European Food Safety Authority

The EFSA Journal (2009) 980, 1-139

SCIENTIFIC OPINION

Cadmium in food[1]

Scientific Opinion of the Panel on Contaminants in the Food Chain

(Question No EFSA-Q-2007-138)

Adopted on 30 January 2009

PANEL MEMBERS

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SUMMARY

Cadmium (Cd) is a heavy metal found as an environmental contaminant, both through natural occurrence and from industrial and agricultural sources. Foodstuffs are the main source of cadmium exposure for the non-smoking general population. Cadmium absorption after dietary exposure in humans is relatively low (3–5 %) but cadmium is efficiently retained in the kidney and liver in the human body, with a very long biological half-life ranging from 10 to 30 years. Cadmium is primarily toxic to the kidney, especially to the proximal tubular cells where it accumulates over time and may cause renal dysfunction. Cadmium can also cause bone demineralisation, either through direct bone damage or indirectly as a result of renal dysfunction. After prolonged and/or high exposure the tubular damage may progress to decreased glomerular filtration rate, and eventually to renal failure. The International Agency for Research on Cancer has classified cadmium as a human carcinogen (Group 1) on the basis of occupational studies. Newer data on human exposure to cadmium in the general population have been statistically associated with increased risk of cancer such as in the lung, endometrium, bladder, and breast.

Cadmium bioavailability, retention and consequently toxicity are affected by several factors such as nutritional status (low body iron stores) and multiple pregnancies, preexisting health conditions or diseases.

A health based guidance value for cadmium of 7 µg/kg body weight (b.w.) per week (Provisional Tolerable Weekly Intake (PTWI)) was established previously by the Joint

[1] For citation purposes: Scientific Opinion of the Panel on Contaminants in the Food Chain on a request from the European Commission on cadmium in food. *The EFSA Journal* (2009) 980, 1-139.

FAO/WHO Expert Committee on Food Additives and endorsed by the Scientific Committee for Food. Although available data indicated that most individuals had intake levels below this PTWI, several international bodies recognised that the margin between this PTWI and the actual weekly intake of cadmium by the general population was small and in some populations may be non-existent.

The Scientific Panel on Contaminants in the Food Chain (CONTAM) was asked by the European Commission to assess the risks to human health related to the presence of cadmium in foodstuffs. To provide an updated assessment of exposure from foodstuffs, about 140,000 data covering the period from 2003 to 2007 on cadmium occurrence in various food commodities were received from 20 Member States and considered by the CONTAM Panel. The highest cadmium concentrations were detected in the following food commodities: seaweed, fish and seafood, chocolate, and foods for special dietary uses. For most foods only a small percentage of the analysed samples (<5 %) exceeded the maximum level (ML), where specified. Up to 20 % of the samples were above the MLs for celeriac, horse meat, fish, bivalve molluscs other than oysters and cephalopods. Highly contaminated areas may show higher cadmium concentrations in locally produced food and the use of cadmium-containing fertilisers in agriculture increases cadmium concentrations in the crops and derived products.

To assess cadmium dietary exposure, the occurrence data and the consumption data as reported in the EFSA's Concise European Food Consumption Database were used. National food consumption dietary surveys were used to estimate the consumption pattern of specific sub-groups such as vegetarians and children. The food groups that contributed to the major part of the dietary cadmium exposure, primarily because of the high consumption, were cereals and cereal products, vegetables, nuts and pulses, starchy roots or potatoes, and meat and meat products. The mean dietary exposure across European countries was estimated to be 2.3 μg/kg b.w. per week (range from 1.9 to 3.0 μg/kg b.w. per week) and the high exposure was estimated to be 3.0 μg/kg b.w. per week (range from 2.5 to 3.9 μg/kg b.w. per week). Due to their high consumption of cereals, nuts, oilseeds and pulses, vegetarians have a higher dietary exposure of up to 5.4 μg/kg b.w. per week. Regular consumers of bivalve molluscs and wild mushrooms were also found to have higher dietary exposures of 4.6 and 4.3 μg/kg b.w. per week, respectively. Tobacco smoking can contribute to a similar internal exposure as that from the diet. House dust can be an important source of exposure for children.

Cadmium levels in urine are widely accepted as a measure of the body burden and the cumulative amount in the kidneys. The CONTAM Panel carried out a meta-analysis on a selected set of studies to evaluate the dose-response relationship between urinary cadmium and urinary beta-2-microglobulin (B2M). B2M, a low molecular weight protein, is recognised as the most useful biomarker in relation to tubular effects. A Hill model was fitted to the dose-response relationship between urinary cadmium and B2M for subjects over 50 years of age and for the whole population. From the model, a benchmark dose lower confidence limit for a 5 percent increase of the prevalence of elevated B2M (BMDL5) of 4 μg Cd/g creatinine was derived. A chemical-specific adjustment factor of 3.9, to account for inter-individual variation of urinary cadmium within the study populations, was applied, leading to a value of 1.0 μg Cd/g creatinine. Such a value was also supported by data from occupationally exposed workers and by the results of several individual studies using a variety of biomarkers.

A one-compartment model was fitted to a large data set based on non-smoking Swedish women (age range from 58 to 70 years), comprising both measurement of dietary cadmium exposure and urinary cadmium concentration to allow an estimation of the relationship between the two. The dietary cadmium exposure that corresponds to the critical urinary

cadmium concentration of 1 μg/g creatinine after 50 years of exposure was then estimated using the model. In order to remain below 1 μg Cd/g creatinine in urine in 95 % of the population by age 50, the average daily dietary cadmium intake should not exceed 0.36 μg Cd/kg b.w., corresponding to a weekly dietary intake of 2.52 μg Cd/kg b.w. The model calculation took into consideration the human variability in absorption rates (1–10 %) so that high absorption rates common in women of reproductive age groups due to high prevalence of low and empty iron stores as well as variations in half-life were included. Because the data used in the dose-response and kinetic modelling relate to an early biological response and a sensitive population, respectively, no adjustment or uncertainty factor was required for individual variability in susceptibility. Therefore, the CONTAM Panel established a tolerable weekly intake (TWI) for cadmium of 2.5 μg/kg b.w.

The mean exposure for adults across Europe is close to, or slightly exceeding, the TWI of 2.5 μg/kg b.w. Subgroups such as vegetarians, children, smokers and people living in highly contaminated areas may exceed the TWI by about 2-fold. Although the risk for adverse effects on kidney function at an individual level at dietary exposures across Europe is very low, the CONTAM Panel concluded that the current exposure to Cd at the population level should be reduced.

Key words: cadmium, food, occurrence, exposure, consumption, biomarkers, beta-2-microglobulin, tolerable weekly intake, risk assessment.

TABLE OF CONTENTS

BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

Cadmium occurs naturally in the environment in its inorganic form as a result of volcanic emissions and weathering of rocks. In addition, anthropogenic sources have increased the background levels of cadmium in soil, water and living organisms. Cadmium is released into the environment by wastewater and waste incineration, and the contamination of agricultural soils can occur by the use of fertilizers, by air deposition and by cadmium-containing sewage sludge. Increases in cadmium levels in soil result in an increase in the uptake of cadmium by plants, depending on plant species, pH and other characteristics of the soil. Edible free-living food organisms such as shellfish, crustaceans and fungi are natural accumulators of cadmium.

The International Agency for Research on Cancer (IARC, 1993; Bergkvist *et al.*, 2003) classified cadmium and cadmium compounds as carcinogenic to humans (Group 1). In 1995 the European Commission's Scientific Committee for Food (SCF) expressed an opinion[2] on cadmium in which it endorsed the 1988 Joint FAO/WHO Expert Committee on Food Additives (JECFA) Provisional Tolerable Weekly Intake (PTWI) of 7 μg/kg b.w. (re-confirmed by JECFA in 2003). Furthermore, the SCF stressed the importance of foodstuffs as the main contributor to human exposure and recommended that efforts should be undertaken to reduce dietary exposure. Besides intake from foodstuffs, cigarette smoke and work place air were mentioned as important contributors to cadmium exposure. In 2004 the European Commission carried out an updated exposure assessment with the data collected in the framework of SCOOP[3] task 3.2.11. The SCF opinion and SCOOP report served as a basis for setting and updating maximum levels for cadmium in foodstuffs.

Regulation (EC) No. 1881/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs[4] contains the most recent maximum levels for cadmium in foodstuffs. However, these levels continue to be constantly reviewed by the Commission. An updated scientific basis is therefore of great importance.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In accordance with Article 29 (1) (a) of Regulation (EC) No 178/2002 the European Commission asks the European Food Safety Authority (EFSA) for a scientific opinion on the risks to human health related to the presence of cadmium in foodstuffs.

In particular, the opinion should:

- consider any new developments regarding the toxicity of cadmium since the SCF opinion of 1995, in order to assess whether the PTWI of 7 μg/kg b.w. is still appropriate;

- contain an updated exposure assessment for cadmium, in particular addressing exposure from food (incl. drinking water) and indicate the relative importance from other non-dietary sources (e.g. air, cigarette smoke etc.);

[2] SCF opinion of 2 June 1995, Thirty-sixth series 1997, p. 67, available at: http://ec.europa.eu/food/fs/sc/scf/reports/scf_reports_36.pdf

[3] SCOOP Report of task 3.2.11: "Assessment of the dietary exposure to arsenic, cadmium, lead and mercury of the population of the EU Member States", March 2004, available at: http://ec.europa.eu/food/food/chemicalsafety/contaminants/scoop_3-2-11_heavy_metals_report_en.pdf. The SCOOP task was carried out in the framework of scientific cooperation with Member States under Council Directive 93/5/EEC, OJ L 52, 4.3.1993, p.18-21

[4] OJ L 364, 20.12.2006, p. 5

- the exposure situation for specific groups of the population (e.g. infants and children, people following specific diets etc.) and an indication of the age group of the population most exposed to cadmium;

- take into account available biomonitoring data when assessing the exposure and compare the results with the calculated exposure.

ACKNOWLEDGEMENTS

The European Food Safety Authority wishes to thank the members of the Working Group on Cadmium in food for the preparation of this opinion: Agneta Åkesson, Eugenia Dogliotti, Alessandro Di Domenico, Corrado Galli, Philippe Grandjean, Jadwiga Gzyl, Lars Järup, Oliver Lindtner, Antonio Mutti, Gunnar Nordberg and Eija-Riitta Venäläinen, and as *ad-hoc* experts Elena Dellatte, Gunnar Johansson and Bettina Julin.

ASSESSMENT

1. Introduction

1.1. General information

Cadmium (Cd) is found in the environment mainly associated with zinc and to a lesser extent with lead and copper. It is thus an inescapable by-product of the metallurgy of these elements. It is used in many technological applications and released into the environment via the smelting of other metals, the burning of fossil fuels, the incineration of waste materials, and the use of phosphate and sewage sludge fertilizers.

Both natural processes (such as volcanic emissions and weathering of rocks) and anthropogenic activities can contribute to the contamination by cadmium of the environment and consequently of the food chain.

Cadmium has no known biological function in animals and humans but mimics other divalent metals that are essential to diverse biological functions. Cadmium can cross various biological membranes by different mechanisms (e.g. metal transporters) and once inside the cells binds to ligands with exceptional affinity (e.g. metallothioneins). However, it is not easily cleared by the cells and the poor efficiency of cellular export systems explains the long residence time of this element in storage tissues such as the intestine, the liver and the kidneys. Cadmium absorbed into the body is eliminated very slowly, with a biological half-life estimated to be 10-30 years. Perturbation of calcium, zinc or iron homeostasis plays a key role in its toxicological action that involves a general threat to basic cellular functions.

Cadmium exposure has been associated with nephrotoxicity, osteoporosis, neurotoxicity, carcinogenicity and genotoxicity, teratogenicity, and endocrine and reproductive effects.

In order to provide a scientific basis for the European Commission to review the maximum levels of cadmium in foodstuffs, the European Food Safety Authority (EFSA) was asked for an updated risk assessment on cadmium in food.

1.2. Previous risk assessments

In 1972, the Joint FAO/WHO Expert Committee on Food Additives and Contaminants (JEFCA) established a Provisional Tolerable Weekly Intake (PTWI) for cadmium of 400-500 µg per person (approximately 7-8 µg/kg b.w. per week and 60-70 µg per day for a 60 kg person) (FAO/WHO, 1972; Nordberg *et al.*, 1985; Chen *et al.*, 2006a). The tolerable levels of exposure to cadmium were based on calculations involving the so-called "normal" and "critical values" of cadmium in the renal cortex (critical level = 200 µg/g) and on the rate of accumulation of cadmium in this target organ. Concentrations of cadmium in the renal cortex of adult subjects without known occupational exposure to the metal were reported to vary with a mean between about 30 and 100 µg/g wet weight. The position of the JEFCA was that "*in order that levels of cadmium in the kidney will not exceed 50 µg/g, and assuming an absorption rate of 5 % and a daily excretion of only 0.005 % of the body load (reflecting the long half-life of cadmium in the body), total intake should not exceed about 1 µg/kg body weight per day*" continuously for 50 years.

The JECFA evaluated cadmium again at its meeting in 1988 (FAO/WHO, 1988). It noted that human studies had yielded estimates that a concentration of cadmium in the renal cortex of 200 µg/g corresponded to a 10 % prevalence rate of low molecular weight proteinuria in the exposed population. Making the same assumptions as previously, the Committee concluded that the total oral intake should not exceed about 1 µg/kg b.w. per day if levels of cadmium in the renal cortex, over a 50-year period, were not to exceed 50 µg/g. A PTWI of was 7 µg/kg body weight (b.w.) was established.

At the JECFA meeting in 1993 (FAO/WHO, 1993) it was noted that, although the modelling assumptions used in deriving the PTWI were conservative, the PTWI did not include a safety factor. They warned that there was only a relatively small safety margin between exposure from the normal diet and the exposure that would produce adverse effects. *The Committee maintained the current PTWI of 7 µg/kg b.w., pending further research.*

In 1993, the International Agency for Research on Cancer (IARC) classified cadmium and cadmium compounds in Group 1 (carcinogenic to humans) based on evidence from human studies, mainly those on lung cancer associated with cadmium inhalation in the work place, and from animal studies (IARC, 1993). In the report from the Joint Research Centre of the European Commission (EU-JRC) cadmium oxide is considered to be a suspected human inhalation carcinogen (EC, 2007).

In 1995, the European Commission's Scientific Committee for Food (SCF) confirmed the PTWI of 7 µg/kg b.w. per week (EC, 1995). The Committee stressed the importance of foodstuffs as the main contributor to non-occupational human exposure in non-smokers and recommended that efforts should be undertaken to reduce dietary exposure.

The U.S. Agency for Toxic Substances and Disease Registry (ATSDR) published in its toxicology profile from 1999 (ATSDR, 1999) a chronic-duration oral minimal risk level (MRL) of 0.2 µg/kg b.w. per day. This limit was obtained from the highest average exposure (2 µg Cd/kg b.w. per day) that was not associated with an excess excretion of beta-2-

microglobulin (B2M) in the urine and an uncertainty factor of 10 to take into account inter-individual variation.

In 2000, the JECFA reassessed cadmium (FAO/WHO, 2000). The JEFCA identified seven commodity groups that contributed significantly to total intake of cadmium, which included rice, wheat, root vegetables, tuber vegetables, leafy vegetables, other vegetables, and molluscs. These commodities accounted for 40 - 85 % of the total intake of cadmium in five regions covered by the World Health Organisation Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme (GEMS/Food). The estimated total intakes of cadmium ranged from 2.8 to 4.2 μg/kg b.w. per week, which equates to 40 - 60 % of the PTWI of 7μg/kg b.w. per week.

As far as the health effects were concerned, the JECFA considered an extensive amount of new information, particularly from environmental epidemiological studies such as the CadmiBel studies from Belgium and a series of Japanese reports. The Committee reaffirmed that: i) *renal tubular dysfunction is the critical health outcome with regard to the toxicity of cadmium*, and ii) *an excess prevalence of renal tubular dysfunction would not be expected to occur if urinary cadmium concentration remains <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 b.w. (FAO/WHO, 2004).

In 2003, a risk assessment report on cadmium oxide and cadmium metal was published as a draft version by the EU-JRC in the context of Council Regulation (EEC) 793/93[5] on the evaluation and control of the risks of existing substances. The final EU-JRC report was published in December 2007 (EC, 2007). This assessment addressed the question of risks associated with the production of cadmium metal and cadmium oxide, and the use of these substances in the production of stabilisers, pigments, alloys and plated products. In the case of subjects exposed indirectly via the environment, the working group identified "*the need for further information to better document the possible effect of low doses of cadmium oxide on neurobehavioral performances and of appropriate control measures to address the concerns expressed for several other health effects including repeated dose toxicity and carcinogenicity*". In a conservative approach it was considered that "*small changes of very sensitive early biomarkers of renal/bone effects of uncertain clinical significance represent adverse health effects that could be used for the risk characterization*". A lowest observed adverse effect level (LOAEL) of urinary cadmium (U-Cd) for renal tubular dysfunction of 2 μg/g creatinine was adopted by aggregation of data from studies indicating LOAELs of 0.5, 2 and 2.6 μg/g creatinine (EC, 2007). Margin of safety (MOS) values were calculated by comparing the LOAEL of 2 μg/g creatinine with empirically measured U-Cd data in five European and one US study. The estimated MOS were below 3 (the MOS value considered as the minimum acceptable) for a significant fraction of the population. MOS values of 12.2-3.58 were estimated in the assessment for adult non-smokers with sufficient iron stores.

In 2004, the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) reviewed the results of the draft EC-JRC assessment. The Committee disagreed with the conclusion regarding health risks for kidney damage in adult non smokers with sufficient iron stores for two reasons*: 1) the proposed LOAEL (U-Cd) of 2 μg/g creatinine is uncertain and not sufficiently conservative and 2) estimation of current exposure levels is inadequate. In addition the CSTEE considers that the group of "adult non smokers with sufficient iron*

[5] OJ L 84, 5.4.1993, p. 1-124

stores" represents a large non-uniform part of the population, which is not well defined and includes several susceptible sub-groups.

The CSTEE modified the approach followed by the EC-JRC by using, instead of an "aggregate" of data, a range of possible LOAEL values suggested by the available studies, including values of 0.5 and 2.0 μg/g creatinine, as the most relevant for the general population exposed through the environment, to obtain a range of estimates of MOS values. The MOS values thus calculated were in the range 0.1-2.6, when the 95th percentiles of exposure were used or 0.25-9 when the mean exposure values were used.

In 2004, the European Commission carried out an updated exposure assessment (EC, 2004b) in the framework of the scientific co-operation initiative (SCOOP) task that, together with the opinion from SCF, served as a basis for setting current maximum levels for cadmium in foodstuffs (Regulation (EC) No. 1881/2006 of 19 December 2006[6]).

In 2005, the JECFA was asked by the Codex Committee on Food Additives and Contaminants to evaluate the impact of different maximum levels (MLs) for cadmium in commodities that contribute significantly to intake. This assessment (FAO/WHO, 2005) took into account the potential impact of different MLs on the distribution of concentrations of cadmium in each commodity and the dietary intakes of cadmium from each individual commodity. The Committee concluded that "*a variation of 1 - 6 % of the intake of cadmium attributable to the use of the proposed CODEX alimentarius MLs, and one level higher or lower, is of no significance in terms of risk to human health considering that the total intake of cadmium in the previous assessment was only 40 - 60 % of the PTWI of 7 μg/kg b.w. per week*".

In 2005, the U.S. Center for Disease Control and Prevention provided an assessment of the exposure to cadmium of the U.S. population using biomonitoring (US-DHHS, 2005). In this Report, it was recognised that "*the urinary and blood cadmium levels at the 95th and 90th percentiles, respectively, approached the values associated with subclinical changes in renal function (Jarup et al., 2000; Noonan et al., 2002; Moriguchi et al., 2004) and bone mineral density (Staessen et al., 1999; Alfven et al., 2002), i.e. greater than or equal to 1 μg/g of creatinine. Further research is needed to address the public health consequences of such exposure in the United States"*.

In 2006, the United Nations Environment Programme – Division of Technology, Industry and Economics, Chemicals Branch, produced an interim review of scientific information on cadmium. On the basis of this review it was concluded that attention should be drawn to the following: "*According to available data, the average weekly intake of cadmium from food in most countries is within the range of 0.7-2.8 μg/kg body weight. Although available data indicate that most people have intake levels below the PTWI (7 μg/kg b.w. per week), WHO recognises that the margin between the PTWI and the actual weekly intake of cadmium by the general population is small, less than 10-fold, and that this margin may be even smaller in smokers. In some populations at high risk, the margin may be non-existent"*(UNEP, 2006, 2008).

In 2008 the Agency for Toxic Substances and Disease Registry (ATSDR) re-evaluated the toxicological profile of cadmium (ATSDR, 2008) and established a new chronic-duration oral minimal risk level of 0.1 μg/kg/day. The assessment was based on a multiple approach that included: 1) a no-observed-adverse-effect level (NOAEL)/(LOAEL) approach, using a single

[6] OJ L 364, 20.12.2006, p. 5-24

environmental exposure study, finding an increased prevalence of abnormal renal effect biomarker levels, 2) a selection of a point of departure from a published benchmark dose analysis, and 3) a selection of a point of departure based on an analysis of the dose-response functions from a number of environmental exposure studies.

1.3. Chemistry

Cadmium is a metallic element of Group IIB (Zn, Cd, Hg) of the Periodic Table which dictates its prevalent valence state of +2.

The metal is soft, ductile and silvery-white or bluish-white. The metal is rarely found in the pure state in nature. Elemental cadmium has a relatively high vapour pressure, but the vapour is rapidly oxidised to produce cadmium oxide in the air. Gases like carbon dioxide, water vapour, sulfur dioxide, sulfur trioxide, and hydrogen chloride react with elemental cadmium in, for example, smoke stacks to form salts that are emitted to the environment. The chemistry of cadmium is dominated by its inorganic compounds in the +2 oxidation state. Cadmium forms a number of inorganic salts. In general, these cadmium compounds exhibit properties similar to the corresponding zinc compounds. The halides and the nitrate of Cd^{2+} are very soluble in water while the hydroxide is insoluble. Cadmium oxide and cadmium carbonate might, however, be soluble in gastric pH.

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 (WHO-IPCS, 1992a). Most of the cadmium found in mammals, birds, and fish is believed to be bound to proteins (WHO-IPCS, 1992b). Organic cadmium compounds are normally not identified in nature, *i.e.* compounds where cadmium binds covalently to carbon (WHO-IPCS, 1992b). However, studies in marine polar regions indicate microbial formation of monomethyl cadmium, $CdCH_3^+$, but currently the significance of these findings is not known (Pongratz and Heumann, 1999; Fairbrother *et al.*, 2007).

The nature of the cadmium salts governs their fate in the environment. In the aquatic environment at low salinity, cadmium is present as the free Cd^{2+} ion with $Cd(OH)_2^0$ and organic complexes at levels dependent on pH and amounts of soluble organic material. In contrast, as salinity increases the degree of complexation with chloride increases and in 100 % seawater, the cadmium is thought to exist almost solely as $CdCl_2^0$ 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 (WHO-IPCS, 1992a). In soil water, the free Cd^{2+} dominates with $CdCl^+$ and $CdSO_4^0$ at about 100 times lower concentration but with increasing pH, $CdOH^+$ and $CdCO_3^0$ increase in abundance (WHO-IPCS, 1992b).

2. Legislation

Regulation EC No. 1881/2006[7] sets several MLs for cadmium in certain foodstuffs, as summarised in Table 1. The MLs established for cadmium reflect the results of a dietary

[7] OJ L 364, 20.12.2006, p. 19

exposure assessment carried out in the SCOOP-task 3.2.11 (EC, 2004b) and the outcome of the opinion on cadmium expressed by the former SCF (EC, 2005).

Maximum levels are generally set for the edible part of the foodstuffs concerned, unless otherwise specified in the Annex of Regulation (EC) No. 1881/2006. For dried, diluted, processed and compound foodstuffs changes of concentration of the contaminants caused by drying, dilution or processing shall be taken into account. For compound foodstuffs the relative proportions of the ingredients in the product shall be taken into account.

As regards the exact definition of the food categories fruits, vegetables and cereals, to which maximum levels of Regulation (EC) No. 1881/2006 apply, Annex 1 of Regulation (EC) No. 1881/2006 makes reference to Regulation (EC) No. 178/2006 amending Regulation (EC) No. 396/2005. In Regulation (EC) No. 178/2006 the exact categories are defined.

Regulation (EC) No. 1881/2006 has recently been amended by Regulation (EC) No. 629/2008[8]. As regards cadmium, the amendment re-groups three fish species in a different category of maximum levels. It also replaces the differentiation between wild and cultivated fungi by a species-based approach and sets new maximum levels for cadmium in food supplements.

Directive 1998/83/EC[9] sets quality standards for the most common substances ("parameters") that can be present in water intended for human consumption, including cadmium. The ML for such water is 5.0 μg/L. By-and-large based on World Health Organization (WHO) guidelines for drinking water, the objective of the Directive, aside from protecting the health of the EU consumers, is also to make sure drinking water everywhere within the EU is wholesome and clean. Member States must monitor the quality of the drinking water supplied to their citizens and of the water used in the food production industry. Natural mineral waters are not included in Directive 1998/83/EC, and a maximum limit for cadmium of 3.0 μg/L in natural mineral waters has been established in Directive 2003/40/EC[10].

[8] Regulation (EC) No. 629/2008 of 2 July 2008 amending Regulation (EC) No 1881/2006 setting maximum levels for certain contaminants in foodstuffs measures (lead, cadmium and mercury in food supplements, lead in mushrooms, cadmium in fish and mushrooms). OJ L 173, 3.7.2008. p. 6.
[9] OJ L 330, 5.12.1998, p. 42
[10] OJ L 126, 22.5.2003, p. 34

Table 1. Cadmium maximum levels (MLs) in foodstuffs (mg/kg wet weight)[a]

Foodstuffs	ML	Foodstuffs	ML
1. Meat (excluding offal) of bovine animals, sheep, pig, and poultry	0.050	11. Cephalopods (without viscera)	1.0
2. Horsemeat, excluding offal	0.20	12. Cereals, excluding bran, germ, wheat, and rice	0.10
3. Liver of bovine animals, sheep, pig, poultry, and horse	0.50	13. Bran, germ, wheat, and rice	0.20
4. Kidney of bovine animals, sheep, pig, poultry, and horse	1.0	14. Soybeans	0.20
5. Muscle meat of fish, excluding species listed in 6 and 7	0.050	15. Vegetables and fruit, excluding leaf vegetables, fresh herbs, fungi, stem vegetables, root vegetables, and potatoes	0.050
6. Bonito (*Sarda sarda*), common two-banded seabream (*Diplodus vulgaris*), eel (*Anguilla anguilla*), grey mullet (*Mugil labrosus labrosus*), horse mackerel or scad (*Trachurus spp*), louvar or luvar (*Luvarus imperialis*), mackerel (*Scomber spp*), sardine (*Sardina pilchardus*), sardinops (*Sardinops spp*), tuna (*Thunnus spp*, *Euthynnus spp*, *Katsuwonus pelamis*), and wedge sole (*Dicologoglossa cuneata*)	0.10	16. Stem vegetables, root vegetables and potatoes, excluding celeriac. For potatoes the maximum level applies to peeled potatoes.	0.10
7. Muscle meat of bullet tuna (*Auxis spp*)	0.20	17. Leaf vegetables, fresh herbs, celeriac and the following fungi: *Agaricus bisporus* (common mushroom), *Pleurotus ostreatus* (Oyster mushroom), *Lentinula edodes* (Shiitake mushroom)	0.20
8. Muscle meat of anchovy (*Engraulis spp*) and swordfish (*Xiphias gladius*)	0.30	18. Fungi, excluding those listed in point 17	1.0
9. Crustaceans, excluding brown meat of crab and excluding head and thorax meat of lobster and similar large crustaceans (*Nephropidae* and *Palinuridae*)	0.50	19. Food supplements excl. food supplements listed in point 20	1.0
10. Bivalve molluscs	1.0	20. Food supplements consisting exclusively or mainly of dried seaweed or of products derived from seaweed	3.0

(a): According to Regulation (EC) No 1881/2006 latest amended by Regulation (EC) No 629/2008.

3. Sampling and methods of analysis

3.1. Sampling

Sampling as well as analytical quality play a crucial role in the accuracy and precision of the determination of cadmium in food commodities.

The sampling of food for cadmium analysis requires specific precautions in order to avoid contamination or losses during handling, storage and transport to the laboratory. Samples must be collected so that the sample integrity and traceability are maintained. In the EU,

methods of sampling for the official control of levels of cadmium in foodstuffs have to fulfil the sampling methods described in Regulation (EC) No 333/2007[11].

3.2. Methods of analysis

The performance criteria for methods of analysis for official control are also laid down in Regulation (EC) No 333/2007[11]. This requires the limit of detection (LOD) to be less than 1/10 of the ML (see Table 1) and the limit of quantification (LOQ) to be less than 1/5 of the ML.

Atomic absorption spectrometry (AAS) is the most common analytical method applied for measuring trace metals in food samples. Flame AAS (FAAS) is a relatively simple technique, with a high sample throughput and low operational costs. FAAS is predominantly a single-element technique that uses a flame to generate ground-state atoms. FAAS sensitivity can be improved by increasing the efficiency of aerosol generation/transport and the residence time of free atoms in the absorption volume. Beam injection flame furnace atomic absorption spectrometry (BIFF-AAS) can enhance the sensitivity of FAAS.

Due to the high sensitivity, selectivity and ease of use, graphite furnace AAS (GFAAS) is also frequently used for the determination of cadmium in foods. This method is also a single-element technique, although multielement instrumentation is also available. GFAAS works on the same principle as FAAS, except that the flame is replaced by a small heated graphite tube to generate the atoms. Because the ground-state atoms are concentrated in a smaller area than a flame, more light absorption takes place, resulting in LODs approximately 100 times lower than those for FAAS.

In addition, inductively coupled plasma-optical emission spectroscopy (ICP-OES) and inductively coupled plasma-mass spectrometry (ICP-MS) are also applied for measuring levels of cadmium in food.

ICP-OES is a multielement technique that uses an extremely hot plasma source to excite atoms to the point that they emit wavelength-specific photons of light characteristic of a particular element. The number of photons produced is directly related to the concentration of that element in the sample. 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, and as a result it offers 5-10 times lower detection limits than the radial configuration. However, detection limits are higher then those obtained by GFAAS.

ICP-MS also uses a plasma source. The fundamental difference between ICP-OES and ICP-MS is that the plasma is not used 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 detection limits better than those attainable using GFAAS.

In addition, it is a multi element method and a wide range of elements can be determined simultaneously.

[11] OJ L 88, 29.3.2007, p. 29–38

Detection limits

Table 2 presents an indication of the LOD for cadmium by the different analytical methods mentioned above. For any given determination, the actual method LOD can be an order of magnitude higher or more.

Table 2. Detection limits of the different methods

Technique	Detection limit (µg/L) [a)]
FAAS	0.8 – 1.5
ICP-OES	0.1 – 1
GFAAS	0.002 – 0.02
ICP-MS	0.00001 – 0001

a) Values available from different instrument suppliers

4. Sources, use and environmental fate

Cadmium occurs naturally in the earth's crust, as part of cadmium rich geological materials (e.g., black shales) and as a consequence of volcanic eruptions, and exfoliation of rocks, and minerals (Pacyna and Pacyna, 2001). Cadmium is primarily found in association with zinc ores, approximately 3 kg of cadmium being produced for each ton of zinc. Anthropogenic sources of cadmium include:

- industrial emissions (non-ferrous mining and smelting, metal using industry, industrial and agricultural wastes, coal combustion, phosphate fertiliser manufactures). World cadmium mine production in the year 2000 was 19,700 tonnes (Nordic Council of Ministers, 2003).

- urban pollution (incineration of municipal solid waste, road dust, heating). As a by-product of zinc processing, cadmium production has closely followed the demand for zinc.

4.1. Air

Industrial activities are the main sources of cadmium release to the air and emissions from anthropogenic sources have been found to exceed those of natural origin by an order of magnitude (ATSDR, 1999). Cadmium and cadmium compounds have negligible vapour pressures but may exist in air as suspended particulate matter derived from sea spray, industrial emissions, combustion of fossil fuels, or the erosion of soils (Elinder, 1985). In processes that involve extremely high temperatures (e.g., the iron and steel industries), cadmium can volatilize and be emitted as a vapour (Wilber *et al.*, 1992).

Total emission to air from natural sources (mainly volcanoes) is estimated at about 150-2,600 tonnes per year. These figures may be compared to an estimate of total anthropogenic air emission in 1995 of approximately 3,000 tonnes (Nordic Council of Ministers, 2003). The largest source of atmospheric cadmium is non-ferrous metal production, which contributes about 75 % of total anthropogenic cadmium emissions (Pacyna and Pacyna, 2001). The total EU-16 emission to the atmospheric compartment in 1996 from cadmium producing and processing plants was 4.6 tonnes, with 83 % originating from cadmium producing plants (EC,

2007). In Europe and North America, emissions of metallic elements have shown a decreasing trend over the last decades, as a consequence of the reduction in coal consumption, the improvement of industrial manufacturing processes and the tightening of environmental legislation. In Eastern Europe, the closure of outdated industrial plants and coal-fired power plants, and the reduction in industrial output all contributed to reduce emissions (Pacyna and Pacyna, 2001).

In urban areas of the EU, cadmium concentrations in air are in the range between 1 and 10 ng/m^3.

Atmospheric cadmium is in the form of particulate matter, which may consist of very small particles (<10 μm) if it is produced by combustion processes. The principal chemical species in air is cadmium oxide, although some cadmium salts, such as cadmium chloride, can enter the air, especially during incineration (IARC, 1993). These are stable compounds that do not undergo significant chemical transformation.

Cadmium pollutants present in the air may be transported from a hundred to a few thousand kilometres and have a typical atmospheric residence time of about l-10 days before deposition occurs by wet or dry processes (Elinder, 1985; ATSDR, 1999).

4.2. Water environment

In surface water and groundwater, cadmium can exist as free ion, or as ionic complexes with other inorganic or organic substances. While soluble forms may migrate in water, cadmium is relatively non-mobile in insoluble complexes or adsorbed to sediments. In seawater, the most common forms are chlorine ion complexes, and in freshwater the free hydrated or carbonated ions (depending on the pH) are the most frequent forms.

With regard to aquatic systems, rivers transport large quantities of cadmium from weathering and erosion processes to the world's oceans. An annual gross input of about 15,000 tonnes of cadmium has been estimated. Moreover, between 900 and 3,600 tonnes of cadmium are estimated to be deposited into aquatic environments throughout the world by atmospheric deposition of emissions originating from anthropogenic and natural sources (UNEP, 2008). For example, the contribution of cadmium via rivers into the marine environment of the North Sea is of the same order of magnitude as the atmospheric deposition as the other main regional dispersion pathway of cadmium. The oceanic residence time of cadmium has been estimated to be about 15,000 years. This indicates that cadmium may be accumulated and transported in significant amounts over long distances in the ocean. There are large natural reservoirs of cadmium in the oceans.

Other major sources of cadmium in the hydrosphere include domestic wastewater, non-ferrous metal smelting and refining, and manufacturing of chemicals and metals. Cadmium concentrations up to 5 mg/kg have been reported in sediments from river and lakes, and from 0.03 to 1 mg/kg in marine sediments. The average cadmium content of seawater is about 5-20 ng/L in open seas, but increased concentrations of 80-250 ng/L have been reported in French and Norwegian coastal zones. Concentrations measured in European rivers generally vary between 10 and 100 ng/L (OSPAR, 2002).

4.3. Soil

Cadmium in soil is derived from both natural and anthropogenic sources. Atmospheric pollution, phosphate fertilisers and sewage sludge appear to be the major contributors to cadmium deposition in agricultural soils. Atmospheric cadmium deposition onto soil has generally decreased over the last 20 years in Europe. Recent studies have documented that atmospheric emissions do not presently have a significant impact upon the cadmium content of soils (Bak *et al.*, 1997).

Cadmium in soil may exist in soluble form in soil water, or in insoluble complexes with inorganic and organic soil constituents. Cadmium in soil tends to be more available when the soil pH is low.

Background cadmium levels in surface soils range from 0.01 to 2.7 mg/kg, though values up to 1,781 mg Cd/kg soil have been reported from very contaminated sites (Kabata-Pendias, 2001). In Europe, the mean cadmium concentration in cultivated soils is 0.5 mg/kg (Davister, 1996; Underwood and Suttle, 1999). A more general picture of common ranges of cadmium in soil is given by the latest report of United Nation Environment Programme (UNEP, 2006) with maximum values of about 50 mg/kg.

The cadmium content of fertilisers depends on its concentration in the raw material used for the production. The assessments conducted in 9 Member States indicated a weighted average of cadmium content of about 30 mg Cd/kg P_2O_5 (corresponding to 68 mg Cd/kg P), higher concentrations being estimated for the EU as a whole. A limit value of 20 mg Cd/kg P_2O_5 fertilisers (corresponding to 46 mg Cd/kg P) was suggested to prevent cadmium accumulation in the soil (EC, 2001). There is currently no EU legislation limiting the maximum level of cadmium in fertilizers but some countries have permanent exceptions to use national guidelines.

Elevated concentrations of cadmium in soils (compared to 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).

Since cadmium is taken up by plants, an increased soil concentration can result in increased levels in food and feeds (UNEP, 2006). However, the concentration of cadmium in soils is not the primary determinant of cadmium in plants. 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 (OECD, 1994).

4.4. Wastes

Global cadmium releases to the terrestrial environment is in total between 2,500-15,500 tonnes per year, with atmospheric deposition being the dominant source. An additional 7,500-29,500 tonnes per year are assumed to be directed to landfills and various deposits in the form of discarded products and production waste (Nordic Council of Ministers, 2003). The long-term fate of cadmium accumulated in landfills is uncertain and may represent a future source of releases. The handling of wastes may lead to elevated local and regional releases, especially in developing countries (UNEP, 2002).

4.5. Transfer in the environment and bioaccumulation

Cadmium can remain present in lake and river suspended particles for 1-3 years. In coastal sediments its estimated half-live is 2 years, and in oceanic water it is estimated to be about 15,000 years (Cabrera *et al.*, 1998). Cadmium in the water accumulated more rapidly in the sediments than in living organisms.

Cadmium concentrates in freshwater and marine animals to concentrations hundreds to thousands of times higher than in the water (ATSDR, 1999). Reported bioconcentration factors range from 113 to 18,000 for invertebrates (van Hattum *et al.*, 1989), from 3 to 4,190 for fresh water aquatic organisms (ASTER, 1995), and from 5 to 3,160 for saltwater aquatic organisms (ASTER, 1994). Bioconcentration in fish depends on the pH and the colloid content of the water (John *et al.*, 1987). In mussels (*Mytilus edulis*), assimilation efficiency of cadmium from water is 0.18 to 0.35 % (Wang *et al.*, 1996; Wang and Fisher, 1997), whereas assimilation efficiency of cadmium from food (phytoplankton) varies from 11 to 40 % (Neff, 2002). Values between 70 and 88 % were reported for the clam species *Macoma balthica,* feeding on diatoms and for the barnacle species *Balanus amphitrite,* feeding on copepods (Wang and Fisher, 1999). The crabs and lobsters are able to accumulate, mainly in the digestive gland, between 10 and 40 % of the cadmium present in their food (Neff, 2002). Rainbow trout (*Oncorhynchus mykiss*) and Lake whitefish (*Coregonus clupeaformis*) accumulate cadmium after water and food exposure of approximately 0.1 % and 1 %, respectively (Harrison and Klaverkamp, 1989).

Cadmium accumulation has been also reported in grasses and food crops, and in earthworms, poultry, cattle, horses, and wildlife (ATSDR, 1999). In general, cadmium accumulates in the leaves of plants and, therefore, is more of a risk in leafy vegetables grown in contaminated soil than in seed or root crops (Alloway *et al.*, 1990). He and Singh (1994) reported that, for plants grown in the same soil, accumulation of cadmium decreased in the order: leafy vegetables > root vegetables > grain crops. Some studies have concluded that soil pH is the major factor influencing plant uptake of cadmium from soils (Smith, 1994). Soil type also affects uptake of cadmium by plants. For soils with the same total cadmium content, cadmium has been found to be more soluble and more plant-available in sandy soil than in clay soil (He and Singh, 1994). Similarly, cadmium mobility and bioavailability are higher in non-calcareous than in calcareous soils (Thornton, 1992).

Although some data indicate increased cadmium concentrations in animals at the top of the food chain, comparisons among animals at different trophic levels are difficult, and the data available on biomagnification are not conclusive (Gochfeld and Burger, 1982; Beyer, 1986). Nevertheless, uptake of cadmium from soil by feed crops may result in high levels of cadmium in beef and poultry (especially in the liver and kidneys).

4.6. Sources of human exposure to cadmium

The general population is exposed to cadmium from multiple sources. Attention is drawn to the following (UNEP, 2008):

- in the non-smoking general population, food accounts for approximately 90 %. The main food commodities that contribute to cadmium exposure are cereals and vegetables.

- cadmium in crops depends on uptake from soils and the rate of uptake is influenced principally by the forms of the element, the soil physico-chemical properties and the plant species.

- meat and fish normally contain lower cadmium contents. Animal offals such as kidney and liver can exhibit high cadmium concentrations, as these are the organs in animals in which cadmium concentrates (UNEP, 2008).

Less than 10 % of total exposure of the non-smoking general population occur due to inhalation of the low concentrations of cadmium in ambient air (Vahter *et al.*, 1991) and through drinking water (Olsson *et al.*, 2002).

If present, smoking and occupational exposure may prevail over food as the main sources of cadmium exposure. Smokers have on average twice the body burden of a non-smoker. Workers may accumulate much higher cadmium levels depending on the type of work. The main sources of human exposure to cadmium are schematically shown in Figure 1. The sources of human exposure to cadmium include industry emissions and contamination of different environmental media, i.e. air, water and soil. The latter may also be contaminated by fertilisers. Cadmium contamination of the environment leads to subsequent food contamination, especially in case of cereals and vegetables.

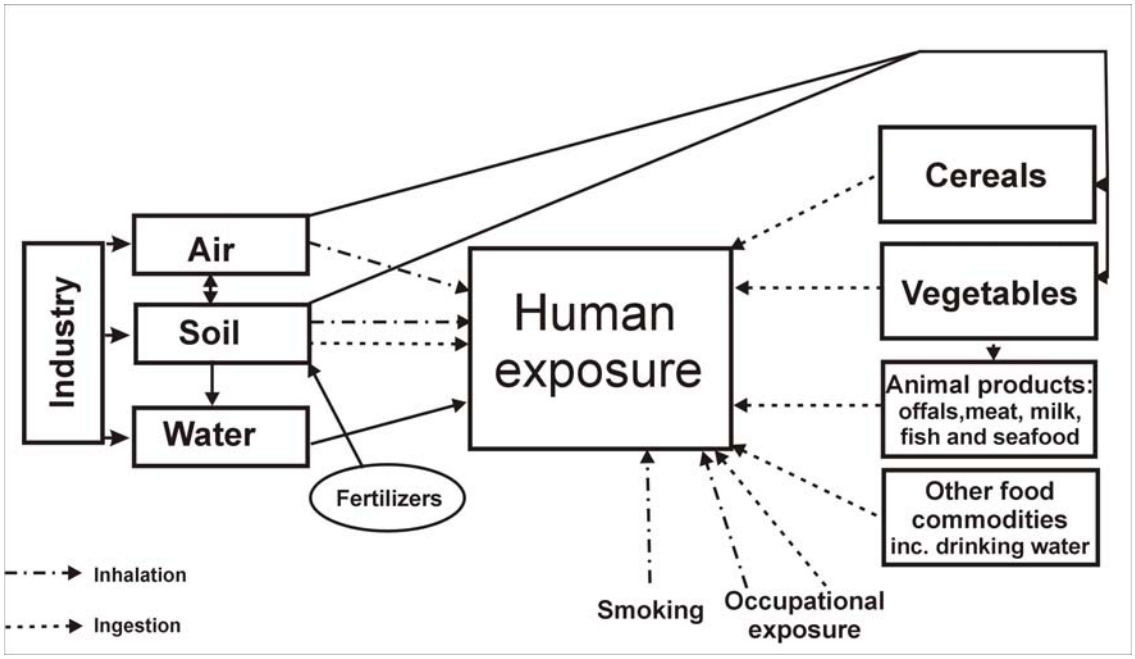

Figure 1. Sources of human exposure to cadmium

5. Occurrence in food

5.1. Previously reported cadmium occurrence results

A number of studies have reviewed cadmium content in a range of different foods. In a collaborative effort under the SCOOP involving 13 EU Member States, cadmium concentrations ranged from non-detected in many foods to a high mean of 1.20 mg/kg for cephalopods (EC, 2004a).

For the 64th meeting of the JECFA average concentrations of cadmium were reported from Australia, Canada, Germany, Japan, New Zealand and the USA including some aggregated data from a further four countries or regions (FAO/WHO, 2004). For rice, Japan reported higher values than the general average, 0.061 compared to 0.017 mg/kg, respectively. The average concentration of cadmium in wheat was 0.054 mg/kg, vegetables ranged from 0.012 to 0.040 mg/kg, and in molluscs results varied from 0.20 mg/kg for cephalopods to 1.38 mg/kg for oysters.

Cadmium was monitored in 119 retail food categories within the framework of a national total diet study of the United Kingdom general population (FSA, 2009). Similar foods were combined into 20 groups of composite samples and assayed "as consumed", that is they were prepared and cooked before testing. Cadmium was present at low concentrations in eleven of the food groups, and was below the levels of detection in meat, poultry, oils and fats, eggs, fresh fruits, beverages, milk and dairy products. Cadmium concentrations were highest in the offal (0.084 mg/kg) and nuts (0.065 mg/kg) groups. Food that was consumed in larger quantities made the greatest contribution to the dietary exposure; high contributors were potatoes (24 %), miscellaneous cereals (21 %) and bread (19 %). Cadmium concentrations found in food in repeated studies undertaken since 1966 was similar with some slight changes but no clear trend.

5.2. Current cadmium occurrence in food

The EFSA issued a call for detailed information on cadmium concentrations in individual food samples to EU Member States in November 2007. Despite a short timeframe, EFSA received an overwhelming response to the call. To accommodate all Member States willing to submit data the deadline had to be extended to January 2008.

Taking into account the period from 2003 to 2007, about 140,000 analytical results were provided by 20 EU Member States, and separate submissions from Iceland, Australia and also from commercial sources. The commercial data were submitted by the following organisations (names in brackets refer to Figure 2):

- Verband Deutscher Mühlen (German Milling Association) (DE);

- Association of Preserve Manufacturers of Shellfish and Fishery Products, Área de Calidad y Seguridad Alimentaria (ANFACO-CECPESCA) (ES);

- European Federation of the trade in dried fruits, edible nuts, honey, spices, canned fruits and vegetables and similar foodstuffs (FRUCOM) (BE).

Additional data were submitted covering the period before 2003. Together with data from the previous SCOOP project (see 5.1 above) and data directly from the European Commission a total of 187,143 results were evaluated. For the detailed analysis of the occurrence of

cadmium in food only the data from 2003 to 2007 were considered to best reflect the current situation. Submissions from two EU Member States lacked sufficient detail and were excluded from the evaluation. Initially commercial and non-commercial data were analysed separately showing slightly higher cadmium occurrence values for the commercial data for some food categories covered by both sources. Combining the two sources had little impact on overall exposure but simplified presentation.

At an early stage of the work, it became apparent that an additional level of food classification detail was required in particular to:

- cluster together foods with high levels of cadmium but with low consumption; and
- verify compliance with maximum levels defined in the legislation (Regulation EC No. 1881/2006, Council Directive 98/83/EC).

To support these additional requirements, a further categorisation level was added to the EFSA aggregated categorisation system in that some food groups were split into sub-categories. Details of the final food categorisation system used are reported in Appendix A-1. Some food items that could not be categorised according to the defined food classification hierarchy and some items covering animal feed were excluded from the analysis as was suspected duplicate data. Finally, clusters of very high values were noted suggesting local high contamination issues or more likely potential errors in the data transmission. Thus to better reflect the situation for the general population, data below the 1st percentile and above the 99th percentile for each food category were censored. Table 3 summarises all data treatment steps.

Table 3. Number of samples received and data remaining after data cleaning steps

Data description	Number of samples
Total samples received	187,143
Exclusion due to deficient food coding or food classification	2,227
Exclusion due to sampling before 2003	41,769
Exclusion due to suspected duplication	3,695
Exclusion as statistical outliers (outside 1st-99th percentile range)	2,250
Total samples included	137,202

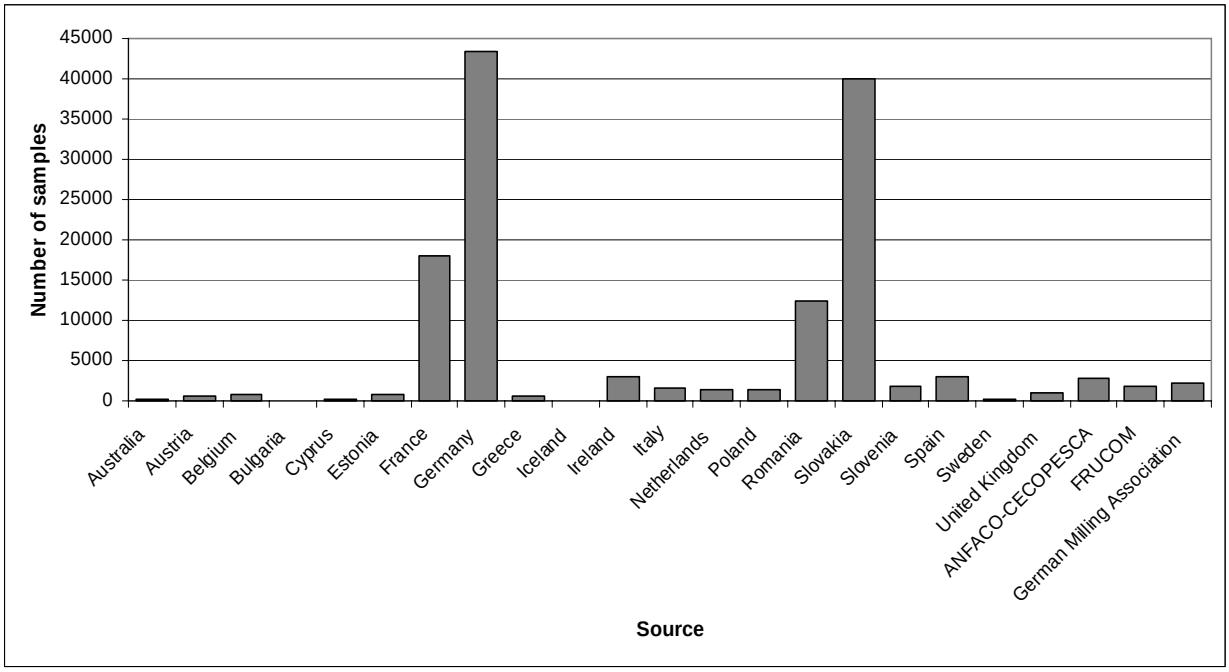

Figure 2. Distribution of samples across EU Member States, Iceland, Australia and commercial organisations

5.2.1. Summary of data collected

The source of 137,202 results reported from the 18 EU Member States, Iceland, Australia and three commercial organisations is illustrated in Figure 2.

Germany was the major non-commercial contributor providing 32 % of the data followed by Slovakia (29 %), France (13 %) and Romania (9 %).

The country of origin of food samples was indicated only for 4.7 % of the submitted results with 91 different countries listed, including EU Member States. A closer analysis was not performed since the few samples with the required information were not representative for the overall material.

5.2.2. Distribution of samples across food categories

Foods were initially classified using the aggregated food categories specified in the EFSA Concise European Food Consumption Database. The distribution of samples across the aggregated food categories is shown in Figure 3.

The dominating food categories covered were meat and meat products and substitutes (15 %), tap water (14 %), edible offal and offal products (12 %) and vegetables, nuts and pulses excluding vegetables soups (12 %).

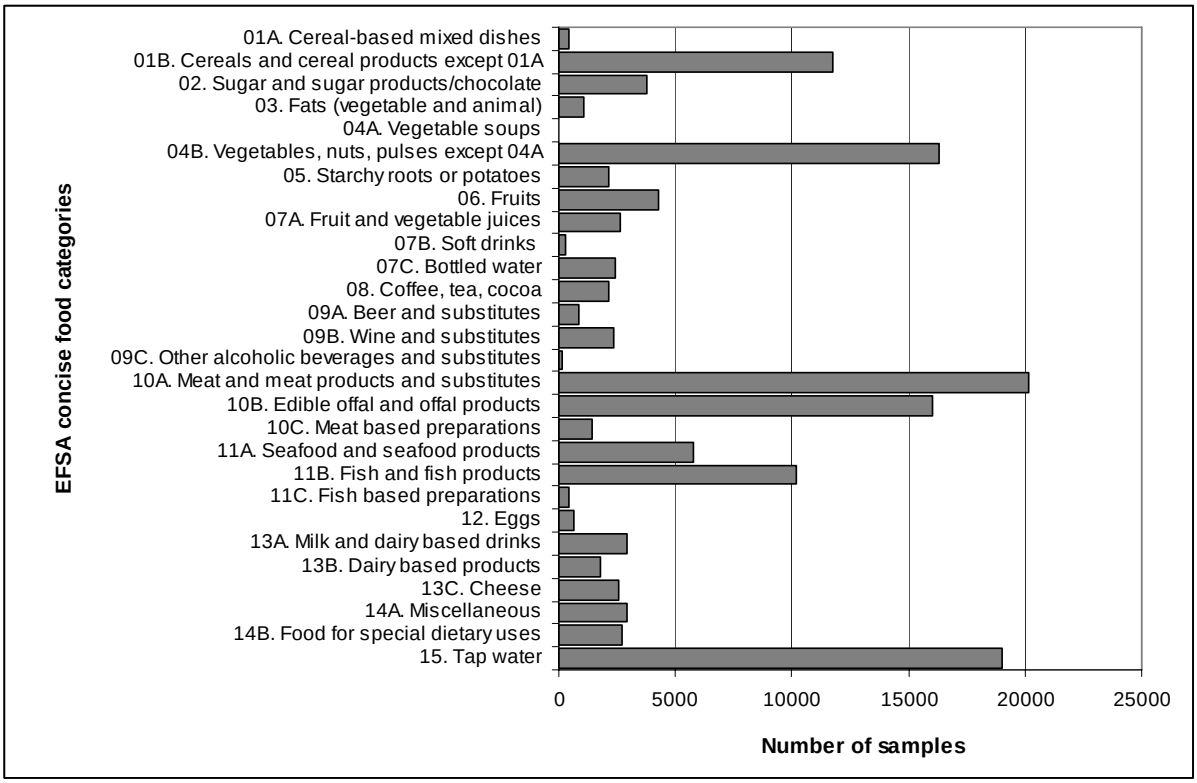

Figure 3. Sample distribution according to the aggregated food categories of EFSA's Concise European Food Consumption Database

5.2.3. Analytical methods used and limits of detection

The original results were reported in mg/kg (25.7 %), in µg/kg (65.4 %), in mg/L (0.4 %) and in µg/L (8.5 %). All the measures have been converted to mg/kg. For the measures expressed in relation to a volume unit, the approximate equivalence of 1 kg = 1 L has been used.

Several analytical methods have been used to perform the analyses (Figure 4). It should be noted that 53,684 (41.2 %) samples reported no information for the actual analytical method used apart from detection and quantification limits. Since so many of the results lacked a description of the analytical method it was not meaningful to cross tabulate the food matrix results with the analytical method.

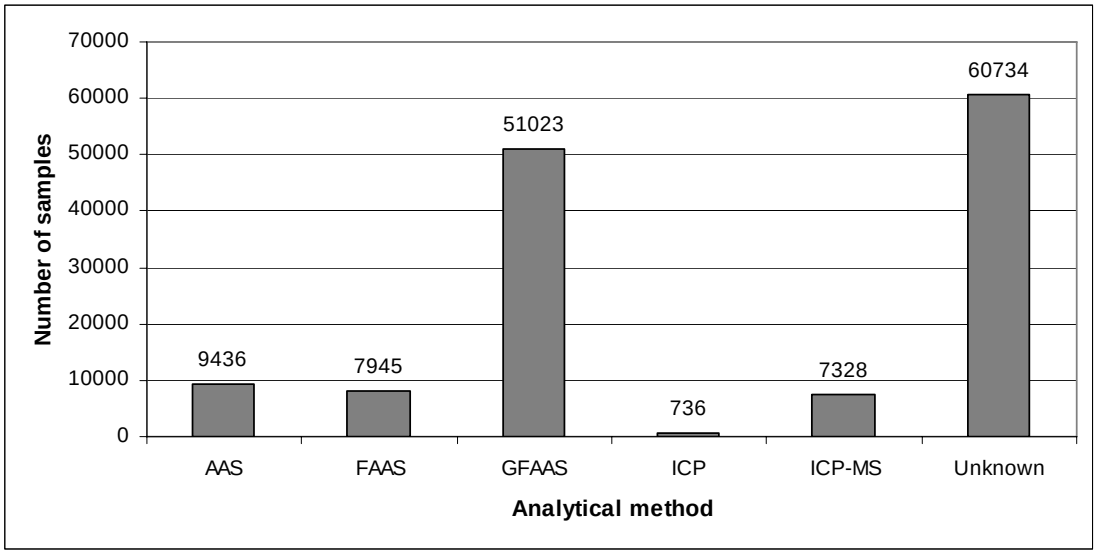

Figure 4. Distribution of analytical methods used (for abbreviations see Section 3.2.)

The LOD for the analyses varied with the analytical technique used and the food matrix (Figure 5).

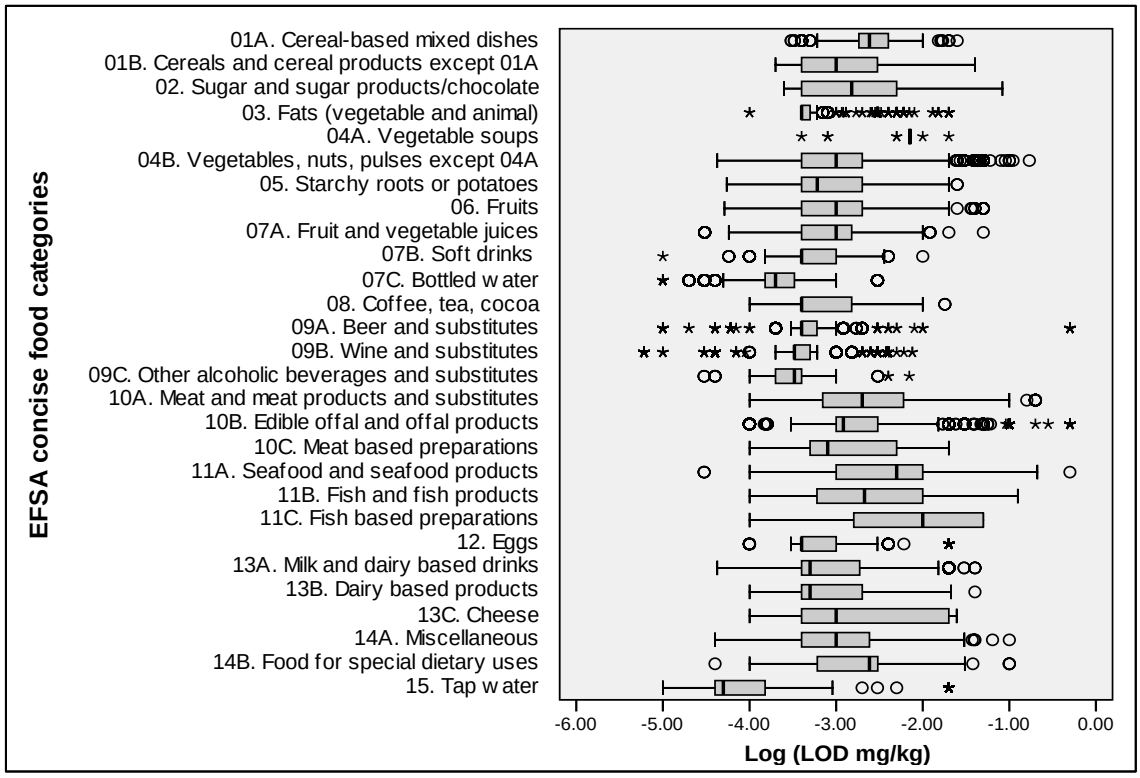

Figure 5. Distribution of the limit of detection according to the aggregated food categories of EFSA's Concise European Food Consumption Database. The box indicates lower and upper quartiles with a line at the median. The whiskers indicate minimum and maximum values with individual values marked as outliers (o) and extremes (x) as defined by the statistical package (SPSS, 2007).

The highest reported sensitivity was for water with a mean LOD almost 100 times lower than that for meat-based dishes although this could have been due to different analytical techniques used.

Most of the aggregated food categories show a considerable spread in the LOD reported. LODs and recoveries for cadmium are food matrix and method dependent, but there are also inter-laboratory differences. The sensitivity of the method is often set by the laboratory to fulfil legislative requirements and not fine tuned to optimal sensitivity for cost and time reasons. This is perfectly satisfactory for routine monitoring purposes, but does cause slight problems when results are used also to calculate human exposure.

In total, the number of samples with results below LOD was 33.9 %. This average result varied between food categories with most categories well below 60 % with the exception of bottled water (69 %), other alcoholic beverages (68 %), poultry and rabbit meat (67 %) and pig meat (66 %). The calculation of the descriptive statistics for the concentration of cadmium was performed by also taking into account the samples with results below the LOD. These samples were assigned a value of half the limit of detection. This approach is recommended by the GEMS/Food to be applied if less than 60 % of the results are below the LOD (WHO, 2003a). For completeness it should be noted that in some cases the LOQ was provided and the samples were reported with a concentration value below the limit of quantification. In these cases the numeric concentration was estimated as half of the limit of quantification.

5.2.4. Occurrence data by food category

Sampling adjustment factors (SAF) calculated from the German Nutrition Survey[12] (Mensink and Beitz, 2004) were applied when aggregating food subcategory averages to category averages. The relative consumption of food sub-groups in the respective food group was used to calculate a percentage for the respective SAF to correct for the unbalanced proportion of samples analysed in food subcategories in relation to their actual dietary contribution (see Table 4). In addition, a low arbitrary SAF (shown in brackets) was assigned to some food sub-categories (Tables 13 and 14) not captured by the methodology used in the German survey.

Table 4. An example of the use of sampling adjustment factors

Food category	N	SAF	Mean	Calculation	Adjusted mean
021. Chocolate	1022	21 %	0.0896	0.21 * 0.0896	0.0188 +
022. Chocolate based products	462	12 %	0.0234	0.12 * 0.0234	0.0028 +
023. Other sugar and sugar products	2326	67 %	0.0071	0.67 * 0.0071	0.0048 =
Total 02. Sugar and sugar products including chocolate	3810		0.0312		0.0264

The calculated SAFs for the vegetable sub-categories were checked against the equivalent GEMS/Food Consumption Cluster Diet information (FAO/WHO, 2006) as illustrated in Figure 6.

[12] The survey was done by the Robert-Koch-Institute in 1998 using the dietary history method and contains 4,030 persons aged between 18 and 79 years.

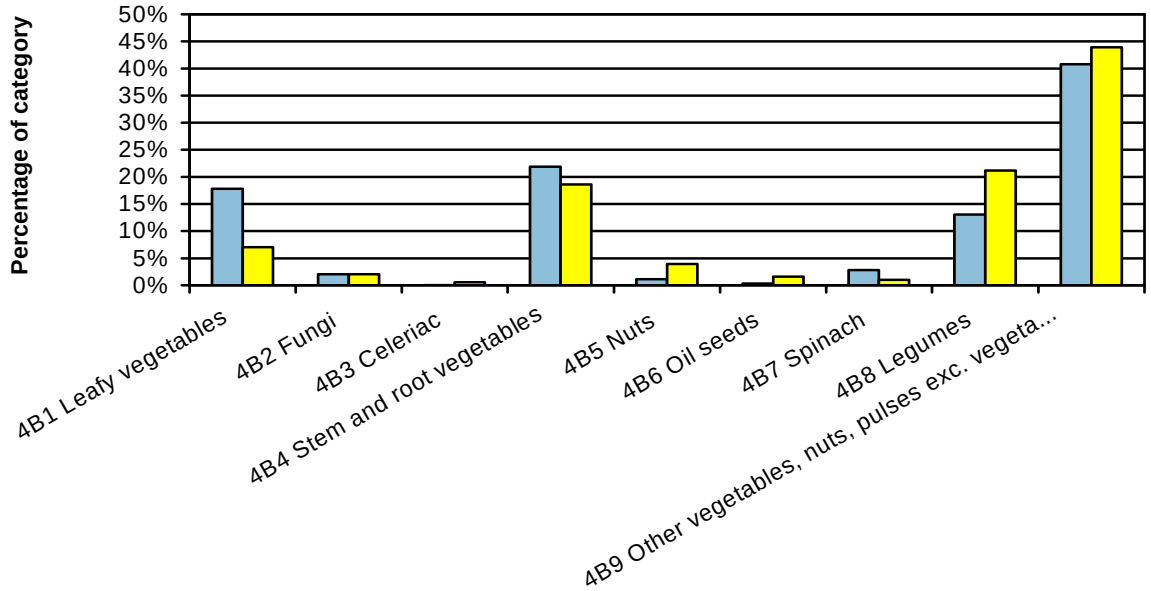

Figure 6. Comparison of German food consumption data (dark bar) with GEMS/Food cluster diet E data (light bar) for the vegetables category

The GEMS/Food database is based on a standardised food classification system of the Codex Alimentarius and hence mainly refers to raw food commodities. For this reason the data cannot be used to adjust means for all EFSA categories. Nevertheless, they were used to compare the SAFs derived from the German data for some food groups and found to be of similar magnitude. Although improving overall precision, it is acknowledged that the adjustment factors are associated with considerable uncertainty. Food commodities not directly consumed without further processing and thus without a SAF, e.g. wheat grains and flour, were not included in calculating cadmium concentrations for the aggregated food categories.

Table 5 to 19 report the data for aggregated and detailed food categories (see Annex 1A). Statistical descriptors include median, mean (with standard deviation – SD) and maximum concentrations as well as the 5th and 95th percentile concentrations (abbreviated as P5 and P95, respectively). N is the number of results reported and the column <LOD indicates the percentage of results below the LOD. The SAF was applied only when calculating adjusted aggregated category means in Table 20. The unadjusted means are shown in the respective tables with results for category totals.

Table 5. Statistical description of concentrations of cadmium for food category "01. Cereal and cereal products" in mg/kg

Food category	N	<LOD	P5	Median	Mean (SD)	P95	Max	SAF
Total 01A. Cereal-based mixed dishes	396	9.3 %	0.0025	0.0140	0.0166 (0.0134)	0.0400	0.0870	23 %
01B1. Bran and germ	348	3.7 %	0.0130	0.0615	0.0647 (0.0347)	0.1300	0.2200	-
01B2. Wheat products (Bread, pasta)	1976	17 %	0.0005	0.0100	0.0137 (0.0141)	0.0410	0.0820	42 %
01B3. Wheat grains and flour	4243	12 %	0.0005	0.0260	0.0300 (0.0250)	0.0800	0.1580	-
01B4. Rice	1000	12 %	0.0010	0.0200	0.0253 (0.0236)	0.0730	0.1340	9 %
01B5. Other cereals and cereal products	4216	16 %	0.0005	0.0100	0.0171 (0.0201)	0.0600	0.1300	26 %
Total 01B. Cereals and cereal products excl. cereal-based mixed dishes	11783	14 %	0.0005	0.0165	0.0233 (0.0241)	0.0700	0.2200	77 %
Total for 01. Cereal and cereal products	12179	14 %	0.0005	0.0160	0.0231 (0.0239)	0.0700	0.2200	100 %

The bran and germ category (01B1) displayed the highest values of cadmium. The reason for subdividing the wheat products into two subgroups: "01B2 Wheat products (bread, and pasta) and "01B3 Wheat grains and flour" is due to the higher values of cadmium found in the latter category compared to the wheat products category. The wheat grains and flour category (01B3) mainly contained data from wheat grain testing, which include also the wheat bran. The flour category also includes wholegrain flour. For this reason this category is expected to have a higher concentration of cadmium in comparison to the wheat product category.

Commission Regulation EC No. 1881/2006 defines MLs for the food classes "Cereals excluding bran, germ, wheat and rice" (0.10 mg/kg wet weight) and "Bran, germ, wheat and rice" (0.20 mg/kg wet weight). The samples exceeding the MLs can be calculated as follows:

- Bran and germ: Two (0.57 %) samples exceeding the ML
- Rice: Absence of sample exceeding the ML.

For the other categories listed in the table it is not possible to determine the number of samples above the ML since the MLs apply only to the raw commodities.

Table 6. Statistical description of concentrations of cadmium for food category "02. Sugar and sugar products including chocolate" in mg/kg

Food category	N	<LOD	P5	Median	Mean (SD)	P95	Max	SAF
021. Chocolate	1022	8.0 %	0.0030	0.042	0.0896 (0.0998)	0.3000	0.4700	21 %
022. Chocolate based products	462	3.0 %	0.0005	0.0090	0.0234 (0.0490)	0.0919	0.3700	12 %
023. Other sugar and sugar products	2326	57 %	0.0005	0.0045	0.0071 (0.0085)	0.0210	0.0680	67 %
Total 02. Sugar and sugar products including chocolate	3810	37 %	0.0005	0.0100	0.0312 (0.0654)	0.1826	0.4700	100 %

There are no MLs specified for chocolate or sugar products in the EU legislation.

Since it has been reported that dark chocolate can have elevated cadmium concentrations compared to milk chocolate an attempt was made to further split the "021. Chocolate" subcategory. The split was possible only for a small subset of samples with enough details provided, but revealed a mean cadmium concentration in 19 samples of dark chocolate of 0.1637 mg/kg compared to 0.0253 mg/kg in 122 samples of milk chocolate or around a sixfold difference. These results should be interpreted with caution because of the limited number of samples with an indication of the type of chocolate.

Table 7. Statistical description of concentrations of cadmium for food category "03. Fats (vegetable and animal)" in mg/kg

Food category	N	<LOD	P5	Median	Mean (SD)	P95	Max	SAF
03. Fats (vegetable and animal)	1064	14 %	0.0005	0.0010	0.0062 (0.0130)	0.0300	0.1040	100 %

No ML is currently defined in the EU legislation for fats.

Table 8. Statistical description of concentrations of cadmium for food category "04. Vegetables, nuts and pulses" in mg/kg

Food category	N	<LOD	P5	Median	Mean (SD)	P95	Max	SAF
04A. Vegetable soups	38	58 %	0.0007	0.0037	0.0127 (0.0306)	0.0400	0.1900	-
04B1. Leafy vegetables[13]	2389	22 %	0.0005	0.0150	0.0231 (0.0294)	0.0730	0.2000	18 %
04B2. Fungi	2017	14 %	0.0020	0.0250	0.2087 (0.4280)	1.2000	2.7090	2.0 %
04B3. Celeriac	20	15 %	0.0126	0.0500	0.1035 (0.1289)	0.3955	0.5000	-
04B4. Stem and root vegetables	2452	19 %	0.0005	0.0100	0.0205 (0.0319)	0.0740	0.3000	22 %
04B5. Nuts	1418	32 %	0.0020	0.0140	0.0434 (0.0672)	0.1900	0.4100	1.0 %
04B6. Oil seeds[14]	1819	4.9 %	0.0050	0.1520	0.2268 (0.2306)	0.7050	1.1050	-
04B7. Spinach	867	21 %	0.0005	0.0500	0.0615 (0.0612)	0.1860	0.3245	3 %
04B8. Legumes[14]	1322	30 %	0.0005	0.0030	0.0077 (0.0137)	0.0340	0.1140	13 %
04B9. Other vegetables not listed above except vegetable soups	3993	26 %	0.0005	0.0038	0.0068 (0.0099)	0.0270	0.0930	41 %
Total for 04B. Vegetables, nuts, pulses except 04A. vegetable soups	16297	21 %	0.0005	0.0100	0.0671 (0.1916)	0.3390	2.7090	100 %
Total 04. Vegetables, nuts and pulses	16335	21 %	0.0005	0.0100	0.0670 (0.1914)	0.3400	2.7090	100 %

The food categories defined in Regulation EC No. 1881/2006. for which MLs applies are "soybeans" (0.20 mg/kg), "vegetables and fruit, excluding leaf vegetables, fresh herbs, fungi, stem vegetables, pine nuts, root vegetables and potatoes" (0.050 mg/kg), "leaf vegetables, fresh herbs, cultivated fungi and celeriac" (0.20 mg/kg), "stem vegetables, root vegetables and potatoes, excluding celeriac" (0.10 mg/kg). For the purpose of the analysis soybeans have been included in the category 04B8. The mean value for soybeans that can be calculated based on 96 samples is 0.069 mg/kg. In regard to the MLs the results show:

Leaf vegetables without spinach: No samples are exceeding the ML.

Fungi: This category includes a variety of species, some which are cultivated and some that can only grow in the wild. For most samples there was no indication of the fungi species. However, cadmium concentrations of 0.4460 mg/kg for the 363 sample results clearly identified as not cultivated were almost three times higher than the 0.1630 mg/kg recorded for other varieties without a specification of their origin. Some samples consisted of dried mushrooms, but without any indication of the resulting water content, causing some uncertainty in the overall results. However, all results were expressed as analysed. In the literature it is common to express cadmium concentrations in mushrooms per dried weight

[13] According to Regulation (EC) No. 178/2006 leafy vegetables includes also spinach, but for the purpose of the occurrence analysis spinaches have been included in the separate category "04B_7. Spinach"

[14] According to Regulation (EC) No. 178/2006 oilseeds includes soybeans. For the purpose of the occurrence analysis, since only few samples where identifiable as soybeans, they have been included to the category "04B8 Legumes"

(d.w.) being about ten times higher than fresh weight results (water content generally assumed to be about 90 %). Thus cadmium concentrations between 0.1 and 5 mg/kg d.w. have been reported for most species. There are, however, a few edible species that have increased cadmium accumulating capacity. Species belonging to the group *flavescens* in genus *Agaricus*, as *Agaricus agustus* and *Agaricus abruptibulbus* have been reported to contain concentrations up to 80 mg/kg d.w.

- Celeriac: 4 (20 %) samples are exceeding the ML.
- Stem and root vegetables: 63 (2.6 %) samples are exceeding the ML.
- Spinach: 34 samples (3.9 %) are exceeding the ML.
- Other vegetables not listed above excl. vegetable soups: 34 (0.9 %) are exceeding the ML.

Table 9. Statistical description of concentrations of cadmium for food category "05. Starchy roots and potatoes" in mg/kg

Food category	N	<LOD	P5	Median	Mean (SD)	P95	Max	SAF
051. Potatoes	2116	15 %	0.0005	0.0150	0.0211 (0.0218)	0.0690	0.1420	96 %
052. Other starchy roots excl. potatoes	19	47 %	0.0009	0.0053	0.0158 (0.0203)	0.0761	0.0761	4.0 %
Total 05. Starchy roots or potatoes	2135	15 %	0.0005	0.0005	0.0211 (0.0218)	0.0690	0.1420	100 %

It was not always possible to distinguish between peeled or non-peeled potatoes, which made it difficult to compare with the ML set for peeled potatoes.

Table 10. Statistical description of concentrations of cadmium for food category "06. Fruit" in mg/kg

Food category	N	<LOD	P5	Median	Mean (SD)	P95	Max	SAF
06.Fruits	4300	56 %	0.0002	0.0005	0.0039 (0.0071)	0.0162	0.0500	100 %

For fruit the ML class applicable is "vegetables and fruit, excluding leaf vegetables, fresh herbs, fungi, stem vegetables, pine nuts, root vegetables and potatoes" (0.050 mg/kg). No samples showed values exceeding the ML.

Table 11. Statistical description of concentrations of cadmium for food category "07. Fruit and vegetable juices, soft drinks and bottled water" in mg/kg

Food category	N	<LOD	P5	Median	Mean (SD)	P95	Max	SAF
07A1. Fruit juices	2357	58 %	0.0002	0.0010	0.0020 (0.0035)	0.0070	0.0330	14 %
07A2. Vegetables juices	256	9.8 %	0.0005	0.0089	0.0081 (0.0057)	0.0170	0.0310	1.0 %
07A. Fruit and vegetable juices	2613	53 %	0.0002	0.001	0.0026 (0.0042)	0.0110	0.0330	15 %
07B. Soft drinks with percentage of fruits lower than nectar, excl. fruit juice	307	44 %	0.0002	0.0007	0.0026 (0.073)	0.0100	0.0900	15 %
Total 07C. Bottled water	2448	69 %	<0.0001	0.0005	0.0004 (0.0004)	0.0010	0.0030	70 %
Total 07. Fruit and vegetable juices, soft drinks and bottled water	5368	60 %	0.0001	0.0005	0.0016 (0.0036)	0.0080	0.0900	100 %

No specific MLs have been set for fruit and vegetable juices or soft drinks.

Table 12. Statistical description of concentrations of cadmium for food category "08. Tea, coffee and cocoa" in mg/kg

Food category	N	<LOD	P5	Median	Mean (SD)	P95	Max	SAF
081. Cocoa (powder or cocoa bean)	542	1.1 %	0.0080	0.1328	0.1776 (0.2568)	0.5000	2.0750	-
082. Coffee (powder)	544	13 %	0.0005	0.0040	0.0078 (0.0159)	0.0240	0.1900	60 %
083. Tea (powder or dry leaves)	816	20 %	0.0003	0.0150	0.0325 (0.0465)	0.1300	0.3120	26 %
084. Other herbal teas (powder or dry leaves)	213	5.6 %	0.0025	0.0620	0.1399 (0.1591)	0.5000	0.6900	14 %
Total 08. Tea, Coffee and Cocoa	2115	12 %	0.0005	0.0210	0.0741 (0.1590)	0.2560	2.0750	100 %

No MLs have been set in the EU legislation for cocoa, coffee and tea.

Table 13. Statistical description of concentrations of cadmium for food category "09. Alcoholic beverages" in mg/kg

Food category	N	<LOD	P5	Median	Mean (SD)	P95	Max	SAF
09A. Beer and substitutes	874	50 %	0.0001	0.0005	0.0050 (0.0303)	0.0050	0.2500	79 %
09B. Wine and substitutes	2371	59 %	0.0001	0.0005	0.0011 (0.0016)	0.0050	0.0125	20 %
09C. Other alcoholic beverages and substitutes	165	68 %	0.0001	0.0004	0.0008 (0.0016)	0.0050	0.0100	1.0 %
Total 09. Alcoholic beverages	3410	57 %	0.0001	0.0005	0.0021 (0.0155)	0.0050	0.2500	100 %

No EU MLs have been set for alcoholic beverages.

Table 14. Statistical description of concentrations of cadmium for food category "10. Meat and meat products, offal" in mg/kg. Arbitrary SAF values are shown in brackets. This category includes also soya meat substitutes.

Food category	N	<LOD	P5	Median	Mean (SD)	P95	Max	SAF
10A1. Soya meat substitutes	367	17 %	0.0005	0.0120	0.0208 (0.0220)	0.0640	0.1240	(0.1 %)
10A2. Bovine, sheep and goat meat	6382	51 %	0.0005	0.0050	0.0090 (0.0198)	0.0370	0.1800	20 %
10A3. Poultry and Rabbit meat	3653	67 %	0.0005	0.0030	0.0047 (0.0052)	0.0100	0.0490	12 %
10A4. Pig meat	6428	66 %	0.0005	0.0050	0.0076 (0.0112)	0.0210	0.1100	42 %
10A5. Horse meat	1219	25 %	0.0040	0.0300	0.1715 (0.6128)	0.6400	8.7460	(0.1 %)
10A6. Game meat	1402	44 %	0.0005	0.0020	0.0038 (0.0055)	0.0150	0.0450	(0.2 %)
10A7. Not specified meat and meat products	691	45 %	0.0005	0.0050	0.0060 (0.0061)	0.0160	0.0400	(0.2 %)
Total 10A. Meat and meat products and substitutes	20142	56 %	0.0005	0.0050	0.0173 (0.1563)	0.0430	8.7460	74.6 %
10B1. Liver bovine, sheep, pig, poultry, horse	10534	11 %	0.0050	0.0430	0.1160 (0.3060)	0.3600	3.6000	5.0 %
10B2. Kidney bovine, sheep, pig, poultry, horse	4586	11 %	0.0100	0.1520	0.2009 (0.2052)	0.5743	1.7300	(0.2 %)
10B3. Liver and kidney of game animals	206	4.9 %	0.0090	0.0740	0.1760 (0.2906)	0.5150	2.0600	(0.1 %)
10B4. Other offal products (tripe, lung, stomach etc.)	223	52 %	0.0005	0.0100	0.0370 (0.1157)	0.1430	1.1200	2.0 %
10B5. Not specified offal product	500	1.0 %	0.0012	0.4500	2.2278 (4.4805)	11.690	34.500	(0.1 %)
Total for 10B. Edible offal and offal products	16049	11 %	0.0050	0.0620	0.2057 (0.9122)	0.6000	34.500	7.4 %
Total for 10C. Meat based preparations	1392	42 %	0.0005	0.0040	0.0076 (0.0112)	0.0240	0.1100	18 %
Total for 10. Meat and meat products, offal	37583	36 %	0.0005	0.0100	0.0974 (0.6141)	0.3010	34.500	100 %

The ML for meat products (excluding offal) of bovine animals, sheep, pig and poultry is 0.050 mg/kg, for horsemeat (excluding offal) 0.20 mg/kg. For liver of bovine animals, sheep, pig, poultry and horse the ML is 0.50 mg/kg and for kidney of bovine animal, sheep, pig, poultry and horse it is 1.0 mg/kg. The number of samples exceeding the MLs is:

- Bovine, sheep and goat meat: 231 (3.6 %); poultry and rabbit meat: none; pig meat: 101 (1.6 %)
- Horse meat: 132 (11 %)
- Liver bovine, sheep, pig, poultry, horse: 393 (3.7 %)
- Kidney bovine, sheep, pig, poultry, horse: 44 (0.96 %).

Table 15. Statistical description of concentrations of cadmium for food category "11. Fish and seafood" in mg/kg. Arbitrary SAF values are shown in brackets.

Food category	N	<LOD	P5	Median	Mean (SD)	P95	Max	SAF
11A1. Bivalve molluscs other than oysters	1388	2.3 %	0.0280	0.1630	0.3797 (0.6426)	1.4000	4.5250	(0.1 %)
11A2. Crustaceans	1896	44 %	0.0005	0.0125	0.0929 (0.2250)	0.5000	2.3000	3.0 %
11A3. Cephalopods	1017	13 %	0.0130	0.1200	0.2845 (0.4049)	1.2000	2.3000	(0.1 %)
11A4. Oysters	164	0.68 %	0.0900	0.2350	0.2916 (0.2074)	0.8400	0.9700	(0.1 %)
11A5. Snails and limpets	124	10 %	0.0100	0.1800	0.2552 (0.2753)	0.6850	1.7480	-
11A6. Other seafood products	1209	3.2 %	0.0125	0.0800	0.1465 (0.2333)	0.4600	2.1800	(0.1 %)
Total 11A. Seafood and seafood products	5780	18 %	0.0025	0.0835	0.2152 (0.4147)	0.9600	4.5200	3.4 %
11B1. Fish muscle matching ML group 3.2.5[15]	6393	53 %	0.0005	0.0050	0.0137 (0.0306)	0.0500	0.3000	43 %
11B2. Fish muscle matching ML group 3.2.6[15]	1250	46 %	0.0005	0.0125	0.0310 (0.0439)	0.1300	0.2800	52 %
11B3. Swordfish	356	29 %	0.0080	0.0359	0.0627 (0.0701)	0.2280	0.3990	(0.1 %)
11B4. Other fish and fish products	2173	33 %	0.0010	0.0120	0.0411 (0.0911)	0.1940	0.6600	0.5 %
Total 11B.Fish and fish products	10172	47 %	0.0005	0.0065	0.0234 (0.0544)	0.1000	0.6600	95.6 %
Total 11C. Fish based preparations	398	49 %	0.0025	0.0100	0.0677 (0.1424)	0.3300	1.3000	(1.0 %)
Total for 11. Fish and seafood	16350	37 %	0.0005	0.0130	0.0923 (0.2673)	0.4000	4.5250	100 %

[15]The groups refer to the Annex of Regulation (EC) No. 1881/2006 in its version of 19 December 2006. In the meantime, the Annex has been amended by Regulation (EC) No. 629/2008 and here the fish species anchovy (*Engraulis* species) is included in ML group 3.2.7 (3.2.8 in amended regulation EC No 629/2008) together with swordfish (see also Table 1).

The ML is 0.10 mg/kg for muscle meat of the following fish species (ML group 3.2.6): anchovy (*Engraulis* spp), bonito (*Sarda sarda*), common two-banded seabream (*Diplodus vulgaris*), eel (*Anguilla anguilla*), grey mullet (*Mugil labrosus labrosus*), horse mackerel or scad (*Trachurus* spp), louvar or luvar (*Luvarus imperialis*), sardine (*Sardina pilchardus*), sardinops (*Sardinops* spp), tuna (*Thunnus* species, *Euthynnus* spp, *Katsuwonus pelamis*), wedge sole (*Dicologoglossa cuneata*). For swordfish (*Xiphias gladius*) the level is 0.30 mg/kg (ML group 3.2.7[15]). For all other muscle meat of fish the level is 0.050 mg/kg (ML group 3.2.5[15]).

The number of samples (percentages in brackets) exceeding the ML is:

- Muscle meat of fish matching ML group 3.2.5[15]: 305 (4.8 %)
- Muscle meat of fish matching ML group 3.2.6[15]: 102 (8.2 %)
- Muscle meat of swordfish (ML group 3.2.7) [15]: 7 (2.0 %)
- Other or not elsewhere classifiable fish products: 365 (17 %)

For seafood, MLs have been defined for the following groups: crustaceans, excluding brown meat of crab and excluding head and thorax meat of lobster and similar large crustaceans (*Nephropidae* and *Palinuridae*) 0.50 mg/kg, bivalve molluscs 1.0 mg/kg, cephalopods (without viscera) 1.0 mg/kg.

The number of samples (and percentages in brackets) exceeding the ML is:

- Bivalve molluscs other then oysters: 130 (9.4 %)
- Crustaceans: 92 (4.9 %)
- Cephalopods: 72 (7.1 %)
- Oysters: None.

A closer look at the "11A2 Crustaceans" subcategory revealed that the mean cadmium concentration for crab meat was lower while for crayfish, with only 17 sample results reported, it was three times higher than the mean for the group as a whole. Crayfish can be seasonally consumed in high amounts in some countries, but with so few sample results reported there should be caution in drawing any firm inference from the results.

Table 16. Statistical description of concentrations of cadmium for food category "12. Eggs" in mg/kg

Food category	N	<LOD	P5	Median	Mean (SD)	P95	Max	SAF
12. Eggs	667	48 %	0.0003	0.0006	0.0030 (0.0041)	0.0100	0.0180	100 %

No ML has been set in the EU legislation for eggs.

Table 17. Statistical description of concentrations of cadmium for food category "13. Milk and dairy based products" in mg/kg. This category includes also soya milk substitutes.

Food category	N	<LOD	P5	Median	Mean (SD)	P95	Max	SAF
13A1. Soya milk	8	50 %	0.0020	0.0045	0.0185 (0.0259)	0.0610	0.0610	-
13A2. Milk and dairy drinks non soya based	2909	47 %	0.0003	0.0010	0.0030 (0.0040)	0.0100	0.0260	57 %
13A. Milk and dairy based drinks	2917	47 %	0.0003	0.0010	0.0030 (0.0043)	0.0100	0.0610	57 %
13B. Dairy based products	1797	35 %	0.0005	0.0020	0.0044 (0.0054)	0.0110	0.0350	30 %
13C. Cheese	2591	54 %	0.0005	0.0050	0.0065 (0.0084)	0.0130	0.0970	13 %
Total 13. Milk and diary based products	7305	47 %	0.0005	0.0020	0.0046 (0.0065)	0.0100	0.0970	100 %

Soya milk has been placed in the category milk and dairy based products since it is a substitute for milk with a similar consumption pattern. No MLs have been set for dairy products in EU legislation.

Table 18. Statistical description of concentrations of cadmium for food category "14. Miscellaneous/Food for special dietary uses" in mg/kg

Food category	N	<LOD	P5	Median	Mean (SD)	P95	Max	SAF
14A1. Herbs	557	16 %	0.0015	0.0174	0.0451 (0.0731)	0.2010	0.4700	-
14A2. Spices	779	16 %	0.0010	0.0339	0.0738 (0.0977)	0.2840	0.6120	8.0 %
14A3. Soya sauce	6	17 %	0.0040	0.0172	0.0192 (0.0158)	0.0450	0.0450	-
14A4. Other miscellaneous products	1547	38 %	0.0005	0.0050	0.0767 (0.2827)	04000	3.0000	12 %
14A. Miscellaneous	2889	28 %	0.0005	0.0100	0.0697 (0.2158)	0.2900	1.8000	20 %
14B1. Supplements	1305	33 %	0.0005	0.0130	0.2357 (1.5560)	0.4800	20.717	-
14B2. Other food for special dietary uses	1387	45 %	0.0005	0.0050	0.0116 (0.0164)	0.0380	0.1800	80 %
14B. Food for special dietary uses	2692	39 %	0.0005	0.0080	0.1202 (1.0890)	0.2800	20.717	80 %
Total 14. Miscellaneous and food for special dietary uses	5581	33 %	0.0005	0.0100	0.0941 (0.7724)	0.2900	20.717	100 %

Apart from a ML for cadmium in fresh herbs (0.20 mg/kg), no MLs have been set in EU legislation for the other food groups listed in Table 18. However, group 14A1 comprises fresh and dried herbs. Comparison with the ML is therefore not possible.

In Regulation (EC) No. 629/2008 amending Regulation (EC) No. 1881/2006 MLs for food supplements have been set. The MLs are 1.0 mg/kg for food supplements in general and 3.0 mg/kg for food supplements consisting exclusively or mainly of dried seaweed or of products derived from seaweed. These MLs will be applicable as from 1 July 2009.

Table 19. Statistical description of concentrations of cadmium for food category "15. Tap water" in mg/kg

Food category	N	<LOD	P5	Median	Mean (SD)	P95	Max	SAF
15.Tap water	19000	34 %	1E-05	0.0001	0.0004 (0.0013)	0.0007	0.0100	100 %

For tap water the ML set in Council Directive 98/83/EC of 5 µg/L applies. The mean of the cadmium concentration in water is 8 % of the ML. The number of samples exceeding the ML is 1.9 %.

Summary of occurrence means and weighted occurrence means

As discussed previously, the means extracted from the data need to be adjusted so that the analytical results are weighted in terms of their relative contribution to the diet, rather than in terms of the number of samples analysed. These separate adjustments for the fifteen EFSA concise food categories are shown in Table 20 and applied in the exposure assessment calculations. To match consumption expressed as liquid, occurrence in the food category "08. Coffee tea and cocoa" was also transformed into liquid by dividing the concentration in the dry product with a factor of 18 assuming that 7 g of coffee powder is used with 125 mL of water (Maier, 1991). Because offal is known to contain high concentrations of cadmium, it was decided to divide category 10 into its three subcategories, including the separate category covering offal. Not all Member States submitted food consumption information for all three subcategories, thus in some cases cadmium concentrations for category 10 as a whole will be used.

As can be seen in the table it is possible for the value of the adjusted mean to be higher than the value of the initial mean calculated only based on the mix of samples submitted. For example this is the case for category "09. Alcoholic beverages" where the sub-category "09A. Beer and substitutes" had an average cadmium concentration much higher than the other sub-categories, but represented only around 25 % of the sample results received. In reality the "beer and substitutes" sub-category constitutes around 79 % of the consumption of alcoholic beverages. Thus, when adjusting the occurrence mean for the actual share of consumption, the resulting mean will increase.

Table 20. Cadmium occurrence means adjusted by applying a sample adjustment factor in comparison with original occurrence means calculated from the sample data

EFSA Concise Food Category	Occurrence Mean (mg/kg)	Adjusted Occurrence Mean (mg/kg)
01. Cereals & cereal products	0.0231	0.0163
02. Sugar & sugar products including chocolate	0.0312	0.0264
03. Fats (vegetable and animal)	0.0062	0.0062
04. Vegetables, nuts and pulses	0.0670	0.0189
05. Starchy roots or potatoes	0.0211	0.0209
06. Fruits	0.0039	0.0039
07. Fruit and vegetable juices, soft drinks and bottled water	0.0016	0.0010
08. Coffee, tea, cocoa (expressed as liquid)	0.0041	0.0018
09. Alcoholic beverages	0.0021	0.0042
10. Meat and meat products, offal	0.0974	0.0165
10.A Meat and meat products and substitutes	0.0173	0.0077
10,B Edible offal and offal products	0.2057	0.1263
10.C Meat based preparations	0.0076	0.0076
11. Fish and seafood	0.0923	0.0268
12. Eggs	0.0030	0.0030
13. Milk and dairy based products	0.0046	0.0039
14. Miscellaneous and food for special dietary uses	0.0941	0.0244
15. Tap water	0.0004	0.0004

6. Food consumption

Dietary exposure to cadmium from food sources is determined not only by cadmium levels in foods, but also by consumption patterns. Some of the food items that contain high cadmium levels as reported in Chapter 5.2.4 are rarely consumed by the general European population (e.g. oilseeds and edible offal) and therefore might not be important for overall intake. Other food items with high consumption in the total population or in some sub-populations can be major contributors to the overall cadmium intake even if they contain only low cadmium levels.

It is thus important to analyse food consumption data of all food groups containing cadmium and to look for sub-populations that could have a higher intake of cadmium because of different consumption patterns. This particularly includes country specific differences between the EU Member States. The EFSA Concise European Food Consumption database (EFSA, 2008) provides data from EU Member States and can thus provide relevant consumption patterns across most of Europe. However, currently it provides data aggregated in broad food categories only and for the adult population. Food sub-categories were thus aggregated into the broad food categories using weighting factors provided by detailed German food consumption information (see section 5.2.4). In addition, separate analyses were undertaken for vegetarians and children using detailed French consumption information for ovolactovegetarians as an approximation for general vegetarians and Italian food consumption data for children, respectively.

6.1. EFSA Concise European Food Consumption database

The EFSA Concise European Food Consumption database was established by EFSA to support exposure assessments in the EU. Initially 16 countries provided national data to EFSA for the database. To obtain comparable results, data were aggregated into 15 broad food groups, although some Member States provided data also for certain subgroups. The consumption figures for the food groups are linked to individual data on gender, age and body weight. Main statistics of the data are available at the EFSA website and contain mean consumption, median and standard deviation as well as several low and high percentiles of consumption for the general population and for consumers only.

The concise database is intended as a screening tool for exposure assessment as well as the first step in generating a more comprehensive database. It allows assessment of the overall exposure of population groups to a wide variety of substances. Limitations arise from the broad food categories defined and from the different methodologies of data collection applied in different countries. The use of this database may be sufficient when the exposure calculation, based on conservative assumptions for occurrence concentrations, is below the level of concern. If this is not the case, as in this opinion, further refinements might be necessary, particularly defining sub-categories of interest and adjusting occurrence means using appropriate SAF. A guidance document for the use of the data has been published on the EFSA website (see Annex 3 to EFSA, 2008). Summaries of the food consumption data used in this opinion are given in Tables 21 to 23.

Table 21. Mean food consumption (g/day)[1] in the total adult population as recorded in 16 European countries (Annex 3 to EFSA, 2008)

Food category		BE	BG	CZ	DK	FI	FR	DE	HU	IS	IE	IT	NL	NO	SK	SE	GB
01	Cereals & cereal products	245	257	274	217	153	317	287	252	276	227	271	220	192	345	291	249
02	Sugar & sugar products including chocolate	31	40	39	43	42	31	45	39	31	41	19	43	47	69	28	27
03	Fats (vegetable and animal)	46	39	48	36	40	28	29	54	33	36	36	48	41	29	24	20
04	Vegetables, nuts and pulses	230	210	131	166	135	210	252	191	125	244	249	193	140	164	118	163
05	Starchy roots or potatoes	95	83	103	112	95	67	125	110	79	229	48	128	133	96	138	112
06	Fruits	113	70	122	150	121	132	190	180	71	106	203	107	119	116	119	95
07	Fruit and vegetable juices, soft drinks and bottled water	945	207	618	340	213	389	947	280	426	179	384	296	491	382	329	325
08	Coffee, tea, cocoa (expressed as liquid)	432	120	559	836	580	282	691	176	429	714	124	887	604	461	575	724
09	Alcoholic beverages	214	102	413	292	139	163	231	76	104	335	126	206	123	64	191	313
10	Meat and meat products, offal	123	114	187	135	120	202	167	186	110	148	137	152	109	156	150	161
10.A	Meat and meat products and substitutes	121	108	175	128		134	127	173	93	122	134	141	103	179		49
10.B	Edible offal and offal products	2	7	9	7		8	11	13	6	1	3	5	6	12		2
10.C	Meat based preparations	0	0	4	0		60	29	0	11	24	0	6	0	12		110
11	Fish and seafood	25	20	19	18	27	37	19	9	37	24	43	13	63	9	34	31
12	Eggs	10	21	20	16	17	18	23	27	11	20	18	15	21	13	14	19
13	Milk and dairy based products	203	169	186	386	437	265	313	265	442	306	212	388	522	91	386	251
14	Miscellaneous / Food for special dietary uses	2	13	15	5	24	2	36	17	23	13	5	6	12	6	16	17
15	Tap water	100		288	840	886	283	71	1	670	284	206	209	312	224	480	205

[1]) As reported by the individual country

Table 22. Mean food consumption (g/day)[1] in adult consumers only as recorded in 16 European countries (Annex 3 to EFSA, 2008)

Food category		BE	BG	CZ	DK	FI	FR	DE	HU	IS	IE	IT	NL	NO	SK	SE	GB
01	Cereals & cereal products	247	262	274	217	154	317	287	252	277	227	271	221	192	372	291	250
02	Sugar & sugar products including chocolate	38	59	41	44	44	33	45	40	45	42	21	48	47	143	31	31
03	Fats (vegetable and animal)	48	42	48	36	40	28	29	54	36	36	36	49	41	59	25	21
04	Vegetables, nuts and pulses	238	219	132	166	137	212	252	191	137	244	249	196	140	253	119	164
05	Starchy roots or potatoes	119	174	128	114	104	70	126	129	155	230	55	146	134	224	140	114
06	Fruits	168	185	147	165	143	156	195	204	150	122	210	141	121	235	132	120
07	Fruit and vegetable juices, soft drinks and bottled water	994	425	698	371	302	452	955	330	656	208	463	387	520	820	355	374
08	Coffee, tea, cocoa (expressed as liquid)	515	202	573	908	603	296	714	229	654	734	140	917	634	551	598	752
09	Alcoholic beverages	403	423	736	352	437	229	245	261	631	468	178	427	155	595	242	425
10	Meat and meat products, offal	129	146	192	135	125	203	167	187	134	150	138	154	110	261	151	169
10.A	Meat and meat products and substitutes	127	140	180	129		135	127	174	120	125	135	144	103	259		55
10.B	Edible offal and offal products	24	116	37	10		23	12	36	95	13	25	22	8	174		17
10.C	Meat based preparations			110			84	33		190	33	19	41		225		120
11	Fish and seafood	60	194	80	20	65	43	23	70	115	35	51	63	64	138	39	44
12	Eggs	26	41	23	16	21	28	23	28	39	21	20	28	21	108	22	28
13	Milk and dairy based products	211	208	191	386	440	266	313	267	453	306	212	391	522	218	387	253
14	Miscellaneous / Food for special dietary uses	7	13	15	5	24	12	36	17	27	13	5	10	12	31	23	20
15	Tap water	467		302	841	887	404	71	167	806	302	247	252	349	722	569	327

[1)] As reported by the individual country

Table 23. 95th percentile food consumption (g/day)[1] in adult consumers only as recorded in 16 European countries (Annex 3 to EFSA, 2008)

Food categories		BE	BG	CZ	DK	FI	FR	DE	HU	IS	IE	IT	NL	NO	SK	SE	GB
01	Cereals & cereal products	503	560	551	359	283	546	490	400	613	395	427	393	337	760	503	466
02	Sugar & sugar products including chocolate	98	180	114	101	122	87	127	93	165	109	55	120	121	240	81	88
03	Fats (vegetable and animal)	140	89	109	75	86	55	54	102	103	75	64	113	99	150	66	51
04	Vegetables, nuts and pulses	581	542	309	337	324	461	504	356	365	544	460	407	321	600	254	357
05	Starchy roots or potatoes	279	396	269	273	241	152	257	258	317	558	132	316	283	493	289	235
06	Fruits	383	512	375	445	378	410	497	485	360	365	470	361	337	600	320	331
07	Fruit and vegetable juices, soft drinks and bottled water	2250	1000	1700	1057	850	1234	2150	940	1700	613	1022	1050	1603	2000	943	1053
08	Coffee, tea, cocoa (expressed as liquid)	1313	450	1150	1971	1210	850	1686	600	1500	1387	344	1757	1367	1400	1157	1636
09	Alcoholic beverages	1156	1100	2250	1027	1470	764	986	863	2000	1759	514	1313	550	1500	661	1549
10	Meat and meat products, offal	296	363	426	258	288	376	341	343	359	289	264	306	212	625	270	329
10.A	Meat and meat products and substitutes	293	300	397	243		261	266	333	288	250	257	288	201	460		124
10.B	Edible offal and offal products	12	52	57	25		40	36	62	18	9	21	30	20	50		51
10.C	Meat based preparations	0	0	0	0		194	99	0	100	81	0	39	0	30		262
11	Fish and seafood	174	424	175	55	174	110	57	160	288	86	128	163	154	250	95	111
12	Eggs	87	160	79	43	72	69	61	75	136	57	44	75	47	250	50	71
13	Milk and dairy based products	539	575	522	921	1015	570	870	610	1146	668	435	868	1173	600	802	553
14	Miscellaneous / Food for special dietary uses	17	32	33	10	82	54	177	35	133	48	13	30	22	150	71	56
15	Tap water	1330		836	2144	2018	1064	202	267	2238	1038	728	997	1200	2000	1600	1144

[1] As reported by the individual country

6.2. French data for vegetarians

Because of the relative high cadmium levels of some vegetables, including oilseeds and cereals like wheat, vegetarians have a higher probability of excessive cadmium intake than the general population. Data on vegetarians are not available from the EFSA database. Thus, published data from France were used to answer the question of whether the specific consumption patterns of vegetarians might yield higher risks (Table 24).

Table 24. Data for vegetarians taken from Appendix 1 of the 1st French Total Diet Study (Leblanc *et al.*, 2004)

	Consumption g/day			
	Ovolactovegetarian [a] over 15 years (n = 74)		General population (n = 1474)	
	Mean	P95	Mean	P95
Other cereals	2.2	9.7	0.9	-
Butter	6.1	18.4	13.6	34.1
Biscuits	13.4	45.2	13.9	57.1
Alcoholic beverages	61.8	268.3	86.6	402.4
Hot beverages	1.0	6.0	3.7	23.3
Coffee	92.8	389.6	200.7	600.0
Breakfast cereals	11.3	44.8	4.9	34.3
Chocolate	6.7	26.1	2.7	14.3
Stewed fruit, compote	15.9	73.5	6.08	42.9
Salads	5.3	44.2	4.1	28.6
Desserts	20.4	75.0	19.8	85.7
Cheeses	57.2	151.5	25.6	75.0
Fruits	109.8	330.0	17.0	121.9
Nuts and oilseeds	32.4	101.4	3.0	17.1
Milk	72.8	286.1	119	352
Vegetables (except potatoes)	20.5	80.5	16.2	52.2
Pulses	28.7	95.7	10.3	42.9
Eggs and eggs products	27.1	72.8	18.3	57.14
Bread, rusk	90.9	218.7	122.6	280.6
Pasta	21.1	76.1	36.1	100.0
Cakes	38.3	140.4	35.6	121.8
Pizza, salt cake and quiches	21.4	92.2	21.8	81.7
Rice and semolina	28.3	90.0	20.8	71.4
Ultra-fresh dairy products	54.9	211.1	70.4	214
Viennese bread and buns	8.5	38.2	17.3	84.8

a) The report of the 1st French Total Diet Study refers to data on "ovolactovegetariens". However, in the opinion the wider term vegetarian was used.

The French data indicate that vegetarians eat in particular a tenfold higher amount of oilseeds than the general French population. Consumption of pulses is nearly threefold higher and consumption of breakfast cereals twofold higher than respective consumptions in the general French population and also the consumption of vegetables is about 25 % higher for different age groups.

6.3. Food consumption data for different age groups from Italian surveys

For the purpose of this assessment, the food groups and subgroups used in the occurrence section were matched with the food consumption information available from the 1994 - 1996 national survey of 1940 Italian subjects carried out by the Italian Istituto Nazionale di Ricerca per gli Alimenti e la Nutrizione (INRAN) (Turrini *et al.*, 2001; Turrini and Lombardi-Boccia, 2002). The INRAN database contains consumption data and other relevant information (e.g. body weight and age) expressed for each individual.

In detail, the 64 food categories of interest (including drinking water and other non-alcoholic drinks) of the INRAN database were clustered into groups to match the EFSA Concise European Food Consumption database (EFSA, 2008). In the attempt of preserving consistency, in some instances the matching process likely introduced some degree of arbitrariness as clarified by the following examples:

- biscuits, cakes, pastries, etc., classified under INRAN "Sugar and sugar products", were reclassified under the EFSA database as "Cereal and cereal products";
- butter, classified under INRAN "Fats" but not explicitly so in the instruction for the EFSA database, was provisionally considered to be part of the EFSA database "Milk and dairy products";
- vegetables and vegetal foods, grouped differently in the INRAN and EFSA databases, were rearranged for exposure assessment, and associated with a consumption-weighted cadmium occurrence mean to take into account the effect of fungi and spinach (consumption rates obtained from (WHO, 2003b);
- ice-cream, classified under INRAN "Sugar and sugar products", was reclassified under the EFSA database "Milk and dairy products";
- dietetic products and sweeteners (low consumption products, not contemplated in the Concise database), classified under INRAN "Dietetic products and sweeteners", were reclassified under the EFSA database "Food for special dietary uses";

The following low consumption INRAN entries could not be matched with the EFSA database: baby foods; dressing and sauces; fruit-based dishes; ready-to-eat dishes; salt, vinegar, and yeast; salted snacks, sandwiches, etc.

On the whole, three food consumption data sets were obtained according to the following age ranges (years): 0.5–6 (toddlers, breastfed not included; N = 88); 7–12 (children; N = 105); 13–94 (adults; N = 1747). A 0.5–12 years old group (N = 193) was later created to improve intake statistics.

7. Human exposure assessment

The dietary exposure assessment is based on the occurrence data on cadmium concentrations (Table 20), with non-detected values entered at half the limit of detection. It is also based on consumption data reported in the EFSA Concise European Food Consumption database (Tables 21 to 23). Although it is well known that dietary exposure is a main contributor to overall cadmium exposure, in addition to cigarette smoke, other exposure sources cannot be neglected and will be briefly discussed. All exposure scenarios detailed below are based on

the mean concentration of cadmium, for each food group. The decision to use the mean concentration is based on the chronic toxicity impact of accumulated cadmium in the body and the assumption that lifetime consumption will involve varying cadmium concentrations in foods consumed, while the average long-term exposure will approach the mean cadmium concentration in the food groups. To express the range of possible exposures, the food consumption information used in the model includes mean and the 95th percentile consumption of the distribution for each individual food group.

The assessment was undertaken in three steps according to the guidance for the use of the concise database: determination of the main food vehicles; estimation of the average dietary exposure; and estimation of the dietary cadmium exposure of the highly exposed consumers (EFSA, 2008).

7.1. Contributions of different food groups to cadmium exposure

Due to the ubiquitous presence of cadmium in food, the food categories that contribute significantly to the dietary exposure are determined either by a high level of contamination of the food or by high amounts consumed of a food with lower contamination levels.

The contribution of each broad food category to total exposure was calculated from the mean consumption of consumers[16] only, as determined in each country for the corresponding food category. The median of the mean values (expressed in g/day) was determined and multiplied by the mean contamination level (expressed in mg/kg). Results are therefore expressed in µg/day and are summarised in Table 25. Because the consumption surveys in the countries involved used different methodologies for data collection, the mean consumption values cannot be averaged and thus the median value for all the countries was used as an approximation.

[16] Consumers are defined as subjects consuming the food category under consideration at least once during the survey duration.

Table 25. Estimated consumer exposure to cadmium by different food groups. The occurrence mean values are the adjusted means reported in Table 20. The consumption median values are calculated from Table 22 (mean consumption in adult consumers only) as median of the values across the Member States for each food category. The product of these two statistics allows for the determination of the top two food categories, highlighted in the table, contributing most to the exposure of cadmium.

Category	Occurrence Mean mg/kg	Consumption Median g/day	Exposure Cadmium µg/day
Cereals & cereal products	0.0163	257	4.189
Sugar & sugar products including chocolate	0.0264	43	1.135
Fats (vegetable and animal)	0.0062	38	0.236
Vegetables, nuts and pulses	0.0189	194	3.667
Starchy roots or potatoes	0.0209	129	2.696
Fruit and vegetable juices, soft drinks and bottled water	0.0010	439	0.439
Coffee, tea, cocoa (expressed as liquid)	0.0018	601	1.082
Alcoholic beverages	0.0042	413	1.735
Meat and meat products, offal	0.0165	151	2.492
Meat and meat products and substitutes	0.0077	132	1.016
Edible offal and offal products	0.1263	24	3.031
Meat based preparations	0.0076	84	0.638
Fish and seafood	0.0268	62	1.662
Eggs	0.0030	25	0.075
Milk and dairy based products	0.0039	287	1.119
Miscellaneous / Food for special dietary uses	0.0244	14	0.342
Tap water	0.0004	349	0.140

The two highest contributors to the dietary exposure were cereals and cereal products, and vegetables, nuts and pulses. These two food categories were used to estimate the exposure of high consumers (see below). It is important to note that because the contributions are estimated for consumers only of foods from each category, and such consumers vary between the different food categories, the various contributions cannot be summed to estimate an overall exposure.

For the body weight the same default value of 60 kg was used for all countries.

Mean and high dietary exposure to cadmium

The next step consists of estimating the mean dietary exposure to cadmium. In order to sum the various contributions from various food categories, the average consumption for the whole population was used. The median of the means for the individual European countries, for which data are available, is 2.27 µg/kg b.w. per week when assuming a body weight of 60 kg (range: 1.89–2.96 µg/kg b.w. per week). These figures are detailed per country in Table 26. These results vary due to consumption patterns only, since cadmium concentrations in food categories are assumed to be the same.

Finally, the exposure for high consumers was estimated following the guidelines for the use of the Concise European Food Consumption database i.e. by summing the 95th percentiles (consumers only) for the two main contributors and the mean exposure (whole population) for the other food categories (Table 24). The resulting "mean high exposure" is 3.02 µg/kg b.w. per week when assuming a body weight of 60 kg (range between 2.54 and 3.91 µg/kg b.w. per week).

Table 26. Mean and high dietary exposure to cadmium (µg/kg b.w. per week) for adults across Europe

Country	Mean exposure *Whole population*	High exposure *Sum of P95 for cereals and vegetables + mean exposure for whole population*
Belgium	2.33	3.28
Bulgaria	1.89	3.13
Czech Republic	2.37	3.08
Denmark	2.26	2.79
Finland	1.95	2.54
France	2.27	3.13
Germany	2.96	3.58
Hungary	2.16	2.72
Iceland	2.08	3.10
Ireland	2.54	3.46
Italy	2.05	2.68
Netherlands	2.25	2.95
Norway	2.31	2.82
Slovakia	2.29	3.91
Sweden	2.32	2.91
United Kingdom	2.15	2.88
Median EU	**2.27**	**3.02**

These results are slightly lower than the calculations of the JECFA at its 64th meeting (FAO/WHO, 2006) as indicated in Table 27, but higher than results from the detailed German Food Monitoring surveys over the years 1995-2002 (BgVV, 2002). This difference might indicate that a refined assessment based on more disaggregated and representative samples can result in lower estimates of cadmium exposure from food. Other estimates in Table 27 include the Catalonian study of a fish consumption population (Llobet *et al.*, 2003); the Canary Islands Diet Study that also includes high fish consumption results (Rubio *et al.*, 2006); the estimated weekly dietary cadmium intake based on a food frequency questionnaire completed by 29,324 postmenopausal Swedish women (Åkesson *et al.*, 2008); the U.S. Total Diet Study carried out by the US-Federal Drug Administration in 2003 (Egan *et al.*, 2007), the earlier European Community SCOOP study (EC, 2004a) and the latest UK Total Diet Study (FSA, 2009).

Table 27. Comparison of estimated ranges of mean cadmium exposure from food according to different national estimates reported in the literature

Study[a)]	Type of estimate	Mean weekly intake [µg/kg b.w.]
Mean exposure, current opinion	Concise food consumption data and occurrence data submitted to EFSA	1.9-3.0
High exposure, current opinion	Concise food consumption data and occurrence data submitted to EFSA	2.5-3.9
FAO/WHO, 2006	GEMS/Food regional diets and the regional average concentrations of cadmium	2.8 – 4.2
EC, 2004	SCOOP study – EU scientific cooperation initiative	0.7-2.9
Swedish women, 2008	Food frequency questionnaire completed by 32,210 postmenopausal Swedish women. Dietary cadmium intake was adjusted for total energy intake of 1700 kcal using the residual-regression method	1.6
Italy, 2001, 2002	Probabilistic mean based on Italian food consumption data (1994-1996) and occurrence data submitted to EFSA	1.9
Germany, 2002	German food consumption data and representative data of Food Monitoring Program	1.2
Catalonia (Spain), 2003	Mean based on National TDS	1.5
United Kingdom, 2006	Mean based on National TDS	1.3-1.5
Canary Islands, 2006	Mean based on National TDS	1.1
US, 2003	Mean based on National TDS	1.5

[a)] When known country in which the population was studied and year of study are indicated (study reference provided in the text).

These results from past studies confirm that the mean estimate derived from using information from the EFSA Concise European Food Consumption database and the occurrence data recently submitted by Member States is of a magnitude similar to the values previously reported.

In Figure 7, the contributions of different food groups to overall cadmium exposure are expressed using the country with the lowest and the highest background exposure levels for the adult population separately for each food category. Cereals and cereal products as well as vegetables, nuts and pulses are consistently the categories with the greatest contributions in all situations. Substantial variation occurs in the minimum and maximum contributions of some other food categories like tap water (partly due to the recording of water consumption), miscellaneous foods/foods for special dietary uses and fish and seafood. Eggs uniformly contribute the least to dietary cadmium intake.

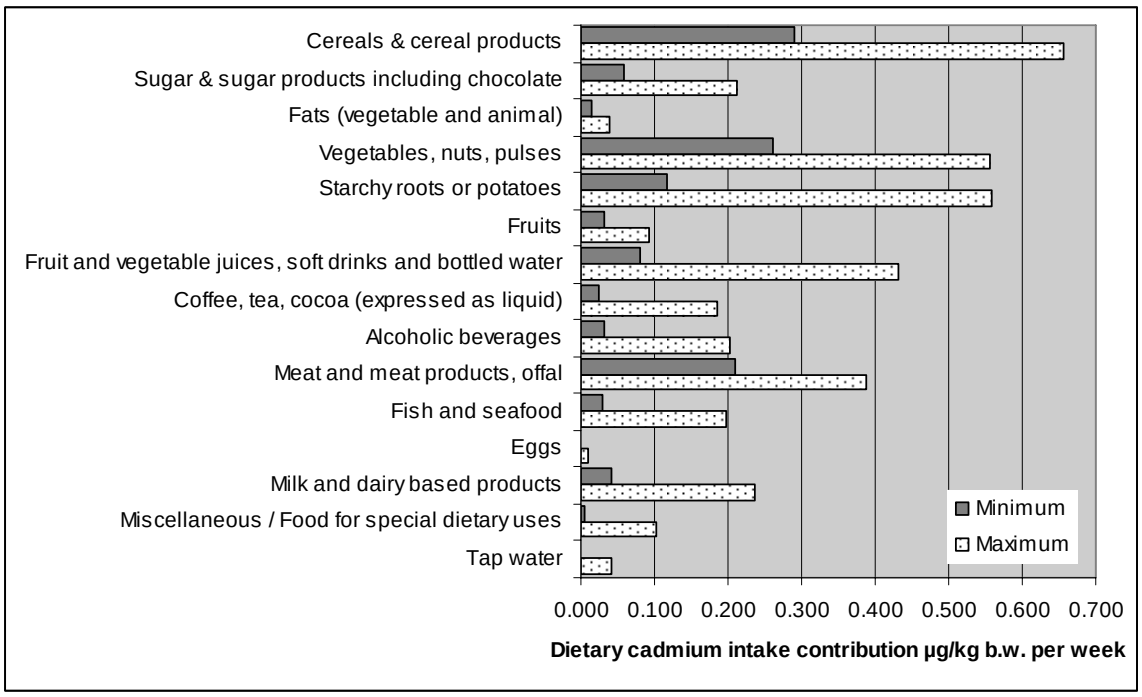

Figure 7. Contribution to overall cadmium exposure by the main food groups of EFSA's Concise European Food Consumption database. Dark bars mark the country specific diet with lowest and light bars the one with highest overall contribution.

7.2. Specific sub-groups of the population

Infants and children

Because of different consumption patterns and lower body weights, infants and children are considered as a separate group in risk assessments. Dietary cadmium exposure in children was calculated using Italian consumption data (see 6.3.) and compared with the exposure of Italian adults (Table 28). For the separate groups of toddlers and children the P95 was not reported due to the limited number of subjects. To allow this comparison the two age groups were combined. Exposure for toddlers and children appears to be higher than for adults, primarily due to the greater amount of food consumed in relation to body weight.

Table 28. Summary of exposure descriptors (µg/kg b.w. per week) for subjects of the Italian general population stratified by age ranges (95% confidence intervals in brackets).

Exposure descriptor	0.5–6 years	7–12 years	0.5–12 years	13–94 years
Number of samples	88	105	193	1747
Min	0.49	0.89	0.49	0.42
Median	3.26	2.37	2.71	1.65
Mean	3.46 (3.17-3.75)	2.56 (2.37 -2.74)	2.97 (2.79-3.15)	1.89 (1.85-1.94)
P95	-	-	5.49 (4.95-6.08)	3.63 (3.42-3.79)
Max	7.92	5.80	7.92	11.8

The estimated mean dietary cadmium exposure for children 12 years of age or less was close to 60% greater than for adults. This difference was exacerbated when splitting toddlers from other children, although the number of subjects is low in the toddler group.

Figure 8 further elaborates the relative contributions of the 15 food categories identified in the EFSA Concise European Food Consumption database to the mean dietary intakes of the three age ranges studied. The high consumption of milk and dairy based products contribute to the high cadmium intake among toddlers, although cereals and cereal-based products and vegetables, nuts and pulses still dominate as cadmium sources also in this age group.

In the latest Total Diet Study in the United Kingdom (FSA, 2009) analysing foods as eaten and not in their raw state, the overall exposure levels were lower both for toddlers/children and adults compared to the Italian estimate, but toddlers in the age range 1.5 to 4.5 years had an exposure 165 % higher than adults.

In the Czech Republic 35 breast milk samples and 8 samples of infant formula were investigated to compare cadmium intake levels (Ursmyova and Hladikova, 1997). All breast milk samples were drawn from non-smoking mothers without occupational exposure to cadmium. Dietary exposure estimates were based on a mean infant body weight of 5 kg and a daily intake of milk of 800 g. The median concentrations of cadmium in the samples were 0.5 µg/kg for breast milk and 0.6 µg/kg for infant formulae resulting in slightly higher intakes from infant formulae compared to breast milk (0.56 µg/kg b.w. per week from breast feeding and 0.67 µg/kg b.w. per week from infant formulae). Proficiency tests of the laboratory results indicated that both intake levels might be slightly underestimated due to measurement error.

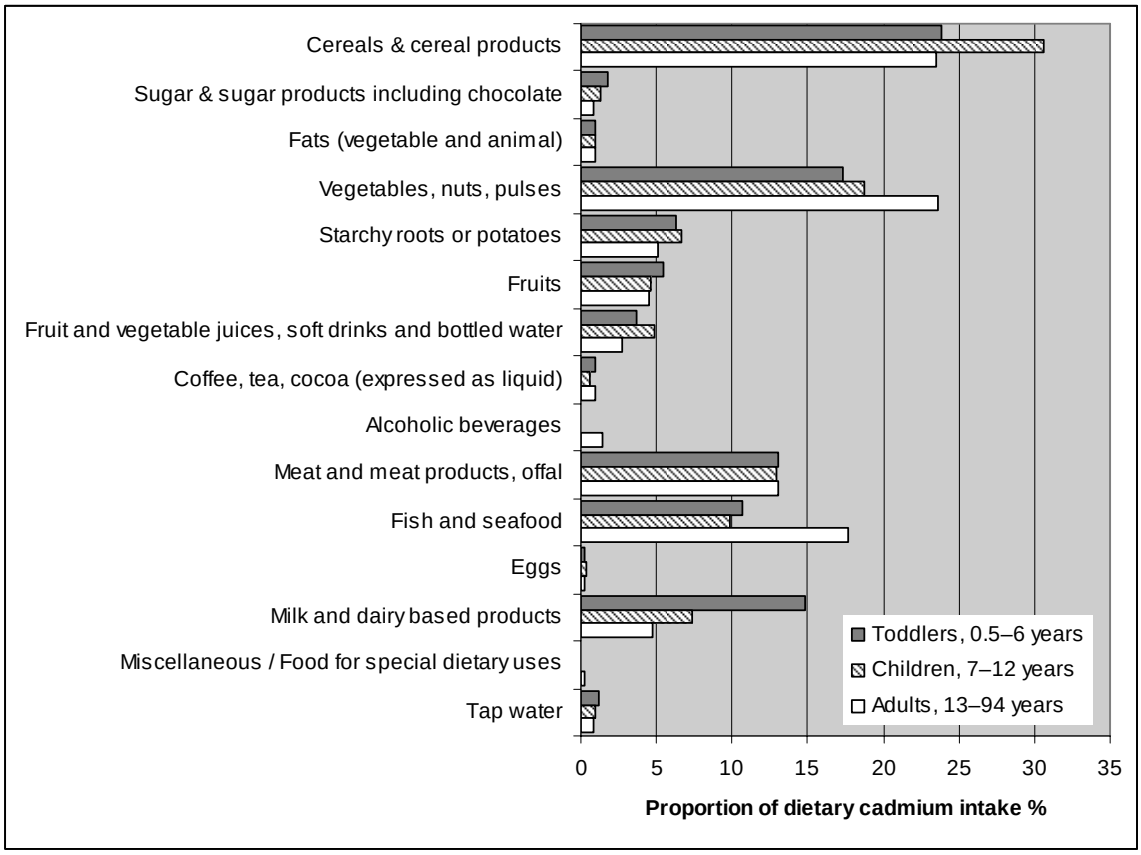

Figure 8. Percent contribution for the 15 food categories to the mean daily cadmium intake of subjects from the Italian general population in three age groups

Higher cadmium levels were found in human milk in another study in Croatia that examined the possible differences associated with the age of the mother, regional differences, number of births and smoking (Frkovic *et al.*, 1997). The authors found cadmium concentrations in the range of 0.5-9.1 µg/L with a median of 1.8 µg/L. No significant difference in cadmium concentrations in the different subgroups was found. Another study reported slightly lower mean cadmium concentrations in human milk from non-smokers (0.06 µg/L) than for smokers (0.07 µg/L) (Palminger Hallen *et al.*, 1995). No cadmium was found in samples of infant formula in the latter two studies. The cadmium intake levels among infants are clearly below those associated with food intakes in toddlers and children described above. In contrast, Eklund and Oskarsson, found that the exposure to dietary cadmium from weaning diets can be up to 12 times higher in children fed infant formula than in breast-fed children (Eklund and Oskarsson, 1999). Infant formula cadmium concentrations range from 1.1 to 23 µg/kg fresh weight concentrated formulas and were related to the composition of the diets in the following order: formulas based on cow milk < soy formulas < diets with a cereal content. The mean weekly intakes of dietary cadmium were estimated to vary between 0.1 and 3 µg/kg b.w. of the child (not including cadmium from drinking water). The highest intake on a body weight basis would be in 6-month-old children, consuming the recommended amount of wheat-, oat- and milk-based formulas.

Consumers with an especially high exposure

Using mean occurrence levels for the comparatively broad food-groups means that even the high consumer approach may underestimate the intake of some population sub-groups. In particular in cases where the contamination values for some specific foods are very high compared to others in the same category the high consumer approach might underestimate the intake of consumer sub-groups, who may eat high amounts of specific more highly contaminated food items. Five separate hypothetical high exposure cases have been developed to assess the potential contribution of extreme diets. The extreme diets include consumption of offal, specific mushrooms, bivalve molluscs other than oysters, algal dietary supplements, and vegetarian diets (Table 29). It was assumed that the extreme diet component would be consumed at a level of 100 g/week except for algal supplements at 10 g/day and vegetarian diets where meat and fish consumption was substituted by nuts and oilseeds. It is of course possible to consume more than the 100 g/week over a shorter period but it was considered realistic for an evaluation of long term intake.

For this modelling approach the 95th percentile cadmium concentrations for mixed species kidney (10B2) were taken from Table 14, for mushrooms (04B2) from Table 8, for bivalve molluscs other than oysters (11A1) from Table 15, and for algal supplements (14B1) from Table 18, respectively. The calculated dietary exposures for the respective individual product were added to the mean country median intake of 2.27 µg/kg b.w. per week from Table 26. The mushroom data are expressed as analysed but could include products sold in the dried state overestimating the overall concentration. On the other hand often consumption of 300 g of fresh mushrooms is assumed per meal (Kalač *et al.*, 2004), but this was considered unrealistic to be a daily occurrence over a full year. From Table 24 it can be seen that vegetarian diets are to a large extent influenced by increases in the consumption of nuts and oilseeds, pulses and cereals. The average exposure of vegetarians was modelled by using the high consumer EU median from Table 26 of 3.02 µg/kg b.w. per week (high consumption of cereals and vegetables) and removing the cadmium dietary intake contribution from the meat and fish groups (0.36 µg/kg b.w per week) and using the amount consumed for those two categories (174 g/day or 1,218 g/week) to estimate an added intake of nuts and oilseed in equal amounts with a mean cadmium concentration of 0.135 mg/kg.

Table 29. Modelled cadmium exposure for five hypothetical extreme dietary exposure scenarios (for details see text above)

Extreme diet	95th percentile concentration mg/kg	Assumed mean consumption g/week	Added weekly exposure µg/kg b.w.	Base weekly median exposure µg/kg b.w	Total weekly exposure µg/kg b.w.
Kidney	0.5743	100	0.96	2.27	3.23
Specific mushrooms[1]	1.2000	100	2.00	2.27	4.27
Bivalve molluscs	1.4000	100	2.33	2.27	4.60
Algal supplements	0.4800	70	0.56	2.27	2.83
Vegetarian	0.1351	1,218	2.74	2.66	5.40

[1)] Simulated to indicate species of mushrooms with an affinity for accumulating cadmium mainly found in the wild

It is difficult to judge how realistic the above scenarios might be. It would not be expected that wild-picked mushrooms representing high cadmium accumulating species would be consumed year round, although using preservation methods can expand the season. Equally,

by using the 95th percentile concentration for bivalve molluscs other than oysters, it is assumed that product from polluted areas are consumed consistently by the same person. This is also fairly unlikely. The kidney scenario is based on offals from older animals and again would vary over time. However, the algal supplements and vegetarian scenarios are probably fairly realistic.

7.3. Hotspot areas due to pollution

As discussed in chapter 4 cadmium is released to the environment from industrial pollution and enters the food chain via soil and drinking water. People living in industrial areas and relying on home-grown produce could have a higher exposure than the general population. This means that the mean intake levels may not be representative for those areas. An assessment of cadmium exposure for the adult Belgian population living close to non-ferrous metal plants concluded that people living in contaminated areas have a higher estimated intake than in non-contaminated areas (Vromman *et al.*, 2008). Analyses showed that cadmium levels in fruit, vegetables and potatoes could be up to 9-fold higher and in meat and offal twice as high as in non-contaminated areas. In a study on home-grown products consumed by children in Germany a relatively high median intake of 2.3 µg/kg b.w. per week was estimated (Wilhelm *et al.*, 2005). Yet, in this 7-day duplicate portion study of 84 children no difference for cadmium intake could be found for children eating substantially locally produced cereals and meat products compared to children only eating foods from the supermarket. However, because of the small sample size it is not possible to draw firm conclusions from the study.

In a study of Greek food samples for 93 different food groups, atmospheric deposition from urban and agricultural areas was found to play an important role in the enrichment of agricultural produce from cadmium (Karavoltsos *et al.*, 2002). The authors also noted that cadmium levels appear to be higher in samples of conventional production compared to 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.

7.4. Relative importance of exposure from sources other than food

Overall cadmium exposure is also influenced by other cadmium sources. The main other source is smoking, which is at the same level as exposure from food. Occupational exposure can also be a major factor for limited sub-populations, but will not be addressed in this opinion.

One cigarette contains cadmium amounts of 1-2 µg depending on the origin of the tobacco (WHO-IPCS, 1992a). According to an EU study carried out by the JRC in 2007 about 10 % of this cadmium is inhaled and it is estimated that 25-50 % of the inhaled cadmium is absorbed (EC, 2007). Dietary absorption rates have not been factored into the previous analysis and will equally not be considered for smoking. Assuming mean cadmium content of 1.5 µg per cigarette of which 10 % is inhaled, 20 cigarettes will result in a daily exposure of 3.0 µg cadmium/day. For a 60 kg adult this corresponds to a weekly exposure of 0.35 µg/kg b.w. The exposure would be higher for heavy smokers with 40 cigarettes resulting in a daily

exposure of 6.0 µg cadmium/day, which would correspond to a weekly exposure of 0.70 µg/kg b.w. for a 60 kg adult.

The EC-JRC assessment (EC, 2007), because of the higher absorption of inhaled cadmium from smoking than that from food, considered internal exposure from smoking to be of a magnitude similar to that from food.

Inhalation apart from smoking is not a major cadmium source for the general population. In the Czech Republic the mean cadmium concentration level in the air is 1 ng/m³. Assuming a daily respiration of 20 m³, this would lead to an external exposure estimation via inhalation of 0.02 µg/day, or 0.0025 µg/kg b.w. per week for a 60 kg person (Puklova *et al.*, 2005), which is several orders of magnitude lower than the cadmium intake from food. As indicated on page 20, maximum cadmium levels in air in Europe could reach 10 ng/m^3, still not providing a major exposure pathway.

Similarly RIVM estimated cadmium exposure from dust based on dust ingestion rates of 50 mg/day for adults and 100 mg/day for children in a worst-case scenario by using the highest cadmium geometric mean values found in the literature of 13 mg/kg (Oomen *et al.*, 2008). For a 60 kg adult and a 15 kg child the exposure from dust would be 0.076 µg/kg b.w. per week for adults and 0.607 µg/kg b.w. per week for children, respectively. The values for ingestion rates are generally associated with a high degree of uncertainty due to methodological problems in the determination of intake by tracer studies in soil and extrapolations of the concentrations of house dust. However, after evaluation of several studies the used values are classified as "a conservative but realistic estimate" (Oomen *et al.*, 2008). The situation could be different in other countries.

Considering the hand-to-mouth behaviour of children this could be a significant cadmium source in areas with high industrial pollution, but would still not become a major exposure pathway. It should also be mentioned that the concentration figure of 13 mg/kg has been measured in an Australian industrial area. In non-industrial areas the contaminations may be considerable lower.

7.5. Summary of different exposure pathways

A summary of different exposure sources of cadmium is presented in Table 30. Oral exposure from food is clearly the dominating source of overall cadmium exposure for adult non-smokers with a small potential contribution from house dust in particularly contaminated areas. More highly contaminated individual foods can double total dietary exposure from a median of 2.27 in the mean diet up to a maximum of 4.64 µg/kg b.w. per week in simulated extreme diets. Some vegetarian diets seem to be able to almost triple the mean dietary cadmium exposure.

Table 30. Overview of mean weekly cadmium exposure estimates for the different exposure pathways

Source		Pathway	Range of calculated or reported exposures [µg/kg b.w. per week]	
			Adults	Children
Dietary exposure	Food mean current opinion	Oral	1.89-2.96	2.56-3.46
	Food high current opinion		2.54-3.91	5.49
	Food in industrial areas	Oral	3.3-5.8[a)]	4.6[a)]
	Extreme diets current opinion	Oral	2.87-4.64	
	Vegetarians	Oral	5.47	
Non-Dietary Exposure	House dust	Oral	0.076	0.607
	Air	Inhalation	0.0024	0.0033 [b)]
	Smoking	inhalation	0.35-0.70	-

[a)] estimated using a factor of 1.86 times average exposure derived from (Vromman *et al.*, 2008)

[b)] assuming a daily inhalation volume of 7 m³ and a body weight of 15 kg

In smokers, the contribution from smoking can increase overall cadmium exposure by 15-30% when smoking between 20-40 cigarettes a day. This does not take into account the higher pulmonary absorption compared to the gastrointestinal absorption. The potential contribution from different sources for a smoker living in an area with contaminated house dust is illustrated in Figure 9A.

The special scenario calculated for children compared to the mean adult scenario showed that children are more exposed. Using the Italian comparison data, there was an almost 60 % increase in the dietary exposure of children compared to adult cadmium exposure. Children are also potentially exposed to cadmium through house dust in contaminated areas with the distribution between potential exposure sources illustrated in Figure 9B. Please note that Figure 9A does not account for the actual absorption through the different exposure pathways. When comparing the internal dose, the contribution from smoking is considered equivalent to the dietary contribution as has been mentioned previously.

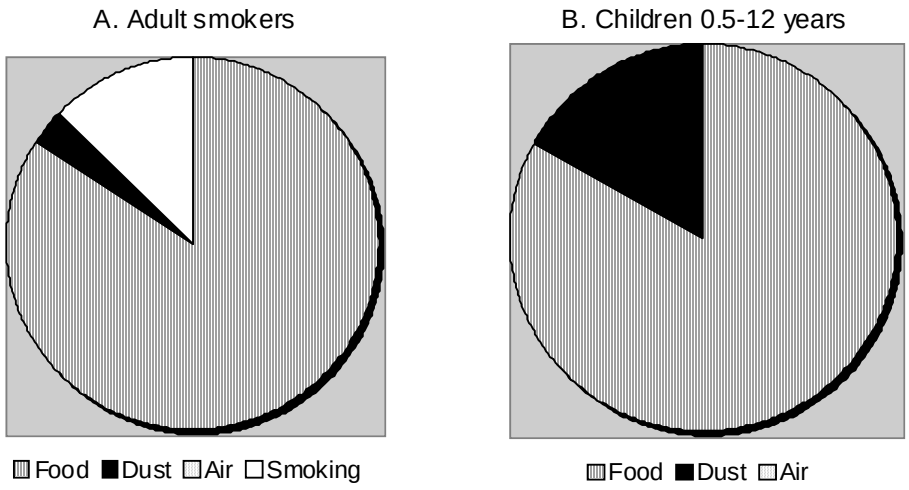

Figure 9. Estimated relative contribution to cadmium exposure of different sources for adult smokers in the presence of contaminated house dust (A) and children in the presence of contaminated house dust (B). The small contribution from air is not visible. The contribution from smoking would increase if the internal dose is considered.

8. Hazard identification and characterisation

8.1. Toxicokinetics

Most data on toxicokinetics have been obtained after injection or inhalation of cadmium and therefore are not directly applicable in the assessment of the fate of dietary cadmium, which is the focus of the present opinion. Due to differences in solubility and bioavailability, gastrointestinal bioavailability is dependent on the source of cadmium and the physiological state of the organism. For instance, that of soil-adsorbed and seafood cadmium is lower than that of ionic cadmium; that of rice-associated cadmium is reported to be higher than from other sources (EC, 2007).

8.1.1. Absorption

Inhalation

Animal data from single and chronic exposure studies indicate a high absorption of cadmium via the respiratory route: 7-50 % of the cadmium inhaled (Friberg *et al.*, 1974; Boisset *et al.*, 1978; Nordberg *et al.*, 1985). Fractional retention of inhaled cadmium depends on particle size: 50-60 % of ultrafine particles would be retained, the remaining part being exhaled with smoke (Chiba and Masironi, 1992; Kalcher *et al.*, 1993; Morawska *et al.*, 2005). The large differences in blood cadmium levels between smokers and non-smokers support the relevance of the respiratory absorption (Elinder *et al.*, 1983; Friberg and Vahter, 1983). Recent studies

indicate that cadmium even at very low concentrations is measurable in exhaled breath condensate from ex-smokers many years after smoking cessation, thus suggesting that an important fraction of cadmium deposited in the lungs is cleared not only by absorption, but also by elimination with exhaled air (Mutti *et al.*, 2006).

Ingestion

Gastrointestinal uptake of cadmium can be compared to a saturable process with fractional absorption which decreases at high concentrations. A previous assumption was that a specific carrier system for cadmium does not exist (Foulkes, 1979, 1985). In general, cadmium absorption from food is not dependent on chemical complexation (except for metallothionein-binding – see below) and its bioavailability varies according to a number of factors i.e. the diet/food itself and its cadmium content, the nutritional status of the individual, the gender, the smoking status and age (ATSDR, 2008) or the presence in food of divalent or trivalent cations such as zinc, iron and calcium that compete with cadmium for absorption (Reeves and Chaney, 2008).

Absorption in rats and mice following oral administration of cadmium chloride varies from 0.2 to 3 % of the administered dose, depending on the dose and of the duration of the exposure (ATSDR, 2008). A refined diet high in fat and protein increases cadmium absorption, partially due to increased gastrointestinal passage time (Schafer *et al.*, 1986; Kim *et al.*, 2007; Min *et al.*, 2008).

Studies in rodents with cadmium given in either inorganic form or as cadmium complexes with organic ligands such as glutathione or metallothionein, have shown that the intestinal uptake of organic complexes is slightly lower than, or comparable with that of inorganic cadmium (Uthe and Chou, 1980; Maage and Julshamn, 1987; Lind *et al.*, 1995). Mice exposed orally to cadmium-metallothionein had low blood and liver cadmium levels but higher kidney levels than mice exposed to the same dose of cadmium in ionic form (Cherian *et al.*, 1978), suggesting that part of metallothionein-bound cadmium is taken up intact from the gastro-intestinal tract. These findings indicate that it may be inadequate to use blood cadmium levels (B-Cd levels) for comparisons of total cadmium uptake from metallothionein containing food items versus other food, as confirmed by McKenzie-Parnell *et al.* (1988) who demonstrated that a high dietary cadmium exposure from New Zealand Bluff oysters (in which cadmium is mainly bound to metallothionein (see Nordberg *et al.*, 1986) did not result in elevated blood cadmium levels.

In humans, estimated daily intakes from the diet indicate that cadmium absorption from food is about 3-5 % (Morgan and Sherlock, 1984). In 14 healthy adults, an average of 4.6 % of $CdCl_2$ administered in water taken with a meal was retained (McLellan *et al.*, 1978). The influence of chemical complexation of cadmium on absorption was evaluated in seven volunteers who ingested brown crab meat (hepatopancreas) labelled with $^{109}CdCl_2$ by prior feeding of the crabs; whole-body counting ranged from 1.2 to 7.6 % with a mean of 2.7% (Newton *et al.*, 1984).

Vahter *et al.* (1996) compared the bioavailability of cadmium from shellfish and mixed diet in women, and found no statistically significant differences in the concentrations of cadmium in blood or urine, in spite of the fact that shellfish diets contained twice as much cadmium as the mixed diet. Reeves and Chaney (2008) tentatively explained the low absorption of the consumption of cadmium-rich oysters on B-Cd levels by the fact that oysters also contain

high levels of zinc and iron, which would compete with cadmium for absorption, thereby accelerating its intestinal transit and elimination with stool.

The differences in the bioavailability and/or kinetics of dietary cadmium are related to the type of diet. No crops other than rice accumulate more cadmium out of proportion to zinc in the edible tissues when grown on soil with high geogenic Zn/Cd (Chaney *et al.*, 1987). Poor nutritional quality of polished rice with respect to zinc and iron is well known (Gregorio *et al.*, 2000; Graham *et al.*, 2007), resulting in anaemia and low zinc status in populations subsisting on rice (Ross *et al.*, 2002). It is recognised that this low zinc/iron status in the consumers who subsist on rice-based diets could cause a much greater absorption of cadmium than occurs with other staple diets (Reeves and Chaney, 2008).

Both experimental and human studies (and some epidemiological studies) confirm the relationship between iron deficiency and cadmium absorption. *In vitro* studies have demonstrated that the divalent metal transporter 1 (DMT1) which is up-regulated by iron deficiency, also has a high affinity for cadmium (Gunshin *et al.*, 1997; Tallkvist *et al.*, 2001; Leazer *et al.*, 2002; Park *et al.*, 2002; Kim *et al.*, 2007). Thus, it is likely that the enhanced intestinal absorption of cadmium in the iron-depleted state is due to the elevated DTM1 expression in the small intestine (Kim *et al.*, 2007). Zinc and calcium deficiencies may also result in an increased accumulation of cadmium in the intestinal wall, liver and kidney (Foulkes and Voner, 1981; Reeves and Chaney, 2008). In line with these data experiments on humans have shown that subjects (mainly women) with a low serum ferritin concentration (<20 μg/L) had an average absorption of 8.9 %, while those with a higher ferritin concentration – and adequate iron stores – had an average absorption of 2.3 % (Flanagan *et al.*, 1978). Serum ferritin is a marker of body iron stores and is reciprocally associated with the iron absorption. Studies on human populations have shown increasing blood cadmium with decreasing serum ferritin in women at fertile age and during pregnancy (Berglund *et al.*, 1994; Åkesson *et al.*, 2002). Thus, long periods of low body iron stores as well as multiple pregnancies may lead to increased cadmium absorption. This is in line with the findings that women generally have a higher body burden of cadmium compared to men as reflected by higher concentrations of cadmium in blood, urine and kidney cortex (Kippler *et al.*, 2007). However, differences in blood cadmium between men and women becomes less obvious or non-existent after menopause, when the iron status in women usually improves (Baecklund *et al.*, 1999). Studies in twins confirm a higher genetic influence on blood cadmium concentrations in women (60 % of the variance) compared to men (13 %) (Bjorkman *et al.*, 2000).

Kikuchi *et al.* (2003) and Horiguchi *et al*. (2004) investigated the dietary absorption of cadmium in young non-smoking Japanese female volunteers and found an apparent absorption rate (estimate based on the difference between total intake and excretion of cadmium into faeces) above 40 %. According to Horiguchi and co-workers (2004), age rather than iron deficiency seems to be the major factor affecting the cadmium absorption rate. The reasons for the discrepancy between the study by Horiguchi *et al.* (2004), and previous studies are most likely methodological as there was a very large variation between individuals in the absorption rates. The high bioavailability of cadmium in young women was not confirmed by European biomonitoring data on cadmium in urine (see section 8.2.3.2), accordingly, an absorption of about 5 % in men and 10 % in women seems as reasonable estimates of gastrointestinal absorption in Western populations and is supported by a toxicokinetics model that employs urine excretion values in the US general population (Choudhury *et al.*, 2001).

A dose-dependent disposition of cadmium administered orally to rats was observed by Lehman and Klaassen (1986) as well as differences in absorption at birth with a decrease from 12 to 5 to 0.5 % at 2 hours, 24 hours and 6 weeks after birth, respectively (Sasser and Jarboe, 1977). Sasser and Jarboe (1980) also reported that absorption of cadmium in the gastrointestinal tract of young guinea pigs was 20-fold higher than in adult guinea pigs.

Crews *et al.* (2000) fed porridge made from ^{106}Cd labelled wheat to nine 12 month old infants from the Norwich area (UK). Holmium was given as a non absorbable faecal marker with each test meal. Each infant was provided with a test meal (100 g ^{106}Cd labelled porridge) as breakfast on 2 consecutive days and stools were collected for 4 days following consumption of the first test meal. Cadmium levels in the meals and collected stools were measured by ICP-MS. Results indicate that the apparent absorption of cadmium varied between 4 and 37 % (mean value 18 %). Although a longer faecal collection time might be required for some individuals, the bioavailability of cadmium in infants may be higher than the 5 % commonly quoted for adults. Based on a model of suckling piglets, it seems that cadmium is not absorbed via the intestinal iron transporters in newborns. There are developmental differences in the handling of both iron and cadmium in newborns as compared to adults (Ohrvik *et al.*, 2007). The absorption of cadmium from the diet is most likely higher in newborns and infants than in adults, although human data are not available.

8.1.2. Transport and distribution

Transport

In the blood, cadmium is mainly found in the erythrocytes, where it is mainly bound to metallothionein (MT), a low-molecular weight protein that strongly binds cadmium on its cysteine (sulfur SH) rich groups (Nordberg *et al.*, 1971a). Cadmium may also bind to other SH-rich low-molecular weight peptides or amino acids such as glutathione and cysteine respectively (Zalups and Ahmad, 2003).

MT is also present in blood plasma and serves as the main transport for cadmium into the kidneys because of its low molecular weight (Nordberg and Nordberg, 2000). MTs are small, cysteine rich metal binding proteins which participate in an array of protective stress responses (Lehman-McKeeman and Klaassen, 1987). They likely evolved as a mechanism to regulate zinc levels and distribution within cells. Seven zinc atoms are shared between two clusters (with 3 and 4 binding sites) of the MT monomer, but cadmium can substitute zinc in both clusters. The small size of MT enables the protein to be filtered through the kidney glomerular membrane. It is then reabsorbed into proximal tubular cells (Nordberg *et al.*, 1971b; Foulkes, 1978). Cadmium, not bound to MT, is not reabsorbed to the same extent. Exogenous MT is degraded in lysosomes thereby releasing cadmium, which may induce renal MT synthesis (Squibb *et al.*, 1984).

Cadmium exposure induces the synthesis of MTs in several tissues (Nordberg *et al.*, 1985). MT-encoding genes are strongly induced by both zinc and cadmium through MTF-1 regulation. A sub-maximal number of bound metal ions triggers MT degradation. Cd-MT has a longer half-life *in vivo* than Zn-MT. Early work indicated that MT binding decreased the toxicity of cadmium, and the ability of the liver to synthesise MT appeared to be adequate to bind all the accumulated cadmium (Nordberg *et al.*, 1971b; Kotsonis and Klaassen, 1978). Cadmium-induced nephrotoxicity is probably due to unbound cadmium as the ultimate

toxicant (Nomiyama and Nomiyama, 1986), as shown in Figure 10. The route of cadmium administration does not appear to affect the MT metabolism in liver and kidney, though inhalation induces lung MT (Glaser *et al.*, 1986; Hart, 1986) and oral exposure induces intestinal MT (Muller *et al.*, 1986). Parenteral administration of cadmium can result in doses high enough to overwhelm MT production and thereby cause effects on tissues otherwise protected by the formation of the Cd-MT complex (Nordberg *et al.*, 1985; Sendelbach and Klaassen, 1988).

A schematic presentation of cadmium metabolism and nephrotoxicity is illustrated in Figure 10. Cadmium bound to albumin is to a large extent taken up by the liver where the complex is split and only minute amounts reach the kidney proximal tubuli (l). In liver cells, cadmium induces the synthesis of metallothionein (MT). Cadmium is then excreted in bile mainly bound to glutathione (GSH). Redistribution occurs from the liver. Cadmium is either excreted in bile mainly bound to glutathione (GSH), or released into the plasma as Cd-MT. The complex Cd-MT is filtered through the renal glomeruli and then reabsorbed by proximal tubular cells until the critical concentration is reached. The critical concentration is represented by the cadmium burden at which tubular cells are no longer able to synthesise enough MT to neutralise free Cd^{2+} produced by lysosomal degradation of Cd-MT. When the critical concentration is exceeded, tubular damage results in increased enzymuria, low molecular weight proteinuria, and increased excretion of cadmium either as Cd-MT or, probably, also as Cd^{2+}.

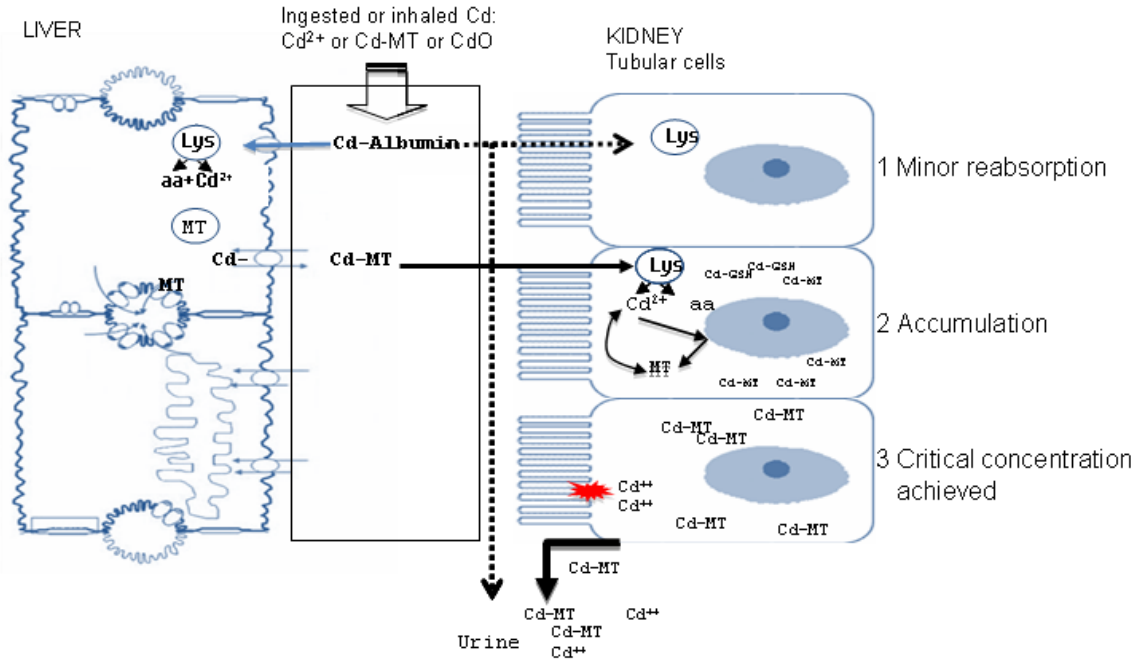

Figure 10. Cadmium metabolism and nephrotoxicity. Upon chronic exposure, cadmium nephrotoxicity depends on the imbalance between the liver ability to synthesise MT carrying cadmium to the kidney and the ability of the latter to synthesise the renal counterpart of MT necessary to neutralise Cd2+ delivered from lysosomal degradation of the Cd-MT complex.

Autoradiography of the kidney of male mice after *i.v.* injection of ^{109}Cd-MT showed that ^{109}Cd distributed preferentially to the S1 and S2 segments of the proximal convoluted tubules (Nordberg and Nordberg, 1975; Dorian *et al.*, 1992), whereas *i.v.* administration of [^{35}S]Cd-MT resulted in a rapid disappearance of ^{35}S (with a half-life of approximately 2 hours), thus indicating that the protein portion of Cd-MT is rapidly degraded after renal uptake of Cd-MT and the released cadmium is retained in the kidney (Dorian *et al.*, 1992). Both the organic (^{35}S) and inorganic (^{109}Cd) portions of Cd-MT are rapidly and efficiently taken up by the S1 and S2 cells of the proximal tubules, and the protein portion is rapidly degraded to release cadmium. Cd-MT increased urinary excretion of glucose, and proteinuria indicated renal injury with dosages as low as 0.2 mg Cd/kg. In contrast, renal function was unaltered by $CdCl_2$ administration, even at dosages as high as 3 mg Cd/kg (Dorian *et al.*, 1992).

MT-null mice were exposed to a wide range of $CdCl_2$ doses up to 10 weeks (Liu *et al.*, 1998). Renal cadmium burden increased with dose and duration up to 0.14 mg Cd/kg kidney in control mice (i.e., MT normal) with a 150-fold increase in renal MT levels (0.8 mg MT/kg kidney). Renal cadmium was much lower in MT-null mice (0.01 mg Cd/kg) and MT levels were not detectable. Lesions were more severe in MT-null mice, indicating that cadmium induced renal injury is not necessarily mediated through a Cd-MT complex, and that MT is an important intracellular protein for protection against chronic cadmium nephrotoxicity, despite the increased uptake in kidney cells.

Studies in MT-I and MT-II knock-out (MT-null) mice suggest that an important carrier of cadmium playing a role in its kidney uptake is Cd-MT (Liu *et al.*, 1996). MT in the intestinal mucosa functions both as a protective barrier against cadmium absorption and as an extracellular transporter of cadmium to the kidney (Kimura *et al.*, 1998). MT did not play a major role in restricting transfer of cadmium from dam to fetus via placenta and to neonate via milk (Brako *et al.*, 2003). Despite the importance of MT in cadmium metabolism and renal toxicity, cadmium-induced nephrotoxic effect can be elicited in exposed MT-transgenic and null mice at one tenth the dose that produces nephrotoxicity in control mice, thereby strongly supporting an MT protective function (Klaassen *et al.*, 1999).

Distribution

Distribution of cadmium in animals after oral exposure shows the highest accumulation in the liver and kidneys (Kotsonis and Klaassen, 1978). Liver and kidney cadmium concentrations are comparable after short-term exposure (Andersen *et al.*, 1988), but the kidney concentration exceeds the liver concentration following prolonged exposure, except at very high exposures (Bernard *et al.*, 1990). After acute oral administration, the higher kidney/liver cadmium ratio after Cd-thionein treatment than after $CdCl_2$ was due to lower concentrations of cadmium in liver rather than increases in renal cadmium levels, which were comparable (Maitani *et al.*, 1984). In rats given 28 % purified diet and 72 % ordinary rice containing cadmium-polluted rice (0. 02, 0.04, 0.12, or 1.01 ppm of Cd) or CdCl(2) (5.08, 19.8, or 40.0 ppm of Cd) for up to 8 months, the distribution of cadmium to the liver and kidney varied depending on the dosage levels of cadmium. The distribution rates to the liver increased dose-dependently, whereas those to the kidney decreased when dose increased (Hiratsuka *et al.*, 1999). Zinc and calcium deficiencies may also result in an increased accumulation of cadmium in the intestinal wall, liver and kidney (Foulkes and Voner, 1981; Reeves and Chaney, 2008).

Non-occupationally exposed people are exposed to cadmium primarily through the diet and either active or passive tobacco smoke. Cadmium can be detected in virtually all tissues in adults from industrialised countries, with the greatest concentrations in the liver and kidney (Sumino *et al.*, 1975; Chung *et al.*, 1986). Average cadmium concentrations in the kidney are near zero at birth, and rise almost linearly with age to a peak (typically around 40-50 mg/kg wet weight) between ages 50 and 60, after which kidney concentrations decline. Liver cadmium levels also begin near zero at birth, increase to typical values of l-2 mg/kg wet weight by age 20-25, then increase only slightly (Sumino *et al.*, 1975; Lauwerys *et al.*, 1984; Chung *et al.*, 1986).

In humans subjected to normal low-level exposures, approximately 50% of the total cadmium body burden at autopsy is found in the kidney and 15 % in the liver, and only a relatively small part is stored in bone (Christoffersen *et al.*, 1988; Nordberg *et al.*, 2007).

In several studies, including both smoking and non-smoking women, the cadmium concentration was approximately half as high in cord blood as in maternal blood (Lauwerys *et al.*, 1978; Kuhnert *et al.*, 1982; Truska *et al.*, 1989). Accumulation of cadmium in the placenta at levels about 10 times higher than maternal blood cadmium concentration has been observed in studies of women in Europe, e. g. (Roels *et al.*, 1978) and the United States (Kuhnert *et al.*, 1982).

The mechanism by which the placenta transports the essential elements, copper and zinc, while limiting the transport of cadmium, is unknown. It may involve the approximately 1,000-fold higher concentration of zinc in the placenta. Chan and Cherian (1992) reported that in Sprague-Dawley rats previously administered $CdCl_2$ (1.0 mg Cd/kg b.w., subcutaneous, daily for 8 days) pregnancy mobilises cadmium from the liver (40 % decrease compared to non-pregnant cadmium-treated controls) and increases the kidney concentrations (60 % increase). Cadmium concentrations in human milk are 5-10 % of levels in blood, possibly due to inhibited transfer from blood because of MT binding of cadmium in blood cells (Radisch *et al.*, 1987). The foetus and the breast-fed infant therefore only share a small proportion of the mother's cadmium burden.

Cadmium was found in autopsy samples from nearly all organs of a worker extensively exposed to cadmium dust, with the greatest concentrations in the liver and kidney (Friberg, 1950b, 1950a). In workers dying from acute poisoning due to inhalation of cadmium fumes, the lung cadmium concentration was somewhat lower than the liver or kidney cadmium concentration, probably due to previous chronic exposure (Beton *et al.*, 1966; Lucas *et al.*, 1980). In the kidney, cadmium rises more slowly than in the liver and begins to decline after the onset of renal damage at a critical concentration of 0.16-0.29 mg/kg (Roels *et al.*, 1981).

8.1.3. Excretion

Most of the inhaled cadmium that is transported to the gut via mucociliary clearance is not absorbed from the gastrointestinal tract (Moore *et al.*, 1973; Rusch *et al.*, 1986). Absorbed cadmium is excreted very slowly, with urinary and faecal excretion being approximately equal (Kjellstrom and Nordberg, 1978; Nordberg *et al.*, 1985).

Among four healthy adults ingesting cadmium in intrinsically labelled crabmeat, faecal excretion was 30 times higher than urinary excretion up to 10 weeks after ingestion of the test meal (Newton *et al.*, 1984).

Urinary excretion depends on blood concentration and kidney concentration, and total excretion is assumed to approximate daily intake at steady state. With these assumptions, daily faecal and urinary excretions are estimated to represent 0.007 and 0.009 % of body burden, respectively (Kjellstrom and Nordberg, 1978; Nordberg *et al.*, 1985).

Cadmium excretion in urine of occupationally exposed workers increases proportionally with the body burden of cadmium, but the amount of cadmium excreted represents only a small fraction of the total body burden, unless renal damage is present; in this case, urinary cadmium excretion markedly increases (Roels *et al.*, 1981). Faecal excretion in workers occupationally exposed to cadmium reflects mainly cadmium dust swallowed from industrial air and/or incidentally ingested from contaminated hands (Adamsson *et al.*, 1979).

Half-lives for cadmium in the whole body of mice, rats, rabbits, and monkeys have been calculated to be from several months up to several years. Half-lives were from 20 to 50 % of the maximum life span of the animal (Nordberg *et al.*, 1985). After reviewing the literature, Nordberg and co-workers (1985) calculated a range of half-lives from their kinetic model for the human kidney of 6 to 38 years, and for the human liver of 4 to 19 years.

Because of the long half-lives and the transfer of cadmium by MT from other tissues to the kidney, after long-term low-level exposure (as from dietary sources), accumulation in the kidney will occur during the major part of the human life span.

The half-life of cadmium in blood displays a fast component of 3 to 4 months and a slow component of about 10 years (Järup *et al.*, 1983). The longer half-life is due to the influence of cadmium body accumulation (body burden) on blood cadmium levels. Thus, after long-term low-level exposure, cadmium in blood may serve as a good reflection of the cadmium body burden. In those situations, blood cadmium is age-dependent and often highly correlated to the concentration of cadmium in urine.

Based on the one-compartment toxicokinetic model of cadmium in 680 postmenopausal Swedish women (see 8.5.2 for further clarification), the predicted urinary cadmium concentrations corresponding to a daily cadmium intake of 0.3 μg/kg b.w. over 70 years have been determined for the 50^{th}, 95^{th} and 99^{th} percentiles of the population. The estimated distribution of apparent half-life of kidney cadmium was estimated to be about 12.1 years (SD = 1.5 years) and the population standard deviation of this half-life to 3.4 years (SD = 0.5 year).

8.2. Biomarkers of exposure

Cadmium exposure reflecting the internal dose is monitored either in blood or urine.

8.2.1. Cadmium in blood

In blood, cadmium is found in the erythrocytes, where it is bound to high- or low-molecular-weight fractions. Plasma cadmium concentrations are low. Blood cadmium is considered the most valid marker of recent exposure and is usually assessed in whole blood. Differences in haematocrit levels (reference interval: 35-46 % in women and 39-50 % in men) may thus cause some variability of the cadmium concentration in whole blood. To control for this variability, the whole blood cadmium may be adjusted to the haemoglobin concentration.

In some recent studies, blood cadmium (B-Cd) has been replaced by erythrocyte cadmium (Ery-Cd), which, dependent on the haematocrit levels, is about 2.3 and 2.5-fold higher than the concentration in whole blood in male and female subjects, respectively (Reeves and Vanderpool, 1997). Thus, B-Cd and Ery-Cd are not interchangeable in exposure assessment.

While B-Cd mainly reflects recent exposure in occupationally exposed workers, it is also a useful measure of long-term exposure in subjects without exposures other than dietary especially among non-smokers (Järup *et al.*, 1998). Indeed, it has been shown that B-Cd correlates closely with U-Cd (correlation coefficient = 0.956, $p<0.01$) (Shimbo *et al.*, 2000). The corresponding correlation coefficient was 0.57 ($p< = 0.001$) in 800 Swedish women (Akesson *et al.*, 2006). The high correlation between U-Cd and B-Cd also facilitates the interpretation of studies using U-Cd as the dose estimate, i.e. both biomarkers are equally good estimates of cadmium body burden in environmentally exposed populations except when dietary Cd exposure changes.

8.2.2. Cadmium in urine

The urinary cadmium concentration is mainly influenced by the body burden of cadmium and is proportional to the concentration in the kidney. Ideally, urinary cadmium is assessed as the amount excreted over 24 hours. Because collection of 24-hour samples is cumbersome and there is a risk of incomplete sampling, spot urine sampling (often first voided morning urine) is commonly used. As spot urine samples vary in composition (volume and solutes) within and between individuals, some adjustment (creatinine concentrations or urinary density) is needed. The expression of data as a function of creatinine is the most common method, but creatinine excretion is affected by muscle mass and meat intake. This source of variation needs to be considered when comparing cadmium data expressed as a function of creatinine between sexes and populations (Suwazono *et al.*, 2005). Alternatively, cadmium excretion can be assessed using timed analyses.

There is a close relationship between cadmium concentrations in urine and kidneys. As a rule of thumb, assuming a linear relationship, urinary cadmium of 5 μg/g creatinine (~5 nmol/mmol creatinine) roughly corresponds to about 100 mg/kg in the renal cortex. In cases of severe tubular damage, the normal reabsorption of cadmium-metallothionein decreases and the urinary cadmium concentration increases. In the long run, cadmium-induced kidney damage will give rise eventually to low cadmium concentrations in both the kidney and in urine, while the tubular damage remains.

Because the half-life of cadmium in the body is very long (see chapter 8.1.3) urinary cadmium is highly dependent on age. However, the age-related increase in blood and urinary cadmium is less evident, disappears or may eventually turn to a decrease at the age range of 50 to 70 years and older. Smoking affects the urinary cadmium levels but not to the same extent as for blood cadmium. On average, 1.5 to 2 times higher levels are observed in smokers compared to non-smokers.

8.2.3. Biological monitoring of cadmium exposure

There have been several compilations of blood and urinary cadmium data in previous risk assessment reports (see e.g. EC, 2007). In this opinion focus is on biomonitoring of urinary

cadmium as this parameter, and not blood cadmium, is needed in order to estimate the dietary cadmium intake using a toxicokinetic model.

8.2.3.1. Biomonitoring data on cadmium in blood

A short summary of data on blood cadmium with focus on data reported after the EC-JRC report are given below. For more details see Table 4.84 in the EC-JRC assessment (EC, 2007).

Children

In children up to 11 years of age from Germany and Sweden, the average concentration was generally below 0.2 µg Cd/L with the highest values seldom exceeding 0.5 µg Cd/L (from EC, 2007, Table 4.84). In Swedish teenagers (1994), the average concentration was <0.2 µg Cd/L but considerably higher averages in those who were current smokers (average between 0.5-1.0 µg Cd/L) (Barany *et al.*, 2002). In 2004 the average concentration of cadmium in blood measured in Belgian teenagers was 0.36 and the 90th percentile was 1.32 µg/L (see "Documentation provided to EFSA"). In the National Health and Nutrition Examination Survey (NHANES) data sampled in 1999 to 2002, most blood cadmium concentrations in 1-5, 6-11 and even in 12-19 year olds were below the limit of detection (<0.2 µg Cd/L). The 95th percentiles were 0.35 µg Cd/L in 1-5 year old, 0.4 µg Cd/L in 6-11 year old, and ~1 µg Cd/L in 12-19 year old subjects (CDC, 2005).

Higher concentrations were found in 8 to 12-year-old children living in polluted areas (and controls) in France, Czech Republic and Poland (de Burbure *et al.*, 2006), with averages of 0.08 to 0.5 µg Cd/L depending on country and area. In children living in the vicinity of smelters in the Netherlands, the average was 0.76 µg Cd/L (EC, 2007).

Adults

Generally, for non-smoking adults living in non-polluted areas, the concentration of cadmium varies between 0.1 and 1.0 µg Cd/L in whole blood. The majority (90 %) of the people in these populations will have a concentration below 0.6 µg Cd/L (EC, 2007). Among smokers the concentration may be up to several times higher, but seldom above 3 µg/L. In Swedish women, aged 53-64 years living in a non-polluted area, the average blood cadmium was 0.35 µg/L (median, 0.30 µg Cd/L; 90th percentile, 0.57 µg Cd/L) in never-smokers. The corresponding data for the German Environmental Survey in 1998 (GerEs III) (Becker *et al.*, 2002) showed a median of 0.38 µg Cd/L for all subjects and 0.28 in non-smokers (95th percentiles, 2.34 and 0.78 µg Cd/L, respectively). In NHANES, for all adults, the median was 0.3 µg Cd/L and the 95th percentile 1.4 µg Cd/L (CDC, 2005). Belgian data showed 0.42 µg Cd/L (average) and 1.0 µg Cd/L (90th percentile) (see "Documentation provided to EFSA").

8.2.3.2. Biomonitoring data on cadmium in urine

Recently published data from France, Poland, Czech Republic, the United States, Germany, Belgium, Sweden, United Kingdom and Canada (not included in EC, 2007) referring to the general population, children in hot-spot areas or high-mollusc consumers are summarised below.

Children

Children and adolescents have lower urinary cadmium concentrations than adults. The median and the 95th percentile in children were 0.1 and 0.3 µg Cd/g creatinine respectively in NHANES (CDC, 2005). The median and the 90th percentile were 0.2 and 0.36 µg Cd/g creatinine respectively in Belgian teenagers (see "Documentation provided to EFSA"), but higher in exposed children from France, Poland and the Czech Republic. In a study on German children, 6-14 years, from the general population (n = 1352) (GerES), assessed during 2003 to 2006, 0.1 % (n = 1) had U-Cd concentration above 1 µg/g creatinine (Schulz *et al.*, 2007).

Adults

Women have higher urinary cadmium concentrations than men, which to some extent can be explained by a lower creatinine excretion in women, due to less muscle mass. The major reason for this sex-difference is, however, considered to be due to increased gastrointestinal cadmium absorption in women compared to men (see further section 8.1.1). Smokers and former smokers have higher U-Cd concentrations than never-smokers. Also high oyster consumers have higher U-Cd concentrations than low or non-consumers. The 95th percentile of U-Cd concentration is available from approximately ten studies. This percentile varied between 0.6 to 1.8 µg cadmium/g creatinine if all studies were considered. In studies presenting separate results for non-smoker/never-smokers the 95th percentiles varied between 0.6 and 1.2 µg cadmium/g creatinine. In a German study, GerES, performed in 1998. 0.4 % (n = 3,983) of the subjects had a urinary cadmium concentration above 2 µg/g creatinine (Schulz *et al.*, 2007).

8.2.3.3. Trends in exposure from biomonitoring data

Temporal trends of cadmium (non-hotspot areas) based on longitudinal data monitored in the same subjects twice or more were available from Belgium. Concentrations of cadmium in blood decreased by 40 % in the non-polluted region between the 1980s and 1990s. In contrast, it was increased by 20 % in the same region between the 1990s and the 2000s (Nawrot *et al.*, 2008). Further data on temporal trends based on biomonitoring data from the general population are available from three studies (not longitudinal data). There was no temporal trend observed in blood cadmium between 1996 and 2003 in over 5,000 ten-year old children from Germany (Link *et al.*, 2007). Similarly, no trend was observed in blood and urinary cadmium of 6-14 year old children from West Germany (n ~ 200), investigated in 1990-1992 and in 2003-2006, while a decreasing trend was observed in the same study of children from East Germany (Schulz *et al.*, 2007). About 4000 adults were also assessed in the latter study, where, in non-smokers, urinary cadmium decreased, while blood cadmium increased over the ten years studied. Data from Northern Sweden displayed no trend in cadmium concentrations measured in erythrocytes of non-smoking adults during the 1990-ties (based on samples stored in a biobank) (Wennberg *et al.*, 2006). Both the German and Swedish data do, however, show a significant decrease in smokers. It can thus be concluded that so far there is no indication of decreasing cadmium exposure in areas with no particular industrial cadmium emission and it cannot be excluded that there is an increasing trend in some areas.

To assess trends in bone cadmium a few studies on deceased people have been undertaken. It has been shown that bone cadmium concentrations in North American natives have increased approximately 50 times in 600 years (Ericson *et al.*, 1991). In another study from France, it was concluded that the concentrations of cadmium in human bones increased about ten times in the 20th century (Jaworowski *et al.*, 1985). A study in Gran Canaria showed that modern individuals showed higher bone cadmium values (mean 517 μg/kg) than prehistoric ones (mean 85 μg/kg), indicating a 6-fold increase (Gonzalez-Reimers *et al.*, 2003).

8.2.3.4. Exposure levels in specific population groups

Smokers

Tobacco smoking is the most important non-dietary source of cadmium exposure. A high cadmium content in tobacco leaves and a comparatively high absorption of cadmium via the lungs result in a substantially higher concentration of cadmium in blood and urine in smokers compared to never-smokers. There is, however, a wide range of cadmium concentrations in blood and urine even among current smokers, probably reflecting a broad range of cadmium concentrations in tobacco products. Former smokers generally have higher blood and urinary cadmium levels than never-smokers. Blood cadmium in smokers may be up to five times higher compared to never-smokers.

Infants and children

Breast milk generally contains fairly low levels of cadmium, with the concentration seeming to be related to the level of maternal exposure. To summarise the exposure situation in early life, a higher maternal cadmium exposure during pregnancy and lactation results in a higher foetal and infant exposure, although at lower concentrations than maternal levels. The intestinal absorption of cadmium during infancy is most likely considerably higher than in adults. A higher gastrointestinal absorption in combination with consumption of infant formula composed by ingredients with a higher cadmium content than breast milk (e.g. wheat or soy) (Eklund and Oskarsson, 1999) may lead to increased internal cadmium exposure in these infants.

Dietary habits

Based on Swedish data more than 80% of the dietary cadmium intake comes from plant food (Olsson *et al.*, 2002), mainly from cereals (especially whole grains), vegetables, root vegetables and potatoes. People consuming a healthy diet with a high intake of whole grains and vegetables (including vegetarians) have a higher dietary exposure than those consuming a mixed diet.

Organ meats (mainly from older animals) and certain seafood (different types of shellfish) may contain high levels of cadmium. Thus, people having a diet high in game offal and shellfish may have a high food-cadmium intake. However, it is possible that cadmium from shellfish is absorbed to a lower extent in the gastro-intestinal tract than cadmium from plants.

8.3. Toxicity

Several documents reviewing cadmium toxicity in experimental animals have been produced by several national agencies and international bodies including the European Commission (WHO-IPCS, 1992a; ATSDR, 1999; JECFA, 2006; EC, 2007).

The target organs (kidneys and bone) as well as the toxicokinetics of cadmium after oral exposure are roughly similar among species. However, there are some important differences. Estimation of cadmium absorption in rodents revealed lower levels as compared to humans particularly after prolonged exposure and it is well established that species specific differences in metallothionein synthesis as well as in cadmium kinetics and toxicity may occur.

Since there are much data from human studies, the Panel decided not to elaborate further on the animal data. Recent data on the mechanisms of cadmium toxicity that are of potential relevance for human health effects are summarised below.

8.3.1. Molecular aspects of cadmium toxicity

Inhibition of DNA repair

Cadmium is not directly genotoxic, it is non-mutagenic in bacteria and weakly mutagenic in mammalian cells with contrasting evidence (for an extensive review of genotoxicity data see (EC, 2007; ATSDR, 2008). Two mechanisms play an important role in cadmium genotoxicity: 1) induction of reactive oxygen species (ROS) and 2) inhibition of DNA repair. At high cytotoxic doses cadmium induces DNA single-strand breaks and genome instability in several types of mammalian cells likely due to oxidative stress. At sub-cytotoxic concentrations cadmium is also harmful because it can sensitize cells to external agents by inhibiting DNA repair. By this mechanism cadmium can enhance the mutagenicity induced by other DNA damaging agents. The precise molecular mechanism involved in the inhibition of DNA repair by cadmium has not been clearly identified. The most comprehensive data indicate an effect of cadmium on the repair or accumulation of 8-hydroxyguanine by inactivating a series of proteins involved in the first steps of base excision repair. Cadmium interferes with DNA-protein interactions required to initiate nucleotide excision repair. Proteins like XPA and TFIIH seem to be specific targets of cadmium. Cadmium affects also proteins involved in mismatch repair (MMR), specifically affects ATP binding and hydrolysis activities of MMR enzymes reducing their DNA binding activity and recognition of mismatches (reviewed in Giaginis *et al.*, 2006).

Cadmium does not directly modify DNA but its capacity to inhibit DNA repair enzymes may contribute to its genotoxic effects.

Effects on gene expression

Cadmium affects both gene transcription and translation. Cadmium regulates the internal cell concentration of calcium and plays the role of an alternative signalling molecule controlling various transduction pathways. Moreover, cadmium may interfere with calcium homeostasis by its ability to modulate extracellular calcium sensing receptors (CaSR) (Chang and Shoback, 2004). In this way cadmium may profoundly affect the function of cells expressing CaSR such as kidney cells that are involved in calcium homeostasis. A recent study on mice

showed that cadmium introduced morphological changes and reduced the level of calcium in the mammary gland and decreased beta-casein gene expression, suggesting that cadmium can disturb the function of the lactating mammary gland, which may impair the development of the suckling offspring (Ohrvik *et al.,* 2006).

Cadmium is not a redox-active metal and cannot itself direct Fenton type-reactions but it induces the production of ROS by indirect processes, a decrease of cellular antioxidants and exhalation of ROS by mitochondria. Cadmium by perturbing the redox homeostasis impacts a large set of transcription factors characterized by reactive cysteines. Among these, MTF1 which is the inducer of MT (Zhang *et al.*, 2003). Moreover, by inducing oxidative modification of proteins cadmium can also target these proteins to degradation.

By modulation of gene expression and signal transduction cadmium may affect cell proliferation, differentiation, apoptosis and other cellular activities (Waisberg *et al.*, 2003). The perturbation of these processes may all contribute to carcinogenicity.

Endocrine functions

The concomitant manifestations of proximal renal tubular dysfunction and anaemia with erythropoietin (Epo) deficiency observed in chronic cadmium intoxication, such as Itai-itai disease (see Chapter 8.4), suggest a close local correlation between the cadmium-targeted tubular cells and Epo-producing cells in the kidney. Recent studies show that cadmium has a strong inhibitory effect on Epo expression both *in vitro* and *in vivo* (Horiguchi *et al.*, 2006). Cadmium-intoxicated rats showed atrophy of Epo-expressing renal tubules. These data indicate that cadmium would induce anaemia through the direct injury of the proximal renal tubular cells that are responsible for Epo production.

It is well known that moderate to high dose exposure to cadmium (1 mg/kg for 5 days/week for 6 weeks by *i.p.*) affects steroid synthesis in reproductive organs in female rats (Zhang *et al.*, 2008). It has been shown that low dose cadmium exposure has potent oestrogen- and androgen-like activities *in vivo* and *in vitro*, by directly binding to oestrogen and androgen receptors (Takiguchi and Yoshihara, 2006). Cadmium, like oestradiol, can cause rapid activation of ERK1/2 and AKT (Liu *et al.*, 2008). However, the precise mechanisms underlying the effects of cadmium as an endocrine disruptor remain to be elucidated.

8.4. Observations in humans

A large number of studies on health effects of cadmium exposure in humans have been published since the groundbreaking paper by Lars Friberg (1950b). In particular, the cadmium induced Itai-itai disease in Japan caused severe sufferings among inhabitants in the Toyama prefecture whose staple food consisted of rice grown on polluted paddy fields. Research has focused on kidney and bone effects, which have been shown to occur at much lower levels of cadmium exposure than initially thought. The sections below present information which was published recently (such as EC, 2007).

8.4.1. Acute effects

Cadmium is toxic to a wide range of organs and tissues. Several fatal inhalation exposures have occurred in occupational accidents. Intentional ingestion of cadmium has occurred in connection with suicidal attempts. The cause of death is massive fluid loss, oedema and widespread organ failure. In humans ingestion of food or beverages contaminated with high amounts of cadmium gives rise to acute gastrointestinal symptoms. The no-observed-effect level (NOEL) of a single oral dose is estimated to be 3 mg elemental cadmium/person, and the lethal doses rage from 350 and 8900 mg (Bernard and Lauwerys, 1986).

8.4.2. Chronic effects

8.4.2.1. Effects on kidney

The kidney is the critical target organ for dietary exposure to cadmium and renal damage is characterised by cadmium accumulation in convoluted proximal tubules, thereby causing cell dysfunction and damage. The earliest signs of tubular toxicity are respectively decreased tubular reabsorption (increased excretion) of low molecular weight proteins (LMWP) and increased excretion of markers of cell shedding. Below an overview of the most commonly mentioned biomarkers of effects of cadmium exposure is given. It should be noted that biomarkers are often non-specific for a certain exposure and may not necessarily be adverse, but can indicate potential health impairment.

Tubular markers

The urinary excretion of LMWP and the activity of some enzymes (mainly N-acetyl-beta-glucosaminidase (NAG), the most stable and reproducible) in urine have been respectively used to assess tubular dysfunction – in terms of reabsorptive capacity – and cell damage – in terms of cell shedding into urine,

- Urinary beta-2-microglobulin (B2M) has been widely used as an indicator. Because it is unstable in acidic urine, there is a need to control the pH of samples to prevent its degradation. However, degradation may occur already in the bladder. As other markers, urinary B2M excretion generally rises with age (Roels *et al.*, 1989) and may be affected by overload proteinuria or competition for tubular uptake at the tubular reabsorption sites.
- Urinary retinol-binding protein (RBP) is more stable than B2M at the physiological pH of urine and therefore has been proposed as a possible substitute, though it is slightly less sensitive to tubular dysfunction (Bernard and Lauwerys, 1981).
- Urinary alpha-1-microglobulin (A1M), also called human complex-forming glycoprotein (pHC) has been used in several studies as a LMWP, though it is less sensitive and less specific for tubular dysfunction.
- Urinary NAG. NAG is a lysosomal enzyme present in high concentrations in the proximal tubule. Increased NAG activity can result from effects other than renal damage (Bernard and Lauwerys, 1989), and only the activity of its membrane-bound B isozyme (NAG-b) is an indicator of cell shedding. Sometimes, total NAG has been used, relying on the assumption (not always true) that there should be a correlation between NAG-b and total

NAG. Alternative explanations for elevated NAG excretion may be exocytosis and interference with enzyme activity by inhibitors

Other enzyme activities, antigens, proteins, prostanoids, amino acids, and urine constituents have been used as biomarkers, but either analytical validity or validation for the purpose of assessing cadmium toxicity are insufficient for use in risk assessment.

Glomerular markers

The urinary excretion of high molecular weight proteins (HMWP) and glomerular filtration rate (GFR) have been respectively used to assess the integrity of glomerular sieve – in terms of ability to retain HMWP – and filtration rate, or volume of blood undergoing ultrafiltration per unit of time.

Albumin: whereas gross increases in albuminuria (> 300 mg/day or 200 mg/g creatinine) suggest damage to glomerular structures resulting in overt nephropathy, values ranging between 20 and 200 mg/g creatinine (microalbuminuria) indicate haemodynamic changes associated with incipient glomerulopathy (e.g., diabetic nephropathy) or tubulo-interstitial damage (lead nephropathy). Alternative explanations to albuminurina include impaired tubular reabsorption and interference by a number of factors (work-load, meat meal, and ortostatism. Owing to such possible interferences, microalbuminuria is diagnosed only when its occurrence is confirmed by repeated measurements over a six-month period. Other proteins can be measured, either as a confirmation test, or to assess the integrity of glomerular structures (e.g., immunoglobulins G and transferrin).

Glomerular filtration rate (GFR): any deviation of GFR from the normal range may indicate renal damage: in early stages of certain chronic conditions, e.g., diabetes and lead poisoning, hyperfiltration (stable increase of GFR by 10-20 %) is indicative of incipient nephropathy, whereas in established disease both conditions are associated with reduced GFR due to glomerular and tubulo-interstitial sclerosis. GFR can be assessed measuring the renal clearance of either exogenous (51Cr-EDTA, inulin, iothalamate) or endogenous substances (creatinine). GFR can also be indirectly assessed measuring serum concentrations of creatinine or LMWP, cystatin C being the most suitable and used protein showing concentrations inversely proportional to GFR.

Biomarkers of effects in workers

Friberg (1948, 1950b) published the first reports of kidney damage as a result of occupational exposure. He found an unusual type of proteinuria detected by trichloroacetic acid precipitation test, but not by the boiling test. The latter test was widely used at that time to detect proteinuria. The reason for his finding was shown in subsequent studies to be the excretion of mainly LMWP as a consequence of tubular kidney damage (Piscator, 1962). Both Friberg and Piscator noted that workers with high cumulative exposure to cadmium and high levels of cadmium in urine, also suffered glomerular damage with increased levels of albumin in urine. These findings were confirmed by other scientists. Bernard and co-workers (1976) reported an increased excretion of albumin in some cadmium workers even at moderate exposures. Various sensitive biomarkers of tubular and glomerular kidney damage have later been established and have been widely used in studies of kidney damage in cadmium workers. One of the earliest developed and most widely used markers is urinary B2M (Nordberg *et al.*, 1985; Järup *et al.*, 1993; Roels *et al.*, 1997).

A thorough review of the occupational studies performed on cadmium workers was recently described in the draft toxicological profile for cadmium (ATSDR, 2008).

The most common route of occupational exposure is via inhalation of fumes or dust, with cadmium oxide representing the predominant chemical form. Heating cadmium-containing products can produce cadmium oxide fumes that are absorbed with ease through the respiratory tract (IARC, 1993; ATSDR, 2008).

In occupational exposed subjects adverse effects of cadmium on the kidney were observed at urinary levels ranging from 1.1 to 15 μg/g creatinine (Elinder *et al.*, 1985; Jakubowski *et al.*, 1987; Shaikh *et al.*, 1987; Verschoor *et al.*, 1987; Kawada *et al.*, 1989; Bernard *et al.*, 1990; Roels *et al.*, 1991; Chiba and Masironi, 1992; Toffoletto *et al.*, 1992; Roels *et al.*, 1993; Järup and Elinder, 1994; Chen *et al.*, 2006a; Chen *et al.*, 2006b).

Concerning urinary biomarkers, Järup and Elinder (1994) reported abnormal levels of B2M (cut-off level: 220 μg/g creatinine) in 10 % of the workers showing urinary cadmium levels of 1.5 (≥ 60 years of age) or 5 (<60 years of age) μg/g creatinine. Elinder *et al.*(1985) found B2M in excess of 300 μg/g creatinine in the urine of 25 % of the workers whose urinary cadmium levels ranged from 2 to 5 μg/g creatinine. According to a study by (Chen et al., 2006a) in cadmium smelter workers, 40 % of the subjects excreting 5 to 10 μg cadmium /g creatinine also had enhanced urinary B2M levels (cut-off: 187 μg/g creatinine). Furthermore, urinary B2M and RBP exceeded the values of 380 and 130 μg/g creatinine, respectively, in 10 % of the workers with urinary cadmium in the range of 10–15 μg/g creatinine (Jakubowski *et al.*, 1987). At >10 μg cadmium/ g creatinine not only the urinary excretion of LMWP was enhanced, but also that of albumin and transferring (Bernard *et al.*, 1990). An age-related decline in maximal glomerular filtration rate was exacerbated in workers with cadmium induced microproteinuria at urinary cadmium levels of 11.1 μg/g creatinine (Roels *et al.*, 1991).

Human occupational studies provide consistent evidence that cadmium targets the kidney after chronic exposure. The earliest manifestations of tubular toxicity (not specific to cadmium) are increased excretion of LMWP, such as B2M, alpha-1-microglobulin (A1M), and RBP.

Clinical significance of tubular damage and the issue of reversibility

Repeated measurements of the GFR using CrEDTA clearance in a follow-up study on workers exposed to cadmium showed that, on average, people with tubular damage also had a reduction in GFR (84 % of age predicted value) and, furthermore, there was a significant correlation between tubular reabsorption loss and GFR (Elinder et al., 1985). Such a relationship was confirmed ten years later, when a highly significant relationship was found between GFR and urinary B2M. The regression equation was: GFR = 117.6 -5.58 * ln(urinary B2M), p = 0.000053 (Järup *et al.*, 1995). In the 10-year follow-up, five subjects with minor increases of B2M at the first examination were found to fall within the reference interval at the follow-up. The authors concluded that such minor changes were probably due to causes other than cadmium, as at those times the irreversibility of cadmium induced tubular proteinuria was a common belief.

The clinical significance of individual biomarkers depends on the magnitude of their deviation from the reference interval. Values between the 95th and the 99th percentile of a

presumably healthy population (e.g., albuminuria between 20 and 200 mg/g creatinine) indicate incipient nephropathy, whereas values exceeding the 99th percentile indicate overt nephropathy, usually irreversible and progressive. These criteria, applied to cadmium-induced tubular dysfunction are depicted in Table 31, which reports a guideline to distinguish values within the reference interval from incipient, irreversible and overt cadmium nephropathy, with cut-offs of 300, 1,000 and 10,000 μg/g creatinine for B2M (Bernard *et al.*, 1997). Increases in the excretion of tubular markers (e.g., B2M > 300 μg/g creatinine) are diagnosed as incipient renal damage. If such changes persist in time (as assessed by subsequent measurements), they should be interpreted as clinically relevant adverse effects, because they reflect early changes that may subsequently lead to compromised renal function, as demonstrated by longitudinal studies.

Table 31. Interpretation of B2M in a clinical perspective (adapted from Bernard, 2004)

B2M in urine (μg/g creatinine)	Clinical interpretation
<300	Within the reference interval.
300-1,000	Incipient cadmium tubulopathy, possibly reversible upon cessation of exposure or forerunner a) of accelerated decline of GFR; increased incidence of renal stones.
1,000-10,000	Irreversible tubular proteinuria. GFR may still be normal.
> 10,000	Overt cadmium nephropathy and usually decreased GFR.

[a)] this refers to values that have been confirmed in the same subject at least twice in two repeated measurements over a six-month period.

The possible reversibility of cadmium-induced tubular dysfunction is another important issue to consider for a correct interpretation of the clinical significance of renal biomarkers. That irreversible tubular proteinuria occurs when B2M values exceed 1,000 μg/g creatinine is demonstrated by a longitudinal study carried out in Belgium (Roels et al., 1997). In former cadmium workers B2M moderate increases of B2M above 300 μg/g creatinine at the time of exposure were almost completely reversible within five-year exposure cessation (data from five subjects). Values exceeding 1,000 μg/g creatinine were either irreversible or progressive. The evolution of tubular renal function was shown to depend both on the extent of the body burden of cadmium (as reflected by Cd-U) and the severity of microproteinuria at the time of diagnosis, prior to reducing or ceasing cadmium exposure. In subjects with severe microproteinuria (B2M-U > 1,500 μg/g creatinine) in association with historical Cd-U values higher than 20 μg Cd/g creatinine, cadmium-induced tubular dysfunction was progressive in spite of reduction or cessation of cadmium exposure. Conversely, microproteinuria reversed when reduction or cessation of exposure of workers occurred when tubular damage was still mild (B2M < 1500 μg/g creatinine) and if Cd-U had never exceeded 20 μg/g creatinine.

Other studies have indeed documented the irreversibility of cadmium induced kidney alterations in subjects that had been previously exposed to high levels of this heavy metal at their workplace (ATSDR, 2008). Years after exposure cessation these former workers showed enhanced microproteinuria or total proteins (Piscator, 1984; Thun *et al.*, 1989; Mason *et al.*, 1999; Roels *et al.*, 1999) or reduced GFR (Piscator, 1984; Jarup *et al.*, 1993; Jarup *et al.*, 1995; Roels *et al.*, 1999).

Conversely, a study in workers of a nickel-cadmium battery factory (Trzcinka-Ochocka *et al.*, 2002) found indication that the tubular proteinuria was, at least in part, reversible, even in the case of relatively high past exposure. This study involved 58 workers divided into three groups according to their RBP-U concentrations at the time of exposure in 1986-1988: < 300 (group 1; n = 26); 301-1,501 (group 2; n = 25) and >1501 μg/g creatinine (group 3; n = 7).

Eleven years later, the RPB-U levels were below 300 μg/g creatinine in 85 %, 64 % and 42 % of persons from groups 1, 2 and 3, respectively. Notably, workers eligible for the study had terminated their employment at least one year before this assessment. From the viewpoint of reversibility of tubular proteinuria, its severity during exposure was the most important determinant. Also, the time since the removal from exposure to cadmium and Cd-U levels seemed to play some role, though not statistically significant. Although the risk of low-molecular-weight proteinuria increased when the past exposure to cadmium was high (Cd-U >20 μg/g creatinine), reversible effects were also detected in a certain percentage of these subjects (all subjects in group 3 had Cd-U above 20 μg/g creatinine).

Because of the very long biological half-life of cadmium in the kidney (10-30 years), both accumulation and decrease are very slow in this tissue. It is not unusual that people, who had marginally increased levels of urinary B2M, reach the age of 50-60 years before Cd levels in their kidney cortex fall below the critical level, despite the fact that exposure ended much earlier in life. In subjects with high liver burden MT-bound cadmium is constantly transferred from liver to kidney and, in spite of exposure cessation, renal damage may progress even though less than 1,000 μg/g creatinine of B2M are present in their urine.

Reversibility is rare among persons who developed overt tubular dysfunction (i.e at least two subsequent values of B2M above 300 μg/g creatinine) as a result of cadmium exposure. In the general population, although a single study has reported some reversibility of increased B2M (Hotz *et al.*, 1999). As reported above, there are also many examples of occupational studies showing no reversibility, with this supporting that when exposure has been excessive, progression of the damage is the rule.

Reversible changes are instead likely in individuals aged less than 50 years, showing mild microproteinuria (B2M between 300 and 1,500 μg/g creatinine) at the time of exposure cessation, and with a past history of low Cd exposure, resulting in a low liver burden.

Biomarkers of effects in the general population

Table 32 summarises recent publications addressing the critical urinary cadmium dose levels of tubular effect markers in the general population. Two older studies in the European Union (CadmiBel and Oscar) that were extensively reported in the evaluation by the EC/JRC (EC, 2007) are included for comparison. As depicted in the table, several markers, approaches and criteria have been used. A more comprehensive literature search has been carried out to set up a data base to be used for a systematic approach and meta-analysis (see chapter 8.5.1.1).

Table 32. Overview of recent studies providing an association between urinary-cadmium exposure and tubular effects

Study	Approach	Sample size, (age years)	Criteria	Marker[a)]	Analytical method[b)]	U-Cd critical dose level µg/g creatinine	Note
CadmiBel (Buchet *et al.*, 1990)	Dose-response	1,699 (20-80)	10 % probability of adverse response	B2M NAG RBP AA Ca	Cd: AAS B2M: LIA RBP: LIA AA: colorimetric Ca: complexometric titration method	B2M: 2 NAG: 1.8 RBP: 1.9 AA: 2.9 Ca: 1.3 Assuming 1 µg/24 h = 0.67 µg/g creat.	Groups and continuous variables
Oscar (Jarup *et al.*, 2000)	Dose-effect, followed by dose-response	470 male (54); 533 female (52) (from a possibly polluted area)	10 % excess of LMWP adding to background prevalence of 5 %	A1M	Cd by ICP-MS (LOD 0.01-0.04 µg/l) HC by RID (LOD 1.7 mg/L)	1.0 (HC)	roups and continuous variables temporality
China I (Jin *et al.*, 2004a)	Dose-response (B2M>800 µg/g creatinine)	790 living in two cadmium exposed areas and one control area in China	BMD05 and LBMD05 (5 % excess of LMWP over background)	NAG NAG-b B2M RBP ALB	Cd: AAS NAG-b (thermostable) B2M: RIA RBP: LIA ALB: ELISA	BMD05/LBMD05 6.70/5.87 (NAG) 4.46/3.99 (NAG-b) 8.36/7.31 (B2M) 7.98/6.98 (RBP) 15.06/12.18 (ALB)	
China II (Hong *et al.*, 2004)	Dose-response (B2M>300 µg/g creatinine)	245 (122 in As-Cd from polluted and 123 from non polluted area)	BMD10 and LBMD10 (10 % excess of LMWP over background)	B2M NAG ALB	Cd: AAS B2M: ELISA ALB: ELISA	BMD10/LBMD10 1.36/1.13 (B2M) 1.05/0.88 (ALB) 1.48/1.24 (NAG)	Co-exposure to As

Table 32. Continued

Study	Approach	Sample size, (age years)	Criteria	Markers[a)]	Analytical methods[b)]	U-Cd critical dose level µg/g creatinine		Note
Japan I (Uno *et al.*, 2005)	Dose-response (B2M>84th percentile: male: 233 µg/g creatinine female: 274 µg/g creatinine)	410 male (42-57 y); 418 female (41-58 y) Urine sampling 1997-1998	BMD05, BMD10 and LBMD05, LBMD10	B2M NAG PROT	Cd: AAS (LOD 0.05 µg/l) B2M: RIA (LOD 1 µg/l) PROT: colorimetry	BMD10/LBMD10 1.0/0.7 (B2M) M 0.7/0.6 (NAG) M 1.9/1.2 (PROT) M 1.8/1.3 (B2M) F 1.6/1.2 (NAG) F 6.6/3.6 (PROT) F	BMD05/LBMD05 0.5/0.4 (B2M) M 0.3/0.3 (NAG) M 0.9/0.6 (PROT) M 0.9/0.7 (B2M) F 0.8/0.6 (NAG) F 3.2/1.8 (PROT) F	
Japan II (Kobayashi *et al.*, 2006)	Dose-response (B2M>84th percentile: male: 507 µg/g creatinine female: 400 µg/g creatinine)	547 male 723 female (≥50 y)	BMD05, BMD10 and LBMD05, LBMD10	B2M NAG PROT	Cd: AAS B2M: RIA PROT: colorimetry	BMD10/LBMD10 4.6/3.6 (B2M) M 6.4/4.4 (NAG) M 5.0/4.3 (PROT) M 3.3/2.8 (B2M) F 5.6/4.0 (NAG) F 5.3/4.6 (PROT) F	BMD05/LBMD05 2.6/2.0 (B2M) M 3.6/2.5 (NAG) M 3.2/2.7 (PROT) M 1.9/1.6 (B2M) F 3.1/2.2 (NAG) F 3.6/3.1 (PROT) F	
Japan III (Shimizu *et al.*, 2006)	Dose-response 84 % and 95 % (1mg/g creat) cut-off for B2M	3178 and 294 (≥50 y) from polluted and non-polluted areas	LBMD05 on dose-effect relationship (continuous variables)	B2M	Cd: HGAAS B2M: RIA	84 % cut-off 2.9 (B2M) M 1.5 (B2M) F	95 % cut-off 4.0 (B2M) M 3.6 (B2M) F	

Table 32. Continued

Study	Approach	Sample size, (age years)	Criteria	Markers[a)]	Analytical methods[b)]	U-Cd critical dose level µg/g creatinine		Note
Japan IV (Kobayashi *et al.*, 2008a)	Dose-response (B2M>84th percentile: 492 µg/g creatinine male and 407 µg/g creatinine female B2M>97.5th percentile: 965 µg/g creatinine male and 798 µg/g creatinine female)	1397 male and 1706 female (≥50 y) from polluted area; 1181 male and 1748 female (≥50 y) from non-polluted area	BMD05, BMD10 and LBMD05, LBMD10	B2M	Cd: AAS B2M: RIA	cut-off 84 % BMD10/LBMD10 5.0/4.6 (B2M) M 5.7/5.4 (B2M) F cut-off 97.5 % BMD10/LBMD10 7.4/6.8 (B2M) M 8.6/8.1 (B2M) F cut-off 1mg/g cr. BMD10/LBMD10 7.5/6.9 (B2M) M 9.4/8.9 (B2M) F	cut-off 84 % BMD05/LBMD05 3.0/2.7 (B2M) M 3.4/3.2 (B2M) F cut-off 97.5 % BMD05/LBMD05 4.9/4.5 (B2M) M 5.9/5.6 (B2M) F cut-off 1mg/g cr. BMD05/LBMD05 5.0/4.6 (B2M) M 6.7/6.3 (B2M) F	BMDs were decreasing with age class
Sweden women (Suwazono *et al.*, 2006)	Dose-response (hybrid) 95 % of 0Cd	820 female (53-64 y)	BMD05, BMD10 and LBMD05, LBMD10	NAG HC GFR	Cd: ICP-MS (LOD 0.31 µg/L) HC: RIA (LOD 0.7 mg/L) NAG colorimetric assay GFR: estimated from serum cystatin C: immunonephelometry	BMD10/LBMD10 1.08/0.83 (NAG) 1.05/0.81 (HC) 1.80/1.18 (GFR)	BMD05/LBMD05 0.64/0.50 (NAG) 0.63/0.49 (HC) 1.08/0.70 (GFR)	Unusual approach to BMD calculation (0 Cd ref)
Sweden women (Akesson *et al.*, 2005)	Dose-effect (quartiles)	820 female (53-64 y)	LOEL	HC NAG GFR Creatinine clearance	HC, NAG, GFR: methods see Suwazono *et al.* (2006) Creatinine clearance: [(140-age) x body weight(kg)] / [0.85 x S-crea (µM)] modified Jaffé method	For NAG, HC (HC not shown) and creatinine clearance in the range 0.65-0.97 (mean 0.79) or equal to the II quartile For GFR: mean = 1.0, or the III quartile		

Table 32. Continued

Study	Approach	Sample size, (age years)	Criteria	Markers[a)]	Analytical methods[b)]	U-Cd critical dose level µg/g creatinine	Note
Thailand (Teeyakasem *et al.*, 2007)	Dose-Response: prevalence of B2M > 0.4 mg/g creatinine NAG > 8 UI/g	58 male; 70 female (30-84); 46 male; 50 female with various diseases (34-87)	LOEL or NOEL	B2M HC NAG ALB	Cd: FAAS B2M: ELISA HC: ELISA ALB: immuno-nephelom.	B2M: 5.0 in controls (LOEL) NAG: 5.0 in subjects with disease NOEL > 10.0 for the other markers	
Czech Rep. France Poland (de Burbure *et al.*, 2006)	Dose-effect (quartiles)	804 children (8.5-12.)	LOEL	B2M RBP NAG Clara cell p. (CC16) CYS	Cd: AAS CYS: LIA B2M: LIA RBP: LIA NAG: colorimetric assay	RBP: 0.71 µg/g creatinine NAG: 0.58 µg/g creatinine HVAL: 1.50 µg/g creatinine CC16: 1.17 µg/g creatinine	Co-exposures to Pb and Hg

a) AA = urinary aminoacids; ALB = albumin; A1M: alpha-1-microglobulin; B2M = beta-2-microglobulin; Ca = urinary calcium; CYS = cysteine; GFR = glomerular filtration rate; HC = A-1-microglobulin; NAG = N-acetyl-beta-D-glucosaminidase; NAG-b = N-acetyl-beta-D-glucosaminidase-b; PROT= total proteinuria; RBP = Retinol binding protein.

b) AAS = atomic absorption spectrometry; ELISA = enzyme-linked-immunosorbent-assay; FAAS = flame atomic absorption spectrometry, HGAAS = hybride generation atomic absorption spectometry; ICP-MS = inductively coupled plasma-mass sepctrometry; LIA = latex immunoassay; RIA = radioimmunoassay.

When interpreting the data displayed in Table 32 it is important to consider the specific criteria and conditions applicable to each specific study some of which have been listed in Table 32. The task of the present assessment is of course to try to find the levels of cadmium that are causally related to a defined effect in terms of increased prevalence of renal dysfunction. In addition to the cut off levels for the various biomarkers listed, other important factors should also be considered such as co-exposure to other kidney-damaging agents and the time period when the exposure took place in relation to the time point when urine samples were taken for chemical determinations of biomarkers.

The first entry in Table 32 describes the CadmiBel study (Buchet *et al.*, 1990) based on environmentally cadmium exposed population groups in Belgium. This study took account of a number of influencing factors other than cadmium exposure and was first to report a statistically significant increase in biomarkers of renal dysfunction at urinary cadmium levels of 2-4 μg/g creatinine. This study is included here for comparison with the more recent studies. It may be of interest that there has been a follow up of the CadmiBel study. Hotz et al. (1999) reported such a follow up and found that the urinary levels of cadmium were lower and some subjects who previously had displayed increased levels of biomarkers of renal dysfunction had returned to lower values, indicating reversibility in some persons.

The Swedish Oscar study, which focused on 1021 persons who had low-level occupational or environmental cadmium exposure, found an age and sex adjusted correlation between cadmium in urine and urinary protein HC (alpha-1-microglobulin). The prevalence of tubular proteinuria ranged from 5 % among people with the lowest exposures to 50 % in the most highly exposed group. Multiple logistic regression analysis showed an increasing prevalence of tubular proteinuria with urinary cadmium as well as with age. After adjustment to the mean age of the study population (53 years), the results showed an increased prevalence of 10% tubular proteinuria (taking into account a background prevalence of 5 %) at a urinary cadmium concentration of 1.0μg/g creatinine (Jarup *et al.*, 2000). In their reanalysis of the Swedish OSCAR data the EU-JRC authors found that 'when the same calculation is done on the group of subjects with environmental exposure to cadmium only, the U-Cd level that is associated with a doubling of the prevalence of elevated HC proteinuria is 0.5 μg/g creatinine (the 65th percentile in this subgroup). It should be noted that exposure to cadmium in this area was higher in the past and had decreased considerably at the time the study by Järup and co-workers (2000) was performed. Estimates of past exposures were presented by Alfven (2000). The values cited in Table 32 and in the text, thus, most probably are lower than the levels of cadmium in urine that caused tubular proteinuria.

In "China I" (Jin *et al.*, 2004a) the prevalence of renal dysfunction was studied in areas with varying degrees of cadmium contamination of rice, from no contamination (control area, levels in rice 0.05 mg/kg) to heavy contamination with cadmium levels in rice of 3.7 mg/kg. Consumption of contaminated rice was going on until 1996 and the urine cadmium levels determined in 1995 and 1998 showed no statistically significant decrease. The reported BMD and BMDL values are somewhat high, reflecting the high cut off values (representing upper 95 percent level among controls) but it is likely that they have been essentially unaffected by the decrease in exposure from 1996 until urine sampling in 1998.

The China II study (Hong *et al.*, 2004) was performed based on a population group with combined inhalation and oral cadmium exposure (until the time of urine sampling) from the domestic use of coal contaminated with arsenic and cadmium and some other inorganic compounds. Arsenic exposure as such caused some renal dysfunction that was increased by concomitant cadmium exposure. There was a strong influence of concomitant arsenic

exposure on the prevalence of renal dysfunction from cadmium as reported in this study and also by Nordberg and co-workers (2005). The considerable influence of concomitant arsenic exposure probably is the main explanation for the lower BMD and LBMD values in this population group compared to "China I".

"Japan I –IV" represent recently reported studies from Japanese areas, both contaminated and non-contaminated. It should be noted that some of these recently reported studies are based on urine samples collected in the early 1980's (Shimizu *et al.*, 2006), while other studies are based on sampling performed in 1997 – 1998 (Uno *et al.*, 2005). The latter study is based on general population groups without known exposure from point sources and cadmium exposure in these groups most probably is mainly from food and has followed the general pattern of cadmium exposure in Japan. It is known from the studies by Watanabe and co-workers (2000) that the daily cadmium intake from food decreased considerably between 1977-1981 and 1991-1997. The intake in the former period was almost 50 % higher than in the latter one. It is thus possible that the low values of BMDL in the study by Uno *et al.* (2005) is related to damage caused at an earlier date when cadmium exposure was higher.

In the study from Poland several biomarkers of renal tubular dysfunction were used including NAG-b. It is interesting to note that the lowest LOAEL value of 1-2 μg/g creatinine was estimated for this very sensitive biomarker.

The studies on a cohort of Swedish women by Suwazono and co-workers (2000) and by Åkesson and co-workers (2005) are of considerable interest. This is a cross-sectional study among women, aged 54 to 63 years, living in a rural area in Southern Sweden with no known industrial cadmium emission and there is no reason to believe that exposure had decreased in this cohort. Both LOEL and benchmark dose were assessed for estimated GFR (based on Cystatin C in serum), creatinine clearance and for alpha-1-microglobulin and NAG in urine. Cadmium was assessed in both blood and urine. In multiple linear regression models, adjusted for likely confounders such as age, body mass index, diabetes, hypertension, the use of non-steroid anti-inflammatory drugs and blood lead concentrations, urinary cadmium was significantly (adversely) associated with GFR, creatinine clearance, alpha-1-microglobulin and NAG. The associations with alpha-1-microglobulin and NAG persisted in the group of women who had never-smoked and, thus, had the lowest exposure. Blood cadmium, on the other hand, was significantly (adversely) associated with GFR, alpha-1-microglobulin and NAG. There was a statistically significant interaction between cadmium and insulin-treated diabetes for the tubular effect makers. The LOEL and BMDL10 were U-Cd = 0.8 μg/g creatinine for alpha-1-microglobulin and NAG in urine and for GFR about 1.2 μg/g creatinine (Akesson *et al.*, 2005; Suwazono *et al.*, 2006).

In the study from Thailand reported LOEL values were slightly higher than BMDL values for the same biomarkers reported in other studies.

The study performed in several countries (de Burbure *et al.*, 2006) found low LOEL values for NAG and RBP. There was coexposure to other nephrotoxic agents and it is difficult to ascertain the relative role of the various exposures.

Summarising the studies in table 32, a range of LOEL or BMDL values have been reported. The range is explained by a number of factors such as the method used for defining cut off values (use of a control group or not, use of 84, 95 or 99 percent cut off in the study population without considering a control group), lag-time between maximum exposure and study as well as co-exposure to other nephrotoxic agents. When considering the lowest values reported for BMDL5 or LOEL i.e. those below 1 μg /g creatinine, the value of 0.88 for

urinary albumin (ALB) reported by Hong *et al.* (2004) can be explained by co-exposure to arsenic. The low values reported by Uno *et al.* (2005) may to some extent be related to the decreasing general exposure in Japan, but even if they are adjusted for such a possible factor they would still be below 1 μg/g creatinine for NAG and B2M among men. The studies of the Swedish cohort of women (Akesson *et al.*, 2005; Suwazono *et al.*, 2006) have been described in detail and display low values for NAG, protein HC (alpha-1-microglobulin) and estimated GFR. In the study by Suwazono *et al.* (2006) a reference value was calculated based on 95 percent cut off in a theoretical extrapolation to zero cadmium exposure that may have generated the low values. However, in a study by Åkesson and co-workers (2005) a quartile approach was taken and LOEL values of around 0.8 μg/g creatinine of U-Cd were reported. The low values in the study by de Burbure *et al.* (2006) may be related to the complex exposure pattern involving several metals.

Based on the data in the table, the identification of a reference point[17] for deriving a health based guidance value is difficult and depends on several study-specific factors, including the size of the study. In cross-sectional studies, the U-Cd concentration is affected by some degree of imprecision, e.g., due to temporal variability, analytical error and urinary flow differences. Such imprecision of the independent variable will cause an underestimation of the true degree of cadmium toxicity. Imprecision of the effect parameters will be of less significance, but any bias will be in the same direction. This bias will also be reflected in benchmark calculations, i.e. that the benchmark dose (BMD) and benchmark dose lower ; 95%-confidence lower bound (BMDL) will be biased towards higher values except for imprecision in the effect parameter that will generate lower BMDL values. From the studies considered, however, it seems reasonable to conclude that minor changes in renal markers are associated with U-Cd around 1 μg/g creatinine.

Long-term health effects of kidney damage

Although there is strong evidence that elevated levels of several biomarkers of renal dysfunction and/or associations between cadmium burden and these biomarkers occur in populations environmentally exposed to cadmium there is less agreement about the significance of these changes.

The question of reversibility has been addressed by several studies providing some indication of reversibility of renal damage associated with exposure to low levels of cadmium following a substantial decrease in cadmium intake. On the other hand**,** a recent Japanese study followed-up 29 persons in the cadmium-polluted Kakehashi River basin with respect to changes in selected biological parameters after removal of cadmium polluted soil present in rice paddies. In particular, they investigated changes in U-Cd and renal glomerular function based on serum creatinine (SCr) and creatinine clearance (C(Cr)). They noted that glomerular dysfunction as indicated by an increase in SCr and a decrease in C(Cr) will continue to progress even after soil replacement (Kobayashi *et al.*, 2008b). On the basis of the available data the CONTAM Panel could not draw a firm conclusion**.**

[17] Analysis of the data obtained in these studies is structured to identify a dose that can be used as a starting point for human health risk assessment. The dose used for this purpose, however derived, is referred to in this paper as the reference point. This term has been used already by EFSA in the opinion of the Scientific Committee on a harmonised approach for risk assessment of substances which are both genotoxic and carcinogenic (EFSA, 2005), and is therefore preferred to the equivalent term point of departure, used by others such as US EPA.

Several studies have found associations between increased mortality and renal dysfunction in residents living in cadmium polluted areas (see below) and there is strong evidence of the predictive value of an early renal marker, namely B2M, and mortality. In a 9-year follow-up survey of 3,178 inhabitants of the cadmium-polluted Kakehashi River basin, Ishikawa Prefecture, the mortality risk ratio of the urinary B2M positive group (>1,000 μg/g creatinine) was significantly higher in both men and women compared to the corresponding negative group (Nakagawa *et al.*, 1993). Using a Cox proportional hazard model, a gradient of risk ratios was found for three subgroups of subjects stratified according to their urinary B2M levels (300–999, 1,000–9,999, and >10,000 μg/g creatinine, respectively), with < 300 μg/g creatinine considered as 1. The risk ratio increased in parallel with increasing urinary B2M concentration in both men (1.27, 1.47, and 1.69, respectively) and women (1.58, 2.04, and 2.43, respectively). In women, the ratio was significantly increased already in the 1st subgroup with B2M levels between 300 and 999 μg/g creatinine (1.58, $p < 0.01$).

Furthermore, when the follow-up period of this population was extended to 15 years, and the subjects were divided into the same four groups according to their urinary B2M concentrations, as in the 9-year survey, and mortality risk ratios calculated, the risk ratios of all of the groups increased even more markedly than at the time of the former survey. The importance of this research lies in the fact that because the upper limit of normal urinary B2M in Japanese adults is approximately 300 μg/g creatinine, these results prove that even small elevations of urinary B2M above the normal range are associated with an increased risk of mortality. Significantly elevated mortality ratios were noted for renal, cardiovascular, and cerebrovascular disorders (Nakagawa *et al.*, 1993). Moreover, by use of urinary RBP, proteinuria, glucosuria, and aminoaciduria as markers of renal tubular injury, similar findings were obtained: mortality risk ratios were elevated significantly in each of the respective positive groups (Nishijo *et al.*, 1994; Nishijo *et al.*, 1995). In these populations, by investigating the relationship between the urinary cadmium concentration and mortality during a 15-year follow-up study, it was demonstrated that the mortality risk ratios also increased with increasing the urinary cadmium concentrations (Nishijo *et al.*, 1999). More recent studies from Japan note that the mortality risk was significantly increased already among subjects with a urinary cadmium concentration of more than 3 μg/g creatinine in proportion to the increases in the amount of 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 1974–75 health impact survey, standardized mortality ratios (SMRs) were assessed instead of proportional mortality ratios (PMRs). An increased mortality risk from cerebral infarction in men was found even in the urinary category with B2M of 300–1000 μg/g creatinine during observation for 15 years. Therefore, the increase of mortality from cerebral infarction may contribute to the increase of mortality for men exposed to cadmium (Nishijo *et al.*, 2006). Whereas the increase in mortality from cerebral infarction did not reach significance in women with B2M of 300–1000 μg/g creatinine [hazard ratio 1.88 (0.82–4.29)], the mortality from heart failure was significantly increased in this subgroup of women [hazard ratio 1.94 (1.08–3.48)].

In Ishikawa Prefecture, the long-term prognosis of inhabitants with renal tubular dysfunction induced by cadmium was unfavourable, with higher mortality rates due to heart failure and cerebrovascular infarction—despite rice paddy restoration being completed many years previously. An increase in mortality from renal disease was observed in subjects with severe renal tubular dysfunction.

For the inhabitants of cadmium-polluted Tsushima in the Nagasaki Prefecture, the mortality rates were also reported to be higher in the groups exhibiting elevated urinary B2M levels (Iwata *et al.*, 1991a; Iwata *et al.*, 1991b). In this manner, long-term follow-up surveys conducted in Japan have clarified that Cd-induced renal tubular injury adversely affects life prognosis and that, in particular, even slightly increased urinary B2M levels provide an adverse risk factor for life prognosis. Increased urinary excretion of B2M can be translated in terms of risk as corresponding to an accelerated aging of renal function and premature death by 5-10 years.

A recent European prospective cohort study (n = 1,107 subjects at baseline of originally 1,419 subjects) 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 6 districts with high cadmium exposure close to zink smelters (>3 mg Cd/kg soil) and 4 districts with low exposure more than 10 km away from the smelters (<1 mg Cd/kg soil). The median urinary cadmium at baseline was 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 and some subjects did not provide blood or urine samples, leaving 956 persons at start of follow-up (50 % from low and 50 % from high exposure areas, respectively). Except for blood cadmium and 24-hrs urinary cadmium excretion, blood pressure, serum creatinine, high-density lipoprotein, total cholesterol, serum γ-glutamyltransferase (as index of alcohol intake), urinary creatinine and retinol-binding protein were assessed. As assessed for urinary cadmium, 208 deaths occurred during an average 20.3 years of follow-up. Multivariate-adjusted hazard ratios (adjusted for age, sex, body mass index, smoking serum γ-glutamyltransferase and socioeconomic status) for all-cause, 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 was 20 % and 44 % for total and non-cardiovascular mortality, and 25 % and 33 % for a doubling of B-Cd. The authors concluded that the increased mortality was directly related to the toxic effects of cadmium, but not directly to renal dysfunction as measured by U-RBP and serum creatinine (Nawrot *et al.*, 2008). This study provides the advantage of being a prospective cohort with longitudinal exposure assessment. The relevance to dietary cadmium exposure cannot be estimated.

Mortality was also assessed in a prospective cohort based on the NHANES (baseline 1988-1994) data including 13,956 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, GFR. The hazard ratios (95 % confidence interval) for all-cause, cancer, cardiovascular disease, and coronary heart disease mortality associated with a two-fold higher creatinine-corrected urinary cadmium 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. Thus, environmental cadmium exposure was associated with an increased risk of all cause, cancer, and cardiovascular disease mortality among men, but not among women (Menke *et al.*, 2009).

Cadmium may also potentiate diabetes-induced effects on kidney (Buchet *et al.*, 1990; Akesson *et al.*, 2005; Chen *et al.*, 2006b). Kidney damage may further progress to end stage renal disease (ESRD) and death if exposure is high and prolonged, or if it occurs along with predisposing factors, and an increased risk of ESRD has been observed at environmental

exposure levels (people living less than two kilometres from a battery plant) (Hellstrom *et al.*, 2001).

8.4.2.2. Effects on bone tissue and biomarkers

Except for fracture incidence (used in a few large scale epidemiological studies on cadmium) which is considered the most adverse endpoint with regard to osteoporosis, bone mineral density is usually measured as a biomarker of early bone effects. The WHO has defined a T-score which is based on the number of standard deviations above or below the mean bone mineral density for young adults. The degree of osteoporosis can also be assessed by computing age- and sex-standardised Z-scores (WHO, 1994). A common definition of low bone mineral density is z-score < –1, which indicates one standard deviation below a sex- and age-standardised mean (Kanis *et al.*, 1997). Markers of bone remodelling and bone-related hormones cannot be used to assess the critical exposure concentration with regard to bone effects, but may add information on the mechanisms of such effects. Based on a meta-analysis, 1 SD decrease in bone mineral density was reported to result in a relative risk of 1.5 (95 % CI:1.4, 1.6) for a fracture at any site, whereas spine measurement for predicting vertebral fractures was (relative risk 2.3 (95 % CI:1.9, 2.8)), and hip measurement for hip fractures was (2.6 (95 % CI 2.0, 3.5)) (Marshall *et al.*, 1996).

Prolonged exposure to cadmium may give rise to bone disease, which was first reported from the Jinzu river basin in Japan, the so called itai-itai (”ouch-ouch”) disease, which is characterised by multiple fractures and distortion of the long bones in the skeleton, causing severe pain in the affected individuals (Järup et al., 1998). The disease exhibits a mixed pattern of osteomalacia and osteoporosis in combination with kidney damage. Several possible mechanisms have been suggested (Kjellstrom, 1992).

The epidemiological studies on environmentally cadmium-exposed populations that indicate association between cadmium exposure and bone effects are discussed below and summarised in Table 33.

In Belgium exposure to cadmium in the general population living in areas close to zinc smelters compared to control areas resulted in average urinary cadmium of 8.8 and 8.6 nmol/24 hrs in men and women, respectively. This corresponds approximately to 0.58 and 0.83 μg/g creatinine in men and women, respectively. The approximate 90th percentile corresponds to 2 μg/g creatinine. This level may promote skeletal demineralisation, which could lead to increased bone fragility and increased risk of fractures. These results were based on a prospective cohort with 506 subjects (Staessen *et al.*, 1999). The relative risks (RR) associated with doubled urinary cadmium were 1.73 (95 % CI 1.16-2.57; p = 0.007) for fractures in women and 1.60 (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. This association between cadmium and bone was also supported by Swedish data (Oscar study) where a doubling of the osteoporosis risk was found at urinary cadmium levels of 0.5-3 μg Cd/g creatinine (Alfven *et al.*, 2000). In addition, an increased risk of fractures was also noted in the Swedish Oscar study, demonstrating an elevated hazard ratio already at low exposure levels (2-4 μg/g creatinine) (Alfven *et al.*, 2004). Studies in China have reported that osteoporosis is related to cadmium dose and kidney dysfunction, and especially to tubular damage and its severity, but not to glomerular damage (Wang *et al.*, 2003; Jin *et*

al., 2004b). The potential interaction between the adverse effects on bones and kidneys needs to be considered. Although recent studies have suggested a direct effect of cadmium on bone, an effect mediated via the kidneys is also plausible. The association between urine protein HC and bone mineral density that was found in the Oscar study supports this hypothesis (Alfven *et al.*, 2000) as does a recent Chinese study, which found that the prevalence of osteoporosis increases with increasing values of parameters of tubular damage (Jin *et al.*, 2004b). It should also be noted that in most animal studies, bone effects were accompanied or preceded by renal damage induced by the Cd-treatment (EC, 2007).

In vitro studies have demonstrated that cadmium compounds might exert a direct effect on bone affecting both bone resorption and formation, and inducing calcium release (ATSDR, 1999). Both in vitro and in vivo studies in animals indicate that cadmium compounds exert toxic effects on the bone tissue and hence support the causality of the association between cadmium exposure and bone effects reported in human studies. Experimental studies have also suggested that cadmium induced bone effects can be caused either by a direct effect on the bone tissue or indirectly via cadmium induced renal damage (tubular dysfunction, hypercalciuria, impaired hydroxylation of vitamin D), see Figure 11.

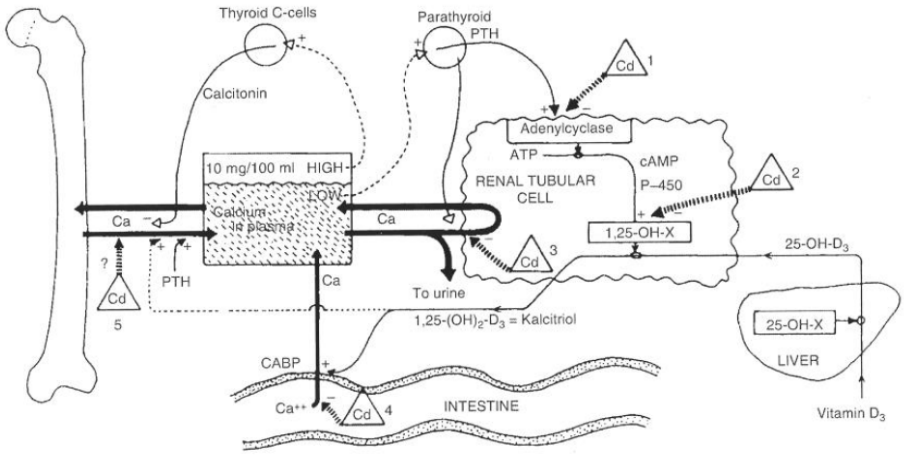

Figure 11. Schematic drawing of vitamin D metabolism and how it may be affected by cadmium. (1) Cadmium decreases PTH stimulation of adenylcyclase. (2) Cadmium inhibits hydroxylation of 25. OH-D3. (3) Cadmium increases urinary calcium excretion. (4) Cadmium decreases gastrointestinal calcium absorption. (5) Cadmium affects bone mineralization and bone collagen directly. CABP = calcium binding protein (Nordberg *et al.*, 2007).

More recent Swedish and Belgian data confirm the negative effects of low-level cadmium exposure on bone mineral density. The exposure in those populations was: median U-Cd = 0.67 (0.31-1.6) µg/g creatinine (Akesson *et al.*, 2006) in the Swedish study and mean B-Cd = 7-10 nmol/L (= 0.79-1.1 µg/L) (Schutte *et al.*, 2008) in the Belgian study, respectively. 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 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 would then be a more likely scenario.

A very recent US study using NHANES data reported an increased risk in 3207 women aged 50 years and older (OR = 1.43 (95 % CI:1.03-2.0)) for osteoporosis in the hip at U-Cd levels between 0.50 and 1.00 µg/g creatinine and 1.40 (95 % CI 0.97-2.03 for U-Cd >1.0 µg/g creatinine as compared to the reference (<0.5 µg/g creatinine) (Gallagher *et al.*, 2008). Only 15 % of the women had urinary cadmium above 1 µg/g creatinine. Osteoporosis was defined according to T-score < -2.5 (in this case <0.56 g/cm2) and is 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-smoke and under weight. Dose-response were reported on urinary cadmium as a continuous variable expressed in µg per g creatinine (OR = 1.15 (95% CI:1.00-1.33)).

Table 33 below summarises the studies relevant for the association between cadmium exposure and bone effects.

Table 33. Critical U-Cd dose levels for bone effect markers

Study (study size)	Effect measure	Threshold/U-Cd critical dose level	Reference
Belgium (PheeCad) (n = 506)	RR of fractures	No threshold reported. The RR associated with 2-fold increase of U-Cd at baseline was 1.73. The mean U-Cd was 1.0 µCd/g creat.	Staessen *et al.* (1999)
Sweden (Oscar) (n = 1,064)	10 % excess prevalence of low bone mineral density (osteoporosis, Z-Score<-1)	0.5-3 µg Cd/g creatinine as compared to <0.5.	Alfvén *et al.* (2000)
Sweden (Oscar) (n = 1,064)	Fracture risk	RR 3.5(1.1-11) for 2-4 µg Cd/g creatinine	Alfvén *et al.*(2004)
China (n = 790)	Osteoporosis (T-Score <-2.5)	Mean 2.3–13 µg Cd/g creatinine	Wang *et al.*(2003)
China (n = 790)	Osteoporosis (Z-Score<-2)	>2 µg Cd/g creatinine	Jin *et al.* (2004b)
Sweden (Lund) (n = 820)	Bone mineral density and several bone effect markers	BMDL5/10 1.0/1.6 µg Cd/g creatinine	Åkesson *et al.* (2006) Åkesson, personal communication, 2008)
Belgium (n = 294)	Bone mineral density and several bone effect markers	Negative associations between U-Cd and bone mineral density in postmenopausal women < 12 nmol Cd/day (approximately 1.3 µg Cd/g creatinine)	Schutte *et al.* (2008)
USA (n = 4,257)	Bone mineral density defined osteoporosis of the hip in women	0.5-1 µg/g creatinine gave higher risk of osteoporosis (43 %)	Gallagher *et al.* (2008)

Some of the studies in Table 33 have used a statistically significant decrease in bone mineral density, regardless of osteoporosis, in relation to cadmium exposure. Such relationships are not equivalent to an increased occurrence of osteoporosis based on the mentioned cut off levels of t-score, but may still be seen as an undesirable effect. It is well known that osteoporosis is related to an increased risk of fractures, but even less severe decalcification of bones probably has an effect in the same direction. The studies summarized above indicate a range of U-Cd for possible effects on bone effects starting from 0.5 μg/g creatinine, which is similar to the levels at which kidney damage occurs.

8.4.3. Other toxic effects

Cardiovascular toxicity and diabetes

The main endpoint examined in epidemiological studies is hypertension, but, as noted by the EU-JRC (EC, 2007), human studies do not support the hypothesis that cadmium is an important cause of hypertension. If cadmium does affect blood pressure, the magnitude of the effect is small compared to other determinants of hypertension. Cerebrovascular mortality is possibly associated with high cadmium exposure, but the evidence does not suggest that cardiovascular effects are important outcomes at exposure levels that are likely to occur from food (EC, 2007).

The EC-JRC report (EC, 2007) also noted that the weight of evidence suggests that cardiovascular effects are not a sensitive end point indicator for cadmium oxide and metal toxicity. However, a recent large US study found an association between U-Cd and myocardial infarction (Everett and Frithsen, 2008). In subjects with environmental cadmium exposure in Belgium, the urinary cadmium excretion was correlated with changes in some physiological indicators of cardiovascular function, i.e. pulse wave velocity, arterial pulse pressures, and arterial compliance and distensibility (Schutte *et al.*, 2008). The pathogenesis of these cadmium-associated abnormalities is unclear at present.

As noted above, cadmium may potentiate diabetes-induced effects on kidney (Buchet *et al.*, 1990; Åkesson *et al.*, 2005; Chen *et al.*, 2006b). A recent large cross-sectional study using US NHANES data showed that urinary cadmium levels are significantly and dose-dependently associated with both impaired fasting glucose and diabetes, suggesting that cadmium may be a cause of prediabetes and diabetes in humans (Schwartz et al., 2003). Renal damage could cause cadmium to leak into urine, potentially leading to a (noncausal) association between cadmium and diabetes. The investigators therefore restricted the analysis to persons without evidence of renal damage, but this restriction did not appreciably affect their findings. There were clear dose-response relationships between U-Cd and fasting glucose as well as diabetes with an OR = 2.05 for fasting glucose at U-Cd levels of 2 μg/g creatinine or above. However, the pathogenesis remains to be explored.

Neurotoxicity

Studies in rats and the few studies in humans are limited to inhalation exposure to cadmium. The results of one study in workers (Rose et al., 1992) suggest that chronic occupational cadmium exposure sufficient to cause renal damage is also associated with impairment in olfactory function. A more recent study of cadmium-exposed workers showed

neurobehavioral changes in the absence of signs of nephrotoxicity (Viaene et al., 2000), thus suggesting that the nervous system may be at least as sensitive as the kidneys to cadmium toxicity.

Reproductive and developmental toxicity

Although cadmium has been studied in regard to possible reproductive toxicity on many occasions, the contribution of this toxicant is generally uncertain due to the presence of a variety of exposures that may have contributed to adverse reproductive outcomes, such as preterm delivery or low birth weight. One study linked delayed psychomotor development at age 6 years to increased cadmium concentrations in hair collected at birth (Bonithon-Kopp et al., 1986). The possible developmental neurotoxicity of cadmium at low exposure levels is unclear and needs to be ascertained.

8.4.4. Cancer

The (IARC, 1993) classified cadmium compounds as a human carcinogen (Group 1) on the basis of sufficient evidence for carcinogenicity in both humans and experimental animals, but the EC has classified some cadmium compounds as possibly carcinogenic (Carcinogen Category 2; Annex 1 to the Directive 67/548/EEC18). The EC JRC report (EC, 2007) concluded that, overall, there is currently no evidence that cadmium acts as a carcinogen following oral exposure, but that the weight of evidence collected in genotoxicity tests, long-term animal experiments and epidemiological studies leads to consider cadmium oxide as a suspected human inhalation carcinogen.

As noted by (IARC, 1993), several constraints influenced the evaluation of cadmium in regard to lung cancer, such as limited number of exposed workers and sparse historical data on exposures to cadmium and concomitant carcinogen exposures. Later UK studies have not been able to confirm cadmium as a lung carcinogen (Sorahan and Esmen, 2004; Jones and Holladay, 2006). However, inference from these studies assumes that cadmium exposure is properly reflected by the proxy variables applied, and any imprecision is likely to have biased the findings towards no effect. In addition, the possible impact of tobacco smoking and concomitant exposures to arsenic may have caused some confounding.

A prospective cohort study from Belgium assessed the association between environmental exposure to cadmium and cancer incidence. Also this study was a prolongation of the Flemish part of the CadmiBel-study including 6 districts with high cadmium exposure close to zinc smelters and 4 districts with low exposure. In total, 994 subjects were included at baseline. Occupationally exposed were not excluded, but a sensitivity analysis was performed based on environmentally exposed alone. The population-attributable risk of lung cancer of 67 % (95 % CI 33-101) in a high-exposure area, compared with that of 73 % (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-hour urinary cadmium excretion, 4.17 (1.21-14.4: p = 0.024) for residence in the high-exposure area versus the low-exposure area, and 1.57 (95 % CI, 1.11-2.24 : p = 0.012) for a doubling of cadmium

[18] Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. OJ 196, 16.8.1967, p. 1. Last amended by Directive 2006/121/EC, OJ L 396, 30.12.2006, p. 850–856

concentration in soil (Nawrot *et al.*, 2006). Overall cancer (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 (Nawrot, personal communication). The relevance to dietary cadmium exposure is not clear. Total mortality as well as the cancer and cardiovascular mortality were also assessed in the same study area (Nawrot *et al.*, 2008). The risk of cancer associated with a doubling of the baseline U-Cd was RR 1.22 (95 % CI 1.06-1.40) for total mortality and RR 1.43 (1.17-11.76) for non-cardiovascular mortality. Thus, even if zinc-smelters close, historical environmental contamination remains a persistent source of exposure and this exposure increase mortality in a continuous fashion (Nawrot *et al.*, 2008). A follow-up study of 275 adults living in a cadmium-polluted area in Japan showed that an increased urinary excretion of B2M (above 1000 μg/g creatinine) in 1982 was associated with an increased age-standardised cancer mortality ratio through 2005 of 2.58 (95 % CI, 1.25-5.36) and cancer incidence ratio through 2002 of 1.79 (95 % CI, 0.84-3.82) (Arizawa et al., 2007). Information on specific cancer sites was limited by small numbers.

In regard to prostate cancer, the previous evidence has not been regarded as convincing (Verougstraete *et al.*, 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 controls) from Italy showed a relation between the toenail cadmium concentration and prostate cancer risk (Vinceti *et al.*, 2007).

Exposure to cadmium appears to be associated with renal cancer, although this conclusion is tempered by the inability of studies to assess cumulative cadmium exposure from all sources including smoking and diet (Il'yasova and Schwartz, 2005). A Belgian case-control study of bladder cancer (172 cases and 359 population controls) showed an odds ratio at increased blood-cadmium concentration of 5.7 (95 % CI, 3.3-9.9) after adjustments that included occupational exposures and cigarette smoking (Kellen *et al.*, 2007).

A small Finnish case-control study (43 cases and 32 controls) found increased cadmium concentrations in breast adipose tissue samples from breast cancer patients, and a suggestive correlation of cadmium with oestrogen receptor levels (Antila *et al.*, 1996). More recently, a US case-control study (246 cases and 254 controls) 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-characterised estrogenic responses of the endometrial lining (hypertrophy and hyperplasia) observed in animals exposed to environmentally relevant doses of cadmium, was further explored in humans. In a large population-based prospective cohort among Swedish postmenopausal women (n = 32,210) the association between dietary cadmium intake and endometrial cancer incidence, the cancer form most suited to explore potential estrogenic effects, was assessed (Åkesson *et al.*, 2008). This is the first study exploring health effects in relation to the dietary cadmium intake, which is in contrast to smaller studies where cadmium 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 reduces the selection bias that often occurs in case-control studies, but is on the other hand, dependent on the assumption that estimated dietary cadmium intake is a valid reflection of the exposure. The average estimated cadmium intake was 15 μg/day (1.5 μg/kg b.w. per week). During 16 years of follow-up, 378 cases of endometroid adenocarcinoma were ascertained through

computerised linkage to the Swedish Cancer Registry with virtually no loss to follow-up. The highest versus lowest percentile of cadmium intake was associated with risk of endometrial cancer, RR 1.39 (95 % confidence interval; CI) 1.04-1.85; P for trend 0.02). To reduce the influence of endogenous estrogen exposure, analyses were stratified by body mass index and by use of postmenopausal hormone use. Analyses were also stratified by smoking status because an anti-estrogenic effect of cigarette smoking is shown on circulating estrogen concentrations due to increased metabolic clearance, a reduction in relative body weight, and an earlier age at menopause (Terry and Stone, 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 intake consistently above the median intake in 1987 and in 1997 in never-smoking women with low bioavailable estrogen (non-overweight and non-users of postmenopausal hormones). These data support the hypothesis that cadmium may exert estrogenic effects and possibly increase the risk of hormone-related cancers but this needs to be confirmed by other studies.

Recent evidence suggests that cadmium may also play a role in the development of other cancers, such as testicular cancer, bladder cancer, pancreatic cancer and cancer of the gall bladder (Huff *et al.*, 2007).

8.5. Establishment of a health based guidance value

It is well established that occupational and environmental cadmium exposure can cause renal injury characterized by proximal tubular reabsorptive dysfunction (Fanconi's syndrome). Severe cadmium-induced tubular damage is irreversible and results in a progressive deterioration of renal function, even after cessation of exposure, with depressed glomerular function and filtration rate.

The health significance of a slight tubular damage, often caused by long-term low-level cadmium exposure, has been long debated. Low-molecular weight proteinuria in itself does not give rise to any subjective symptoms or objective disease and is, in its early stage not accompanied by any histological changes. Furthermore, there are data suggesting reversibility of mild tubular proteinuria after a distinct reduction of the cadmium exposure. It is not known whether these early tubular changes indicate increase in the risk of progression of the renal injury to a clinically manifest renal disease such as ESRD, although LMW proteinuria exceeding 300 μg/g creatinine has been associated with an accelerated decline of renal function associated with aging and with increased mortality.

On the other hand, it can be argued that increased excretion of low-molecular weight proteins is a widely accepted indicator of kidney damage that, irrespective of progression to severe or clinically relevant renal disease, can be considered as an adverse effect. The purpose of sensitive markers of early effects is to detect the earliest possible onset of disease at a stage where it is possible to prevent health effects, even in the most sensitive groups of the population. In addition, a possible reversibility needs to be considered in the light of the long half-life of cadmium in the environment and in the kidney, which will hamper a marked reduction of the body burden.

The wide range in the urinary cadmium concentration that includes low exposure levels has inspired some alternative interpretations of the association between urinary concentrations of cadmium and tubular effect markers, particularly at low exposure levels. The alternative explanations are competition between cadmium-metallothionein and the low-molecular

weight proteins at the tubular reabsorption sites, or parallel phenomen on causing increased excretion of both cadmium and the low-molecular proteins due to cadmium-independent kidney deterioration. Arguments for and against the alternative interpretations have been carefully considered by the CONTAM Panel. A causal relationship is, however, supported by the observed dose-response associations, in particular because cadmium in blood is also associated with the tubular effect markers, thus implying that cumulative cadmium exposure – and not only cadmium excretion – is associated with the tubular effects.

As the earliest effect of cadmium exposure is tubular damage, it seems most appropriate to base the risk assessment on this outcome. However, in light of recent studies, it seems appropriate also to consider data on adverse skeletal effects in the risk assessment once more data become available.

8.5.1. Dose-response modelling of urinary cadmium concentrations

8.5.1.1. Meta-analysis

8.5.1.1.1 Objectives and scope of the meta-analysis

A meta-analysis is a statistical procedure to review and summarise information gathered from different studies. In order to evaluate the dose-response and/or dose-effect relationships between urinary cadmium and biomarkers, the body of evidence present in the scientific literature can be compiled, encompassing and quantifying the wide variation between individuals and between studies.

Some studies have calculated reference points using a variety of methods and outcome variables. Combination of these results into a single reference point is not possible. The CONTAM Panel noted that the lowest reference points were below 1 µg cadmium per g creatinine. However, choosing the lowest published reference point is not appropriate, for instance because small studies with large uncertainty will create low reference points that may not be representative. The CONTAM Panel therefore decided that a meta-analysis of published data was necessary. The objective of the meta-analysis is the derivation of a benchmark dose (BMD) and its 95 %-confidence lower bound (BMDL) for humans using cut off points relevant to clinical changes in the target organ. This meta-analysis and BMD calculation were attempted for all identified renal biomarkers. As such, this meta-analytic approach complements the supporting data (see 8.5.1.2).

8.5.1.1.2 Data and methods

Literature search and data collection

Extensive literature searches (from 1966 until October 2008) were performed using specific keywords related to cadmium exposure, kidney (renal: beta-2-microglobulin (B2M), alpha-1 microglobulin (A1M), N-acetyl-beta-D-glucosaminidase total (NAG-total), N-acetyl-beta-D-glucosaminidase-A (NAG-A), N-acetyl-beta-D-glucosaminidase-B (NAG-b), Retinol binding protein (RBP), proteinuria) and bone biomarkers (bone mineral density (Bone MD), alkaline phosphatase activity (bALP), serum calcium, parathyroid hormone (PTH) and cross-checked

by two different scientists in selected databases (Web of Knowledge, Pubmed, Medline). Manual searches were also performed in specialized review papers and book chapters.

More than 5000 abstracts were retrieved and each study was individually checked for its relevance with respect to urinary cadmium concentration in humans and each biomarkers of effect.

Peer reviewed publications were selected for inclusion in a consolidated excel database based on the following criteria:

The study is published in an international peer-reviewed journal

The study measured urinary cadmium (in μg/g creatinine) as indicator of internal dose together with at least one biomarker of renal and/or bone effect both as continuous variables (mean, standard deviation or geometric mean and geometric standard deviation)

The data are not already (fully or partially) used in previous studies. In the cases where data are used in more than one study, the study providing the most complete and detailed information was chosen (e.g., the study which provides the most dose sub-groups)

Major covariates that might affect the dose-effect relationship were also collected from the original publication (e.g., body weight, age, gender, ethnicity) when reported. Additionally, important study characteristics were also collected, such as analytical methods, year of publication, type of exposure (environmental and/or occupational exposure), and presence of co-exposure to other metals.

Final database

The final numbers of studies included by biomarkers are reported in Table 34 and 35 hereafter.

Table 34. Summary of number of studies for renal biomarker entered in the final database

Renal Biomarker	Total	B2M	A1M	NAG (total)	NAG-a	NAG-b	RBP	Proteinuria (total)
N studies Continuous data	54	35	16	27	1	2	10	11

B2M: beta-2-microglobulin, A1M: alpha-1-microglobulin, NAG-total: N-acetyl-beta-D-glucosaminidase total, NAG-a: N-acetyl-beta-D-glucosaminidase-a, NAG-b: N-acetyl-beta-D-glucosaminidase-b, RBP: Retinol binding protein.

Table 35. Summary of number of studies for bone biomarker entered in the final database

Bone Biomarker	Total	Bone MD	Calcium Serum	bALP	PTH
N studies Continuous data	9	5	5	5	4

Bone MD: bone mineral density, bALP: alkaline phosphatase activity, PTH: parathyroid hormone.

The largest set of data was found for B2M and the CONTAM Panel also noted that this biomarker has been recognised as a highly useful indicator of cadmium induced tubular damage. B2M has also been accepted as the standard biomarker in previous meta-analyses

(Ikeda *et al.*, 2003; Gamo *et al.*, 2006; Omarova and Phillips, 2007) and by the JECFA and ASTDR (FAO/WHO, 2004; ATSDR, 2008). Fewer studies were available for bone effects and these were seen as very heterogeneous. As a consequence, the CONTAM Panel decided to perform the benchmark dose modelling only on 2BM. Thus the Oscar study was excluded, because it did not include B2M. The CadmiBel was also excluded, because it had only 24 h measurements of B2M and the data were not expressed in terms of creatinine excretion. A detailed description of these large studies and their calculated reference points is provided elsewhere in this opinion (see chapter 8.4.2.1: "Biomakers of effects in the general population" and Table 32). The list of studies used in the meta-analysis is reported in Annex 2-A.

For the B2M dataset, 165 matched pairs of group based urinary cadmium and B2M concentrations could be gathered from 35 studies, with the corresponding geometric standard deviations (GSDs) in most cases. This covers about 30,000 individuals, although the individual results were not available. The meta-analysis therefore had to be performed on the basis of reported group averages.

Meta-analysis and benchmark dose modelling

The meta-analysis was then performed to determine the overall relationship between urinary cadmium and B2M for subjects over 50 years of age and for the whole population. A mixed-effect model was fitted to group-based geometric means and geometric standard deviations, under log-normality assumption. The model allows accounting for inter-study and inter-individual variability and to weight studies according to their sample sizes. Further technical details can be found in the EFSA/AMU Technical Report (EFSA, 2009).

Dose-effect models were driven by the data visualisation (showing the shape of the curve) and data exploration (identifying the most significant influential variables). On the log-log scale, the relation between urinary cadmium and B2M is illustrated by Figure 12. Figure 13 and Figure 14 show the same data with one different colour for each study, and illustrating the difference in GSD (Figure 13) and difference in sample size (Figure 14) between the groups.

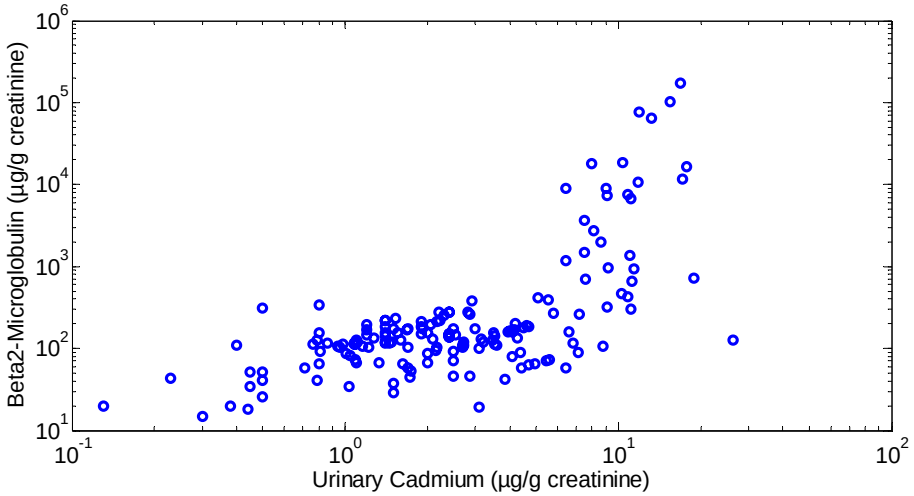

Figure 12. Scatter plot of data from all studies linking urinary cadmium to beta-2-microglobulinuria on the log-log scale. Each data point represents geometric means for a subgroup as defined in each study.

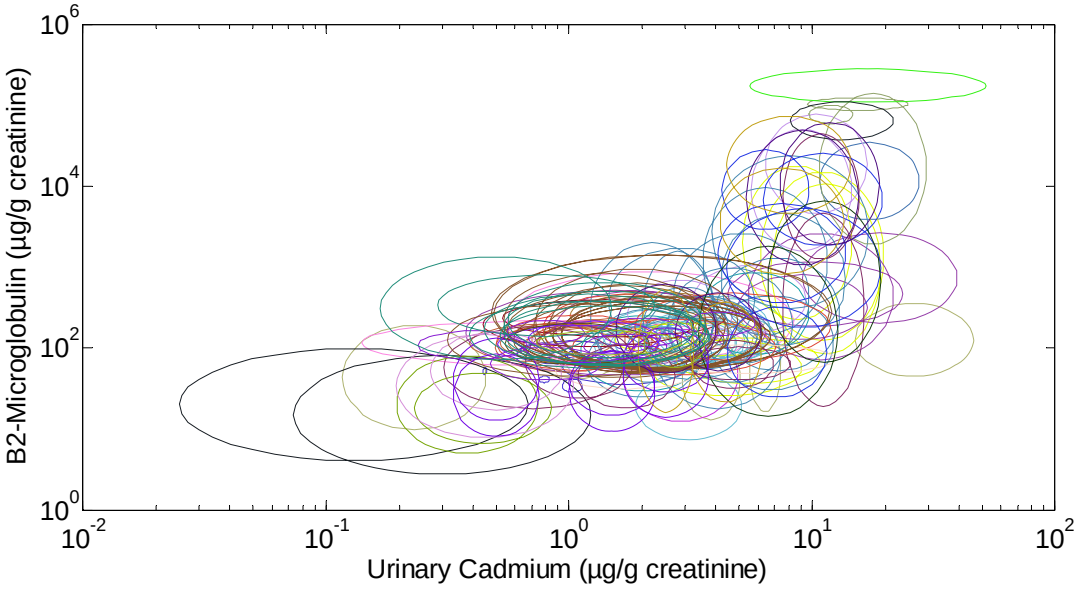

Figure 13. Scatter plot of data from all studies linking urinary cadmium to beta-2-microglobulinuria, using a different colour for each study and illustrating within group variability. Each study population is represented by an ellipse on the log scale, with log(GSD) as the radius.

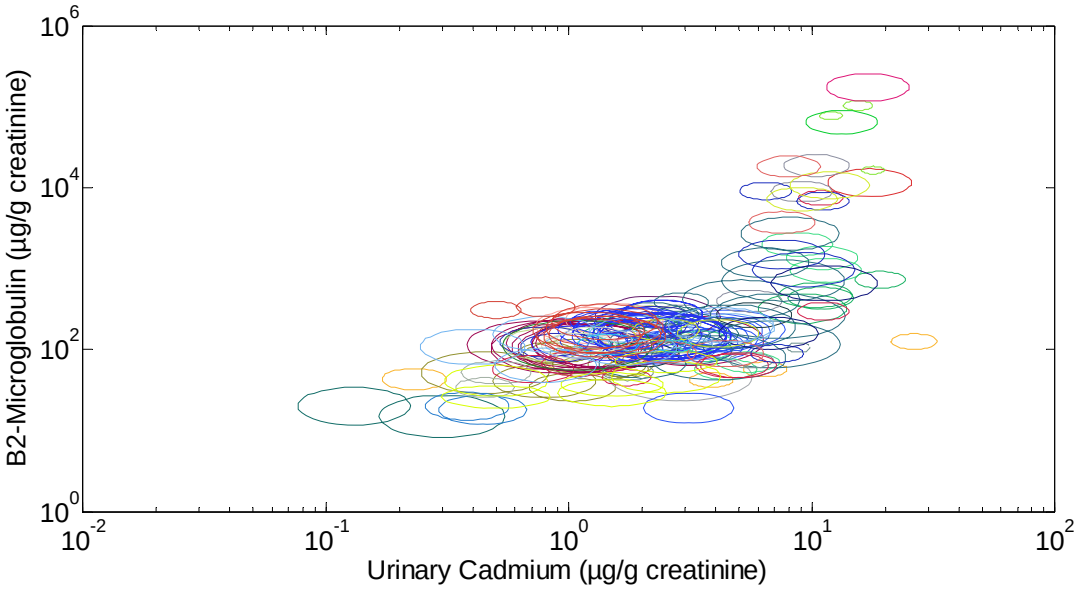

Figure 14. Scatter plot of data from all studies linking urinary cadmium to B2M, using a different colour for each study and illustrating differences in sample size. Each study population is represented by an ellipse on the log scale, with radii proportional the logarithm of their sample size.

From the data visualisation, an adequate dose-effect model should describe an S-shaped relation between urinary cadmium and B2M, in the log-log scale. Common S-shaped models that are widely used, including for BMD calculations, are exponential models (e.g. Gompertz model) and Hill models (Sand *et al.*, 2008). The two model options are expected to lead to similar results, as they both describe an S-shaped curve with 4 parameters in that log-log scale (Sand *et al.*, 2006). The Hill model was chosen, especially because:

- it uses more interpretable parameters than the exponential one,
- it has some symmetrical properties on the log-dose scale, which cause less numerical problems in the fitting process
- the goodness-of-fit was adequate (see Figure 15)

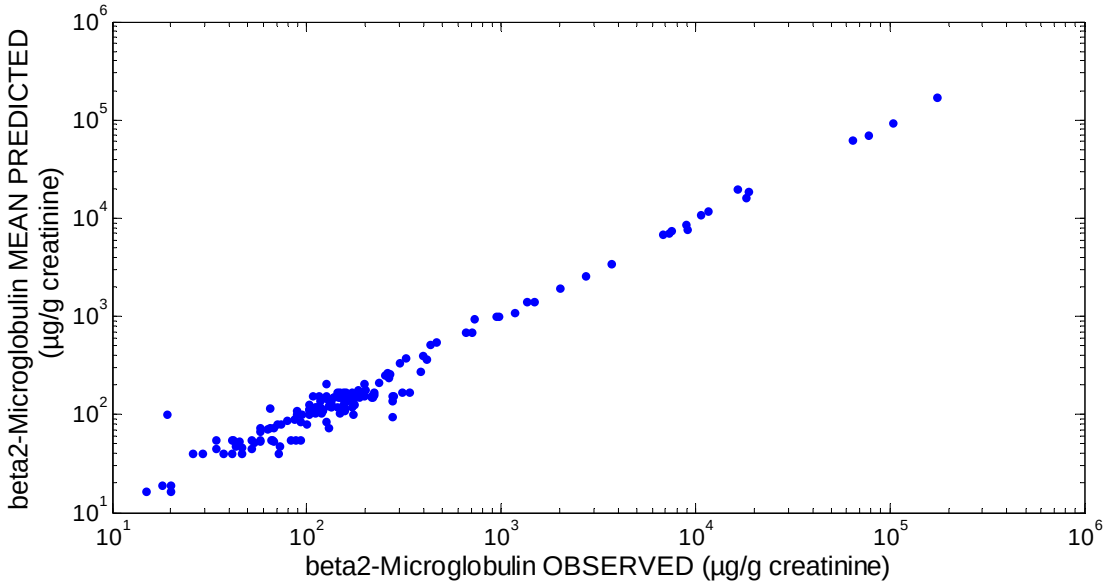

Figure 15. Predicted versus observed scatter plot for the Hill model fitted to the complete data set

More complicated models (e.g., with more parameters) were disregarded since attempts to fit some of them were not successful (fitting algorithms failed to converge) suggesting an over-parameterization. However, as a sensitivity analysis, an alternative piecewise (hockey-stick) linear model was also fitted. But not reported in the opinion. This piecewise linear model gave similar fits except for the low urinary cadmium concentrations.

All technical details on the model description and results are given in a separate report (EFSA, 2009).

Ethnicity was seen as an influential variable on the dose-effect curve. The possible degradation of B2M in acidic urine was considered as a potential confounding factor, but most studies on Caucasians have adjusted urine pH.

BMD approach

The benchmark dose approach used was the so-called hybrid approach (Budtz-Jorgensen *et al.*, 2001; Crump, 2002; Suwazono *et al.*, 2006; Sand *et al.*, 2008) which allows for calculation of risks without dichotomizing the outcome, hence using all information available from continuous data. Risks or prevalence can then be derived with respect to any given biologically relevant threshold. This approach is valid under the assumption that B2M levels are log-normally distributed over the population at a given dose of urinary cadmium. The main idea of this hybrid approach is to model the population variability around the mean dose-effect curve using a statistical (log-normal) distribution at each given dose, as illustrated in Figure 16.

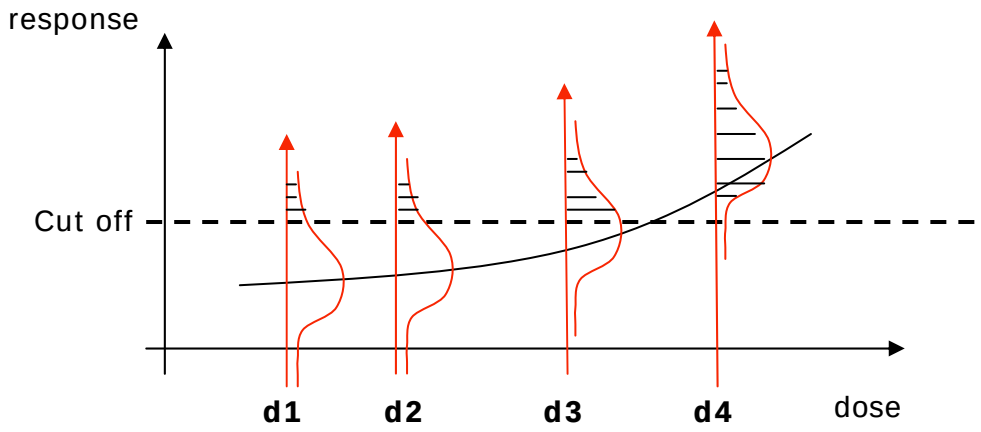

Figure 16. Hybrid approach used for benchmark dose evaluation, based on prevalence corresponding with a given cut off point

The CONTAM Panel chose to calculate a BMDL5, meaning an extra risk[19] of 5 %. Alternative calculations of reference points included in the EFSA/AMU Technical Report (EFSA, 2009) are in general agreement with the results presented in Table 36.

Selection of cut-off limits

As an indication of abnormality, a value of 1000 µg B2M /g creatinine was set as a high-level criterion. B2M excretion levels above this limit are likely to be irreversible. As a lower and more protective cut-off level, a value of 300 µg B2M /g creatinine was chosen. Excretion levels above this limit are considered adverse. As a third criterion, the 95th percentile of the B2M distribution at background urinary cadmium concentrations was calculated. This limit is

[19] Extra risk is defined as an absolute change in risk (additional risk) divided by the non affected fraction in the control population (100 minus the background response in %). For instance, when the additional risk is 4.5 % and the background response is 9.5 % the extra risk is 4.5 /(100 – 9.5) x 100 = 5 %

the most protective, but has to take into account the ethnicity-associated differences in B2M excretion levels.

Three different cut-off values were chosen to derive the BMD and BMDL:

- two biologically-based cut-offs: 300 and 1000 µg B2M/g creatinine (defined above) to calculate the percentage of the population above this level at background U-Cd concentrations
- one statistically-based cut-off: corresponding to the 95th percentile of B2M distribution at background U-Cd concentrations (statistical cut-off)

The BMD evaluation was performed for the whole population and for subjects over 50 years of age, while excluding the population sub-groups exclusively comprised of workers, with an adjustment for ethnicity, to account for differences between Caucasians and Asians (including Japanese).

All models were fitted using Bayesian inference with WinBUGS (Version 1.4) and Monte-Carlo simulation and plot performed using Matlab (Release 14).

Statistically-based cut-offs for the whole populations and for subjects over 50 years were calculated to be 211 and 374 µg B2M/g creatinine, respectively. It should be noted that a previously determined biologically based cut-off value of 300 µg/g creatine falls within this range.

The Hill model fitted to the complete dataset (the group means of the Caucasian and Asian population) is shown in Figure 17.

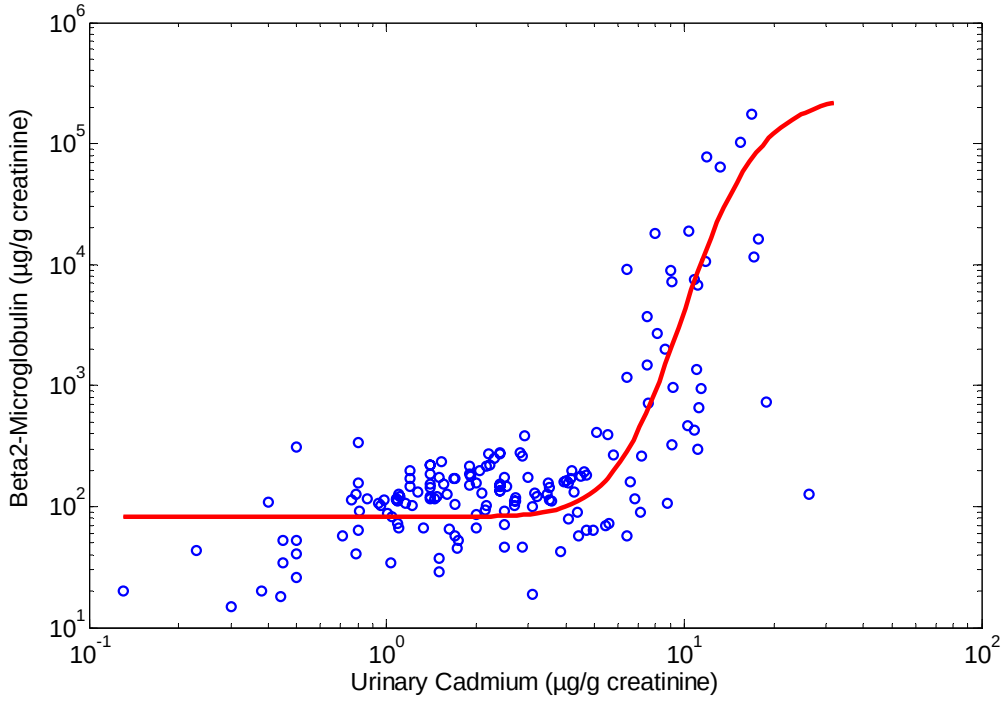

Figure 17. Hill model fitted to the complete group based dataset (Caucasian and Asian data pooled), using posterior mean estimates for the curve parameters

Table 36 reports the various BMDs and BMDLs for both the total population and for the subpopulation with a mean age greater than 50 years, and only non-occupationally exposed, at the three cut-offs, and for extra risk of 5 % (BMD_5 and BMDL5) .

Table 36. BMD and BMDL (in μg Cd / g creatinine) estimates for the Hill model at various cut-offs leading to extra risks of 5 % in the total population, and non-occupationally exposed subjects above 50 years of age adjusted to Caucasian ethnicity.

	Statistical cut-off [a] for U-beta-2-microglobulin (μg/g creatinine)		**U-beta-2-microglobulin >300 μg/g creatinine**		**U-beta-2-microglobulin >1000 μg/g creatinine**	
	BMD5	BMDL5	BMD5	BMDL5	BMD5	BMDL5
U-Cd (μg/g creatinine)from the whole population	3.98	3.62	4.65	3.84	6.80	5.95
U-Cd (μg/g creatinine) from non-occupationally exposed subjects over 50 years	5.28	4.89	5.25	4.45	6.33	5.46

[a] 211 and 374 for whole and subjects over 50 years, respectively.

Taking into account the slightly higher values for the subjects over 50 years and the range of the BMDL5 results for the statistical and the biological cut-off limit of 300 μg B2M / g creatinine, the CONTAM Panel selected an overall group-based BMDL5 of 4 μg cadmium / g creatinine. In order to protect a large proportion of the European population, the variability and uncertainty sources should all be accounted for. There are three main sources of variability described by the models:

- The inter-study variability
- The population variability of the effect given a urinary cadmium level
- The population variability of urinary cadmium within each dose group

In addition there are two main sources of uncertainty in this analysis:

- The uncertainty around the statistical estimates, given a model
- The uncertainty on the model (and the underlying assumptions)

The inter-study variability has been removed using a random effect model. The population variability of effect is addressed by the BMD approach itself, as it uses this variability to determine the dose leading to a predefined extra risk. The uncertainty around statistical estimates is addressed by considering the BMDL instead of the BMD. Finally, the uncertainty on the modelling assumptions is, at least partially, addressed by comparing two models and

performing some sensitivity analyses. The results of the various calculations showed general concordance.

The remaining source of uncertainty in this analysis is due to the fact that group means with associated ranges of U-Cd levels were used, and not data points from individual subjects. Therefore the estimated BMDs are likely to be greater than when calculated with individual data. This problem can be overcome by applying an adjustment factor based on the estimated coefficient of variation of inter-individual variability in U-Cd within all recorded study populations. This factor can be considered to be a chemical-specific adjustment factor (CSAF) as recommended by the HO and can be defined as the ratio of a 95th population percentile to the median BMD (WHO-IPCS, 2005):

$CSAF$ = 95th Percentile (BMD)/Median (BMD)

Since concentrations have been assumed to be lognormal, this CSAF can be computed using the standard formula for lognormal percentiles, namely:

$$CS\,AF = \exp\left(1.64\sqrt{\ln\left(1+CV^2\right)}\right)$$

The inter-individual coefficient of variation (CV) of urinary cadmium within each dose sub-group was estimated to be about 100 % for the non-occupationally exposed subjects over 50 years. From this CV of 100 %, a *CSAF* of 3.9 can be calculated to cover 95 % of the population.

Dividing the BMDL5 of 4 μg U-Cd/g creatinine by the AF of 3.9 leads to a urinary cadmium excretion of 1.0 μg/g creatinine. The CONTAM Panel therefore concludes that the urinary cadmium concentration of 1 μg per g creatinine or below, representing the internal dose, would indicate that 95 % of the European population would not exceed cut-off limits in the range of about 300 μg/g creatinine for B2M in urine.

As a comparison, reference points based on B2M biomarker range from 0.5 μg/g creatinine up to 10-12 μg/g creatinine (Ikeda *et al.*, 2003; Gamo *et al.*, 2006; ATSDR, 2008), but with various cut-offs, various definitions of BMDs and various populations (mostly Japanese).

8.5.1.2. Supporting data

Results of the meta-analysis are supported by a study carried out in workers (Elinder *et al.*, 1985; Järup *et al.*, 1993). In this study cadmium induced renal effects were examined in 60 workers (58 men, 2 women) previously exposed to cadmium. Tubular damage in the form of beta 2-microglobulinuria was found in 40% of the subjects. The prevalence of abnormal high values ranged from 7 % in subjects with U-Cd < 2 μg/g creatinine to 91 % in workers with U-Cd > 15 μg/g creatinine.

BMDs and BMDLs were calculated using the EPA software (version 1.4.1.) as shown in Figure 18. Using a Probit model, BMD and BMDL values were 2.38 and 1.88 μg urinary cadmium/g creatinine, respectively. The corresponding figures obtained with a logistic model were 2.53 and 1.96, respectively.

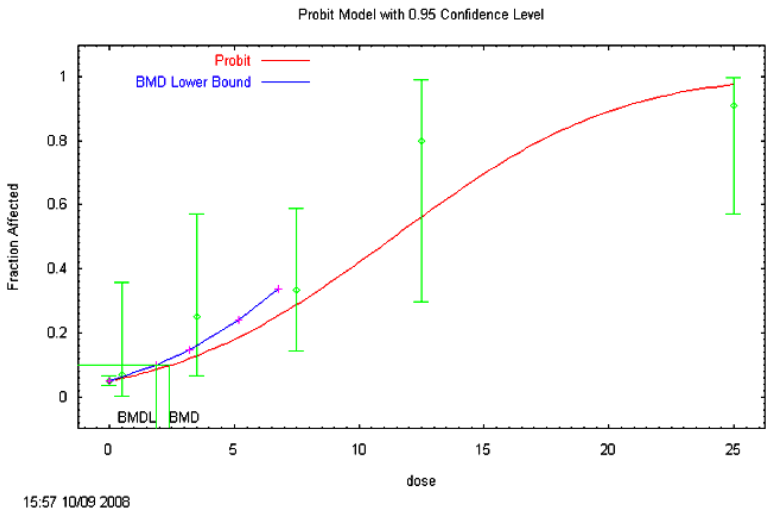

Figure 18. Dose-response relationship between U-Cd (dose as µg cadmium /g creatinine) and prevalence of B2M values exceeding 300 µg/g creatinine. Data from Elinder *et al.*(1985).

It was then considered that clinical data had been obtained 7 years after the end of exposure, thus leading to an underestimation of the true BMD and BMDL, which on the basis of cadmium kinetics in urine should be increased by 33 %. It was then noted that not only the dose, but also the effect could be decreased over a 7-year period. Considering the reversibility of B2M values below 1,000 µg/g creatinine (Jarup *et al.*, 1993; Roels *et al.*, 1997) and the average decline of response rate, BMD and BMDL values were re-calculated assuming both a 33 % reduction in dose levels (Cd-U) and a 21 % decrease in response rate in the same 7-year period. Table 37 summarises BMD and BMDL values obtained under different assumptions, which provide consistent estimations.

Table 37. BMD and BMDL10 values based on crude values and after correction for time-lag of either U-Cd alone or both U-Cd and U-µ2microglobulin

	Model: PROBIT		Model: LOGISTIC	
	BMD10	**BMDL10**	**BMD10**	**BMDL10**
Crude values U-Cd (µg/g creatinine)	4.03	3.21	4.15	3.24
+33 % U-Cd* U-Cd (µg/g creatinine)	5.36	4.26	5.52	4.31
-33 % U-Cd & -21% B2M** U-Cd (µg/g creatinine)	3.52	2.81	3.96	3.19

*corrected for time-lag
**assuming a reversibility of response rate similar to that observed in the period 1985-1993

Considering that a B2M value >300 µg/g creatinine represents an adverse effect (see chapter long-terms health effects on kidney) a BMDL10 was used, considering that the BMD was derived from a dose-response relationship and that a prevalence of 5 % of subjects exceeding the upper limit of the reference interval for B2M is expected to occur in a reference

population. Hence, a BMDL10 would indicate a doubling of this prevalence and it would correspond to a 5 % extra risk. Because these studies were carried out in male workers, an uncertainty factor must be included to take into account the "healthy worker effect". The default value to extrapolate to the general population is a factor of 3 (square root 10 for intra-species inter-individual variability). Thus a value of 1.0 μg U-Cd/g creatinine for the general population can be calculated.

8.5.1.3. Conclusions of dose response modelling

The CONTAM Panel selected a reference point of 1 μg U-Cd /g creatinine for risk evaluation on basis of the following:

The meta-analysis based on B2M as a marker of tubular effect, identified overall **group-based** BMDL5 of 4 μg U-Cd/g creatinine that after adjustment by a calculated chemical specific adjustment factor of 3.9 led to the value of 1 μg U-Cd/g creatinine. The CSAF takes into account the inter-individual variation of urinary cadmium within each dose-sub group in the analysis.

This reference point is similar to that estimated in workers occupationally exposed to cadmium in the example study (BMDL10 2.81 μg U-Cd/g creatinine) on the basis of B2M after adjustment by an uncertainty factor of 3 to account for interindividual differences in vulnerability from workers to the general population.

In addition, this reference point is also supported by several epidemiological studies based on a variety of early markers of kidney damage (see Table 32) and effects on bone (see Table 33).

8.5.2. Model-based estimation of the relationships between urinary cadmium and dietary cadmium intake to set a tolerable weekly intake

To be able to derive a dietary cadmium intake from a urinary cadmium concentration, a one-compartment model was fitted to data from the population-based Swedish Mammography Cohort study[20]. To account for the inter-individual variation of cadmium toxicokinetics in the population, population parameters were added to the model. Examples of such inter-individual variation are differences between individuals in cadmium elimination and gastrointestinal absorption of cadmium from food (for further details see Amzal *et al.*, 2009).

Within the cohort, urinary cadmium was assessed in 680 women, aged from 56 to 70 years, who reported to have never smoked. The women were randomly selected from the cohort during 2004 – 2007 for urine sampling. For each of the participating women, the food intake was assessed on three different occasions over time; in 1987, 1997 and 2004-2007 using a food frequency questionnaire. The daily dietary cadmium intake was estimated from the questionnaire, using age-specific serving sizes together with data on the concentration of cadmium in each specific food item (Åkesson *et al.*, 2008; Amzal *et al.*, 2009). The food cadmium content was obtained for all foods on the Swedish market and was provided by the Swedish National Food Administration (Uppsala, Sweden) (partly published in: Becker and Kumpulainen, 1991; Jorhem and Sundstrom, 1993; Jorhem *et al.*, 2001).

[20] Available at URL: www.imm.ki.se/smc

The average urinary cadmium concentration in the 680 women was 0.35 µg/g creatinine (range 0.09 to 1.2 µg/g creatinine). The estimated average daily dietary cadmium exposure at the three assessment occasions was 14 µg/day (range 19-21 µg/day) corresponding to 0.2 µg/kg b.w. per day (range 0.1-0.4 µg/kg b. w. per day). The availability of individual information on long-term cadmium intake as well as urinary cadmium concentration in the same subjects, allowed for the first time a data-based derivation of population variability. (for further details see Amzal *et al.*, 2009). The fact that women may constitute a vulnerable group due to increased gastrointestinal cadmium absorption supports the use of this specific group for modelling.

On the basis of data, the model suggested a mean cadmium half-life in the study population of about 11.6 years (95 % CI = [10.1-14.7]) with a population variability of about CV = 25 % (Figure 19, extracted from Amzal *et al.*, 2009).

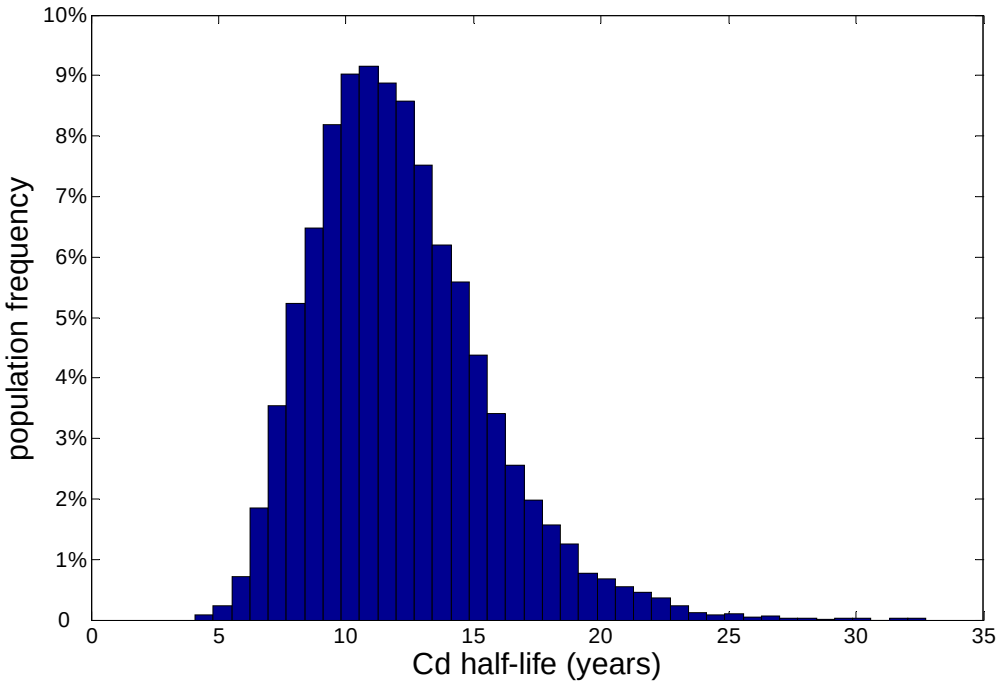

Figure 19. Estimated distribution of apparent cadmium half-life over the (study) population (extracted from Amzal *et al.*, 2009)

The concordance between measured and predicted individual urinary cadmium concentrations was very high, as the population-based model fitted well to the empirical data i.e. between observed and predicted U-Cd concentrations for each individual. This indicates that most of the inter-individual variability could be addressed by the model and translated in population variability in cadmium toxicokinetics. All parameters were then set to their statistical estimates and Monte Carlo simulations were run in order to derive lifetime exposure for various percentiles of the population. The various model validation steps performed (including sensitivity analysis with respect to the modelling assumptions) showed that population estimates were robust (for further information see Amzal *et al.*, 2009). The population-averaged predictions were also consistent with those previously obtained for the

US-population (Choudhury *et al.*, 2001; Diamond *et al.*, 2003) further supporting the robustness of the results.

Figure 20 shows the cumulative distribution function of the daily intake required to reach a maximal level of exposure corresponding to U-Cd concentrations of 0.5, 1, 2 and 3 µg/g creatinine by age 50. For each of those target excretion levels, one could derive the maximum daily cadmium intake required to ensure that a given population percentile (e.g. P95) has excretion levels below the corresponding target. The results displayed are based on non-smoking women.

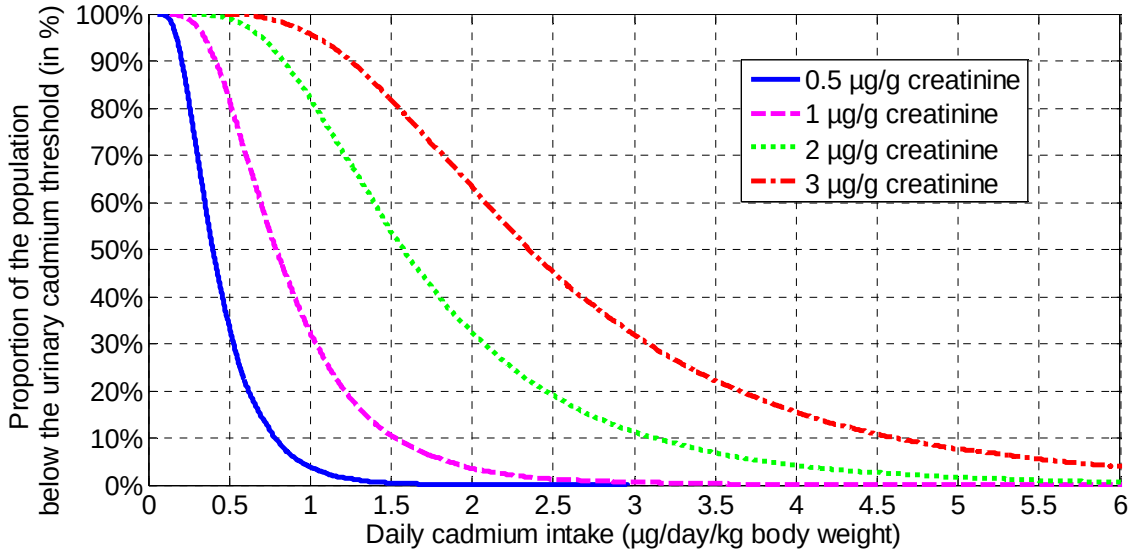

Figure 20. Proportion of the population below 0.5, 1, 2 and 3 µg/g creatinine of U-Cd concentration versus the daily cadmium intake. The figure is based on the model from Amzal *et al.*, 2009 and data from a cohort of 680 Swedish non-smoking women with ages ranging from 50 to 70 years.

The dietary cadmium exposure that corresponded to the urinary cadmium concentration of 1 µg/g creatinine after 50 years of exposure was estimated by one-compartment modelling of the data. Table 38 shows the dietary cadmium exposure that would be compatible with the urinary cadmium reference point in a predefined proportion of the population.

Table 38. The dietary cadmium exposure (µg/kg b.w. per day or µg/kg b.w. per week) that would not exceed the critical concentrations of cadmium in urine of 1 µg/g creatinine for certain proportions of the population (women)

Proportion of the population below 1µg urinary cadmium/g creatinine	Dietary cadmium exposure	
	µg/kg b.w. per day	µg/kg b.w. per week
50 %	0.78	5.46
90 %	0.42	2.94
95 %	0.36	2.52

As illustrated in Table 38, in order to remain below 1 µg cadmium/g creatinine in urine in 95 % of the population by age 50 years, the long term daily dietary cadmium exposure should not exceed 0.36 µg Cd/kg b.w., and the weekly dietary cadmium exposure should stay below 2.52 Cd/kg b.w. Because of the long half-live of cadmium in the human body a health based guidance value should be set on weekly rather than daily basis. Therefore, the CONTAM Panel established a tolerable weekly intake (TWI) of 2.5 µg/kg b.w.

9. Risk characterisation

The average dietary exposure to cadmium for adults across European countries was estimated to be between 1.9 and 3.0 µg/kg b.w per week, and the high exposure adults have estimates in the range of 2.5-3.9 µg/kg b.w. per week. The CONTAM Panel noted that such average dietary exposure in European countries is close to or slightly exceeding the TWI of 2.5 µg/kg b.w. Furthermore it was noted that subgroups of the population, such as vegetarians, children, smokers and people living in highly contaminated areas may exceed the TWI by about 2-fold.

Although for the individual exceeding the TWI by about 2-fold is unlikely to lead to adverse effects on the kidney it clearly demonstrates the need to reduce exposure to Cd at the population level.

10. Uncertainty analysis

The evaluation of the inherent uncertainties in the assessment of exposure to cadmium has been performed following the guidance of the Opinion of the Scientific Committee related to Uncertainties in Dietary Exposure Assessment (EFSA, 2006). In addition, the draft report on "Characterizing and Communicating Uncertainty in Exposure Assessment" which is in preparation to be published as WHO/IPCS monograph, has been considered (WHO-IPCS, 2005).

According to the guidance provided by the EFSA opinion (EFSA, 2006) the following sources of uncertainties have been considered: assessment objectives, exposure scenario, exposure model, and model input (parameters).

10.1. Assessment objectives

The objectives of the assessment were clearly specified in the terms of reference and the CONTAM Panel assessed the new occurrence data that were collected by EFSA, and evaluated, and which food commodities in the different Member States contribute most to the cadmium exposure. The uncertainty in the assessment objectives is considered to be negligible.

10.2. Exposure scenario / Exposure model

In response to the request from EFSA to the Member States, data on cadmium occurrence in food from 20 Member States and additionally data from Iceland, Australia and some

commercial parties were submitted to EFSA. After data evaluation 137,202 data points from the period 2003 to 2007 were included in the analysis. Germany submitted most of the results (32 %) followed by Slovakia (29 %). From those figures it is obvious that the data set is not fully representative of food on the EU market and that there is an uncertainty in possible regional differences in cadmium contamination of food commodities. However, considering that the data set includes a considerable number of analytical data from a wide range of European countries and for a number of food categories, the uneven distribution of occurrence data over the Member States will not add significantly to the overall uncertainty. It was tested that pooling commercial and non-commercial data has no significant effect to the exposure assessment.

The samples originated from both targeted and random sampling, but this could only have resulted in an overestimation of exposure.

Since a significant part of the samples having levels below LOD this may have introduced uncertainties to the overall estimate. Using the medium bound approach is consistent with the existing guidance and the objective of estimating long term exposures so that the resulting uncertainties will be small.

Most exposure calculations were based on mean cadmium occurrence values and mean consumption amounts; for the Italian population, exposure calculations were based on mean occurrence values and individual consumption rates of a large array of food items obtained from a survey of 1940 Italian subjects. In addition, scenarios for high consumers were estimated, as well as scenarios combining high occurrence levels and high theoretical consumption values for highest contaminated food groups. However there was uncertainty about how realistic the scenarios for those extreme consumers were. People living in and consuming relevant amounts of food from high contaminated areas were also considered by a separate assessment so that exposure scenarios cover from average to high possible exposure values within the population.

Besides different scenarios for the adult population two main risk groups (children and vegetarians) were included in the assessment. Data for children were based only on one selected country (Italy) and there might be uncertainties in regard to generalization to Europe as a whole.

The approach to calculate the contribution of the different food groups to the overall exposure is not sensitive to differences between countries. It should be noted that the contribution of the food groups to the exposure can change because of different dietary patterns. However, taking into account the results from the literature the uncertainties in the ranking of the main food groups are expected to be small and only fish might have a higher impact (up to 7 %) in some diets.

Also other exposure pathways were calculated and considered in the assessment. Due to lack of data, estimates were taken from the literature and therefore might be affected by higher uncertainties than for dietary exposure. Nevertheless it is not expected that those uncertainties might have high impact on the estimation of the importance of the different pathways.

10.3. Model input (parameters)

A main problem to estimate dietary exposure by the deterministic modelling was to match food consumption data with occurrence data in food, because the food categorization used in consumption surveys is generally different from the food categorization used in occurrence databases.

For the probabilistic assessment of dietary exposure in Italy, it was in some instances difficult to match consumption data from the Italian food survey and the EFSA occurrence data organised in food categories according to the EFSA concise database. This entailed creating sub-categories or using sampling adjustment factors: expert judgements were necessary to fit the category system, introducing some degree of arbitrariness.

As regards the occurrence data, most of the aggregated food categories show a considerable spread in the LOD reported. The sensitivity of the analytical method is often set by the laboratory to fulfil legislative requirements and not fine tuned to optimal sensitivity, which causes slight problems when results are used also to calculate human exposure. Using half of the LOD might therefore result in overestimation of occurrence levels.

Limitations and in consequence some uncertainties arise from using broad food categories. Comparison with other estimates indicates that this will result more likely in over- than underestimation of exposure. The magnitude of those uncertainties is reduced by using adjusted occurrence means based on sampling adjustment factors (SAF). However, the SAF are estimated from German food consumption behaviour and it is acknowledged that the adjustment factors are associated with considerable uncertainty. Although the comparison with the GEMS/Food Cluster diets for the vegetables food group did not result in significant differences it could not be excluded for other categories. Hence, there will remain uncertainties induced by the broad food categories.

Contamination data were not available for all food items: therefore, contributions provided by these items could not be included in the exposure evaluation.

10.4. Toxicokinetic and BMD modelling

Biomarkers of kidney damage and BMD modelling

The identification of a reference point from population-based cross-sectional studies using biomarkers of kidney effects presents several difficulties and depends on several study-specific factors. Biomarkers of kidney effects are influenced inter alia by gender, age, body mass index, physical exercise, and diurnal variation, all factors which can either confound or modify dose-effect and dose-response relationships.

The risk assessment is based on the use of B2M as biomarker of Cd-induced tubular toxicity, which is not per se associated with any objective symptom or disease. However, exceeding the biological cut-off of 300 μg/g creatinine for B2M (one of the cut-offs considered in the BMD modelling) has been associated with an accelerated decline of renal function associated with aging together with increased mortality. The use of this critical effect of cadmium exposure to base our risk assessment leads to a possible overestimation of the risk but it allows protecting the most sensitive groups of the population.

The BMDL5 was identified by a meta-analysis of published data. Factors potentially influencing the BMD calculation such as gender, ethnicity and age, have been controlled for

in the analysis. Modelling assumptions and inter-individual variability within all dose groups were accounted for by applying a calculated CSAF (see 8.5.1.1.2; "Selection of cut-offs" for details). Some uncertainties arise also from the meta-analysis which includes possible publication bias and lack of selection from any controlled or random process. The calculated reference point is consistent with earlier calculations in individual studies using other biomarkers of kidney and bone effects.

Overall, this is a conservative assessment which is based on solid evidence from epidemiological studies, taking into account long-term outcomes of early cadmium-induced renal effects.

The model used to link cadmium intake to urinary cadmium is based on a number of assumptions that may be additional sources of uncertainty. This was accounted for and integrated in the model using the Bayesian inference methodology. Furthermore, some uncertainty can arise from some modelling assumptions (e.g. lognormal population distribution, choice of 1-compartment model, intra-individual variability not fully accounted for). The sensitivity analysis performed revealed little variation and supports the robustness of the estimates. It also showed that the low population percentiles were relatively robust to the model assumptions (variation below 10 %).

Data used for the TK model

The data used for the TK model input to derive the population variability is also associated with uncertainty. It is expected that the cadmium intake assessment method used for this study may over-estimate intakes. As for a validation, the model was also fitted using an alternative data set from the Varberg study (Berglund *et al.*, 1994) using a different intake assessment method. The low population percentiles were seen to be relatively robust with respect to the change of population (variation below 10 %).

10.5. Uncertainty evaluation

In Table 39 a summary of the uncertainty evaluation is presented, highlighting the main sources of uncertainty and indicating an estimate of whether the respective source of uncertainty might have led to an over- or underestimation of the exposure or the resulting risk.

Table 39. Summary of qualitative evaluation of the impact of uncertainties on the risk assessment of the exposure to cadmium.

Sources of uncertainty	Direction [a)]
Use of sampling adjustment factors	-/+
Use of broad food categories	+
Influence of non-detects on exposure estimate	+
Estimation of exposure of extreme consumer	+
Estimation of exposure from other pathways	-/+
Absorption for different exposure routes	-/+
Dietary exposure assessment method	+
Modelling assumptions	-/+
Estimation of reference point	-/+

[a)] + = uncertainty with potential to cause over-estimation of exposure/risk
- = uncertainty with potential to cause, under-estimation of exposure/risk (EFSA, 2006).

The CONTAM Panel considered that the impact of the uncertainties on the risk assessment of exposure to cadmium is limited and concluded that its assessment of the risk is likely to be conservative – i.e. more likely to overestimate than to underestimate the risk.

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

- Cadmium is a non-essential metal that is found as an environmental contaminant both from natural occurrence and from industrial and agricultural sources. Food is the major source of exposure to cadmium for the non-smoking general population.

Occurrence

- Highest cadmium concentrations were detected in the following food commodities: seaweed, fish and seafood, chocolate, and foods for special dietary uses. Specific food items that showed high concentrations are fungi, oilseeds and edible offal.

- For most foods, only a small percentage of the analysed samples (< 5 %) exceeded the maximum level (ML), where specified. Up to 20 % of the samples were above the MLs for celeriac, horse meat, fish, bivalve molluscs other than oysters and cephalopods.

- Area with elevated levels may show higher cadmium concentrations in locally produced food. In addition, usage of cadmium-containing fertilisers in agriculture increases cadmium concentrations in the crops and derived products.

Exposure

- The food groups that contribute to the major part of the dietary cadmium exposure, primarily because of the high consumption are cereals and cereal products, vegetables, nuts and pulses, starchy roots or potatoes and meat and meat products.

- The mean dietary exposure for adults across EU countries is between 1.9 and 3.0 μg/kg body weight (b.w.) per week and high consumers have estimates in the range of 2.5 to 3.9 μg/kg b.w. per week Exposure for toddlers and children appears to be higher than for adults, primarily due to the greater amount of food consumed in relation to body weight.

- Vegetarians have a higher dietary exposure calculated to be up 5.4 μg/kg b.w. per week.

- Tobacco smoking can lead to a similar internal exposure as that from the diet.

- House dust can be an important source of exposure to cadmium for children.

- Inhalation exposure in the general non-smoking population contributes only to a minor extent to the overall exposure.

Hazard identification and characterisation

- Dietary cadmium absorption in humans is usually low (3-5 %). Factors such as nutritional status (low body iron stores) and multiple pregnancies, preexisting health conditions or diseases can lead to higher adsorption.

- Pulmonary absorption of cadmium is higher compared with gastrointestinal absorption.

- Cadmium is retained in the human kidney and liver with a very long biological half-life ranging from 10 to 30 years.

- Cadmium is primarily toxic to the kidney, especially to the proximal tubular cells where it accumulates over time in the cortex. Prolonged and/or high exposure may lead to tubular damage and progress to renal impairment with decreased glomerular filtration rate, and eventually to renal failure.

- Cadmium can also cause bone demineralization, either through direct bone damage or indirectly as a result of renal dysfunction.

- Cadmium does not interact directly with deoxyribonucleic acid (DNA). It is genotoxic by induction of oxidative stress and inhibition of DNA repair. Cadmium can cause lung cancer in rats after inhalation. The International Agency for Research on Cancer has classified cadmium as human carcinogen (Group 1) on the basis of occupational studies. Newer data on human exposure to cadmium in the general population have found statistical associations with increased risk of cancer such as in the lung, endometrium, bladder, and breast. However, the CONTAM Panel did not consider the dose-response data as a sufficient basis for quantitative risk assessment.

- There are a large number of epidemiological studies, conducted in different countries, examining the relationship between urinary cadmium levels and tubular effects. As tubular damage is the earliest effect of cadmium exposure it is appropriate to base risk assessment on these studies.

- The CONTAM Panel carried out a meta-analysis to evaluate the dose-response relationship between selected urinary cadmium and urinary beta-2-microglobulin (B2M) as the biomarker of tubular damage recognised as the most useful biomarker in relation to tubular effects.

- A group-based BMDL5 of 4 μg U-Cd/g creatinine for humans was derived. A chemical specific adjustment factor of 3.9 was applied to account for human variability in urinary cadmium within each dose-subgroup in the analysis resulting in a reference point of 1.0 μg cadmium per g creatinine. This reference point is consistent with earlier calculations in individual studies using other biomarkers of kidney and bone effects.

- Based on modelling of a large data set of non-smoking Swedish women, 95 % of the population at age 50 would have urinary cadmium concentrations below the reference point of 1 μg Cd/g creatinine if the average daily dietary cadmium exposure does not

exceed 0.36 μg Cd/kg b.w. Taking into account the cumulative effects of cadmium this should be expressed as a weekly dietary intake of 2.5 μg Cd/kg b.w.

- Because the data used in the modelling relate to an early biological response and a sensitive population, no adjustment or uncertainty factor was required for individual variability in susceptibility. Therefore, the CONTAM Panel established a tolerable weekly intake (TWI) of 2.5 μg/kg b.w.

Risk characterisation

- The CONTAM Panel noted that the mean dietary exposures in European countries are close to or slightly exceeding the TWI of 2.5 μg/kg b.w.

- Subgroups such as vegetarians, children, smokers and people living in highly contaminated areas may exceed the TWI by about 2-fold. Although adverse effects on kidney function are unlikely to occur for an individual exposed at this level, the CONTAM Panel concluded that exposure to Cd at the population level should be reduced.

RECOMMENDATIONS

- More detailed food consumption information should be acquired to allow calculation of the impact of individual foods or food groupings on overall exposure to cadmium.

- There is a need for representative occurrence data in food commodities, including total diet studies to reduce the uncertainty in the exposure assessment. In addition, it would be valuable to establish exposure based sampling procedures in the food monitoring and surveillance programs to reduce uncertainties due to sampling adjustment factors.

- More data are required to evaluate the effects of cadmium on reproduction and development as well as the possible effect on cancer incidence (especially hormone-related cancers) and mortality.

- The vulnerability of diabetics and patients with kidney disease needs to be ascertained with regard to cadmium effects on kidney function.

- Collection of biomonitoring data from diverse European populations should be promoted.

DOCUMENTATION PROVIDED TO EFSA

Schoeters Greet, Submission of biomonitoring data on cadmium in blood for Belgian teenagers in the year 2004, 2008. Submitted by Vlaamse instelling voor technologisch onderzoek (VITO), Belgium.

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APPENDICES

APPENDIX A CATEGORISATION OF OCCURRENCE DATA

The table below reports the detail on how the food items, transmitted by the organisation providing the data has been mapped in the category/subcategory used for the occurrence analysis. Examples of food items are also reported for each food category. The list may not be exhaustive.

Cadmium Occurrence – Food Category Name	Examples
01. Cereals and cereal products	
01A. Cereal-based mixed dishes	Pastry, cakes, croissants, paste, pizza, dumplings, sandwiches, waffles, egg pasta, noodles
01B. Cereals and cereal products excl. cereal based mixed dishes	
01B_1. Bran and germ	Only bran and germ when explicitly reported
01B_2. Wheat products (Bread, pasta)	Bread, whole meal bread, bread of mixed cereals, bread with added seeds, potato bread, pumpkin bread. Rolls, rolls of mixed cereals, rolls with other non cereal products, Base mixture for bakery, Semolina products
01B_3. Wheat grains and flour	Wheat grains and flower
01B_4. Rice	Rice and rice products
01B_5. Other cereal and cereal products excl. cereal-based mixed dishes	Muesli, oat, buckwheat, barley, mixed cereals products (pasta egg-free, biscuits, muesli bars, basic mixture, snacks, breakfast cereals)
02. Sugar and sugar products including chocolate (move chocolate to cocoa category)	
02_1. Chocolate	Dark chocolate, milk chocolate, white chocolate
02_2. Chocolate based products	Chocolate mixed products
02_3. Other sugar and sugar products	Jam, marmalade, honey, toppings, chewing gum, toffees, fudges, candies, chocolate confectionery, liquorices, marzipan, sugar free confectionery, cocoa powder, meringue, nutritive sweeteners (e.g. fructose) List of items excluded: intense sweeteners
03. Fats (vegetable and animal)	Mayonnaise, dressings, sauces (béchamel, hollandaise), low fat dressings or mayonnaise, goose fat, coconut extract. List of items excluded: vegetable sauces
04. Vegetables, nuts, pulses including carrots, tomato and leafy vegetables	
04A. Vegetable soups	Vegetable soups
04B. Vegetables, nuts, pulses except vegetable soups	
04B_1. Leafy vegetables	Lettuce, lollo, rocket salad, scarole, leafy vegetables excluding spinaches.
04B_2. Fungi	Champignon, boletus, cultivated or wild mushrooms in general
04B_3. Celeriac	Only celeriac
04B_4. Stem and root vegetables	Artichokes, carrots, celery, etc with exclusion of starchy roots

Cadmium Occurrence – Food Category Name	Examples
04B_5. Nuts	Cashew nuts, peanuts, almonds, pine nuts, hazel nuts, coconuts
04B_6. Oil seeds[21]	Poppy seeds, sunflower seeds, sesame seeds, line seeds
04B_7. Spinach	Spinaches
04B_8. Legumes[11]	Butterbeans, peas, check peas, lens, this category includes also soybeans
04B_9. Other vegetable not listed above except. Vegetable soups.	Brassica, capsicum, cucurbits, tomato, wine leaves
05. Starchy roots or potatoes	
05_1. Potatoes	Potatoes peeled and unpeeled
05_2. Other starchy roots excl. potatoes	Tapioca, cassava, sweet potatoes.
06. Fruits	
07. Fruit and vegetable juices, soft drinks and bottled water	
07A. Fruit and vegetable juices	
07A_1. Fruit juices	Only fruit juice
07A_2. Vegetable juices	Carrot juices, vegetable juices in general including mixed fruit and vegetables juices.
07B. Soft drinks with percentage of fruits lower than nectar	
07B_1. Soft drinks	Cola, tonic water
07B_2. Other soft drinks	Prepared herbal tea, water based drinks
07C. Bottled water	Bottled mineral water
08. Coffee, tea, cocoa, insert new category for chocolate	
08_1. Cocoa (Powder or bean)	Cocoa reported as cocoa powder or cocoa beans
08_2. Coffee (Powder or beans)	Coffee reported as coffee powder or coffee beans
08_3. Tea (Powder or dry leaves)	Tea reported as tea powder or tea dry leaves
08_4. Infusions and herbal teas (Powder or dry leaves)	Infusion and herbal teas reported as powders for infusions, dry leaves.
09. Alcoholic beverages	
09A. Beer and substitutes	Beer and substitutes including non-alcoholic beer, panache, cider, alcohol soft drinks
09B. Wine and substitutes	Sangria, sparkling wine, "non-alcoholic" wine, fortified wine (e.g. porto, cherry wine, madeira, vermouth), fruit wine
09C. Other alcoholic beverages and substitutes	Alcohol-free anise, spirits
10. Meat and meat products, offal	
10A. Meat and meat products and substitutes	
10A_1. Soya meat substitutes	Soya products excluding soy beans, soya milk and soya sauce
10A_2. Bovine, sheep and goat meat	Bovine, sheep and goat muscle meat
10A_3. Poultry and rabbit meat	Chicken, duck, goose and rabbit
10A_4. Pig meat	Pig muscle meat
10A_5. Horse meat	Horse muscle meat
10A_6. Game meat	Reindeer, dear, pheasant (where explicitly reported as livestock farming they are entered in 10A_7 "Not elsewhere classifiable meat and meat products")
10A_7. Other or not elsewhere classifiable meat and meat products	Mixed meat, reptiles, frog legs, ox and other meat of African animals

[21] Soybeans have been classified under the category 04B_8 while in Regulation No. 178/2006 they have been classified under oilseeds.

Cadmium Occurrence – Food Category Name	Examples
10B. Edible offal and offal products	
10B_1. Liver bovine, sheep, pig, poultry, horse	Pate and liver of bovine animals, sheep pig poultry and horse
10B_2. Kidney bovine, sheep, pig, poultry, horse	Kidney of bovine animals, sheep, pig, poultry and horse
10B_3. Liver and kidney of game animals	Reindeer, dear, pheasant (where explicitly reported as livestock farming they are entered in 10B_4 "Other)
10B_4. Other offal products (Trip, lung, stomach, etc.)	Heart, tripe and offal not otherwise specified
10B_5. Not specified offal products	Offal products which could not be identified because reported as "Offal", and therefore not classifiable in any of the 10B categories.
10C. Meat based preparations	Mixed meat food
11. Fish and seafood	
11A. Seafood and seafood products	
11A_1. Bivalve molluscs other then oysters	Scallops, mussels, cockles, clams
11A_2. Crustaceans	Prawns, crayfish, langoustines, etc…
11A_3. Cephalopods	Squids, octopus, cuttlefish.
11A_4. Oysters	Oysters.
11A_5. Snails and limpets	Soil and sea snails, limpets and gastropods in general.
11A_6. Other or not elsewhere classifiable seafood products	Not elsewhere classifiable seafood, in particular only food category reported.
11B. Fish and fish products	
11B_1. Muscle meat of fish, excluding species listed in ML groups 3.2.6 and 3.2.7	Muscle meat of all fish species not falling under categories 3.2.6 and 3.2.7 of the Annex to Regulation (EC) No. 1881/2006 in its version of 19 December 2006
11B_2. Muscle meat of fish matching ML group 3.2.6	Only the species listed in the legislation, excluded processed fish.
11B_3. Muscle meat of swordfish	Only when swordfish has been reported
11B_4. Other or not elsewhere classifiable fish products	Process fish has been included here. Canned anchovy, anchovy in oil in salt etc., Fish liver and caviar and roe. Processed fish is included in this category
11C. Fish based preparations	Fish soup, fish quenelle, etc.
12. Eggs	Omelettes, fried eggs List of items excluded: fish eggs
13. Milk and dairy based products	
13A. Milk and dairy based drinks	
13A_1. Soya milk	Milk substitute from soy processing
13A_2. Milk	Cow milk and other milk from animal origin
13B. Dairy based products	Chantilly, rice pudding, ices and sherbets, creams, desserts (e.g. mousse chocolate, Siberian omelettes, tiramisu, profiteroles), yoghurt, French fromage blanc, sour cream, custard. List of items excluded: drinkable yoghurt
13C. Cheese	Mozzarella, spread cheese, cottage cheese, cheese substitutes (e.g. made of vegetable oil). Excluded: tofu.
14. Miscellaneous / Food for special dietary uses	

Cadmium Occurrence – Food Category Name	Examples
14A. Miscellaneous	
14A_1. Herbs	All herbs dried and fresh or not specified.
14A_2. Spices	All spices, ginger etc.
14A_3. Soya sauce	
14A_4. Other miscellaneous products	Additives, flavouring, sweeteners, Algae and seaweeds
14B. Food for special dietary uses	
14B_1. Supplements	Fish oil, multivitamins, herbal products, yeasts, supplements based on seaweeds
14B_2. Other food for special dietary uses excluding food supplements	Food for infants, Food for diabetics, Material for food production, dietetic food
15. Tap water	

APPENDIX B LIST OF THE PUBLICATIONS USED FOR THE BENCHMARK DOSE MODELLING OF BETA-2-MICROGLOBULIN

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ABBREVIATIONS

A1M	alpha-1-microglobulin / protein HC
AA	urinary aminoacids
AAS	Atomic absorption spectrometry
AKT	V-akt murine thynoma viral oncogene homolog
ALB	albumin
ATP	Adenosine-5'-triphosphate
ATSDR	Agency for Toxic Substances and Disease Registry
b.w.	body weight
bALP	alkaline phosphatase activity
B2M	beta-2-microglobulin
B2 MG	Beta-microglobulin
B-Cd	blood cadmium
BIFF-AAS	Beam injection flame furnace atomic absorption spectrometry
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit; 95 %-confidence lower bound
C(Cr)	creatinine clearance
Ca	urinary calcium
CABP	Calcium binding protein
CaSR	calcium sensing receptors
Cd	cadmium
CDC	US Centre for Disease Control and Prevention
Cd-TH	Cadmium-thionein
CI	confidence interval
CONTAM	The Scientific Panel on Contaminants in the Food Chain
CSAF	chemical-specific adjustment factor
CSTEE	Scientific Committee on Toxicity, Ecotoxicity and the Environment
CV	coefficient of variation
CYS	cysteine
DMT1	divalent metal transporter 1
DNA	deoxyribonucleic acid

d.w.	dried weight
EDTA	ethylenediaminetetraacetic acid
EFSA	European Food Safety Authority
ELISA	enzyme-linked-immunosorbent-assay
EPA	Environmental Protection Agency
Epo	erythropoietin
ERK1/2	Extracellular regulated kinase 1 and 2
Ery-Cd	erythrocyte cadmium
ESRD	end stage renal disease
EU	European Union
EU-JRC	Joint Research Centre of the European Commission
FAAS	flame atomic absorption spectrometry
FSA	Food Standards Agency
GEMS/Food	World Health Organisation Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme
GerEs	German environmental survey
GFAAS	graphite furnace AAS
GFR	glomerular filtration rate
GSH	glutathione
GSD	geometric standard deviation
HC	A-1-microglobulin
HEDSET	Risk assessment of Chemical Substances – Belgium Scientific Institute of Public Health
HGAAS	hybride generation atomic absorption spectometry
HMWP	high molecular weight proteins
IARC	International Agency For Research on Cancer
ICP-MS	inductively coupled plasma-mass spectrometry
ICP-OES	inductively coupled plasma-optical emission spectroscopy
ICPS	International Programme on Chemical Safety
INRAN	Istituto Nazionale di Ricerca per gli Alimenti e la Nutrizione
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JRC	Joint Research Center
LBMD	lower benchmark dose
LIA	latex immunoassay

LMW	low molecular weight
LMWP	low molecular weight proteins
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOQ	limit of quantification
MD	mineral density
ML	maximum level
MMR	mismatch repair
MOS	margin of safety
MRL	minimal risk level
MT	metallothionein
MTF-1	Metal-regulatory transcription factor 1
NAG	N-acetyl-beta-D-glucosaminidase
NHANES	National Health and Nutrition Examination Survey
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
OECD	Organisation for Economic co-Operation and Development
OR	odds ratio
pHC	human complex-forming glycoprotein
PMR	proportional mortality ratio
PROT	total proteinuria
PTH	parathyroid hormone
PTWI	provisional tolerable weekly intake
RBP	retinol-binding protein
RIA	radioimmunoassay
ROS	reactive oxygen species
RR	relative risk
SAF	sampling adjustment factors
SCF	Scientific Committee for Food
SCOOP	Scientific cooperation initiative
SCr	serum creatinine
SD	standard deviation
SMR	standardized mortality ratio
TK	toxicokinetic

TWI	tolerable weekly intake
U-Cd	urinary cadmium
UNEP	United Nations Environment Programme
WHO	World Health Organization