	Animal fats	20	17	0.001	0.006
	Vegetable oils & fats	40	39	0.000 1	0.004
	Coffee, tea & cocoa	20	19	0.000 1	0.001
	Sugar, honey & sweets	20	19	0.002	0.042
	Total number	2 306	937		
USA (USFDA monitoring data)					
	Rice	6	0	0.021	0.047
	Baked goods	27	2	0.020	0.040
	Cereals/grains, other	9	3	0.025	0.058
	Roots & tubers	1	1	ND	ND
	Pulses & legumes	5	3	0.000 8	0.003
	Fruits	84	57	0.002	0.023
	Dried fruit	47	31	0.004	0.070
	Fruit juice	36	28	0.001	0.011
	Vegetables	37	18	0.026	0.360
	Vegetables, dried	2	0	0.085	0.130
	Finfish	124	90	0.006	0.139
	Shellfish	354	8	0.429	3.420
	Molluscs	90	9	0.091	0.799
	Dairy products	117	109	0.000 3	0.009
	Nuts & oilseeds	7	0	0.117	0.508
	Spices	5	0	0.228	0.251
	Total number	951	359		

Table 6 (contd)

Data source	Food category	No. of samples	No. of non-detects	Mean concentration (mg/kg) (ND = 0)[a]	Maximum concentration (mg/kg)
USA (USDA)					
	Meat muscle	958	941	0.001	0.277
	Meat kidney	961	1	0.498	9.054
	Meat liver	307	0	0.073	0.415
	Poultry muscle	852	823	0.002	0.837
	Poultry kidney	876	3	0.464	11.40
	Poultry liver	200	0	0.176	1.820
	Total number	4 154	1 768		
Viet Nam					
	Molluscs	317	0	0.487	0.980
Industry (ingredients used worldwide)					
	Wheat (including breads)	1 327	146	0.035	0.390
	Rice	2 265	426	0.023	0.510
	Cereals/grains, other	371	179	0.010	0.120
	Oats	187	34	0.016	0.096
	Roots & tubers	59	13	0.035	0.160
	Pulses & legumes	88	38	0.030	0.220
	Fruits	369	263	0.007	0.380
	Fruit juices	796	713	0.002	0.085
	Vegetables	790	118	0.095	1.800
	Vegetables, dried	118	16	0.330	2.400
	Meat muscle	37	30	0.002	0.024
	Poultry muscle	65	51	0.010	0.150
	Eggs	7	5	0.007	0.030
	Molluscs	7	0	4.213	22
	Shellfish	13	3	0.648	6.000
	Dairy products	1 592	1 403	0.002	0.763
	Nuts & oilseeds	246	68	0.038	0.590

Table 6 (contd)

Data source	Food category	No. of samples	No. of non-detects	Mean concentration (mg/kg) (ND = 0)[a]	Maximum concentration (mg/kg)
	Vegetable oils & fats	447	409	0.002	0.031
	Coffee, tea & cocoa	1 284	196	1.750	1327
	Spices	861	307	0.106	1.400
	Total number	10 929	4 418		

NA, not available; ND, non-detects

[a] In calculation of mean cadmium concentration, cadmium concentration set at 0 mg/kg for non-detects, except for EFSA results, in which cadmium concentration set at LOD/2 or LOQ/2 for non-detects.

6.1.3 Canada

Aggregated data on cadmium levels in wild and farmed molluscs (scallops) were submitted by Canada. A weighted mean cadmium level of 4.82 mg/kg was calculated from the 43 aggregated results representing 706 samples collected in 2003–2004. The maximum cadmium level was 94.65 mg/kg. Neither the LOD nor the LOQ was specified.

6.1.4 Chile

Chile submitted one aggregated mean value representing nine samples of mussels collected in 2008. The mean cadmium level was found to be 0.949 mg/kg, and the maximum value was 1.364 mg/kg. The LOQ was 0.01 mg/kg.

6.1.5 China

Data from three different sources were provided by China.

Results from the 2007 Chinese TDS included cadmium levels in 12 food group composites collected from 12 provinces; the national average cadmium levels and maximum values reported are provided in Table 6. The highest mean cadmium levels were found in fish and seafood (0.077 mg/kg) and in meat and poultry (0.042). The highest maximum values were reported for fish and seafood (0.414 mg/kg) and meat and poultry (0.249 mg/kg). The LOD was 0.0005 mg/kg.

Individual results were also submitted by China for 1332 samples of fruits and vegetables collected in 2004–2005. Mean cadmium levels were 0.006 mg/kg in fruits and 0.019 mg/kg in vegetables. The highest cadmium level (0.270 mg/kg) was found in one sample of fruit. Neither the LOD nor the LOQ was specified.

Aggregated data were submitted on 15 samples of molluscs collected in China in 2003–2007; as sample sizes were not provided for all results, only the average of the aggregated means (0.599 mg/kg) is presented in Table 6. The LODs and LOQs were not reported.

6.1.6 Europe

EFSA recently completed an assessment on cadmium in the food-chain, including the risks to humans from dietary exposure to cadmium (EFSA, 2009a). The work was carried out by the Scientific Panel on Contaminants in the Food Chain at the request of the European Commission. For the EFSA assessment, cadmium data on about 140 000 samples, including a wide range of foods covering the period from 2003 to 2007, were submitted by 19 European countries (Austria, Belgium, Bulgaria, Cyprus, Estonia, France, Germany, Greece, Iceland, Ireland, Italy, the Netherlands, Poland, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom). EFSA grouped the data into 15 major food categories and in some cases subcategories that were directly related to the consumption data (EFSA's Concise European Food Consumption Database) used to estimate dietary exposure (EFSA, 2008). The EFSA food categories that were included in this assessment, as reported in Table 6, were similar but not identical to the categorization scheme used for the current assessment by the Committee. Results for foods that did not match the food categories used for the current assessment (i.e. foods for special dietary use, supplements and meat- and fish-based preparations) were excluded; the total number of samples from EFSA as reflected in Table 6 is 131 167.

EFSA submitted to the Committee both the final report of its assessment and the individual cadmium occurrence data used in the assessment. As EFSA had undertaken a very detailed analysis and aggregation of the occurrence data for its assessment, the Committee agreed that the summary results from the EFSA report would be used in the present assessment rather than the individual occurrence data. In the EFSA report, two mean cadmium values were reported for each food category. The first value was calculated as the mean of combined occurrence data from all countries, assuming one half the LOD or LOQ for results below the LOD/LOQ; these values are reported in Table 6. It should be noted, however, that in its estimation of dietary exposure, EFSA weighted these mean values by applying the sampling adjustment factor that corrected for the unbalanced proportion of samples analysed in food categories in relation to their relative consumption amounts. The weighted means are not reported here but are available in the EFSA report. Highest mean cadmium levels were found in meat and poultry offal (0.206 mg/kg) and in seafood and seafood products (0.215 mg/kg). Individual foods with the highest cadmium concentrations included fungi (2.71 mg/kg), horse meat (8.75 mg/kg) and offal, not further specified (34.50 mg/kg).

6.1.7 France

Individual results for samples collected between 2003 and 2007 were submitted by the French Food Safety Agency. The samples included a wide range of foods collected by the General Directorate for Competition, Policy, Consumer Affairs and Fraud Control and the General Directorate for Food. Meat and poultry

products make up the majority of samples. LODs ranged from 0.0002 to 0.01 mg/kg. In all, results for 17 939 samples were included in the current assessment. The highest mean cadmium levels were found in meat offal (1.086 mg/kg) and dried vegetables (1.952 mg/kg). The maximum cadmium value of 47.60 mg/kg was found in meat offal.

The majority of cadmium occurrence data submitted by France were also included in the EFSA cadmium assessment and are reflected in the EFSA data summary. Although the data submitted by France are presented separately in Table 6, to avoid double-counting of data, they have not been included in the total count of sample results submitted for the present assessment (Table 5) or in the summary of data by food category (see Table 7 below).

6.1.8 Ghana

Data on cadmium levels in two species of marine finfish in Ghana were submitted for the present assessment. A total of 144 samples of fish were collected in 2008–2009. Of those, only 12 samples had detectable levels of cadmium (LOD = 0.002 mg/kg); the mean cadmium level overall was 0.000 02 mg/kg.

6.1.9 Japan

Aggregated data on cadmium levels in molluscs were submitted by the Environmental Science Research Laboratory in Japan. The data represented 67 samples of molluscs collected from 2004 to 2007. The weighted mean level was found to be 0.346 mg/kg, with a maximum cadmium level reported to be 1.4 mg/kg.

6.1.10 Singapore

Cadmium data on a range of foods were provided by Singapore. A total of 482 individual results were submitted for samples collected in 2008. The majority (228) of samples were dried vegetables; these foods also had the highest cadmium levels, with a mean of 0.986 mg/kg and a maximum value of 14.87 mg/kg. Other foods that contained relatively high cadmium levels were shellfish/molluscs (mean of 0.288 mg/kg) and coffee, tea and cocoa (mean of 0.149 mg/kg). The LOD was 0.04 mg/kg.

6.1.11 USA

Three different sources of individual data were provided by the USA. The United States Food and Drug Administration (USFDA) provided 2306 results from samples collected in its TDSs between 2004 and 2008. LODs ranged from 0.001 to 0.004 mg/kg. Nuts and oilseeds were found to have the highest cadmium levels (mean of 0.131 mg/kg and maximum of 0.874 mg/kg). Meat liver had a mean cadmium concentration of 0.06 mg/kg. All other foods had mean concentrations of 0.021 mg/kg or less.

Cadmium results from other USFDA monitoring programmes were also submitted; these included 951 results from samples collected from 2003 to 2006. Nine food categories were represented, although finfish and shellfish comprise the

majority of samples. LODs or LOQs were not reported. Nuts and oilseeds, spices and shellfish had the highest mean cadmium levels (0.117, 0.228 and 0.429 mg/kg, respectively).

The United States Department of Agriculture (USDA) submitted a total of 4154 results for three subcategories (muscle, liver and kidney) of meat and poultry tissue. The samples were collected from 2003 through 2008. Kidney and liver tissues were found to contain higher mean cadmium levels than muscle. Highest levels were found in meat kidney (mean of 0.498 mg/kg and maximum of 9.054 mg/kg) and poultry kidney (mean of 0.464 mg/kg and maximum of 11.40 mg/kg).

6.1.12 Viet Nam

Aggregated data on cadmium levels in oysters and clams from samples collected in 2007 were submitted by Viet Nam. The weighted mean of all samples was found to be 0.487 mg/kg. The maximum level found was 0.980 mg/kg. Neither the LOD nor the LOQ was specified.

6.1.13 Food industry

Aggregated data on raw materials used worldwide were submitted by the food industry. The samples were collected between 2002 and 2009; it was not possible to separate the data by sampling year, so results prior to 2003 are included in the data summaries. Overall, the data represented analytical results of 10 929 samples. Weighted mean cadmium levels were calculated for all food categories. Highest mean levels were found in molluscs (4.213 mg/kg) and in coffee, tea and cocoa (particularly the latter) (1.75 mg/kg). LODs and LOQs were not reported.

6.2 Cadmium occurrence data by food category

Cadmium occurrence data submitted for this meeting are summarized by food category in Table 7. For each food category, the total number of samples and the number of countries or region (i.e. Europe or industry) represented by the data are reported. As noted above, because the data for Europe that were submitted by EFSA included data from France, the data submitted separately by France have not been included in Table 7. The range of national or regional mean cadmium concentrations is reported, as well as the current Codex MLs that have been established for commodities within the food category.

For all food categories, calculations of mean concentrations included results below the LOD or LOQ (i.e. non-detects). EFSA assumed a value of one half the LOD or LOQ when calculating mean concentrations; mean cadmium levels for other countries were calculated assuming a concentration of 0 mg/kg for non-detects.

National mean concentrations of cadmium ranged between not detected (ND) and 0.04 mg/kg in most food categories. Higher national mean concentrations, ranging from 0.1 to 4.8 mg/kg, were reported for vegetables (including dried); meat and poultry offal; shellfish/molluscs; nuts and oilseeds; coffee, tea and cocoa; and spices.

Table 7. Cadmium occurrence data summarized by food category

Food category	Total no. of samples	No. of countries/region contributing data	Range of national or regional mean cadmium concentrations (mg/kg)	Codex MLs (mg/kg)
Wheat (including breads)	1 503	3	0.009–0.04	0.2
Rice	2 295	3	0.004–0.02	0.4
Oats	211	3	0.003–0.02	0.1
Baked goods	55	3	ND–0.02	—
Cereals/grains, other	12 637	6	ND–0.02	0.1
Roots & tubers	2 319	5	0.006–0.04	0.1
Pulses & legumes	169	4	0.003–0.03	0.1 (pulses)
Fruits	6 314	5	0.001–0.007	—
Fruit juices	3 932	5	ND–0.003	—
Dried fruit	79	2	0.003–0.009	—
Vegetables	18 183	6	0.006–0.1	0.05–0.2[a]
Dried vegetables	348	3	0.09–1.0	—
Meat and poultry, NFS	20 154	2	0.008–0.04	—
Meat and poultry offal, NFS	16 049	1	0.1	—
Meat muscle	1 715	4	0.001–0.003	—
Meat offal	1 406	3	0.03–0.5	—
Poultry muscle	2 500	4	0.0002–0.01	—
Poultry offal	1 224	3	0.006–0.5	—
Eggs	736	5	0.0001–0.007	—
Finfish	10 531	6	ND–0.008	—
Shellfish/molluscs	7 403	10	0.01–4.8	2[b]
Dairy products	9 208	5	ND–0.004	—
Nuts & oilseeds	350	4	0.02–0.1	—
Animal & vegetable fats	1 610	5	ND–0.006	—
Coffee, tea & cocoa	3 505	5	0.0001–1.8	—
Sugar, honey & sweets	3 908	5	ND–0.03	—
Spices	2 237	5	0.006–0.2	—

Table 7 (contd)

Food category	Total no. of samples	No. of countries/region contributing data	Range of national or regional mean cadmium concentrations (mg/kg)	Codex MLs (mg/kg)
Alcoholic beverages	3 443	4	ND–0.004	—
Drinking-water (bottled & tap)	21 472	3	ND–0.0004	0.003 (natural mineral water)
Total no. of samples	155 496			

ND, not detected

[a] MLs for vegetables: 0.05 mg/kg for brassica, bulb and fruiting vegetables, excluding tomatoes and fungi; 0.1 mg/kg for stalk, stem and legume vegetables; and 0.2 mg/kg for leafy vegetables.

[b] ML for cephalopods and bivalves, excluding scallops and oysters.

7. FOOD CONSUMPTION AND DIETARY EXPOSURE ESTIMATES

7.1 National and regional estimates of dietary exposure

New information on national estimates of dietary exposure to cadmium was submitted by Australia, China, Japan and the USA. EFSA submitted dietary exposure estimates for Europe. Additional information on national dietary exposure for Chile, Lebanon and the Republic of Korea was obtained from the scientific literature. National and regional exposure estimates were expressed on either a daily or weekly basis, as these estimates are based on 1- to 7-day food consumption surveys. During the meeting, the Committee concluded that a provisional tolerable monthly intake (PTMI) was appropriate for cadmium (see section 10). For contaminants such as cadmium that are widely distributed in foods at approximately constant levels, day-to-day variability in dietary exposure over the long term would be low, so extrapolating dietary exposure from a daily or weekly basis to a monthly basis would not have a substantial impact on exposure estimates. Therefore, the national and regional exposure estimates as reported below were extrapolated to a monthly basis by multiplying daily exposures by 30 or weekly exposures by 4.

7.1.1 Australia

Food Standards Australia New Zealand has conducted two recent TDSs that included assessments of cadmium in foods: the 20th Australian TDS in 2000–2001 and the 23rd Australian TDS in 2008–2009. Analytical results from the 23rd Australian TDS were described and summarized in the previous section of this report. As dietary exposure estimates from the most recent TDS have not yet been completed, those from the 20th TDS (2000–2001) are presented in Table 8.

Table 8. Dietary exposure to cadmium in Australia (2000–2001)

Population subgroup	Average body weight (kg)	Exposure (µg/kg bw per month)	
		Lower bound (ND = 0)	Upper bound (ND = LOR)
Infants 9 months	9.2	3.9	20.4
Toddlers 2 years	14	5.4	17.1
Boys 12 years	49	3.3	8.7
Girls 12 years	52	2.7	6.6
Adult males 25–34 years	82	2.4	7.2
Adult females 25–34 years	66	2.1	6.6

Lower- and upper-bound estimates of exposure were calculated for six population subgroups. Both estimates were based on mean food consumption data from the 1995 Australian National Nutrition Survey. The lower-bound estimates were based on median cadmium concentrations in foods, assuming that results below the LOR were equal to zero, whereas upper-bound estimates assumed that results below the LOR were equal to the LOR. Table 8 summarizes the range of exposure estimates per kilogram of body weight per month. Estimates of exposures for infants and toddlers range (from lower to upper bound) from 3.9 to 20.4 µg/kg bw per month. Exposures for boys and girls 12 years of age range from 2.7 to 8.7 µg/kg bw per month, whereas those for adults range from 2.1 to 7.2 µg/kg bw per month. No information was provided regarding contributions of specific food categories to overall exposure.

7.1.2 China

China completed its most recent TDS in 2007, from which the mean cadmium concentrations in 12 food group composites from 12 geographic regions (provinces) were reported above (Table 6). Dietary exposures were estimated from these cadmium occurrence data, but assuming a value of one half the LOD for non-detects rather than zero, as reported in Table 6.

Estimated regional cadmium exposures ranged from 0.5 µg/kg bw per month in Ningxia province to 36.5 µg/kg bw per month in Sichuan province (Table 9). The national average cadmium exposure was estimated to be 9.9 µg/kg bw per month.

Based on the national average estimate of exposure, the food categories that contributed most to cadmium exposure were cereals/grains (32%) and vegetables (25%). For Sichuan province, which had the highest cadmium exposure, cereals accounted for 85% of the total exposure; the cadmium level in the cereals composite sample from this province was 0.067 mg/kg, which is about 6 times the national mean concentration in cereals.

Table 9. Dietary exposure to cadmium in China (2007)

Province	Mean exposure (µg/kg bw per month)[a]	Major sources of exposure (% of total exposure)
Heilongjiang	6.8	Meat (93%)
Liaoning	5.2	Seafood (88%)
Hebei	2.6	Legumes (36%) + seafood (34%)
Shanxi	1.2	Vegetables (62%)
Henan	2.7	Cereals (50%) + vegetables (45%)
Ningxia	0.5	Cereals (39%) + potatoes (23%)
Shanghai	4.7	Vegetables (69%)
Fujian	14.7	Cereals (40%) + vegetables (37%)
Jiangxi	22.4	Cereals (92%)
Hubei	9.7	Meat (53%) + vegetables (41%)
Sichuan	36.5	Cereals (85%)
Guangxi	10.3	Cereals (37%) + legumes (24%)
National average	9.9	Cereals (32%) + vegetables (25%)

[a] Based on mean cadmium concentration (ND = LOD/2) and body weight of 63 kg.

Although cereals were the main source of dietary exposure to cadmium in most provinces, vegetables, meat and seafood were significant sources in several provinces. Vegetables accounted for 62% and 69% of total cadmium exposure in Shanxi and Shanghai provinces, respectively. Meat was the major source of cadmium in the diet in Heilongjiang and Hubei provinces. Seafood contributed 88% of the total dietary cadmium in Liaoning province.

7.1.3 Europe

Dietary exposure estimates for Europe were calculated for the recent EFSA assessment on cadmium in foods (EFSA, 2009a). The cadmium occurrence data summarized in Table 6 were used in the exposure estimates, after applying the sampling adjustment factor to the mean cadmium concentrations to correct for the unbalanced proportion of samples analysed in food categories in relation to their relative consumption amounts.

Several food consumption databases were used in order to estimate exposure for different population subgroups: the EFSA Concise European Food Consumption Database (EFSA, 2008), French data on food consumption by ovolactovegetarians and Italian data on food consumption by children.

The EFSA Concise European Food Consumption Database was compiled from data provided by 16 European countries on food consumption by adults. (Note that the countries that provided the cadmium occurrence data summarized in Table 6 are not necessarily the same countries represented in the consumption database.) The EFSA database includes mean consumption estimates for each of 15 broad food categories for each of the 16 countries. The cadmium occurrence data submitted for the EFSA assessment were aggregated to these same food categories so that the consumption and occurrence data could be linked. Dietary exposure was estimated by multiplying mean consumption per food category for each country by the adjusted (weighted) mean cadmium concentration for each food category. A body weight of 60 kg was used as the default for all countries when converting exposure estimated from a per person basis to exposure per kilogram of body weight.

Mean exposure for adults ranged from 7.6 µg/kg bw per month (Bulgaria) to 11.8 µg/kg bw per month (Germany), with an estimated median European exposure of 9.1 µg/kg bw per month (Table 10). As the same mean cadmium concentrations per food category were used in all calculations, differences in exposure estimates reflect variability in national consumption patterns only.

National estimates of high exposures were also estimated for the adult population based on the EFSA Concise European Food Consumption Database by summing the 95th percentile exposures (consumers only) from the two food categories contributing most to exposure and the mean exposure (whole population) for other food categories. High exposure estimates ranged from 10.2 µg/kg bw per month (Finland) to 15.6 µg/kg bw per month (Slovakia), with an overall European estimate of 12.1 µg/kg bw per month.

Regarding cadmium exposures for certain subpopulations, food consumption data from Italy were used to estimate exposure for children. Exposure for children 0.5–12 years of age was estimated to be 11.9 and 22.0 µg/kg bw per month at the mean and 95th percentile, respectively. For estimating dietary exposure for vegetarians, detailed French consumption data for ovolactovegetarians were used to represent vegetarians as a whole. From the French consumption data, it was shown that vegetarians consume greater amounts of nuts, oilseeds, pulses and cereals. Average exposure of vegetarians in Europe to cadmium was modelled by using results of exposure estimates for adults but replacing consumption of meat and fish groups with added consumption of nuts and oilseeds. The resulting estimate of average exposure was 21.60 µg/kg bw per month; high exposure was not estimated for this subgroup.

EFSA reported cadmium exposures from specific food categories (Table 11) for adults only. These were estimated by multiplying the median consumption values (consumers only) across the 16 European countries that submitted consumption data by the adjusted mean cadmium occurrence values for each food category. Food categories contributing most to adult exposure to cadmium included cereals and grains; vegetables, nuts and pulses; and edible offal and offal products. As these estimates were based on consumers-only consumption data, they could not be summed to calculate the total exposure or the relative contributions of each food category to total exposure.

Table 10. Dietary exposure to cadmium in Europe (2003–2007)

Country or subpopulation	Exposure (µg/kg bw per month)[a]	
	Mean	High[b]
Adults		
Belgium	9.3	13.1
Bulgaria	7.6	12.5
Czech Republic	9.5	12.3
Denmark	9.0	11.2
Finland	7.8	10.2
France	9.1	12.5
Germany	11.8	14.3
Hungary	8.6	10.9
Iceland	8.3	12.4
Ireland	10.2	13.8
Italy	8.2	10.7
Netherlands	9.0	11.8
Norway	9.2	11.3
Slovakia	9.2	15.6
Sweden	9.3	11.6
United Kingdom	8.6	11.5
Adults, all countries (median)	9.1	12.1
Vegetarians	21.6	NA
Children 0.5–12 years	11.9	22.0[c]

NA, not available

[a] Based on mean European cadmium concentration (ND = LOD/2) (weighted) and mean national food consumption (whole population).

[b] Sum of 95th percentile exposure (consumers only) for the two food categories with highest exposure plus mean exposure (whole population) for the other food categories.

[c] 95th percentile.

Table 11. Main sources of dietary exposure for adults in Europe

Food category	Mean cadmium occurrence[a] (mg/kg)	Median consumption[b] (consumers only) (g/day)	Cadmium exposure (consumers only) (µg/day)
Cereals/grains	0.016	257	4.2
Vegetables, nuts, pulses	0.019	194	3.7
Meat + offal combined	0.017	151	2.5
Offal only	0.126	24	3.0
Meat	0.008	132	1.0
Starchy vegetables/roots	0.021	129	2.7
Alcoholic beverages	0.004	413	1.7
Fish and seafood	0.027	62	1.7
Sugars	0.026	43	1.1
Milk and dairy products	0.004	287	1.1
Coffee, tea, cocoa	0.002	601	1.1
Juices, soft drinks, bottled water	0.001	439	0.4
Miscellaneous foods	0.024	14	0.3
Fats (vegetable + animal)	0.006	38	0.2
Tap water	0.000	349	0.1
Eggs	0.003	25	0.08

[a] Mean (ND = LOD/2) (adjusted).
[b] Median of national estimates, consumers only.

7.1.4 USA

The USFDA conducts its TDS continuously, and foods are routinely analysed for cadmium. Cadmium levels in samples collected between 2004 and 2008 (Table 6) and consumption data from the 2003–2006 NHANES were used to estimate dietary exposure. Monte Carlo simulations were run for 14 population subgroups using the full distribution of both consumption and cadmium occurrence data; for the latter, all samples with results below the LOD were assigned a value of zero.

Estimates of mean and 90th percentile exposures are reported in Table 12. Infants and children 2 years and 6 years of age had the highest cadmium exposures, with means of 9.4, 12.9 and 10.9 µg/kg bw per month, respectively. Exposures at the 90th percentile were 17.6, 21.5 and 17.1 µg/kg bw per month, respectively.

Mean exposures for teenagers and adults were similar, ranging from 4.1 to 5.5 µg/kg bw per month. Boys 14–16 years of age had the highest 90th percentile exposures, at 10.1 µg/kg bw per month.

Table 12. Dietary exposure to cadmium in the USA (2004–2008)

Population subgroup	Exposure (µg/kg bw per month)[a]	
	Mean	90th percentile
M + F 6–11 months	9.4	17.6
M + F 2 years	12.9	21.5
M + F 6 years	10.9	17.1
M + F 10 years	7.2	12.7
M 14–16 years	5.5	10.1
F 14–16 years	5.3	8.9
M 25–30 years	5.3	9.5
F 25–30 years	4.6	8.6
M 40–45 years	4.7	7.2
F 40–45 years	4.5	8.4
M 60–65 years	4.7	8.9
F 60–65 years	4.3	7.2
M 70+ years	4.1	6.9
F 70+ years	4.5	8.3

F, female; M, male

[a] Based on distributions of cadmium occurrence data (ND = 0) and individual consumption data and self-reported body weights of consumption survey participants.

7.1.5 Estimates of dietary exposure from the published literature

In addition to the dietary exposure estimates that were submitted for the present assessment, information on dietary exposure to cadmium in four countries (Chile, Japan, Lebanon and the Republic of Korea) was obtained from the literature.

Results of a TDS conducted in Chile in 2001–2002 showed an estimated cadmium exposure of 21 µg/day or 0.3 µg/kg bw per day, based on a body weight of 68 kg (Munoz et al., 2005). This was extrapolated for the present assessment to an estimated exposure of 9 µg/kg bw per month. The major sources of cadmium in the diet were fish and shellfish, spices and cereals.

In a study by Matsudo (2007), cadmium exposure in Japan was estimated to be 21.1 µg/person per day, calculated as 0.4 µg/kg bw per day using a body weight of 53 kg. This was extrapolated to 12 µg/kg bw per month.

A TDS was conducted in Lebanon in 2004 in order to estimate dietary exposure of urban adults to heavy metals and radionuclides (Nasreddine et al., 2006). Five market baskets consisting of 77 foods were collected in Beirut, and the foods were prepared “as consumed” before analysis. Cadmium levels in those foods

Table 13. National estimates of dietary exposure to cadmium for adults

Country or region	Treatment of ND occurrence data in exposure estimates	Mean exposure (µg/kg bw per month)	High exposure (µg/kg bw per month)
Australia	ND = 0 and ND = LOD	2.2–6.9	—
Chile	Not specified	9	—
China	ND = LOD/2	9.9	—
Europe	ND = LOD/2	9.1[a]	12.1[b]
Japan	Not specified	12	—
Lebanon	ND = LOQ/2	5.2	6.9[c]
Republic of Korea	ND = LOD	7.7	—
USA[d]	ND = 0	4.6	8.1

[a] Median of mean exposure estimates for 16 European countries.
[b] Sum of 95th percentile exposure (consumers only) for the two food categories with highest exposure plus mean exposure (whole population) for the other food categories.
[c] Calculated from mean food consumption and highest cadmium concentrations in each food category.
[d] Calculated from distributions of both food consumption and cadmium occurrence data; high exposure equals 90th percentile of exposure.

were multiplied by national food consumption data, resulting in estimated mean and maximum exposures of 1.2 and 1.6 µg/kg bw per week (or 0.17 and 0.23 µg/kg bw per day), respectively. These were extrapolated to 4.8 and 6.4 µg/kg bw per month. Grains, vegetables and drinking-water were the major sources of cadmium in the diet.

A study in the Republic of Korea reported an estimated cadmium exposure of 14.3 µg/person per day or 0.26 µg/kg bw per day, based on a body weight of 55 kg (Lee et al., 2006). On a monthly basis, this would result in an exposure of 7.7 µg/kg bw. The two major sources of dietary exposure to cadmium were vegetables (especially seaweed) and fish.

7.1.6 Summary of national estimates of dietary exposure to cadmium

In summary, the national estimates of mean cadmium exposure for adults ranged from 2.2 to 12 µg/kg bw per month (Table 13). Estimates of high exposure for adults reported for Europe, Lebanon and the USA were 12.1, 6.9, and 8.1 µg/kg bw per month, respectively.

For Australia, Europe and the USA, mean dietary exposure for children 0.5–12 years of age ranged from 2.7 to 12.9 µg/kg bw per month; the highest exposure for this age group was reported for Europe (22.0 µg/kg bw per month). Dietary exposure for vegetarians, as reported by EFSA, was estimated to be 21.6 µg/kg bw per month. Overall, the food categories that contributed most to cadmium exposure

were cereals/grains, vegetables, meat and poultry offal, and seafood (especially molluscs).

7.2 Regional estimates of dietary exposure

The Codex Alimentarius Commission guidelines for conducting exposure assessments for contaminants in foods (FAO/WHO, 2010) recommend that regional dietary exposure estimates should be calculated using regional average contaminant values and the Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme (GEMS/Food) consumption cluster diets. Such estimates were not calculated for the present meeting because occurrence data were submitted by countries that represented only 2 of the 13 GEMS/Food clusters. Furthermore, national exposure estimates based on national food consumption data were submitted by the countries that also submitted the majority of new occurrence data. As the national estimates provided more refined estimates than could be calculated with the consumption cluster diets, only the national estimates were considered in this assessment.

8. DOSE–RESPONSE ANALYSIS AND ESTIMATION OF CARCINOGENIC/TOXIC RISK

8.1 Biomarker studies

The predominant sites of cadmium accumulation that contribute to body burden are the liver, kidney and several other tissues, but particularly muscle, skin and bone. The highest concentrations are found in the liver and renal cortex. The primary toxic effect resulting from chronic cadmium exposure is impaired tubular reabsorption of filtered solutes. However, the critical concentration of cadmium in the renal cortex that is likely to produce renal dysfunction remains a source of investigation and discussion. Nevertheless, excess urinary excretion of low molecular weight proteins and solutes appears to be associated with reduced tubular reabsorption. It should be noted that low molecular weight proteins (e.g. β2MG, α1MG, RBP and *N*-acetyl-β-D-glucosaminidase) are nonspecific for a given cadmium exposure and may not necessarily be adverse, but may indicate potential renal impairment. Clinically, impaired kidney function is usually apparent through increased levels of protein, amino acids, uric acid, calcium, copper and phosphorus in urine and/or serum. After prolonged cadmium exposure, increased levels of high molecular weight proteins in urine or decreased serum clearance of creatinine are indicative of glomerular dysfunction, which is generally associated with progressive renal damage.

A number of investigators have examined different data sets and cut-off criteria to estimate a safe cadmium body burden as a function of cadmium concentration in urine. BMD analyses of data from populations living in areas in Sweden (Suwazono et al., 2006) or Japan (Uno et al., 2005; Kobayashi et al., 2006) that are not polluted with cadmium or in cadmium-polluted areas in Japan (Shimizu et al., 2006) have been completed. These analyses used urinary cadmium level as a biomarker of cadmium exposure and the prevalence of abnormal levels of β2MG,

α1MG (also known as pHC or protein heterogeneous in charge), total protein, *N*-acetyl-β-D-glucosaminidase, RBP, albumin or GFR as biomarkers of renal tubular effects. As summarized in Table 14, the BMDs for urinary cadmium levels vary widely between the studies, depending on the renal biomarker and the cut-off level used.

8.2 Pivotal data from human clinical/epidemiological studies

To overcome the limitations inherent in a "key study" analysis, EFSA (2009b) undertook a comprehensive systematic literature review (published between January 1966 and October 2008), using Cochrane methodology (see Higgins & Green, 2008), to compile a database for the purpose of deriving a BMD and its 95% confidence lower bound (BMDL) using cut-off points relevant to clinical changes in target organs. Most published studies reported a relationship between urinary cadmium levels and renal biomarkers of cadmium toxicity. The most frequently studied low molecular weight protein biomarker of renal dysfunction was β2MG. The database compiled by EFSA covered approximately 30 000 predominately non-occupationally exposed individuals (99%) reported in 35 studies, but β2MG and cadmium concentrations in urine were expressed only as group means with standard deviations. The majority of the individuals were of Asian descent (93.5%) and female (75%). The age distribution was approximately equally divided around 50 years (i.e. ≥50 years: 51.5%; <50 years: 48.5%). The data for the population aged 50 years and over in the 35 studies were assigned to concentration classes, resulting in 98 groups containing matched pairs of urinary cadmium and β2MG levels. The 98 groups ranged in size from 3 to 908 individuals, with a median of 56.

EFSA (2009b) noted that there were few studies on effects of cadmium on bone; of those, most were considered to be heterogeneous and unsuitable. They also considered associations between cadmium exposure and other non-renal health effects, including diabetes, hypertension, carcinogenicity, reproductive outcomes and neurotoxicity. EFSA (2009b) found the results of these studies to be too preliminary to serve as the basis for its evaluation. Further work is needed to clarify the contribution of exposure to cadmium to these diseases.

8.3 General modelling considerations

8.3.1 Data check

The database containing the 35 suitable studies and described in detail by EFSA (2009b) was checked for consistency and accuracy. Only one alteration was made to the database. In the study reported by Hotz et al. (1999), it was considered unnecessary to transform the reported means and standard deviations to geometric values because it appeared as though they were already geometric values.

Table 14. Overview of recent studies reporting benchmark dose estimations for cadmium levels in urine and effects on renal tubular function

Study population	Cut-off level	Sample size (age in years)	Effect biomarker	BMD model	Urinary cadmium critical dose level (β2MG, μg/g creatinine; NAG, U/g creatinine; PROT, α1MG, mg/g creatinine)		Reference
					BMD_5 / $BMDL_5$	BMD_{10} / $BMDL_{10}$	
General population (Japan)	84% upper limit value of the target population	410 M; 418 F (40–59 years) Urine sampling occurred 1997–1998	β2MG NAG PROT	Quantal linear model	β2MG M: 0.5 / 0.4 F: 0.9 / 0.8 NAG M: 0.3 / 0.3 F: 0.8 / 0.6 PROT M: 0.9 / 0.6 F: 3.2 / 1.8	β2MG M: 1.0 / 0.7 F: 1.8 / 1.3 NAG M: 0.7 / 0.6 F: 1.6 / 1.2 PROT M: 1.9 / 1.2 F: 6.6 / 3.6	Uno et al. (2005)
General population (Japan)	84% upper limit value of the target population of those who had never smoked	1114 M; 1664 F (≥50 years), non-smokers	β2MG NAG PROT	Log-logistic model	β2MG M: 2.9 / 2.4 F: 3.8 / 3.3 NAG M: 4.8 / 3.3 F: 4.7 / 3.7 PROT M: 3.6 / 3.1 F: 4.8 / 4.2	β2MG M: 5.0 / 4.0 F: 6.6 / 5.5 NAG M: 8.3 / 5.7 F: 8.3 / 6.4 PROT M: 5.6 / 4.9 F: 7.5 / 6.6	Kobayashi et al. (2006)

Table 14 (contd)

Study population	Cut-off level	Sample size (age in years)	Effect biomarker	BMD model	Urinary cadmium critical dose level (β2MG, µg/g creatinine; NAG, U/g creatinine; PROT, α1MG, mg/g creatinine)		Reference
					BMD_5 / $BMDL_5$	BMD_{10} / $BMDL_{10}$	
General population (Sweden)	95th percentile of effect biomarkers on the "hypothetical" control distribution at a urinary cadmium level of zero	790 F (53–64 years)	NAG α1MG		NAG 0.64 / 0.5 α1MG 0.63 / 0.49	NAG 1.08 / 0.83 α1MG 1.05 / 0.81	Suwazono et al. (2006)
Residents in cadmium-polluted (Kakehashi River basin) and non-polluted areas (Japan)	84% upper limit values from a group of 424 males and 1611 females who did not smoke and lived in three different areas not polluted with cadmium	3178 M + F and 294 M + F (≥50 years) from polluted and non-polluted areas	β2MG	Quantal linear model	β2MG M: 1.5 / 1.2 F: 1.4 / 1.1	β2MG M: 3.1 / 2.5 F: 2.9 / 2.3	Shimizu et al. (2006)
				Log-logistic model	β2MG M: 3.7 / 2.9 F: 2.6 / 1.5	β2MG M: 5.1 / 4.2 F: 4.2 / 2.7	

[a] BMD_x, benchmark dose for an x% response; $BMDL_x$, lower limit on the benchmark dose for an x% response; F, female; M, male; NAG, *N*-acetyl-β-D-glucosaminidase; PROT = protein; U = unit. One unit will hydrolyse 1.0 µmol of *p*-nitrophenyl *N*-acetyl-β-D-glucosaminide per minute at pH 5.0 and 25 °C.

8.3.2 Selection of mathematical model

Three different models were considered:

1) the Hill model, which is a four-parameter sigmoidal model (minimum, maximum, median effective dose [ED_{50}] and a shape parameter);
2) an exponential model with a threshold, which has three parameters (minimum, threshold and slope);
3) a biexponential model with four parameters (minimum, slope 1, slope 2 and a breakpoint).

All three models provided a similar visual goodness of fit, but the biexponential model was selected because it best showed the obvious transition or breakpoint between the slope observed at low and high concentrations of cadmium in urine (Figure 1). As the breakpoint is indicative of the onset of pathological changes in renal tubular dysfunction, the Committee considered this model to be suitable to characterize the urinary cadmium/β2MG dose–response relationship. The biexponential model is essentially the same as the piecewise-linear model described by EFSA (2009b). As individual subject data were not available and because much of the variation in outcome is attributable to within-group variation of urinary cadmium, it is not possible to model potential variation in the cause–effect relationship between the two biomarkers. This precluded the calculation of a BMD defined by a population percentile (e.g. a BMD_{10}), although a population average BMD associated with a specific urinary concentration (e.g. 300–1000 µg/g creatinine) could be calculated. In addition, an additional parameter was used to account for differences between Asians and Caucasians.

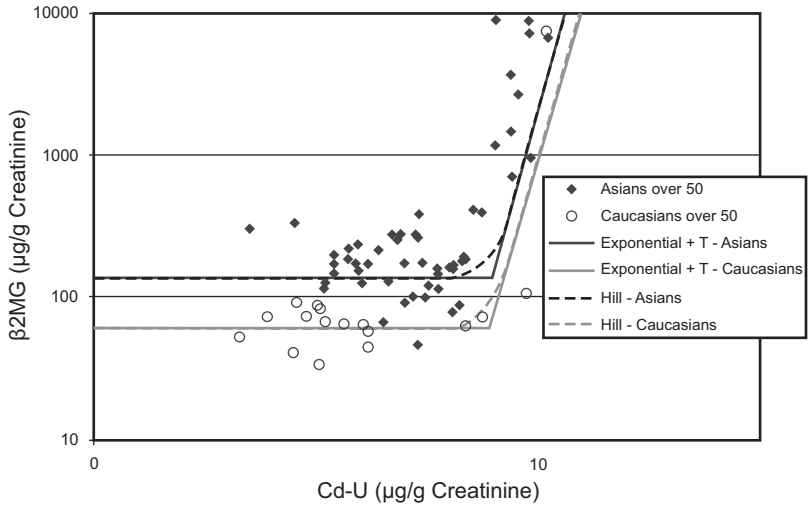
Parameter estimates were generated with linear regression, minimizing the sum of squares of the logs of the residuals. Log residuals were used in order to prevent domination of the parameter estimates by very high β2MG levels.

From Figures 1 and 2, it is apparent that Caucasians excrete less β2MG than Asians for an equivalent concentration of cadmium. A possible explanation for this difference may be the way in which urinary β2MG and urinary cadmium excretion are expressed as a function of excreted creatinine. Creatinine excretion is known to be affected by BMI and protein intake. This source of variation needs to be considered when comparing urinary cadmium data expressed as a function of creatinine between sexes and populations (Suwazono et al., 2005; Gerchman et al., 2009). In general, the mean or median BMI for Asian populations is lower than that observed for non-Asian populations (WHO Expert Consultation, 2004).

8.3.3 Use of the biexponential model in the evaluation

As described in section 8.3.2, the Committee chose the breakpoint for the second slope, which characterizes where the urinary β2MG concentration begins to rapidly increase with increasing urinary cadmium concentration, as the basis of the evaluation. The breakpoint derived for the population aged 50 years and over corresponds to 5.24 (5th–95th percentiles 4.94–5.57) µg/g creatinine. Hence, the breakpoint value of 5.24 (5th–95th percentiles 4.94–5.57) µg of cadmium per gram creatinine and associated uncertainty are similar to those reported by EFSA (2009b)

Figure 1. Data and models with log–log plot

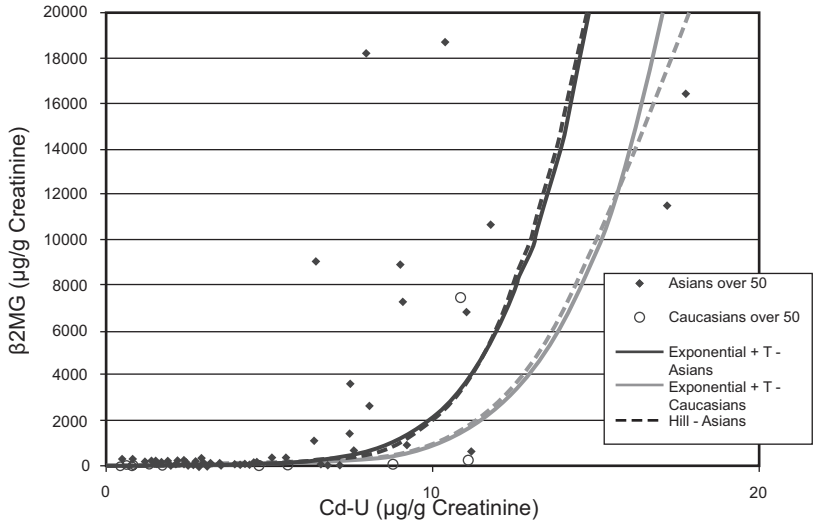


for the entire data set without covariates (i.e. 5.54; 95% CI 5.24–5.82). An inspection of the plotted data using the biexponential model (Figure 3) illustrates that this urinary cadmium concentration of 5.24 µg/g creatinine corresponds to the point at which the urinary β2MG concentration rises dramatically.

8.3.4 Toxicodynamic variability

Toxicodynamic variability in the dose–response relationship (i.e. variability in toxic response of the kidney to cadmium that has reached the target organ) is not taken into account by the model, because the data represent only a population average rather than individual data points. The lack of empirical evidence of a response below a urinary cadmium concentration of 5.24 (5th–95th percentiles 4.94–5.57) µg/g creatinine indicates that the variance is small. Toxicodynamic variability in the model was accounted for by introducing a log triangular distribution to represent individuals with increased or decreased susceptibility. The extreme values of the distribution were defined with a maximum variability in either direction (increased or decreased susceptibility) that ranged from 1 to 3, with a median of 2. The value of 3 approximately corresponds to the toxicodynamic component of a conventional 10-fold uncertainty factor for interindividual variability (IPCS, 2005). Individual subjects were presumed to have a critical concentration (breakpoint) somewhere between the range defined by the mean multiplied or divided by the maximum value. As the same maximum value was used for both increased and reduced individual susceptibility, the adjustment resulted in broadened distributions of both population variability and uncertainty without affecting the geometric central estimates.

Figure 2. Data and models with linear plot



8.3.5 Toxicokinetic modelling

The relationship between urinary cadmium concentration and dietary cadmium exposure was characterized by a one-compartment model reported by Amzal et al. (2009), which was based on a long-term study of Swedish women. Amzal et al. (2009) compared a complex eight-compartment model with a simplified one-compartment model and found that the simplified model provided an adequate description of the toxicokinetic relationship, while also allowing for an accounting of population variability. This one-compartment model consisted of two toxicokinetic parameters (cadmium half-life and a constant that subsumed several physiological parameters) and a statistical parameter for variation in apparent half-life that was used to account for individual variability.

This one-compartment model was used by the Committee for the evaluation. The confidence intervals associated with each of the parameters provided by Amzal et al. (2009) were used to generate the confidence intervals associated with the model estimates. The calculated relationship between dietary cadmium exposure and urinary cadmium concentration is linear; therefore, the outcome may be expressed as a population distribution of the ratio with confidence intervals (Figure 4).

Figure 3. The EFSA biexponential (piecewise-linear) dose–response model for urinary cadmium and β2MG concentrations

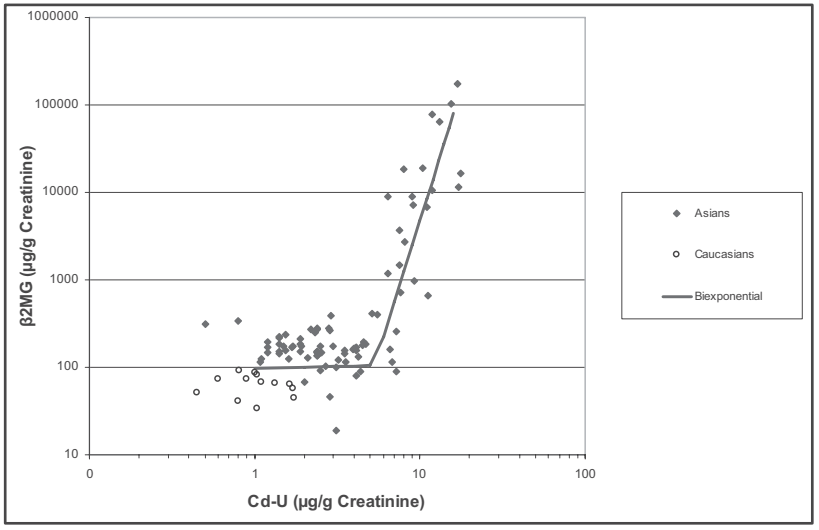


Figure 4. Population distribution of urinary to dietary cadmium ratios

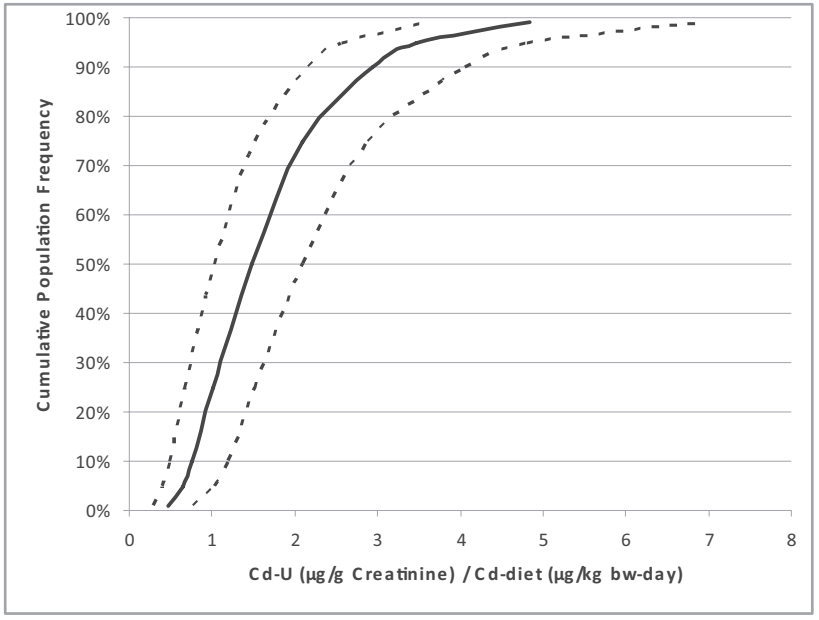
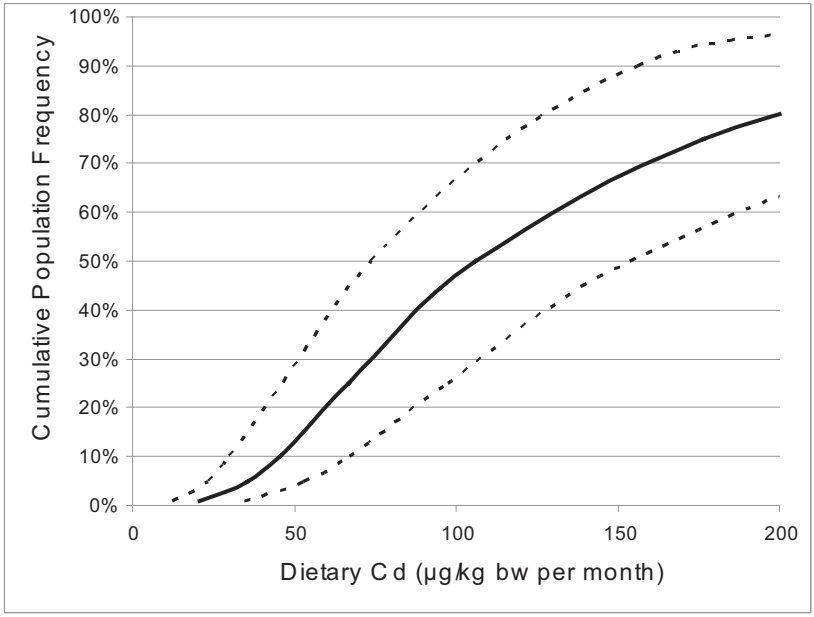


Figure 5. Population distribution of dietary cadmium exposure with 5th–95th percentile confidence intervals



8.4 Estimating the relationship between urinary cadmium excretion and dietary cadmium exposure

A two-dimensional Monte Carlo simulation was used to estimate the population percentiles with associated 5th to 95th percentile confidence intervals from the variability and uncertainty in the breakpoint, the adjustment for toxicodynamic variability and the toxicokinetic model (Figure 5). The simulation employed 1000 iterations for the variability dimension and 300 for the uncertainty dimension. The dietary cadmium exposure (µg/kg bw per day) that equates to a urinary cadmium concentration of 5.24 (5th–95th percentiles 4.94–5.57) µg/g creatinine was estimated to be 1.2 (5th–95th percentiles 0.8–1.8) µg/kg bw per day at the 5th population percentile. This is equivalent to 36 (5th–95th percentiles 24–54) µg/kg bw per month. The Committee decided to use the lower bound of the CI to account for particularly susceptible individuals so that they would remain below the point at which renal pathology is indicated by increased urinary β2MG levels.

9. COMMENTS

9.1 Absorption, distribution, metabolism and excretion

In previously reviewed studies, the Committee noted that most ingested cadmium passes through the gastrointestinal tract largely without being absorbed. In mice, rats and monkeys, the absorption of cadmium from the gastrointestinal tract

depends on the type of cadmium compound, dose and frequency, age and interaction with various dietary components. A recent study has shown that expression of *DMT1* and *MTP1* genes is upregulated in response to iron-deficient diets. This upregulation may explain the observation that both the urinary cadmium excretion and kidney cadmium concentration were significantly higher in women with low iron stores (serum ferritin concentration below 30 µg/l).

The oral bioavailability of cadmium in laboratory animals ranges from 0.5% to 3.0%, on average. Following absorption, cadmium binds to metallothionein, but this binding can be overloaded at relatively moderate doses. Cadmium is distributed mainly to the liver, kidneys and placenta. The cadmium concentrations in liver and kidneys are comparable after short-term exposure, but the kidney concentration generally exceeds the liver concentration following prolonged exposure, except at very high exposures. Cadmium present in liver and kidney accounts for more than half of the body burden. The retention of cadmium in various tissues is variable, and its release appears to be multiphasic. The apparent half-life estimates range between 200 and 700 days for mice and rats and up to 2 years in the squirrel monkey.

In humans, about 50% of the cadmium body burden is found in kidneys. Other major bioaccumulating organs or tissues contributing to the body burden are liver (15%) and muscle (20%). The quantity of cadmium in bone is small. The slow excretion of cadmium results in a long biological half-life, which has been estimated to be between 10 and 33 years. A recent estimate, based on long-term dietary exposure data covering a period of 20 years from a Swedish cohort of 680 women aged between 56 and 70 years, indicated an apparent half-life of kidney cadmium of 11.6 years, with a standard deviation of 3.0 years (Amzal et al., 2009). A one-compartment toxicokinetic model was applied to these dietary exposure data. The average daily dietary exposure was reported to be 14 µg (0.2 µg/kg bw), and the mean urinary cadmium level was 0.34 µg/g creatinine. Based on the model, the population distribution of the daily dietary cadmium exposure corresponding to a given level of urinary cadmium could be obtained (see section 9.9.3).

9.2 Toxicological data

In previously reviewed studies, the Committee noted that long-term oral exposure to cadmium resulted in a variety of progressive histopathological changes in the kidney, including epithelial cell damage of proximal tubules, interstitial fibrosis and glomerular basal cell damage with limited tubular cell regeneration. Biochemical indications of renal damage were seen in the form of low molecular weight proteinuria, glucosuria and aminoaciduria. Tubular dysfunction also caused an increase in the urinary excretion of cadmium.

9.3 Observations in humans

A number of new epidemiological studies have assessed factors influencing cadmium concentrations in kidney and urine following environmental exposure, as well as the relationship between cadmium exposure and several health effects.

The kidney is the critical target organ for the long-term effects of cadmium, showing a variety of progressive histopathological changes, including epithelial cell damage in the proximal tubule, interstitial fibrosis and glomerular basal cell damage. The earliest manifestation of cadmium-induced nephrotoxicity is renal tubular dysfunction, which most often manifests as the urinary excretion of low molecular weight proteins and enzymes, such as β2MG, RBP, α1MG and *N*-acetyl-β-D-glucosaminidase. Urinary β2MG level has been the most widely used marker of renal tubular dysfunction.

Several studies monitoring populations following a reduction in cadmium exposure have attempted to address the question of the reversibility of early renal changes. A modest increase in urinary excretion of β2MG or RBP, in the range of 300–1000 µg/g creatinine, is unlikely to indicate compromised renal function and is usually reversible after cadmium exposure is reduced. With β2MG or RBP excretion above 1000 µg/g creatinine, proteinuria due to renal tubular dysfunction becomes irreversible, although GFR is normal or only slightly impaired; when the urinary excretion of these proteins is increased up to 10 000 µg/g creatinine, renal tubular dysfunction progresses to overt nephropathy usually associated with a lower GFR. These values have been used as cut-off criteria to estimate cadmium nephrotoxicity (measured by urinary β2MG excretion) as a function of cadmium concentration in urine. Although there is good evidence demonstrating relationships between urinary excretion of cadmium and various renal biomarkers (e.g. urinary β2MG or RBP concentration), the health significance of these nonspecific biomarkers in relation to cadmium-induced renal damage remains somewhat uncertain. These biomarker changes in the lower range (i.e. 300–1000 µg/g creatinine) might reflect an early renal response to cadmium, which may be purely adaptive or reversible.

Previously reviewed studies have shown that effects on bone generally arise only after kidney damage has occurred and are likely to be secondary to resulting changes in calcium, phosphorus and vitamin D metabolism. Recent studies have evaluated the association between cadmium and bone mineral density or osteoporosis in populations with low-level cadmium exposure. Although these studies found a significant inverse association between the score of bone mineral density and urinary excretion of cadmium at low levels of exposure, they did not assess renal damage. In one of these studies, in Sweden, the incidence of forearm fractures was significantly increased (by 18%) per unit of urinary cadmium (1 µg/g creatinine). In a Belgian study, a significant relative risk of fractures of 1.73 was associated with a doubling of mean cadmium excretion in the urine (1.66 versus 0.83 µg/g creatinine) among women. There was no association between fractures and cadmium levels among men. Another study in Belgium that investigated the association between urinary cadmium and bone mineral density also measured markers of bone resorption, renal tubular dysfunction and calcium metabolism. In this study, even in the absence of renal tubular dysfunction, urinary cadmium level was associated with reduced bone mineral density, increased calciuria and reduced levels of serum parathyroid hormone. However, four additional studies failed to show any association between urinary cadmium and bone mineral density or calcium metabolism, or the association was no longer significant after controlling for age, body weight and smoking, in the absence of renal tubular damage. The

assessment of the association between urinary cadmium and bone mineral density is based upon different types of epidemiological designs, including prospective and cross-sectional studies, with variable power and different degrees of control of the relevant confounders. Although the overall evidence at present points to an association between urinary cadmium and a decrease in bone mineral density, it is unclear whether the effect is secondary to renal tubular dysfunction. Therefore, the data do not provide a basis for a dose–response analysis of the direct effects of cadmium on bone mineral density.

Cadmium has been classified by the International Agency for Research on Cancer (IARC) as carcinogenic to humans (group 1), with sufficient evidence for lung cancer and limited evidence for kidney, liver and prostate cancer. Most of the evidence is derived from high cadmium exposure of workers exposed through inhalation. Some case–control studies have reported associations of bladder cancer with increased levels of blood cadmium, breast cancer with increased urinary excretion of cadmium and prostate cancer with increased levels of cadmium in toenails; the relationship between cadmium concentration in toenails and dietary exposure is unknown. A prospective study in Sweden reported a significantly increased risk of endometrial cancer in relation to dietary intake of cadmium in postmenopausal women.

In several cross-sectional studies, increased levels of cadmium measured in blood or urine have been found to be associated with various cardiovascular end-points, including myocardial infarction, stroke, heart failure, hypertension and changes in measures of arterial function (aortic pulse wave velocity and carotid, brachial and femoral pulse pressures). The epidemiological evidence for an association between cardiovascular diseases and cadmium is weak.

Prospective studies of the relationship between mortality and environmental exposure to cadmium were also available. In one study, based on a representative sample of the population of the USA with 9 years of follow-up, a doubling of the urinary cadmium level (0.64 versus 0.32 μg/g creatinine) was observed. This was associated with a 28% increased mortality by all causes, 55% increased mortality by cancer, 21% increased mortality by cardiovascular diseases and 36% increased mortality by coronary heart disease, which were statistically significant among men. No significant effects were observed among women. In a study from Belgium of subjects from a cadmium-polluted area and a control area with a follow-up of 20 years, a doubling of the mean urinary cadmium concentration (1.36 versus 0.68 μg/g creatinine) was significantly associated with 20% increased risk of mortality by all causes, 43% increased mortality for cancer and 44% increased mortality for non-cardiovascular diseases. Two prospective studies assessed mortality, renal tubular dysfunction and environmental exposure to cadmium in cohorts of residents in highly polluted areas in Japan. One of them reported a significant increase of 41% in mortality for subjects with β2MG excretion greater than or equal to 1000 μg/g creatinine, compared with the regional reference death rate, after 20 years of follow-up. The other study, with a follow-up of 15 years, found a significant increase in overall mortality of 27% in men and 46% in women with β2MG urinary levels above 1000 μg/g creatinine; moreover, among subjects with β2MG urinary levels between

300 and 1000 µg/g creatinine, there was a significantly increased risk of death by cerebral infarction, digestive diseases (men) and heart failure (women).

9.4 Analytical methods

Analytical methods for the determination of cadmium in foods, water and biological materials are well established; the detection techniques include FAAS, ETAAS, BIFF-AAS, HG-AFS, ICP-OES and ICP-MS. HR-CS-ETAAS allows direct analysis of solids with improved LODs. In recent years, the use of DRC-ICP-MS has allowed the removal of the interferences with a minimum loss of sensitivity. Although ETAAS has been extensively used, ICP-MS could be considered as the method of choice, as it offers lower LODs and wide dynamic range and allows simultaneous determination of several elements. Additionally, ICP-MS offers high specificity through spectral interpretation and isotopic information. Microwave-assisted acid digestion has been the preferred sample preparation technique, although other techniques, such as ashing and slurry preparation, have been used.

Most data submitted were obtained using the above methods, which were validated. Laboratories followed good quality assurance programmes; some had also participated in proficiency testing schemes and achieved good *z*-scores.

9.5 Sampling protocols

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

9.6 Prevention and control

There have been worldwide efforts to reduce cadmium exposure, including implementation of MLs for cadmium in foods, food additives and water. Other prevention and control measures include controlling cadmium levels in fertilizers and feeds and following good agricultural and manufacturing practices.

9.7 Levels and patterns of contamination in food commodities

At its present meeting, the Committee reviewed new cadmium occurrence data submitted by EFSA, covering 19 European countries (Austria, Belgium, Bulgaria, Cyprus, Estonia, France, Germany, Greece, Iceland, Ireland, Italy, the Netherlands, Poland, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom), as well as data submitted by 11 other countries (Australia, Brazil, Canada, Chile, China, France, Ghana, Japan, Singapore, the USA and Viet Nam). The food industry also submitted data on cadmium levels in products that are distributed and used worldwide. The total number of analytical results (single or composite samples) was 155 496, with 84.4% coming from Europe, 5.2% from North America, 1.5% from Asia, 1.4% from Latin America, 0.3% from the Pacific region and 0.1% from Africa. The data submitted by industry accounted for 7.0% of the data.

A summary of the new occurrence data by food category is provided in Table 7 (see section 6.2). For all food categories, calculations of mean concentrations

included results below the LOD or LOQ (i.e. non-detects or ND), although the values assigned to those results varied by country. National average concentrations of cadmium range between not detected and 0.04 mg/kg in most food categories. Higher national mean concentrations, ranging from 0.1 to 4.8 mg/kg, were reported for vegetables (including dried); meat and poultry offal; shellfish/molluscs; nuts and oilseeds; coffee, tea and cocoa; and spices.

9.8 Food consumption and dietary exposure assessment

New information on national estimates of dietary exposure to cadmium was submitted by Australia, China, Japan and the USA. EFSA submitted dietary exposure estimates for Europe. Additional information on national dietary exposure for Chile, Lebanon and the Republic of Korea was obtained from the scientific literature. National and regional exposure estimates were expressed on either a daily or weekly basis, as these estimates are based on 1- to 7-day food consumption surveys. During the meeting, the Committee concluded that a PTMI was appropriate for cadmium (see section 10). For contaminants such as cadmium that are widely distributed in foods at approximately constant levels, day-to-day variability in dietary exposure over the long term would be low, so extrapolating dietary exposure from a daily or weekly basis to a monthly basis would not have a substantial impact on exposure estimates. Therefore, the national and regional exposure estimates were extrapolated to a monthly basis by multiplying daily exposures by 30 or weekly exposures by 4.

Mean cadmium exposure for adults ranged from 2.2 to 12 µg/kg bw per month (see Table 13 in section 7.1.6). Estimates of high exposures reported for Europe, Lebanon and the USA ranged from 6.9 to 12.1 µg/kg bw per month. For Australia and the USA, dietary exposure for children 0.5–12 years of age ranged from 3.9 to 20.6 µg/kg bw per month. Dietary exposure for vegetarians, as reported by EFSA, was estimated to be 23.2 µg/kg bw per month.

The food categories that contributed most to cadmium exposure were reported by Chile, China, Europe, Lebanon and the Republic of Korea. For Chile, the major sources of cadmium in the diet were fish and shellfish, spices and cereals/grains. For China, the main contributors to dietary exposure to cadmium on a national basis were cereals/grains and vegetables; meat and seafood were found to be the main dietary sources of cadmium in several regions within China. Cereals/grains, vegetables/nuts/pulses and animal offal were the main dietary sources of cadmium in Europe. In the Republic of Korea, the main sources of cadmium in the diet were rice, vegetables/seaweed and seafood. The major sources of cadmium in the Lebanese diet were reported to be cereals/grains and vegetables.

The Codex Alimentarius Commission guidelines for conducting exposure assessments for contaminants in foods (FAO/WHO, 2010) recommend that regional dietary exposure estimates should be calculated using regional average contaminant values and the GEMS/Food consumption cluster diets. Such estimates were not calculated for the present meeting because occurrence data were submitted by countries that represented only 2 of the 13 GEMS/Food clusters. Furthermore, national exposure estimates based on national food consumption data

were submitted by the countries that also submitted the majority of new occurrence data. As the national estimates provided more refined estimates than could be calculated with the GEMS/Food consumption cluster diets, only the national estimates were considered in this assessment.

9.9 Dose–response analysis

The basis of the current PTWI is an estimate of a critical cadmium concentration in the kidney cortex at or below which there is no observed increase in β2MG concentrations in urine. A toxicokinetic model was used to estimate the dietary exposure required to reach this critical cadmium concentration in the kidney cortex. An alternative approach is to identify a threshold level of a urinary biomarker of renal tubular damage, such as β2MG, and then use a toxicokinetic model to calculate the dietary exposure corresponding to that threshold level.

9.9.1 Biomarker meta-analysis

In order to determine a dose–response relationship between a suitable biomarker and urinary cadmium levels for the general population, the data available in published studies were compiled and used for a meta-analysis to characterize the relationship between urinary β2MG and urinary cadmium levels (EFSA, 2009b). Urinary β2MG level was chosen as the most suitable biomarker for the meta-analysis because it is widely recognized as a marker for renal pathology and consequently had the largest number of available data. The database covers approximately 30 000 predominantly non-occupationally exposed individuals (99%) reported in 35 studies, but the data are expressed only as group means with standard deviations. The majority of these non-occupationally exposed individuals were of Asian descent (93.5%) and female (75%). The age distribution was approximately equally divided above and below 50 years (i.e. ≥50 years: 51.5%; <50 years: 48.5%). As the apparent half-life of cadmium in human kidneys is about 15 years, steady state would be achieved after 45–60 years of exposure. Therefore, data relating β2MG excretion in urine to cadmium excretion in urine for individuals who are 50 years of age and older should provide the most reliable basis to determine a critical concentration of cadmium in the urine. The data for the population aged 50 years and over in the 35 studies were categorized according to urinary cadmium concentration, resulting in 98 groups containing matched pairs of urinary cadmium and β2MG levels. The 98 groups ranged in size from 3 to 908 individuals, with a median of 56.

The Committee identified the biexponential model as being suitable to characterize the cadmium–β2MG dose–response relationship. In the model, the first (low urinary cadmium concentration) slope is virtually flat, and only the second (high urinary cadmium concentration) slope was considered by the Committee to be indicative of renal pathology (see Figure 3 in section 8.3.3 above). Therefore, the Committee chose the breakpoint for the second slope, which is the point at which the urinary β2MG concentration begins to rapidly increase with increasing urinary cadmium level, as the basis of the evaluation. This breakpoint derived for the population aged 50 years and over corresponds to 5.24 (5th–95th percentiles 4.94–5.57) µg of cadmium per gram of creatinine (Figure 3).

9.9.2 Toxicodynamic variability

Toxicodynamic variability in the dose–response relationship is not taken into account by the model, because the data represent only a population average rather than individual data points. The lack of empirical evidence of elevated β2MG levels below a urinary cadmium concentration of 5.24 (5th–95th percentiles 4.94–5.57) µg of cadmium per gram creatinine indicates that the variance is small.

Toxicodynamic variability in the model was accounted for by incorporating a maximum variability that ranges from 1 to 3. The value of 3 approximately corresponds to the toxicodynamic component of the conventional 10-fold uncertainty factor for interindividual variability (IPCS, 2005). Individual subjects were presumed to have a critical concentration (breakpoint) somewhere within the range defined by the mean multiplied or divided by the maximum value. As the same maximum value was used for both increased and reduced individual susceptibility, the adjustment resulted in broadened distributions of both population variability and uncertainty without affecting the geometric central estimates.

9.9.3 Toxicokinetic modelling

A one-compartment model was used to characterize the relationship between urinary cadmium concentration and dietary cadmium exposure (see section 9.1 above). This model included a statistical parameter for variation in apparent half-life. The calculated relationship between dietary cadmium exposure and urinary cadmium concentration is linear; therefore, the outcome may be expressed as population distribution of the ratio with confidence intervals (see Figure 4 in section 8.3.5 above).

9.9.4 Estimating the relationship between urinary cadmium excretion and dietary cadmium exposure

A two-dimensional Monte Carlo simulation was used to estimate the population percentiles with associated 5th–95th percentile confidence intervals from the variability and uncertainty in the breakpoint, the adjustment for toxicodynamic variability and the toxicokinetic model (see Figure 5 in section 8.4 above). The dietary cadmium exposure (µg/kg bw per day) that equates to 5.24 (5th–95th percentiles 4.94–5.57) µg of cadmium per gram creatinine in urine was estimated to be 1.2 (5th–95th percentiles 0.8–1.8) µg/kg bw per day at the 5th population percentile. This is equivalent to 36 (5th–95th percentiles 24–54) µg/kg bw per month. The Committee decided to use the lower bound of the confidence interval to account for particularly susceptible individuals so that they would remain below the dietary exposure at which renal pathology is indicated.

10. EVALUATION

Since cadmium was last considered by the Committee, there have been a number of new epidemiological studies that have reported cadmium-related biomarkers in urine following environmental exposure. The Committee noted that a large meta-analysis of studies that measured the dose–response relationship between β2MG and cadmium excretion in urine was available. As the apparent half-life of cadmium in human kidneys is about 15 years, steady state would be achieved

after 45–60 years of exposure. Therefore, data relating β2MG excretion in urine to cadmium excretion in urine for individuals who are 50 years of age and older provided the most reliable basis on which to determine a critical concentration of cadmium in the urine. An analysis of the group mean data from individuals who were 50 years of age and older showed that the urinary excretion of less than 5.24 (5th–95th percentiles 4.94–5.57) µg of cadmium per gram creatinine was not associated with an increased excretion of β2MG. Higher urinary cadmium levels were associated with a steep increase in β2MG excretion.

To determine a corresponding dietary exposure that would result in a urinary cadmium concentration at the breakpoint of 5.24 (5th–95th percentiles 4.94–5.57) µg of cadmium per gram creatinine, a one-compartment toxicokinetic model was used. The lower bound of the 5th population percentile dietary cadmium exposure that equates to the breakpoint was estimated to be 0.8 µg/kg bw per day or about 25 µg/kg bw per month.

The Committee noted that the existing health-based guidance value for cadmium was expressed on a weekly basis (PTWI), but, owing to cadmium's exceptionally long half-life, considered that a monthly value was more appropriate. The PTWI of 7 µg/kg bw was therefore withdrawn.

In view of the long half-life of cadmium, daily ingestion in food has a small or even a negligible effect on overall exposure. In order to assess long- or short-term risks to health due to cadmium exposure, total or average intake should be assessed over months, and tolerable intake should be assessed over a period of at least 1 month. To encourage this view, the Committee decided to express the tolerable intake as a monthly value in the form of a PTMI. The PTMI established was 25 µg/kg bw.

The estimates of exposure to cadmium through the diet for all age groups, including consumers with high exposure and subgroups with special dietary habits (e.g. vegetarians), examined by the Committee at this meeting are below the PTMI.

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