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IUPAC Technical Report

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Risk assessment of effects of cadmium on human health (IUPAC Technical Report)

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Abstract: Chemistry and Human Health, Division VII of the International Union on Pure and Applied Chemistry (IUPAC), provides guidance on risk assessment methodology and, as appropriate, assessment of risks to human health from chemicals of exceptional toxicity. The aim of this document is to describe dose-response relationships for the health effects of low-level exposure to cadmium, in particular, with an emphasis on causation. The term “cadmium” in this document includes all chemical species of cadmium, as well as those in cadmium compounds. Diet is the main source of cadmium exposure in the general population. Smokers and workers in cadmium industries have additional exposure. Adverse effects have been shown in populations with high industrial or environmental exposures. Epidemiological studies in general populations have also reported statistically significant associations with a number of adverse health effects at low exposures. Cadmium is recognized as a human carcinogen, a classification mainly based on occupational studies of lung cancer. Other cancers have been reported, but dose-response relationships cannot be defined. Cardiovascular disease has been associated with cadmium exposure in recent epidemiological studies, but more evidence is needed in order to establish causality. Adequate evidence of dose-response relationships is available for kidney effects. There is a relationship between cadmium exposure and kidney effects in terms of low molecular mass (LMM) proteinuria. Long-term cadmium exposures with urine cadmium of 2 nmol mmol⁻¹ creatinine cause such effects in a susceptible part of the population. Higher exposures result in increases in the size of these effects. This assessment is supported by toxicokinetic and toxicodynamic (TKTD) modelling. Associations between urine cadmium lower than 2 nmol mmol⁻¹ creatinine and LMM proteinuria are influenced by confounding by co-excretion of cadmium with protein. A number of epidemiological studies, including some on low exposures, have reported statistically significant associations between cadmium exposure and bone demineralization and fracture risk. Exposures leading to urine cadmium of 5 nmol mmol⁻¹ creatinine and more increase the risk of bone effects. Similar associations at much lower urine cadmium levels have been reported. However, complexities in the cause and effect relationship mean that a no-effect level cannot be

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defined. LMM proteinuria was selected as the critical effect for cadmium, thus identifying the kidney cortex as the critical organ, although bone effects may occur at exposure levels similar to those giving rise to kidney effects. To avoid these effects, population exposures should not exceed that resulting in cadmium values in urine of more than 2 nmol mmol⁻¹ creatinine. As cadmium is carcinogenic, a 'safe' exposure level cannot be defined. We therefore recommend that cadmium exposures be kept as low as possible. Because the safety margin for toxic effects in kidney and bone is small, or non-existent, in many populations around the world, there is a need to reduce cadmium pollution globally.

Keywords: biomarkers; cadmium; cancer; exposure; hazard assessment; kidney; risk assessment; skeleton; toxicokinetics; urine.

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1 General introduction and aims

1.1 Introduction

IUPAC is the world authority on chemical nomenclature and terminology and on setting standards for the critical evaluation of chemical data. Division VII, Chemistry and Human Health, has the objective of providing guidance on risk assessment methodology and, as appropriate, of providing assessments of risks to human health from chemicals of exceptional toxicity. This document is an example of such a risk assessment. It is based on literature up to 2014 and a few further publications from 2015 to 2016.

Cadmium is a metallic element found naturally in low concentrations, usually combined with zinc and lead as sulfide ores. Dispersion into the environment occurs from multiple sources, including cadmium-containing phosphate fertilizers and the inappropriate disposal of electronic waste. Elevated concentrations in air, water, and soil may occur close to industrial emission sources, particularly those of nonferrous mining and metal refining industries. Electroplating cadmium metal onto steel has been one of the methods used to prevent corrosion. Cadmium compounds are used in batteries and as pigments. Nanoparticles derived from cadmium compounds are used in solar panels and other electronic applications.

Exposure to cadmium through inhalation of fumes or dust in occupational settings has long been known to cause adverse health effects on lungs and kidneys. Long-term intake of high doses of cadmium from polluted rice induced “Itai-itai disease”, a disease of the kidneys and bones, that was recognized in the Japanese population after World War II [1].

There is widespread contamination of soil in many areas of the world, from one natural geological source or another, and from pollution by cadmium-containing fertilizers or industrial emissions. Cadmium is taken up from the soil by vegetable crops, e.g. rice, wheat, and potatoes. In many areas, human exposure to cadmium is high enough to be of significance to health [2]. The critical effect has long been considered to be the toxic effect on the renal proximal tubules that may result in clinical kidney disease. Measures of such tubular kidney effects, and of the urinary excretion of cadmium, have been the basis for assessment and management of risk, both in the occupational setting and for cadmium in food [2]. However, other adverse effects, particularly those on the skeleton and the risks for cancer, must also be considered.

1.2 Hazard and risk assessment methods

Methods used in hazard and risk assessments of human health impacts from chemicals have been developed during the last few decades. International risk assessments of chemical compounds and consensus documents on methods used have been published by the International Program on Chemical Safety (IPCS). IPCS is run cooperatively by the United Nations Environment Programme (UNEP), the International Labour Organization (ILO), and the World Health Organization (WHO). Since the 1970s, the Scientific Committee on the Toxicology of Metals of the International Commission on Occupational Health (ICOH) has been active in this field. Risk assessments of many metals have been summarized in the Handbook on the Toxicology of Metals, which includes a chapter on cadmium [1]. Several National Agencies have also performed such risk assessments. A relevant “Glossary for Chemists of Terms Used in Toxicology” was published in 1993 [3] within the framework of IUPAC. It was updated in 2007 [4], incorporating new terms in toxicokinetics based on “Glossary of Terms Used in Toxicokinetics” [5]. The 2007 “Glossary of Terms used in Toxicology” is focused particularly on terms of importance for hazard and risk assessment. In hazard and risk assessment, a general scheme of assessment is usually applied. Initially, human exposures to the chemical (exposure assessment) are combined with information on hazards in terms of adverse effects that may be caused by the chemical in question. This is done in order to determine qualitatively whether the effect is the result of exposure to the chemical or not. Further information may be available, allowing estimates of the relationships between dose or exposure and adverse effects (dose-response relationships). Such information, in combination with exposure assessment data, may allow quantitative estimation of the risks to human health. Knowledge of the chemistry of a substance is fundamental to any risk assessment. Further, the availability of methods for chemical analysis of the substance in environmental media, and preferably also in biological media, including human tissues and fluids, is essential. The present document takes into account these considerations. When estimating dose-response relationships, toxicokinetic (TK) and toxicodynamic (TD) information is crucial, regardless of whether dose-response relationships are estimated from mathematical modelling of such data or from direct observations based on epidemiological data. In the latter case, toxicokinetic–toxicodynamic (TKTD) data forms an important background for evaluating the causality of observed relationships.

1.3 Aim

The central focus of the present document is on the risk assessment of low-level exposures to cadmium in order to provide a basis for preventive action. Treatment of clinical cadmium poisoning has been discussed elsewhere [1]. This review critically assesses the available information and identifies dose-response relationships for health effects caused by exposures to all chemical species of cadmium and its compounds. Special consideration is given to effects that have been reported at low-level exposures, with particular emphasis on causality.

2 Physical and chemical properties and uses of cadmium and its compounds

2.1 Introduction

Cadmium (CAS no: 7440-43-9; EU no: 231-152-8) is a metallic element of Group 12 (Zn, Cd, Hg) of the Periodic Table. Compounds formed from cadmium most commonly contain cadmium with a valency of +2. Cadmium shares some properties with its neighbors in Group 12 of the Periodic Table; the essential element zinc is the lower atomic mass neighbor, while the very toxic element mercury is the higher atomic mass neighbor. A summary of the physicochemical data for cadmium and selected compounds is given in Table 1. All are odourless.

In the elemental state, cadmium is soft, malleable, and has a silvery-white or bluish-white lustre. It is a relatively rare element and is not found in its pure state in nature. There is (0.1–0.5) mg kg⁻¹ of cadmium in the earth's crust. Cadmium is mainly associated naturally with the sulfide ores of zinc, lead, and copper. Purification was first performed by Stromeyer in 1817 from an ore whose principal component was zinc carbonate.

Cadmium is used for the plating of steel, as a plastic stabilizer, as an electrode material in nickel-cadmium batteries, and in semi-conductors. Mining, smelting, and industrial use have resulted in increased bioaccessibility in the environment, and anthropogenic sources are the most significant threat to human health. Cadmium is commonly regarded as a pollutant of worldwide concern and has been reviewed by both IPCS [6, 7] and the UNEP Chemicals Branch [8]. The UNEP report has a chapter on initiatives and actions for the management and control over the release of and exposures to cadmium, including which adverse effects on human health and the environment have been considered by national and international organizations to be significant enough to require regulation.

Elemental cadmium vapour is rapidly oxidised in air to produce cadmium oxide. Gases and vapours like carbon dioxide, water vapour, sulfur dioxide, sulfur trioxide, and hydrogen chloride react with elemental cadmium to form salts that may enter environmental media. Examples of these reactions during cadmium emissions from coal-fired power plants are described by Kirsch *et al.*, 1982 [9]. The chemistry of cadmium is dominated by its inorganic compounds in the +2 oxidation state. Cadmium forms many inorganic salts. In general, these salts are similar to the corresponding zinc compounds in their properties. Cadmium compounds can be divided into three groups (Table 1): the soluble salts, the insoluble pigments, and those compounds that are insoluble at neutral pH but dissolve in dilute acid. The halides and the nitrate and sulfate of cadmium are very soluble in water, while chalcogenides are insoluble. The hydroxide and the carbonate are soluble only in dilute acid. Cadmium sulfide (yellow), cadmium selenosulfide (orange), and cadmium selenide (red), singly or in combination, are used as pigments. Cadmium green is a pigment consisting of a mixture of cadmium yellow and viridian (a blue-green pigment, a hydrated chromium(III) oxide). Cadmium sulfide and cadmium selenide have semi-conductor-like properties and can be used in solar panels and electronic equipment. Nanoparticles of cadmium selenide (quantum dots) are used in solar panels and other

Table 1: Physicochemical data for cadmium and selected compounds.

Common name	Formula	CAS no	EU no	Molecular mass (atomic mass)	Appearance	Melting point	Boiling point	Vapour pres- sure <i>P</i> /MPa	Density/ (g cm ⁻³)	Solubility in water/ (mg L ⁻¹)
Cadmium	Cd	7440-43-9	231-152-8	112.4	grey/silver-white solid (brownish or grey as powder)	321 °C	765; 767 °C	negligible at 25 °C	8.6	2.3 (powder); 8.7 (bar)
Insoluble compounds										
Cadmium oxide**	CdO	1306-19-0	215-146-2	128.4	brown or red ochre powder##	950 °C (sub)#	NA	NA	6.9; 8.26#	none; 4.8; 2.1 ⁻
Cadmium sulfide	CdS	1306-23-6	215-147-8	144.5	orange ochre powder	871–890 °C (sub)#	NA	NA	4.8	insoluble; 12 (exptl)~
Cadmium selenide++	CdSe	1306-24-7	215-148-3	191.4	white cubic crystals	1240 °C	NA	NA	5.81	insoluble
Soluble salts										
Cadmium chloride**	CdCl ₂	10108-64-2	233-296-7	183.3	white hygroscopic solid	568 °C; 533 °C (N ₂ ; dec), in air 480 °C (dec)	NA	NA	4.1; 3.9	good; 113.9 at 20 °C; 45.7 ⁻
Cadmium nitrate	Cd(NO ₃) ₂	10325-94-7	233-710-6	236.4	white hygroscopic solid	360 °C trihydrate	NA	NA	3.6; 2.5	156 at 25 °C; 50.7 ⁻
Cadmium sulfate +	CdSO ₄	10124-36-4	233-331-6	208.5	white hygroscopic solid*/ green liquid#	59.5 °C; 48–61 °C [~] 1000 °C*/ below 0 °C#	NA (dec)*/ ca 100 °C#	NA	4.7* 1.3#	76 at 25 °C* NA#
Partially soluble										
Cadmium carbonate***	CdCO ₃	513-78-0	208-168-9		white solid	500 °C (dec); 356 °C (dec)	NA	NA	4.3; 4.4	very slightly; experimental value 0.114
Cadmium hydroxide	Cd(OH) ₂	21041-95-2	244-168-5	146.4	white crystalline solid/ greenish-white powder [~]	130 °C (dec) 300 °C (dec), 188 °C ⁻⁻⁻	NA	NA	4.8/4.7 [~]	0.026/0.007 [~]

Note: Data are from Chemsponder, European Chemicals Agency website (ECHA), International Chemical Safety Cards (ICSC) and Handbook of Chemistry and Physics, 87th edition, 2006 (Handbook), and are in agreement unless otherwise stated.

+ The data on the ECHA website for cadmium sulfate (+) appears to suggest that the substance evaluated is different from the substance evaluated in ICSC, Handbook and Chemsponder. The substance tested was registered as an intermediate. It would appear that the test was conducted on a liquid, perhaps because being an intermediate, the substance was not isolated during manufacture and the non-isolated material was tested. The substance that should be tested is 'a chemical element and its compounds in the natural state or obtained by any manufacturing process including any additive necessary to preserve its stability and any impurity deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition'. It is notable that the ECHA data for the other substances for which data were available concurred with the pure data quoted elsewhere.

++ Cadmium selenide (++) data only available from Handbook Cadmium selenide nanoparticles exhibit quantum confinement and include quantum dots.

---Values given in order as found in Handbook; Chemsponder; ECHA.

~In order: Handbook, ECHA.

-In order: ICSC, Handbook, ECHA.

#In order: ICSC, ECHA.

#As given in ECHA website (in air).

***As given in Chemsponder (first) or the ECHA website (second).

**Data for amorphous form.

*ICSC, Handbook; Chemsponder.

Dec, Decomposition.

Exptl, Experimental.

NA, No measurable value under relevant conditions.

Sub, Sublimation.

electronic applications. Cadmium sulfide and cadmium telluride are used in thin film solar panels. Cadmium hydroxide and cadmium carbonate are soluble in dilute acid and should be soluble at the acidic pH prevailing in the human stomach.

2.2 Coordination chemistry of toxicological relevance

Since cadmium(II), the only valence state important in toxicology, has a filled 4d-shell of electrons, its chemical properties resemble those of zinc(II) in flexibility of coordination and lack of redox chemistry. The crystal ionic radius (109 pm) of Cd^{2+} is larger than that of Zn^{2+} (88 pm). This leads to slightly longer bond lengths in its coordination compounds. Cadmium(II) is a softer Lewis acid than zinc(II). Hence, it has slightly lower stability than zinc in complexes with oxygen and nitrogen ligands [10]. However, relative affinities of the two ions are reversed for sulfur ligands, as cadmium is considerably more thiophilic than zinc. Thus, an important characteristic of cadmium for understanding its toxic intracellular effects is its sulfur coordination chemistry. The similar ionic radius to Ca^{2+} (108 pm) allows substitution for calcium in many sites, *e.g.* in calmodulin, and may underlie effects such as activation of signaling pathways, oncogenes, cell survival mechanisms, and apoptosis [11]. Outside cells, the reduction potential is higher than inside, and most thiols are oxidized to disulfides. Because of the relatively large number of sulfur donors available intracellularly, cadmium is generally bound more strongly than zinc inside the cell. In molecules with multiple cysteine ligands, affinity for cadmium is very strong. For example, in metallothionein (MT), cadmium shows tetrathiolate binding that is three orders of magnitude higher than that of zinc. On the other hand, the relative affinities of cadmium(II) ions and zinc(II) ions to oxygen and nitrogen donors show that cadmium(II) ion concentrations must be higher than zinc concentrations to displace zinc from coordination sites with oxygen and nitrogen. To bind preferentially to sulfur sites, cadmium(II) ion concentrations need be only one thousandth of those of zinc [12].

Cadmium(II) ions, when their intracellular concentrations reach a few nanomolar, have the potential to compete for binding to nitrogen and oxygen donor atoms with calcium(II) ions, the intracellular concentrations of which are a few millimolar. However, because of the buffering capacity of high affinity thiolate coordination sites, where calcium does not bind, such competition is unlikely. Cadmium(II) ions bind in calcium binding sites of proteins *in vitro* because the ionic radius of Ca^{2+} is similar to that of Cd^{2+} , but any *in vivo* mechanisms with free cadmium(II) ions as the cytotoxic species have been considered unlikely to occur because of the strong sulfur binding [13]. It has been shown, however, in living cells, that the Cd^{2+} ion can participate in a number of Ca^{2+} dependent pathways as a Ca^{2+} mimetic. Such a role has been shown related to calmodulin and CaMK-11, the latter involved in apoptotic cell death [11].

2.3 Organic cadmium compounds

Organic cadmium compounds, *i.e.* compounds where cadmium binds covalently to carbon, are not common in nature [7]. However, studies in marine polar regions indicate that there is the possibility of microbial formation of monomethyl cadmium, CdCH_3^+ [14, 15], which may be more toxic than cadmium ions.

2.4 Environmental cadmium

In aquatic environments at low salinity, cadmium is present principally as the free Cd^{2+} ion, with cadmium dihydroxide and organic complexes occurring at levels dependent on pH and the amount and nature of soluble organic material present. As salinity increases, the degree of complexation with chloride increases and, in seawater, cadmium is thought to exist almost solely as cadmium dichloride and CdCl^+ complexes [16].

3 Methods and problems of chemical analysis

Great differences exist in cadmium concentrations in different materials. Contamination from a high-level material to a low-level material may easily occur. On the other hand, losses may also occur because cadmium in liquid solutions may be adsorbed onto the surface of storage containers. These sources of error must be considered when sampling and when storing samples for chemical analysis. Sample collection guidelines for trace elements should be followed as published by IUPAC [17] in order to avoid errors.

Inductively coupled plasma mass spectrometry (ICP-MS) and, sometimes, atomic absorption spectrometry (AAS) are used for the determination of cadmium in biological samples. Other techniques that may be used are anodic stripping voltammetry, neutron activation analysis, and X-ray fluorescence spectrometry [18].

The flame AAS method has a detection limit in pure water of (1–5) mg L⁻¹, whereas more sensitive AAS-methods can detect levels more than 100-fold lower. In environmental or biological samples, the sensitivity is usually not as great, because of matrix interference. With ICP-MS, a detection limit as low as 0.04 µg L⁻¹ (even lower with some instruments) can be achieved in biological fluids.

When determining cadmium in urine by ICP-MS, interference by molybdenum can be a problem, as molybdenum oxide is formed in the plasma and appears at the same mass to charge ratio in the mass spectrometer as cadmium, producing falsely high results. The molybdenum concentration in urine varies considerably. This interference is greatest in studies of children, whose urine may contain very low cadmium concentrations and higher molybdenum concentrations than adults' urine [19]. Modern ICP-MS instruments can overcome these problems, for example by using what are known as reaction cells or collision cells, in which the oxide molecules break down, but data from ICP-MS instruments with a low-resolution quadrupole mass spectrometer may be erroneously high.

Electrochemical methods must be able to access Cd²⁺. The complete destruction of all organic materials in the sample is usually required. Differential pulse anodic stripping voltammetry is particularly suitable for water analysis, but it has also been used for analyses of blood, urine, food, and tissues [20].

Cadmium in tissues can also be determined *in vivo* through the use of neutron activation analysis (NAA) [20] or X-ray fluorescence [21].

In the past, a substantial amount of published data has been based on inadequate methods. Errors, with values 10–100 times too high, have been observed from both emission spectroscopy and AAS measurements, emphasizing the continuing need for adequate quality assurance [17, 20, 22, 23].

4 Environmental levels and exposure

4.1 General and occupational environment

The mining, smelting, and industrial usage of cadmium has caused considerable exposure of workers to cadmium, but it is now fairly well controlled in long-established industrialized countries. There are still problems in developing countries and in some newly industrialized countries. Such activities and the inappropriate disposal of electronic waste have increased the accessibility of cadmium in the general environment. Thus, anthropogenic sources have become a significant threat to human health. Although cadmium toxicity has been recognized for only a century, [24] environmental pollution has taken place for several 1000 years, ever since humans started to produce metals from ores that happened to contain cadmium. The main routes of exposure are through nutrition and smoking. Some plants, e.g. rice, tobacco, and mushrooms, accumulate cadmium from the soil on which they grow, and make cadmium ions available to wildlife, livestock, and humans. The use of phosphate fertilizers and sewage sludge, along with the resulting contamination of soils, facilitates the mobilization of cadmium in the environment and its accumulation in crops. The turnover of cadmium in soils is very slow. It was estimated by WHO 2007 [25] that a near balance between input and

output from soils was reached in Sweden, while increasing concentrations prevail in most European countries, despite decreased atmospheric dispersion and precipitation in recent decades.

Environmental levels and exposures have been extensively reviewed elsewhere [1, 2, 26]. In countries with relatively low cadmium levels in food, smokers have about double the cadmium levels found in non-smokers [27]. In contaminated areas of China, intake from contaminated rice was the dominating source of cadmium uptake in smokers of locally grown tobacco [28]. Offal, shellfish, and certain seeds contain high levels of cadmium, but are usually consumed only in small amounts. In populations with a high consumption of rice, the main source of cadmium is rice [28]. Cereal products, grains, and root vegetables are also important sources in many populations. Ambient air is believed to contribute only marginally to human exposure by inhalation. However, traffic intensity near the home is reported to affect cadmium levels in blood, possibly by indirect exposure to precipitated dust [29].

4.2 Exposures in different parts of the world

Cadmium exposures vary widely. Rice, irrigated with cadmium-contaminated water, has been a source of toxic cadmium exposure in many populations, especially in Asia, and still poses a problem [1]. As a consequence, Asian populations consuming large quantities of rice have been reported to have higher cadmium exposure than those in Europe and the U.S. [30]; see also Section 4.3. Exposure differences among various countries and regions in North America and Europe appear to be relatively small. Hrubá *et al.*, 2012 [29] found geometric mean mass concentrations in blood among school children from 0.11 (Sweden) to 0.17 $\mu\text{g L}^{-1}$ (Croatia). Pawlas *et al.*, 2013 [31] found a similarly small range in adult women (0.25–0.65 $\mu\text{g L}^{-1}$) in six European cities and towns. Industrial pollution causes locally elevated exposures, mainly as a result of past emissions [32].

4.3 Temporal trends in human exposure

The industrial use of cadmium has increased by a factor of more than 50 from 1920 to 1990. Perhaps related to this industrial use is the implied increase in human exposure (implying twice as high an intake) identified through the temporal trend in cadmium concentrations in wheat from 1920 to 1970 [33]. There is very little information on whether, during the last four decades, cadmium exposures of human populations are increasing, decreasing, or unchanged. In adults from north Sweden 1990–1999 there were no indications of a temporal trend in cadmium levels in erythrocytes, except for a decrease in smokers, statistically significant in males but not in females [34], suggesting a decrease in cadmium exposure from smoking, but no change in dietary exposure. Average daily intakes in European countries and the USA have been below 20 $\mu\text{g day}^{-1}$ (178 nmol day^{-1}), except in Greece, The Netherlands and Italy, where somewhat higher values have been reported [30]. In Japan, there has been a decrease of cadmium exposures in the general population, from (59–113) $\mu\text{g day}^{-1}$ (525–1005 nmol day^{-1}) in the 1960s to lower values in recent decades. The dietary intake of cadmium among women in Japan further decreased, from 38 $\mu\text{g day}^{-1}$ (338 nmol day^{-1}) in 1977–1981 to 26 $\mu\text{g day}^{-1}$ (231 nmol day^{-1}) in 1991–97 [35]. Itoh *et al.*, 2014 [36] reported a dietary intake of 25 $\mu\text{g day}^{-1}$ (222 nmol day^{-1}) in 2001–05. The decrease of cadmium intakes in Japan is to a large extent related to decreased rice consumption.

5 Toxicokinetics

5.1 Absorption and uptake

The following sections deal with the uptake of cadmium after inhalation and ingestion. Dermal uptake of cadmium contributes little to the total uptake.

5.1.1 Inhalation

Absorption of inhaled cadmium in the respiratory tract is influenced by numerous factors, including the size of inhaled cadmium-bearing particles and the solubility of the cadmium species. Studies in animals have indicated that between 7 and 40 percent of an inhaled aerosol of cadmium particles is absorbed into blood, the lower values being valid for larger particles with low solubility and the higher values for small particles and for particles with high solubility. Similar uptake estimates have been derived from calculations based on general knowledge about the deposition and absorption of particle aerosols in human lungs [37]. Such calculations indicate that up to 50 percent uptake would be possible for ultrafine particles, like those in cigarette smoke [1]. A considerable deposition in the nose and pharynx may also occur for certain forms of nano-sized cadmium particles [38, 39].

5.1.2 Ingestion

Uptake of cadmium into the body after ingestion has been estimated to be, on average, 10 percent of the food content among women and 5 percent among men, based on population data from USA and calculations with a toxicokinetic model [40]. Lower estimates were reported by Fransson *et al.*, 2014 [41], based on similar calculations using kidney cortex, blood, and urine values measured in 30 persons in Sweden. It is possible that a somewhat lower uptake occurs in Sweden than in many other countries with higher dietary exposures. In Sweden, the average daily dietary cadmium intake is approximately 12 micrograms [42]. A strong dose-dependence, with greater gastrointestinal uptake and retention of cadmium at higher doses, is known from animal experiments [43]. In humans, uptake from the diet has been shown to be influenced by iron status, with up to four-fold higher uptake when serum ferritin was below 20 $\mu\text{g L}^{-1}$ [44–48], leading to higher cadmium values in blood or urine in women with low iron stores [49–51]. Women often have lower iron stores than men, explaining a higher fractional intestinal uptake of cadmium and higher cadmium concentrations in biomonitoring media. Animal experiments have shown influences by a number of other factors, such as intake of fibre, protein, calcium, iron, and zinc [1]. An interaction with essential metals, such as zinc and calcium, is also likely to take place in humans, in addition to the well-documented influence of iron. Such interactions are explained by the fact that cadmium utilizes the same intestinal transporters as zinc, iron, and calcium. The increased cadmium uptake subsequent to low iron intakes is explained by an up-regulation of DMT1 (Divalent Metal Transporter 1). Zinc and calcium transporters may similarly influence intestinal cadmium uptake [52]. In humans, concentrations of cadmium in blood and urine were shown to be associated with polymorphisms in zinc transporter genes [53]. These findings support the idea that cadmium is absorbed *via* zinc transporters and an up or down regulation of these transporters should cause parallel variations in the intestinal absorption of cadmium and zinc. As mentioned, an increased cadmium uptake as a result of calcium deficiency has been shown in animals, and the role of low calcium intake is believed to be a contributing factor for the induction of severe bone changes from high dietary cadmium exposures seen in Itai-itai disease. However, as far as we know, specific studies demonstrating an influence of calcium deficiency on the intestinal uptake of cadmium have not been documented in humans.

5.2 Transport and distribution

From the site of absorption, cadmium is transported in the blood to other tissues (observed concentrations in humans are given in Section 6, Biological Monitoring). Cadmium in blood is found mainly in the blood cells. However, cadmium in blood plasma is more important for transport to bodily organs. Cadmium is distributed *via* plasma to many organs, but the blood-brain barrier protects the brain from high concentrations and the placental barrier protects the fetus. In plasma, cadmium is partly bound to high molecular mass protein and partly to low molecular mass protein. The former component is mainly albumin. Cadmium

bound to albumin is mostly transported to the liver. The cadmium bound to low molecular mass protein is probably bound to metallothionein (MT), a small protein rich in sulfhydryl groups. Cadmium bound to MT is readily filtered through the glomeruli of the kidneys and subsequently reabsorbed by the kidney tubules, where the cadmium is accumulated [1]. Cadmium that is not bound to protein in plasma forms complexes with non-protein sulfhydryls, such as glutathione and cysteine. In humans in Sweden with a typical dietary exposure (estimated at $12 \mu\text{g day}^{-1}$), approximately 50 percent of the body burden is found in the kidneys and 15 percent in the liver [1]. In population groups with higher exposures, *e.g.* in the (erroneously considered) “uncontaminated” areas of Japan in the 1960s and 1970s ($60\text{--}113 \mu\text{g day}^{-1}$), a larger proportion is found in the liver and a lower proportion in the kidneys. The highest concentration or mass fraction of cadmium is, however, invariably found in the kidney cortex [1]. Kidney cadmium concentrations increase with age, are higher in women than in men, and also are higher in smokers than in nonsmokers [27, 54]. Increased cadmium absorption in women with low iron stores is reflected in the corresponding increased amounts of their kidney cadmium [27].

5.3 Excretion, biological half-life

Absorbed cadmium is excreted both in urine and in feces. Only a very small proportion (0.01–0.02 percent) of the body burden of cadmium is excreted by humans each day. Inter-individual as well as day-to-day variation is considerable. The relationship between the concentration of cadmium in the kidney and urine cadmium concentration is discussed in Section 6.1.2. There is a dramatic increase in the proportion of cadmium excreted in urine when renal damage is induced by cadmium. This phenomenon has been demonstrated both in animals and in humans [1].

Direct measurements of the biological half-lives in various tissues of animals have demonstrated variable retention among different tissues. Measurements of concentrations of cadmium in human tissues, in combination with measurements of excretion at various ages, indicate that the biological half-life of cadmium is 10–30 years in muscle, kidney cortex, and liver tissue [55, 56]. In blood, the biological half-life has two components according to studies by Jarup *et al.*, 1983 [57]: a fast component with a biological half-life of 100 days and a slow component with a half-life of 7–16 years (see also [1, 58]). Animal experiments show that the biological half-life is dependent on exposure level. At doses below the level that induces renal tubular dysfunction, the clearance of cadmium is slightly slower as dose increases, probably because a larger proportion of tissue cadmium is bound to metallothionein at higher doses, promoting tissue retention. In addition, there was a positive intercept for the relationship between urine cadmium and body burden of cadmium in these animal studies. This observation may be explained if there is a direct route for cadmium to pass from blood plasma to urine and the amount excreted by this route is related to recent exposure [43, 59].

Thus, in addition to the dose-dependent half-life of cadmium accumulated in the kidney (kidney tissue cadmium), urinary cadmium levels seem to be dependent on two excretion mechanisms: one pathway from kidney tissue into urine and another pathway from blood plasma into urine, probably arising from glomerular filtration of plasma cadmium and incomplete renal tubular reabsorption. In accord with this, Akerstrom *et al.*, 2013 [60] calculated a biological half-life in the human kidney of 21 years at a kidney cortex level of 8 mg kg^{-1} and 43 years at 23 mg kg^{-1} , based on the slope of the observed linear relationship between the urine excretion rate ($\mu\text{g day}^{-1}$) and the kidney cadmium burden (μg). These estimates reflect the combined contributions of all urinary pathways for cadmium, including transfer from plasma and transfer from kidney tissue. The longer half time at higher kidney tissue cadmium levels suggests that slow transfer from kidney tissue to urine dominates urine cadmium kinetics when kidney tissue levels are high (but lower than the critical concentration for proteinuria). Fransson *et al.*, 2014 [41] calculated the rate of transfer of cadmium from kidney tissue to urine by estimating this parameter in a physiologically based toxicokinetic model (PBTk), based on the data from Akerstrom *et al.*, 2013 [60]. The corresponding half-life for the transfer of cadmium from kidney tissue to urine was 45 years. Longitudinal studies of urinary excretion of cadmium in populations following a decrease in dietary cadmium exposure from relatively high levels (*e.g.* $300 \mu\text{g day}^{-1}$) have estimated

urinary excretion half-lives ranging from 14 to 33 years [61–63]; these estimates reflect the contributions of all pathways to the transfer of cadmium to urine.

5.4 Mathematical (toxicokinetic) models of cadmium accumulation in kidney (or bone)

Accumulation of cadmium in critical organs has important health effects. Accumulation in the kidney cortex is relevant to renal dysfunction. Accumulation in the [soft part of] bone tissue may lead to demineralization and weakening of the skeleton and a subsequent increased risk of fractures. Mathematical models (toxicokinetic models) describing quantitative relationships between cadmium exposure by various routes, accumulation in the kidney, and excretion, have been developed. No such models have been published describing the accumulation of cadmium in bone (soft tissue part). They are urgently needed. Also required are the data to develop and evaluate models of cadmium bone kinetics. It is not clear to what extent existing TK models for cadmium are valid for cadmium nanoparticles.

Several authors [6, 64–66] have used one-compartment models, which consider the body as a single compartment and the critical organ (kidney cortex) as a part of the whole body. These models have been employed for the calculation of the biological half-life of cadmium and as a tool in risk assessment, describing the relationships between exposures by inhalation or ingestion and accumulation in the critical organ and excretion. The modeling by Amzal *et al.*, 2009 [66] describes the relationship between oral cadmium intake and urinary excretion and the population variability in toxicokinetics. The quantitative results of modeling by Amzal *et al.*, 2009 [66] are incorporated in Section 8 of the risk estimates presented by the European Food Safety Authority (2009) [2].

While one-compartment models can satisfy certain risk assessment applications, including predicting doses that correspond to kidney cadmium levels below the threshold of toxicity, they do not capture the complex realities of cadmium biokinetics needed to predict dose-response relationships below and above organ thresholds. Important toxicokinetic factors that influence cadmium dose-response relationships include: (1) multi-organ distribution and multiple target organs for toxicity (kidney, liver, skeleton); (2) multiple forms of cadmium in the body having distinct distribution and elimination kinetics (*e.g.* cadmium complexes with non-protein sulfhydryls, plasma albumin complex and metallothionein); (3) dose-dependent distribution and elimination associated with induction of metallothionein and toxicity; (4) effects of nutritional status and co-exposure to other metals (*e.g.* iron, and zinc) on cadmium absorption, and distribution and elimination kinetics. An improved understanding of such factors, as well as improved computational tools for solving complex models, has led to the development of more advanced multi-compartment physiologically-based toxicokinetic and toxicodynamic models. An eight-compartment model was presented by Kjellstrom and Nordberg, 1978 [67] and Nordberg and Kjellstrom, 1979 [68]. This model was used by Thun *et al.*, 1991 [69] for quantitative risk assessment. It was amended by Choudhury *et al.*, 2001 [40] and the amended model was used by Diamond *et al.*, 2003 [70] for estimating daily cadmium intake, giving rise to specified critical concentrations or mass fractions of cadmium in the kidney cortex of population groups in the USA (see Section 7.3.1). This model was also used by the CDC in USA to derive Minimal Risk Levels for oral exposure to cadmium [71]. Such calculations are dependent on the accuracy of the estimated relationships between blood cadmium, urine cadmium, and kidney cortex cadmium over the range of exposure scenarios.

The model by Choudhury *et al.*, 2001 [40] was also used by Diamond *et al.*, 2003 [70]. For inhalation exposures, it was complemented by the ICRP Human Respiratory Tract Model to assign absorption and regional particle deposition fractions in the respiratory tract, as described in ATSDR, 2012 [71]. This model has been used to predict the relationship between cadmium intake by oral or inhalation routes and cadmium concentrations in kidney cortex and urine. For dietary exposures, the model predicts that the cadmium concentration in kidney cortex reaches its maximum at approximately 55–60 years of age. For women in general, low iron stores are common and an uptake fraction 0.1 (10 percent) is common (see Section 5.1.2). Women are the most vulnerable section of the population for cadmium-induced effects on kidney tubules. Accordingly,

the following estimates are for women. Assuming an absorption fraction of 0.1, a cadmium mass fraction in kidney cortex of $120 \mu\text{g g}^{-1}$ (reached at age 55) is predicted to correspond to an average mass fraction in urine of $2 \mu\text{g g}^{-1}$ creatinine (2 nmol mmol^{-1} creatinine). This value is reached after 55 years of dietary exposure (from birth) to $1.6 \mu\text{g}$ of cadmium per kg of body mass per day. A cadmium concentration in the kidney cortex of $84 \mu\text{g g}^{-1}$ (the estimated lower confidence limit on the renal cortex concentration associated with a 10 % probability of low molecular mass proteinuria (Diamond *et al.*, 2003) [70]), corresponds to $1.4 \text{ nmol mmol}^{-1}$ creatinine of urinary cadmium. The same mass fraction in kidney cortex is reached at age 55 years at a constant oral intake of cadmium of $1 \mu\text{g}$ per kg body mass per day from birth. Assuming a background oral intake of $0.3 \mu\text{g kg}^{-1}$ body mass per day (e.g. dietary), inhalation of $2.7 \mu\text{g m}^{-3}$ of an aerosol of cadmium sulfide (ICRP absorption class M) with a uniform particle size of $1 \mu\text{m}$, 8 h per day, 5 days per week, will give rise to a kidney cortex mass fraction of $84 \mu\text{g g}^{-1}$, if inhalation occurs from industrial air from age 20–60. For the same inhalation exposure scenario, exposure to $5.1 \mu\text{g m}^{-3}$ cadmium oxide (ICRP absorption class S) will give rise to a kidney cortex mass fraction of $84 \mu\text{g g}^{-1}$. According to Amzal *et al.*, 2009 [66], the average oral cadmium intake corresponding to a urinary cadmium/creatinine ratio of 2 nmol mmol^{-1} is $1.6 \mu\text{g kg}^{-1}$ body mass, i.e. the same value as obtained by the other model (Diamond *et al.*, 2003) [70]. According to the Amzal *et al.* [66] model estimates, more than 90 percent of a population of non-smoking women, age 50–70 years, would have a urine cadmium below 2 nmol mmol^{-1} creatinine if the dietary intake of cadmium is $0.6 \mu\text{g kg}^{-1}$ per day.

Data from healthy subjects with known kidney cadmium levels have been reported by Akerstrom *et al.*, 2013 [56]. Their reported relationships between kidney cadmium and urine cadmium are described in Section 6.1.2. The data published by Akerstrom *et al.*, 2013 [56] has been used in quantitative modeling by Fransson *et al.*, 2014 [41]. Some results of these modeling calculations have been reported in Sections 5.1.2 and 5.3.

A problem in mathematical modeling is that existing models do not mechanistically simulate dose-dependencies of cadmium clearance that arise from cadmium-induced damage to the kidney, which may occur far below mass fractions of cadmium in the kidney cortex of $(150\text{--}200) \mu\text{g g}^{-1}$. This was the concentration previously believed to be the critical concentration in the kidney cortex in the 10 % most susceptible individuals in a population (the present evaluation like the one by Diamond *et al.*, 2003 [70] estimated $84 \mu\text{g g}^{-1}$ as the lower confidence limit of the 10 percent value for the most susceptible individuals).

6 Biological monitoring

6.1 Biomarkers of exposure

For risk assessment, the exposure causing toxicity is what matters. This exposure produces the toxic dose at the site of action in the target organ. At this dose, referred to as the target dose, the toxicant, cadmium, binds to the receptors that ultimately produce the toxic effect. The target organ that suffers toxicity at the lowest external exposure level is the critical organ and the adverse effect that occurs at the lowest external exposure is the critical effect. This effect is critical because it is crucial for preventive action. According to IUPAC definition [4] “Critical effect: For deterministic effects, the first adverse effect that appears when the threshold (critical) concentration or dose is reached in the critical organ. Adverse effects with no defined threshold concentration are regarded as critical”.

It is often difficult to estimate the target dose in the critical organ and the average concentration or mass fraction in the critical organ is used as an approximation. However, in many instances, these values are also difficult to determine and thus external or internal doses (e.g. absorbed dose) are used as surrogates. Cadmium content in blood or urine is a measure of internal dose, but each relates differently to the accumulation of cadmium in the kidney and the dose at the site of action in this organ. The relationship may be complex because blood concentrations mostly reflect short-term exposure, rather than effect. Hence, the use of such data is reviewed critically in this section. Important reference values are also included, i.e. values for people in the general population who have not been subjected to excessive exposure.

Modelling the uptake of cadmium in food and uptake *via* the lung and the subsequent accumulation in the kidney is discussed in Section 5.4.

6.1.1 Cadmium in blood

Cadmium in blood occurs mainly in the blood cells. Although the binding of cadmium in plasma has been studied in animals by the use of radioactive isotopes [1], most of the chemical analyses that have been available up to the present have not been sensitive enough to permit an accurate measurement of the low levels occurring in human plasma. All studies referred to in the following text relate to levels of cadmium in whole blood.

Blood reference mass concentrations (also called “normal” values) in nonsmokers are below $1 \mu\text{g L}^{-1}$ in most countries, whereas considerably higher values, up to $7.6 \mu\text{g L}^{-1}$, have been found in heavy smokers with the same intake from food [72–74]. There are great discrepancies in early published data on reference values of cadmium in blood and quality control was not always adequate. The data for most countries taken from recent studies where there was appropriate quality control agree with the values presented in earlier studies with adequate control [22, 29, 31, 58, 75]. Reference values for cadmium in blood of nonsmokers in the general population in Japan in the 1990s were higher than for other countries, *i.e.* approximately $2 \mu\text{g L}^{-1}$ [35].

Although the relationship to age is less prominent for blood-cadmium than for urine-cadmium, somewhat higher levels of cadmium in blood are generally found among older persons. In Sweden, nonsmoking men and women with a mean age of 87 years [76] had cadmium concentrations in their blood of 3.9 nmol L^{-1} ($0.43 \mu\text{g L}^{-1}$). Previous smokers and current smokers had concentrations of 4.4 nmol L^{-1} ($0.49 \mu\text{g L}^{-1}$) and 7.5 nmol L^{-1} ($0.83 \mu\text{g L}^{-1}$), respectively. In a study [77] of women aged 50–59 years in Sweden, nonsmokers had a mean blood-cadmium value of $0.30 \mu\text{g L}^{-1}$. In the United States, geometric mean blood cadmium in 2011–2012 was $0.34 \mu\text{g L}^{-1}$ (3.0 nmol L^{-1}) in adults [78]. Pawlas *et al.*, 2013 [31] studied women from six European countries, mainly from urban areas, and found geometric mean blood cadmium mass concentrations of 0.25 – $0.65 \mu\text{g L}^{-1}$, while in the same report three other areas showed 0.39 (Fez Morocco), 0.61 (Camilo Ponce Enriques, Ecuador) and $0.99 \mu\text{g L}^{-1}$ (Guiyang, China). Among 11-year-old children in Sweden, lower values have been reported with a geometric mean of 0.8 nmol L^{-1} ($0.09 \mu\text{g L}^{-1}$) [79]. Somewhat higher values have been reported in other countries. Children 7–8 years of age, living near a nonferrous metal smelter in Poland, had median values of cadmium in their blood of $0.5 \mu\text{g L}^{-1}$, with a range of 0.3 – $0.8 \mu\text{g L}^{-1}$, and pregnant women had a value of $0.7 \mu\text{g L}^{-1}$, with a range of 0.4 – $1.3 \mu\text{g L}^{-1}$ [80]. Among 8–9-year-old children living in an industrialized area of Poland, the median blood cadmium concentration was 4 nmol L^{-1} ($0.45 \mu\text{g L}^{-1}$), with a range of 2 – 22 nmol L^{-1} [81]. More recent studies have reported somewhat lower values: children, 7–14 years, from urban areas in six European countries including Poland, showed geometric means of 0.11 – $0.17 \mu\text{g L}^{-1}$, while corresponding values in Morocco were 0.21 and in Ecuador $0.26 \mu\text{g L}^{-1}$ [29].

Blood cadmium can be used as an indicator of exposure level. A study of blood cadmium in newly hired workers in a cadmium-battery factory [67] showed that, during the first months of exposure [cadmium in air $50 \mu\text{g m}^{-3}$], the blood cadmium increased to levels many times higher than the initial level. Similar findings were reported by Lauwerys *et al.*, 1979 [82], where the half-life for the increase in blood cadmium was approximately 2.5 months. Workers who were no longer exposed to cadmium displayed a biphasic reduction in their levels of blood cadmium. The half-life in the fast component was approximately 100 days on average, while in the slow component it was 7–16 years [57]. Most blood cadmium is found in blood cells (see above). The “fast” component may, therefore, reflect the turnover of cells in the blood, which is slow compared with the sudden changes in daily exposure that may occur. The slow component reflects the exchange of cadmium in blood with that in tissue stores.

The differences in average blood cadmium between smokers and nonsmokers [58] and in the data cited above, reflect differences in daily cadmium exposure, but, because of the effect of the slow component in blood, may also be interpreted as reflecting differences in cadmium body burden in long-term exposures.

Cadmium concentration in blood is a useful indicator of the degree of exposure in recent months. After long-term cadmium exposure, an increasing proportion of blood cadmium will be related to the body burden, and blood cadmium is a good indicator of internal dose and accumulation in the kidney and other soft tissues in long-term orally exposed population groups [83]. An even better indicator of body burden would be the cumulative exposure calculated from repeated blood samples or time-integrated blood cadmium. The decrease in blood cadmium is much more rapid than the decrease in body burden after a major decrease in exposure [61, 84]. These considerations are in accordance with the general understanding of cadmium kinetics and the toxicokinetic multicompartment model for cadmium (see Section 5.4). Because of the “fast” compartment of blood cadmium [57], high blood cadmium values may be found in high exposure situations before critical levels are reached in the kidneys or in bone. Whereas these disadvantages with blood cadmium should be kept in mind, there are also advantages over urine cadmium when dose-response relationships are examined, because blood cadmium is not subject to confounding by diuresis and co-excretion of proteins (see Section 6.1.2). Effects related to influence on the vascular system may be more directly related to blood cadmium than to urine cadmium. The level of blood cadmium is used for occupational biomonitoring in some countries. As mentioned, it is better than urine cadmium as a biomarker of current exposure.

6.1.2 Cadmium in urine

It is well established that in cadmium-exposed populations, urinary cadmium is a reliable biomarker of the accumulation of the metal in the kidney cortex. Studies of industrial workers in the 1970s and 80s showed a curvilinear relationship between urinary cadmium and cadmium concentration in the renal cortex [1] (see also below). This relationship holds as long as the proximal tubular function is not impaired. Dysfunction of the proximal tubule caused by excessive cadmium accumulation or other insult may abolish or even invert the relationship between urinary and kidney cadmium. The failure of the proximal tubule to reabsorb cadmium (mainly transported by metallothionein, MT) from the glomerular filtrate results in increased urinary excretion and thereby decreased renal accumulation of the metal. For a satisfactory measurement using creatinine as reference, it is also important that urinary cadmium be determined in urine samples that are not too diluted or concentrated *i.e.* measurements are conducted on samples in which urinary creatinine concentrations are between 3 mmol L⁻¹ and 30 mmol L⁻¹ [85]. The quality of chemical cadmium analysis should always be verified (see Section 3).

At low values of urinary cadmium, its usefulness as a biomarker of kidney accumulation is influenced by several factors unrelated to the cadmium body burden, including diuresis, albuminuria, LMM proteinuria, and sampling conditions.

One of the most important factors affecting urinary cadmium is diuresis. The concentration of Cd in urine shows a strong positive correlation with the concentration of creatinine in urine, which makes it necessary to adjust for the hydration status via either creatinine or relative density (specific gravity). Creatinine adjustment of urinary cadmium is, however, not perfect. Recent studies have shown that there is a strong negative correlation between creatinine-adjusted urinary cadmium and urinary creatinine [86–89]. This means that dividing the concentration of urinary cadmium by that of creatinine, as systematically done in most studies, decreases the influence of diuresis and changes the direction of the relationship. Various methods can be used to ensure a complete elimination of the influence by urinary flow. When urinary cadmium is expressed per g of creatinine, the residual association with urinary creatinine can be eliminated by further adjusting the ratio of urinary cadmium to creatinine on the basis of the regression coefficient between the two variables. The method recommended by Barr *et al.* [89] is similar: urinary cadmium is expressed per liter and adjusted with creatinine on the basis of the regression coefficient between the two analytes. For multiple regression analyses of population groups, a model can be included in which associations are made independent of the effects of urine flow.

Another determinant of urine cadmium is the co-excretion of cadmium with proteins and especially with LMM proteins. Cadmium is excreted in urine as a complex with MT, a LMM protein that follows the

same glomerular filtration-tubular reabsorption pathway as other LMM proteins. Akerstrom *et al.*, 2013 [60] studied 30 non-smoking men and women in Sweden with only background exposure to cadmium (mean urine cadmium $0.11 \text{ nmol mmol}^{-1}$ creatinine, range $0.01\text{--}0.52 \text{ nmol mmol}^{-1}$ creatinine). Repeated urine sampling was performed, with the recording of urine flow taken on two separate days. Within each individual's samples, statistically significant associations were demonstrated between creatinine adjusted urine cadmium and urine albumin [or urine alpha-1-microglobulin]. Similar associations were found with urine cadmium adjusted for relative density. These associations are not a result of cadmium toxicity, but reflect intra-individual variability in the renal handling of proteins, including MT, the main transport protein for cadmium in plasma. This co-excretion phenomenon between cadmium and protein is an important source of confounding in epidemiology, as it may generate associations mimicking those induced by cadmium toxicity. Some of the associations between low urine-cadmium and urine LMM proteins in adult general populations are a result of such confounding (see Section 7.3). Relationships found in children [90] may also be a result of similar confounding.

Urinary cadmium varies also with the sampling protocol. Based on their detailed studies of urine cadmium, Akerstrom *et al.*, 2014 [86] found a considerable diurnal variation, with 50 percent higher excretion in the morning (at 9:30 hrs) than in the afternoon (at 17:30 hrs). When considering results of different studies, it is important that the urine sampling is done at the same time of day. Another factor, sometimes overlooked, is that urinary cadmium expressed per liter or mmol of creatinine levels off or even declines after the age of 60–70. This decline may reflect an age-related decrease in kidney function (glomerular filtration rate) in combination with a decrease of the cadmium body burden, dietary intake, and/or intestinal absorption of the metal. Caution should be exercised when using urinary cadmium for assessing the lifetime exposure to cadmium in populations aged more than 60–70 years.

Various factors may influence the relationship between cadmium in kidney cortex and in urine. Direct measurements in living kidney donors [60], however, indicate a reasonable relationship on group basis. A cadmium mass fraction of $25 \mu\text{g g}^{-1}$ in kidney cortex corresponds to a urinary cadmium/creatinine ratio of $0.42 \text{ nmol mmol}^{-1}$ and $8 \mu\text{g g}^{-1}$ in cortex to $0.26 \text{ nmol mmol}^{-1}$ creatinine (see further discussion below). It seems that the quotient of cadmium in the kidney and in urine is not constant, but varies with exposure level. The explanation for this variable quotient of urine cadmium and kidney cadmium might be that the study did not distinguish the influence of body cadmium on urine cadmium from that of the recent exposure to the metal, as 60 % of the studied population was a mix of current and ex-smokers. This study was conducted in healthy subjects, with well-preserved renal function and, therefore, cannot be extrapolated to the general population at large. There is a need for more data with accurate information based on actual observations on kidney cortex cadmium in relation to urine cadmium following low-level exposures in a variety of populations and age groups.

The following discussion will use creatinine-adjusted values, in spite of the bias identified above. The implications of diuresis will be considered, particularly in low-level exposures. In urine, reference values (sometimes called “normal” values) vary with age, area, and smoking habits, but they are generally $<1 \text{ nmol mmol}^{-1}$ creatinine (or $1 \mu\text{g L}^{-1}$ adjusted to specific gravity 1.024), although values of $1\text{--}4 \text{ nmol mmol}^{-1}$ creatinine have been reported from some non-polluted areas in Japan [22, 35, 91–93]. In Sweden average excretion is less than $0.1 \mu\text{g day}^{-1}$ in children and almost $0.5 \mu\text{g day}^{-1}$ in elderly adults [94]. The difference between children and adults is less pronounced if expressed in $\mu\text{g L}^{-1}$. In Belgium, mean urinary cadmium mass concentrations in children and adolescents were $0.23\text{--}0.27 \mu\text{g L}^{-1}$; in adult never smokers $0.56 \mu\text{g L}^{-1}$ and in elderly never smokers $0.94 \mu\text{g L}^{-1}$ [87]. Similar values have been reported in other studies [88, 95]. In the U.S., geometric mean urinary cadmium, measured in 2011–2012, was approximately $0.08 \text{ nmol mmol}^{-1}$ creatinine in children and adolescents (6–19 years) and $0.22 \text{ nmol mmol}^{-1}$ creatinine in adults [78]. Geometric means for non-smoking adults were 0.13 for ages 20–49 years and 0.24 for age 50 years and older; the corresponding values for smokers were 0.22 and $0.53 \text{ nmol mmol}^{-1}$ creatinine. Urinary cadmium in adult non-smoking females was higher than that of males.

The role of different factors explaining relationships between gastro-intestinal absorption, body burden, and urinary cadmium in various age groups needs further clarification. The cadmium content in urine is

usually related to recent exposure only to a limited extent (see Section 5.3). However, recent exposure may still be an influencing factor at low exposures, particularly in children who have not yet accumulated a large body burden of cadmium, and this may distort the relationship between urinary cadmium and kidney burden [90, 96]. Urinary excretion increases after renal damage has occurred (see above). Cadmium in urine is bound to MT and measurements of urinary MT reflect body burden and kidney accumulation of cadmium [97–99]. Among people who have not been subject to occupational exposure [94], there is no direct relationship between the average age-related changes in daily cadmium intake (as indicated by fecal cadmium elimination) and daily urinary excretion, but there is a continuous increase in urinary cadmium with age, at least when excretion per 24 hours is considered (see above). Animal experiments (see Section 5.3) support the view that, during the early phase of exposure, before renal tubular impairment has occurred, a correlation exists on a group basis between the body burden and the urinary excretion of cadmium. This relationship is dose dependent, with a higher proportion of the body burden being excreted at lower doses.

Comparisons of group-average urinary cadmium excretion in humans of various ages with group-average tissue amounts [100] indicate good agreement between the levels of urinary and kidney cadmium, fair agreement between the levels of urinary and liver or whole-body cadmium, and no agreement between the level of urinary cadmium and daily cadmium intake. These observations have been confirmed in many more recent epidemiological studies; urinary cadmium is widely accepted as an indicator of body burden and kidney accumulation of cadmium [58, 83, 101, 102], but at low oral doses, the influence of diuresis and co-excretion of proteins (see above) must be taken into account.

The relationship between cadmium in the kidney cortex and higher values of cadmium in the urine was studied [103] in industrial workers. Among workers with no tubular dysfunction, a kidney cortex cadmium mass fraction of 200 mg kg^{-1} corresponds to approximately $10 \text{ nmol mmol}^{-1}$ creatinine of cadmium in urine. Observations in humans *in vivo* at lower concentrations of cadmium in kidney cortex have previously not been available. Estimates [104], based on autopsy samples of both kidney tissue and urine, are uncertain because of post-mortem increases in urinary cadmium. Akerstrom *et al.*, 2013 [56] studied living humans, thus providing better data from biopsies of human kidney cortex and related urine samples. These data implied a slope, 0.014, and intercept, 0.071, for the relationship between urinary cadmium and kidney cortex cadmium. This predicts urinary cadmium of $0.18 \text{ nmol mmol}^{-1}$ creatinine at a mass fraction of $8 \mu\text{g g}^{-1}$ in the kidney cortex. The linear model predicts a variable quotient between urinary cadmium and kidney cortex cadmium at low kidney levels (e.g. 8 vs $25 \mu\text{g g}^{-1}$ kidney cortex) because of a positive intercept in the linear regression model. The positive intercept suggests that some urinary cadmium is not associated with kidney cortex cadmium, supporting the notion of a direct pathway from blood plasma to urine in addition to the one from kidney tissue to urine. The blood-urine pathway contributes, in relative terms, more to urinary cadmium at low kidney cadmium burdens than at high kidney cadmium ones. This observation is similar to observations in animals (see Section 5.3) and has implications for estimating the kidney cadmium elimination half-life. If the half-life is based on the slope of a regression model relating urinary cadmium to kidney cadmium (e.g. the change in urinary cadmium per unit change in kidney cadmium), then the resulting half-life will vary with the extent to which blood and kidney contribute to the observed urinary cadmium. Akerstrom *et al.*, (2013) [56] found that the relationship between urinary cadmium and kidney cadmium was curvilinear, with the slope decreasing with increasing kidney cadmium. This would be expected if the contribution of kidney cadmium to urine increased with increasing kidney cadmium and if the transfer from kidney to urine was slower than the transfer from blood to urine.

6.1.3 Cadmium in placenta, cord blood and other media

Cadmium accumulates in the human placenta and placental samples can be used as an indicator of cadmium exposure during pregnancy. Miller *et al.*, 1988 [105] reviewed the data available for the levels of cadmium in human placenta. Mean levels in various countries ranged from 8 to 176 ng g^{-1} wet weight, with higher values observed in smokers than in nonsmokers. Lagerkvist *et al.*, 1996 [106] found 2.6 , 3.6 , and 5.0 ng g^{-1} wet mass

in Swedish nonsmokers, ex-smokers, and smokers, respectively. Placental values were four times higher than those in the maternal blood. Moberg-Wing *et al.*, 1992 [107] reported values of 20 and 36 ng g⁻¹ dry mass in placenta samples of nonsmokers and smokers, respectively. Ronco *et al.*, 2005 [108] reported 20 and 60 ng g⁻¹ dry mass in nonsmokers and smokers, respectively, in Chile. Kippler *et al.*, 2010 [109] found 0.16 µg L⁻¹ in umbilical cord blood and 110 µg kg⁻¹ dry mass and 20 µg kg⁻¹ (20 ng g⁻¹) wet mass in placenta in tissues from a metal-contaminated area in Bangladesh. The values just cited are all from non-occupationally exposed populations. In a study of female smelter workers in the UK, Berlin *et al.*, 1992 [110] found 21 ng g⁻¹ wet mass in placental samples.

Kile *et al.*, 2009 [111] reported 0.04 µg dL⁻¹ (0.4 µg L⁻¹) in umbilical cord blood from Bangladesh and 0.6–1 µg L⁻¹ in such blood from Taiwan (samples taken 1991). These values are higher than those reported by Kippler *et al.*, 2010 [109] (see above) and may involve increases due to sampling and/or analysis. There is a need for further well-performed studies using adequate methods of sampling and chemical analysis.

For people exposed to cadmium almost exclusively from food, the average daily cadmium content in feces is a good indicator of the daily intake, because the major part of the ingested cadmium passes through the gastrointestinal tract unabsorbed and reaches the feces. Fecal excretion is the pooled biliary excretion and excretion from the mucosa of the gastrointestinal tract. It constitutes only a small fraction of fecal content of cadmium, particularly among young persons. Fecal excretion from the body is only a small fraction of the daily intake (see also Section 5.1.2 and 5.3).

Fecal cadmium has been used in several studies to estimate the average daily intake from food in cadmium-polluted areas and in populations exposed to background levels of cadmium [58].

Cadmium in hair may be used as an indicator of exposure and of the internal dose following oral cadmium-exposure [112]. Because cadmium levels in hair are low, there is a risk of confounding by external contamination. This is especially important in occupational exposures. Thus, cadmium in hair has not often been used for biological monitoring.

6.1.4 Cadmium in kidney and liver, measured *in vivo*, body burden

Newborn babies are almost free from cadmium; the total body burden is only approximately 1 µg [113]. A person who is 50 years of age in the United States, Sweden, or Germany will have a total body burden of cadmium between 10 and 30 mg. These values correspond to mass fractions in the liver of approximately (1–3) mg kg⁻¹ and in the kidney cortex of (15–50) mg kg⁻¹ (corresponding to approximately (12–40) mg kg⁻¹ calculated for a whole kidney). Higher values are found among smokers than among nonsmokers. Values in Japan are usually higher than in other countries. Present-day values are somewhat lower than those measured 1970–1980, because daily intake of cadmium has decreased in Japan during the past two-three decades as a result of decreased rice consumption.

In vivo NAA or *in vivo* X-ray fluorescence measurements of liver and kidney cadmium have made it possible to calculate the correlation between the concentrations of cadmium in the indicator media and in the critical organ, the kidney cortex. Roels *et al.* [103] found no increase in the blood cadmium with increased body burden. The generally high blood values of cadmium (5–30 µg L⁻¹) among the workers studied reflected their high daily exposures. However, in workers not exhibiting renal damage, urinary cadmium correlated with the body burden. Tohyama *et al.* [97] and Ellis *et al.* [114] calculated the relationship between the cadmium concentrations in the kidney or liver measured with *in vivo* NAA and the prevalence of renal tubular dysfunction. Other studies have not succeeded in establishing these relationships because of the lower levels measured and the related larger proportion of values falling below the detection limit [58].

6.1.5 Biomarkers of exposure – summary

Cadmium in whole blood is used extensively as a biomarker of current exposure. It also reflects long-term exposures, but is subject to changes depending on recent exposure, because a considerable component of

blood cadmium, even in long-term exposures, is dependent on a body compartment with relatively short turnover (half-life 100 days).

Cadmium in urine is the most extensively studied biomarker of cumulative exposure kidney- and body-burden of cadmium. Cadmium in urine is often adjusted by creatinine concentration in order to compensate for variations in each individual's fluid intake. Such adjustment is, however, not perfect, since it leaves a residual dependence on urine flow. This dependence on urine flow can lead to confounding with false positive associations between urine cadmium/creatinine and the concentration in urine of proteins such as beta-2-microglobulin and retinol binding protein. Such confounding is more likely to be a problem at low urinary cadmium concentrations or ratios to creatinine ($0.1\text{--}1\text{ nmol mmol}^{-1}$ creatinine) than at higher values, because at higher exposures ($2\text{--}4\text{ nmol mmol}^{-1}$ creatinine and higher) cadmium-induced levels of low molecular mass (LMM) proteins occur and the relative importance of urine flow is less prominent. Despite the uncertainties, the present review uses urine cadmium, adjusted for creatinine as an indicator of cadmium accumulation in kidney cortex. Usually, cadmium in urine is related to the mass fraction of cadmium in the kidney cortex, but the quotient between kidney cortex and urine cadmium varies somewhat, and is not the same at all exposure levels. At exposure levels lower than those leading to renal tubular dysfunction, only a small proportion of urine cadmium is related to recent exposure, and urine cadmium is usually related to the concentration of cadmium in the kidney cortex. However, in young children, who have not yet accumulated a substantial amount of cadmium in the kidney cortex, recent exposure may influence urine cadmium to a larger extent than in older people. Although substantial experience exists for the use of urine cadmium as an indicator of cadmium in kidney cortex or body burden, there are still some uncertainties concerning its interpretation, particularly in the low range ($0.1\text{--}1\text{ nmol mmol}^{-1}$ creatinine).

6.2 Biomarkers of effects

Kidney effects of cadmium are well established as critical effects and biomarkers of such effects are available. For glomerular kidney effects, useful biomarkers are glomerular filtration rate (GFR) and albumin in urine. For tubular kidney effects, crude indicators are glucosuria and aminoaciduria. Indicators that are more sensitive are the urinary excretion of retinol-binding protein (RBP), B2M, ProteinHC (α_1 -microglobulin), *N*-acetyl- β -D-glucosaminidase (NAG) and its isoenzymes A and B, as well as CC16. Each protein indicates quite specifically where in the tubule the effect occurs.

Metallothionein (MT) can also serve as a biomarker of the effect. When the critical concentration (or mass fraction) of cadmium is exceeded in the kidney cortex, increased amounts of urinary MT are excreted [99]. Section 7.3 describes the dose-response relationships for these effect biomarkers.

As a biomarker of bone effects, *i.e.* in terms of osteomalacia and osteoporosis, bone mineral density (BoneMD) is usually measured; serum calcium, phosphorus, and serum alkaline phosphatase measurements are also classical indicators of osteomalacia (*cf.* Section 7.4). Urinary deoxypyrimidinoline is a biomarker of bone resorption.

7 Toxicodynamics and overall TKTD relationships: effects and dose-response relationships

7.1 Smoking as a potential confounder in studies of cadmium exposure and adverse health effects

Tobacco smoking may interact with cadmium toxicity in several different ways. These aspects will be discussed together here.

Tobacco leaves contain cadmium, which will be vaporized during smoking, and, after condensation, cause inhalation of small-size particles. Thus, active smoking is a major source of cadmium exposure (see Section 4.1) and causes increased values in blood and urine. Exposure to environmental tobacco smoke will also cause exposure, though not sufficiently high to significantly affect blood-cadmium values [115].

In addition to cadmium, tobacco smoke contains several other toxic agents, such as polycyclic hydrocarbons, nitrosamines, carbon monoxide, and lead, which are known to cause, *inter alia*, cancer, as well as cardiovascular, renal, and bone disease. Hence, any study of associations between those effects and cadmium biomarkers must consider confounding by smoking, either by studying non-smokers only, or by adjustment for smoking habits in the statistical model. If never-smokers are not separately analyzed, there may be a problem caused by the long-term retention in the body of cadmium among previous smokers. However, if all or some of the smoking-associated effect is due to the cadmium content in the smoke, adjustment for smoking will result in an over-adjustment, which will underestimate the effect caused by cadmium. Thus, the truth probably lies somewhere between the risks in unadjusted and adjusted models.

One further aspect is the fact that the toxicity of smoking-derived cadmium absorbed mainly in the lungs into the pulmonary and main blood circulation may not be equivalent to cadmium ingested through food and drinking water and absorbed through the intestinal wall into the portal blood circulation. Cadmium passes through the liver and may be retained or bound to metallothionein immediately after intestinal, but not pulmonary, absorption. This may affect the toxicity. The influence of varying absorption routes on cadmium toxicity has not yet been fully investigated.

7.2 Respiratory tract

Cadmium compounds cause adverse effects on the respiratory tract through direct action on tissues following deposition of inhaled aerosol. Aerosol characteristics favoring high absorption were summarized in Section 5.1 “Absorption and uptake”. Cadmium in the form of nanoparticles behaves partly differently from cadmium in larger particles and may need special consideration. This is still under investigation (Iavicoli *et al.*, 2016 [38]).

Acute poisoning has occasionally occurred in the past, mainly as a result of inhalation of cadmium-containing dust, fumes from smelting or from welding cadmium-containing materials, or fumes from soldering with silver-cadmium solder. The first reported cases were observed by Sovet 1858 [116] after the use of a cadmium-containing powder as silver polish. In severe cases, there is a progression to pulmonary edema and chemical pneumonitis, sometimes culminating in death. The minimum exposure causing clinical symptoms after short-term exposure (one day) has been estimated to be 1 mg m^{-3} (8-hour time weighted average [TWA]) [117]. Long-term, *i.e.* years, of exposure by inhalation may give rise to respiratory disorders including emphysema, chronic inflammation of the nose, pharynx, and larynx, as well as olfactory disturbances. In the lower airways, chronic obstructive lung disease of varying severity is found. In reports subsequent to that of Friberg 1950 [118], impaired pulmonary function was also noted in cadmium workers [119–121]. It was considered by Elinder 1986 [117] that long term (several years) inhalation of workroom air, *i.e.* 8 hours per day, 5 days per week, of $20 \text{ } \mu\text{g m}^{-3}$ of respirable particulate cadmium was the lowest exposure giving rise to lung effects. The Scientific Committee on Occupational Exposure Limits (SCOEL) of the EU derived a LOAEL corresponding to a cumulative exposure to cadmium by inhalation of workroom air (respiratory size particles) of $500 \text{ } \mu\text{g year m}^{-3}$, corresponding to a value of cadmium in urine of 3 nmol mmol^{-1} creatinine [122]. The committee based this value on the observations of respiratory effects (with changes in residual lung volume) in cadmium-exposed workers by Cortona *et al.* [122, 123]. None of the more recent studies has documented effects of cadmium at lower exposures that can be considered caused by cadmium and not by smoking. In a cohort of cadmium workers in England (see Section 7.5.2), chronic disease of the respiratory system was increased significantly, in relation to the amount of cumulative exposure to cadmium [124]. In a survey of 16 024 subjects selected from the general American population, a negative correlation was identified between pulmonary function and urinary cadmium levels, and cadmium exposure was implicated in the

exacerbation of pulmonary disorders associated with cigarette smoking [125]. Similar results were reported in another study of US men [126]. Untangling the cadmium-related effects from other toxic effects of cigarette smoke is, however, difficult.

7.3 Kidneys

7.3.1 Renal tubular dysfunction

Long-term exposure to cadmium for decades in occupational and general environments leads to substantial accumulation of cadmium in the kidney cortex, particularly in the proximal renal tubular cells. This renal cortical accumulation gives rise to renal tubular dysfunction. There is substantial evidence both from humans and from experimental animals demonstrating such relationships [1]. The mass fraction of cadmium in kidney cortex giving rise to toxic effects and low molecular mass proteinuria varies among individuals in a population and has been estimated at (80–200) mg kg⁻¹ (0.71–1.78 mmol kg⁻¹) in kidney cortex (wet mass). Toxicokinetic (TK) calculations of the exposures required to reach such tissue mass fractions have previously been used in risk assessment of cadmium exposures in working environments, as well as in general environments, for example by IPCS, 1992 [6] (see also Nordberg *et al.*, 2015 [1]). The toxic action of cadmium in kidney cortex cells is counteracted by binding to metallothionein (MT) and each person's susceptibility to the development of renal tubular dysfunction is dependent on his or her ability to synthesize MT. Persons with less efficient synthesis of MT more readily develop renal tubular dysfunction from cadmium exposure (Nordberg *et al.*, 2012 [84]). Diamond *et al.*, 2003 [70] estimated, based on a toxicokinetic and toxicodynamic (TK/TD) model, that in the US population, a cadmium mass fraction of 84 µg g⁻¹ wet weight in the kidney cortex corresponds to the lower confidence limit for the lower 10 percent (*i.e.* the most sensitive part) of the population. This value is higher than the 95 % upper value of cadmium in kidney cortex in the US population from background dietary exposures calculated by Choudhury *et al.*, 2001 [40] (see also Section 5.4). Diamond *et al.*, 2003 [70] concluded that cadmium-related risks from dietary cadmium in the US would be negligible in the absence of other exposures.

In Section 5.4, the mass fraction of cadmium in urine corresponding to 84 µg g⁻¹ in kidney cortex was estimated to be 1.4 nmol mmol⁻¹ creatinine and the corresponding dietary cadmium intake 1 mg kg⁻¹ body mass per day. Long-term exposure to cadmium giving rise to cadmium levels in urine >2 nmol mmol⁻¹ creatinine is related to deficiencies in renal tubular reabsorptive function that gradually increase at higher cadmium exposures (see later). Such renal tubular dysfunction is a feature of Itai-itai disease, a disease with bone symptoms and fractures that occurred in a cadmium-polluted area in Japan (see Section 7.4).

The relationship between cadmium exposure and renal tubular dysfunction has been shown in epidemiological studies measuring increased urinary excretion of marker low molecular mass (LMM) proteins, such as β2-microglobulin (B2M), α1-microglobulin (A1M), and retinol-binding protein (RBP), as well as the enzyme NAG (*N*-acetyl-β-D-glucosaminidase) [1, 2, 127, 128]. The use of LMM proteins as markers of adverse effect is supported by long-term follow-up surveys in Japan, where populations with cadmium-induced tubular dysfunction had increased mortality in renal, cardiovascular, and cerebrovascular disorders when B2M exceeded the reference interval of 0.3 mg g⁻¹ creatinine [129]. This upper reference limit is applicable to most populations in Asia and Western countries. In some areas in Asia, higher upper reference limits have been observed in population groups with low background exposures to cadmium, but additional cadmium exposure gave rise to further increases in B2M [28]. There are also certain diseases (*e.g.* systemic lupus erythematosus and hematopoietic malignancies like chronic lymphatic leukemia) with elevated levels of B2M in serum and urine. Therefore, the clinical evaluation of persons with increased urinary B2M should ideally include the determination of serum B2M in order to exclude the possibility that the increase is caused by these diseases. In epidemiological studies of cadmium-exposed populations, B2M in serum has usually not been measured. The error introduced by not identifying persons with these diseases is small, because they are not common. Another disadvantage with B2M as an indicator of renal tubular dysfunction is that the

protein is degraded in urine with a low pH. This problem can be avoided by giving bicarbonate to the persons giving urine samples, but such procedures have not been used in all studies. Other biomarkers, such as RBP or NAG, are not sensitive to low pH and may therefore be preferred. Increased urinary excretion of LMM proteins also occurs in lead exposure [130] and, transiently, following excessive alcohol consumption.

The European Food Safety Authority [EFSA] summarized the available data on urinary-cadmium and urinary excretion of B2M in a meta-analysis, and used the resulting dose-response estimation [2] for their risk assessment. Later, the same database was used by a joint committee of the UN's Food and Agriculture Organization (FAO) and the WHO, the Joint Expert Committee on Food Additives and Contaminants (JECFA) [26]. The modeled relationships between urinary cadmium and urinary B2M excretion, as calculated by the two organizations, are shown in Fig. 1. Both organizations used urine cadmium in the range 4–5 μg cadmium g^{-1} creatinine (4–5 nmol mmol^{-1} creatinine) as the point when an increase in urinary B2M was considered to occur, but arrived at different tolerable intakes (see Section 9).

A weakness of the meta-analysis and the modeled relationship displayed in Fig. 1 is the fact that several studies of high quality were excluded from the meta-analysis. The reason for exclusion was either that they used 24-hour urine sampling (instead of expressing the excretion per gram of creatinine in spot samples), or because they did not use urinary-B2M at all, owing to its susceptibility to breakdown at low urinary pH. The present group of scientists consider it reasonable to take into account also these high-quality studies not included in the EFSA 2009 [2] meta-analysis, showing risks of LMM-proteinuria at lower urine-cadmium than 4 nmol mmol^{-1} creatinine.

Several studies have reported positive associations between urinary cadmium and excretion of β 2-microglobulin (B2M) [131–134] and other LMM proteins [77, 135–138] at cadmium in urine below 4 μg g^{-1} creatinine.

The CadmiBel studies in Belgian cadmium-polluted areas [136] found statistically significant associations between urinary cadmium and the levels of RBP, NAG, B2M, amino acids, and calcium in urine at urinary cadmium excretion 2–4 μg day^{-1} , corresponding to slightly lower numbers in terms of μg g^{-1} creatinine (nmol mmol^{-1} creatinine). Bernard *et al.*, 1994 [135] reported increased urinary excretion of the LMM protein CC16 in women at even lower urinary cadmium. Jin *et al.*, 2004 [134], studying areas in China, found a highly significant dose-response relationship between urine cadmium from <2 to >20 nmol mmol^{-1} creatinine and a prevalence of increased (above the upper reference value in the control group) NAG, B2M, Albumin and RBP. Some studies in Sweden [60, 77] found statistically significant associations between urinary LMM proteins and urinary cadmium even at cadmium/creatinine ratios as low as <1 μg g^{-1} creatinine. One study also

Fig. 1: Relationship between urinary cadmium and beta-2 microglobulin in urine in a number of studies compiled by JECFA 2011 [26] and by EFSA 2009 [2].

reported an association between LMM proteinuria and blood cadmium $<1 \mu\text{g L}^{-1}$ (Akesson *et al.*, 2005 [77]). Several studies in Japan have examined relationships between cadmium exposure and urinary excretion of LMM proteins. Hayano *et al.*, 1996 [133] studied population groups in the cadmium polluted Kakehashi river basin in Japan and found statistically significant associations between urinary cadmium and B2M. They calculated “permissible values” of urinary cadmium: $1.6\text{--}3.0 \mu\text{g g}^{-1}$ creatinine for men and $2.3\text{--}4.6 \mu\text{g g}^{-1}$ creatinine for women. Several studies have also been performed in population groups in Japanese areas not considered cadmium polluted, but still with urinary cadmium in adults of $1\text{--}4 \mu\text{g g}^{-1}$ creatinine. Suwazono *et al.*, 2010 [139] summarized BMDL-5 values of urinary cadmium for LMM protein effects in Japan as $1.5\text{--}3.2 \text{ nmol mmol}^{-1}$ creatinine, with $0.09\text{--}0.13 \text{ mg cadmium kg}^{-1}$ ($0.8\text{--}1.15 \mu\text{mol kg}^{-1}$) for cadmium concentration in rice and $0.9\text{--}1.4 \text{ g}$ ($8\text{--}12.5 \text{ mmol}$) for lifetime cadmium intake. Studies in China (Jin *et al.*, 2004 [101]) reported BMDL-5 values of urinary cadmium as $3\text{--}4 \text{ nmol mmol}^{-1}$ creatinine for the most sensitive biomarkers of LMM proteinuria.

Whether these associations represent a causal relationship is discussed in depth below (see Section 7.3.4).

7.3.2 Glomerular effects

It is well known that high occupational or environmental exposures to cadmium give rise to decreased GFR and increased serum creatinine. Often there is a combination with tubular dysfunction, but isolated glomerular dysfunction also occurs (Jarup *et al.*, 1998 [58]; Nordberg *et al.*, 2015 [1]).

Associations have been reported between low-level cadmium exposure and indicators of glomerular function in cross-sectional analyses. Estimated glomerular filtration rate (eGFR) based on serum cystatin C or serum creatinine was studied in 700 elderly women and found to be statistically significantly lower (approximately 95 mL min^{-1}) at urinary cadmium $0.75\text{--}1.0$ than at urinary cadmium $<0.5 \text{ nmol mmol}^{-1}$ creatinine (approximately 100 mL min^{-1}) [77, 140]. However, eGFR was decreased to a similar extent at blood-cadmium $>1 \mu\text{g L}^{-1}$ compared to $<0.5 \mu\text{g L}^{-1}$ (Akesson *et al.*, 2005 [77]). The associations became non-significant in never-smokers. Navas-Acien *et al.*, 2009 [141] analyzed blood-cadmium data from $>14\,000$ individuals in the USA. These authors found increased odds of low eGFR at $>0.6 \mu\text{g cadmium L}^{-1}$ (median $1 \mu\text{g L}^{-1}$) compared to individuals with $<0.2 \mu\text{g cadmium L}^{-1}$ (odds ratio (OR): 1.32; 95 % confidence interval (CI): 1.04–1.68), but not for the subgroup for whom urine cadmium data were available [142] or among never smokers with blood cadmium $>0.6 \mu\text{g cadmium L}^{-1}$ [141]. Smoking may therefore be involved in the observed relationship. An association between blood cadmium and low eGFR was also found among Korean women, but not Korean men [143, 144].

Because of the limited correlation between estimated glomerular filtration rate (eGFR) and measured GFR in individuals with normal kidney function and the effect of body mass on S-creatinine as well as on S-cystatin C, the studies on eGFR cannot yet be used as evidence of glomerular dysfunction caused by low-level cadmium exposure.

A mild effect on the glomeruli is indicated by moderately increased urinary excretion of albumin. Such an effect has been demonstrated in cadmium-exposed workers and populations [61, 99, 101, 141, 142, 145, 146]. In an environmentally exposed Chinese population, increased urinary albumin was shown to be reversible 8 years after cessation of the consumption of cadmium-contaminated rice, leading to substantially lower dietary exposure (Liang *et al.*, [61]). There was a substantial decrease in blood cadmium during these 8 years, while the decrease in urine cadmium was much more limited. Albuminuria, representing a vascular effect, may be more closely related to blood cadmium than urine cadmium, as suggested by Bernard *et al.*, 1979 [145]. However, changes in LMM protein excretion, indicating tubular dysfunction, were not reversible in the studies in China by Liang *et al.*, 2012 [61].

7.3.3 Renal failure

Studies of population groups with high cadmium exposures in Japan have shown associations between urinary cadmium and mortality from renal diseases [129, 147]. An increased risk of end-stage renal disease

(ESRD) was found in an ecological Swedish study combining occupationally and environmentally exposed subjects residing in areas close to battery plants (Hellstrom *et al.*, 2001 [148]). On the other hand, an ecological study in Japan showed no association between mortality associated with renal failure and cadmium levels in local brown rice [149]. Only one study of prospective design has been published on ESRD in relation to low-level cadmium biomarkers [150]. This case-referent study, performed in northern Sweden, did not find cadmium concentrations in erythrocytes at baseline to be a statistically significant predictor for ESRD later in life after adjustment for potential confounders.

The relevant literature up to 2014 has been comprehensively reviewed by Byber *et al.*, 2016 [151]. They systematically assessed the evidence for an association between cadmium exposure and Chronic Kidney Disease (CKD). Although they found a number of case reports of CKD related to cadmium exposure, they considered that the etiological role of cadmium was questionable in some of these cases. Decreases in GFR related to cadmium had been reported in several early studies but none of these were considered to be conclusive. It is well established that tubular dysfunction is a chronic condition constituting an important facet of Itai-itai disease, but Byber *et al.* [151] considered it questionable to use the term CKD for the tubular defects. Finally, Byber *et al.* [151] concluded that there was no convincing evidence for an increased risk of progression to CKD in populations exposed to cadmium. They noted that there was insufficient information about the methods used in the relevant studies and that other factors affecting the collected data precluded a meta-analysis. Because their review was specifically focused on chronic kidney disease, they did not consider evidence of effects on other organs, *e.g.* the Japanese studies demonstrating increased mortality in several diseases in relation to increased cadmium-induced tubular proteinuria (see Section 7.6.6).

There may well be a need for further evidence to establish an indisputable link between cadmium induced tubular dysfunction, decreased GFR, development of CKD, and end-stage renal disease (ESRD). However, the judgement of the present group of scientists is that the data showing decreased GFR and increased serum creatinine (see Section 7.3.2) following high cadmium exposure provides valid evidence. With increasing cadmium-induced LMM proteinuria, there are increased risks of mortality in renal and cardiovascular diseases according to several studies (sect 7.6.6). There is also evidence that the renal tubular defects cause renal osteomalacia and anemia (sect 7.4; 7.6.1). The present group of scientists considers cadmium induced LMM proteinuria as an adverse effect *i.e.* an effect with negative consequences for health, and it is thus a suitable critical effect for risk assessment. However, because of the variables involved, assessment of the dose-response function for renal failure after cadmium exposure is not possible. Therefore, quantitative assessment of the risk of renal failure is also not possible.

7.3.4 Are associations between low-level urinary cadmium and LMM proteinuria causal?

It has been proposed that the associations observed between very low-level urinary cadmium and increases in urinary protein excretion may not be causal [152], partly because urine cadmium at low levels is an uncertain indicator of cadmium concentrations in the kidney cortex (Bernard 2016 [90], Section 6.1.2). The possible roles of tobacco smoking and renal physiology are discussed below.

Tobacco smoking substantially increases cadmium exposure, and thereby increases both blood and urinary cadmium. If smoking also causes increased protein excretion [153], independently of the cadmium content in smoke, then it is an important confounder that needs to be taken into account by stratification or by adjustments in statistical models. In occupationally exposed workers, a weaker association between LMM proteinuria and urinary cadmium has been observed in never-smokers as compared to smokers [153, 154].

There are physiological mechanisms that could potentially result in an association between excretion of cadmium and LMM protein excretion, without cadmium toxicity being the cause. After filtration through the glomeruli, LMM proteins, albumin (in small amounts), and cadmium-MT compete for reabsorption in the proximal tubules. LMM proteins and cadmium-MT seem to have similar affinity for tubular binding sites [152–155] and normal physiological changes in renal tubular reabsorption function can therefore cause a co-excretion of cadmium and LMM proteins. It should be noted that, compared to the LMM proteins used for

screening cadmium nephrotoxicity, MT occurs in tubular fluid in much lower concentrations and its tubular reabsorption can be competitively inhibited by these LMM proteins, as well as by albumin. Variation in diuresis (urinary flow rate) is an example of such normal renal physiological variability and can result in altered tubular reabsorption of solutes and water [57]. This mechanism could be the reason for the positive associations observed between excretion of cadmium and LMM proteins among healthy teenagers with very low urinary cadmium [142]. Clear positive associations were observed between the excretion rates of cadmium, A1M, and albumin within individuals with very low urinary cadmium ($<1 \text{ nmol mmol}^{-1}$ creatinine) when repeated samples were taken in each individual on the same day [60], irrespective of adjustment for variation in dilution (by creatinine or specific gravity). Moreover, urine flow rate had a clear positive impact on the excretion of cadmium within individuals. Thus, it is possible that normal physiological variability in renal reabsorption of LMM proteins causes an increase in urinary cadmium by inhibiting tubular uptake of MT-bound cadmium; in other words, this is a possible case of reverse causality [155].

The effects of cadmium exposure on renal tubules at high levels of exposure to cadmium (urinary cadmium $>4 \text{ nmol mmol}^{-1}$ creatinine) are well established. At urinary cadmium $>2 \text{ nmol mmol}^{-1}$ creatinine, the present group of authors consider that the effect of diuresis probably does not cause major confounding, but this assumption should be supported by actual studies. However, the associations observed at lower levels of exposure ($<2 \text{ nmol mmol}^{-1}$ creatinine) are likely to have been influenced by such confounding. Other factors should be considered, such as the ability to synthesize metallothionein and the occurrence of metallothionein antibodies [83]. The TK/TD model calculations (see above) indicate that risks of tubular dysfunction would be negligible at dietary intakes of cadmium occurring in the USA (see Section 5.4) and provide no indications that causal epidemiological relationships between urinary or blood cadmium and biomarkers of tubular dysfunction should be expected. Thus, although a toxic effect cannot be entirely ruled out at exposures corresponding to urinary cadmium $<1 \text{ nmol mmol}^{-1}$ creatinine (values that generally occur among non-smokers in many populations worldwide), normal physiology is likely to be an important determinant in the observed associations between LMM protein excretion and urine cadmium at these levels [60, 155]. This makes it difficult to interpret any associations that may be observed at such low exposure levels as causal.

The effects of renal physiology on the exposure biomarker are eliminated when blood cadmium, instead of urinary cadmium, is used in relation to kidney effect markers in urine. Studies using blood cadmium and LMM protein excretion in never-smokers may shed light on this issue, but such studies are demanding as to population size and analytical performance. When using blood cadmium, it should be remembered that a single blood cadmium value is sensitive to variations in exposure, and it is not a good biomarker of body burden (Section 6.1.1). Time integrated cadmium concentration may be preferred, but is not available. One study observed a statistically significant association in never-smokers between blood cadmium (single value for each individual) as a biomarker of cadmium exposure and LMM protein excretion (urinary A1M) occurring within the normal range of urinary A1M [77].

Although long-term cadmium-induced tubular proteinuria (urinary B2M concentration above the reference interval) may be a risk factor for anemia (7.6.1), bone (see Section 7.4), renal and cardiovascular disease and related mortality [129], the public-health impact of cadmium-related increases in biomarkers of tubular dysfunction within the normal range is unknown.

7.3.5 Summary of effects on kidneys

Long-term, high-level cadmium exposures give rise to both glomerular and tubular effects on the kidneys. Severe cadmium induced tubular damage causes renal osteomalacia (see Section 7.4) and renal anemia (see Section 7.6.1). The majority of available studies on kidney effects at relatively low exposures describe relationships between urine cadmium and LMM proteinuria. Conclusions from these studies will be summarized in the following text. There are also studies that describe relationships between blood cadmium and albuminuria (see Section 7.3.2) and LMM proteinuria, including, in one study, at a low blood cadmium concentration

[77]. However, because of the limitations of these observations (see Section 7.3.4), conclusions will not be based on blood cadmium. Unfortunately, data on time-integrated blood cadmium is not available.

For cadmium toxicity, measures of renal tubular dysfunction are the most sensitive markers of an adverse effect on the kidneys, because glomerular effects usually occur at higher doses and mild forms of these effects are reversible. Many studies concerning tubular dysfunction (LMM protein excretion) were included in the meta-analysis by EFSA (2009) [2], but some high-quality studies were excluded. The meta-analysis showed a dose-effect relationship starting from a cadmium mass fraction in urine of approximately $4 \mu\text{g g}^{-1}$ creatinine (4 nmol mmol^{-1} creatinine). Additional high-quality studies in Belgium [135, 136], Sweden [132], Japan [139], and China [134] have shown increases of LMM protein excretion at urinary cadmium of $2\text{--}4 \text{ nmol mmol}^{-1}$ creatinine. Also, at lower values of cadmium in urine ($<2 \text{ nmol mmol}^{-1}$ creatinine), associations have been reported [77], but at such low values confounding by urine flow is likely to explain at least part of the association, because procedures to control for this factor were not included.

In summary, the present group of scientists consider the lowest value of cadmium in urine that is causally related to a low risk of LMM proteinuria to be 2 nmol mmol^{-1} creatinine, *i.e.* this is the lowest observed adverse effect level, (LOAEL). This estimate of the LOAEL is supported by TKTD calculations (Section 5.4), showing that such a value of cadmium in urine corresponds to an average kidney cortex mass fraction of cadmium of approximately $120 \mu\text{g g}^{-1}$. The TKTD calculations estimated $84 \mu\text{g g}^{-1}$ in kidney cortex as the lower confidence limit for the lowest (most sensitive) decile of the population, related to cadmium induced LMM proteinuria. Because of the uncertainties concerning occurrence of LMM proteinuria at urinary cadmium less than 2 nmol mmol^{-1} creatinine, a no observed adverse effect level (NOAEL) cannot be determined.

7.4 Bone: osteomalacia, osteoporosis, and fracture

It is well established that excessive exposure to cadmium affects bone mineral metabolism, leading to Itai-itai disease, a combination of kidney dysfunction, osteomalacia, and osteoporosis. This disease occurred most frequently after menopause among women who had given birth to several children, mainly in an area in Toyama Prefecture, Japan. It was discovered in the period after World War II and most cases were diagnosed in 1967–1970, after the disease had been officially recognized as related to cadmium exposure. Up to 2011, more than 190 cases have been officially recognized. In addition, there are more than 250 suspected cases requiring observation (for reviews, see Nordberg, 1974 [128], Nordberg *et al.*, 2015 [1]). High-level exposures in industry, mainly by inhalation of cadmium-containing dust and fume, have also been related to the development of osteomalacia and osteoporosis, more than 50 cases having been reported from various countries (see review by Nordberg *et al.*, 2015 [1]).

Whether the kidney dysfunction and the bone effects are causally linked or are parallel effects is important. Mechanisms for the induction of bone effects include a deficient renal synthesis of active Vitamin D metabolites, as in classical renal osteomalacia, and the loss of calcium and phosphate because of deficient reabsorption in renal tubules. In women, additional losses occur during pregnancy and lactation. In Itai-itai disease patients, a mean value of cadmium in urine of more than $30 \mu\text{g g}^{-1}$ creatinine ($30 \text{ nmol mmol}^{-1}$ creatinine) was reported. Low dietary intakes of vitamin D and essential metals such as calcium and zinc may also be important (see reviews by Nordberg, 1974 [128], Kjellstrom, 1986 [156], Nordberg *et al.*, 2015 [1]). A possible link between osteoporosis and much lower cadmium exposure levels than those causing the Itai-itai disease has been studied closely during the last 10–15 years. Osteoporosis is characterized by low bone mass and micro-architectural deterioration of the skeleton, leading to fragility and an increased risk of fractures. The relationship between any type of osteoporosis and increased risk of fractures is well established [157, 158].

Four studies were published between 1999 and 2004 on bone mineral density, osteoporosis, and/or the incidence of fractures as indicators of an adverse effect of cadmium exposure on bone. One study was performed in Belgium [159]; one in Sweden, where urinary cadmium was measured after values had peaked (Alfvén *et al.*, 2000 [32], 2004 [160]); and one in Japan [161]. The fourth study was performed in a heavily polluted area in China [83, 162]. In this fourth study, urinary cadmium values of about 2 to $>20 \mu\text{g g}^{-1}$ creatinine

(nmol mmol⁻¹ creatinine) and blood-cadmium values in subgroups with >20 µg L⁻¹ were related to decreased BoneMD and an increased risk of osteoporosis, as well as fractures. Jin *et al.*, (2004) [134], based on the same dataset, showed that there was an increased risk of osteoporosis and that there was a statistically significant relationship between kidney effects and bone effects. In the Chinese study, both kidney effects and osteoporosis were present, but osteomalacia, a prominent feature of Itai-itai disease, was not reported. General risk factors for osteoporosis and fractures are female sex, old age, low body mass, early menopause, family history of osteoporosis, deficiency of Vitamin D and calcium, smoking, excessive consumption of alcohol, inactivity, several medical disorders, and certain drugs [163, 164].

Sixteen studies on BoneMD and fractures and (or) bone effect biomarkers published after 2004 will be summarized and discussed in the following text.

7.4.1 Women in the general population in South Sweden

Findings from this study were published previously, but new statistical analyses on the exposure-response relationship have been performed. BoneMD of the non-dominant wrist was measured using dual-energy X-ray absorptiometry (DXA). The median value of urinary cadmium was 0.67 µg g⁻¹ creatinine (5–95 percentiles 0.31–1.6) and the median blood cadmium mass concentration was 0.38 µg L⁻¹ (5–95 percentiles 0.16–1.8) [165]. The benchmark dose (BMD) and the benchmark dose lower confidence limit (BMDL), adjusted for relevant covariates, corresponding to an additional benchmark response (BMR, i.e. the additional risk above background) of 5 or 10 %, were calculated. For a 5 % BMR of osteoporosis, the BMD was 2.9 µg g⁻¹ creatinine of urinary cadmium and the BMDL 1.6 µg g⁻¹ creatinine. The lowest BMDL value of urinary-cadmium was the one for wrist bone mineral density (BMDL-5) of 1.0 µg g⁻¹ creatinine (see also Suwazono *et al.*, 2009 [166]).

7.4.2 Women and children in the general population, Belgium

A Belgian study included 294 women (mean age 49 years) randomly recruited from a population in 10 districts in northeastern Belgium, with environmental cadmium exposure mainly from zinc smelters [167]. The median blood cadmium mass concentration was 0.90 µg L⁻¹, while the 24-hr urinary cadmium excretion was 0.7 µg day⁻¹ in premenopausal and 1.2 µg day⁻¹ in postmenopausal women, probably corresponding to about 0.7 and 1.2 µg g⁻¹ creatinine, respectively.

Multivariate-adjusted associations of exposure with specific markers of bone resorption, calcium excretion, various calciotropic hormones, and forearm bone density were evaluated. In all women, the effect size associated with a doubling of urinary cadmium was -0.009 g cm⁻² ($p=0.055$, i.e. not fully statistically significant) for proximal forearm bone density (average 0.45 g cm⁻²). In 144 postmenopausal women, the corresponding effect size was -0.012 g cm⁻² ($p=0.008$) for distal forearm bone density (average 0.405 g cm⁻²). Notably, only one woman had renal tubular dysfunction, as measured by urinary retinol-binding protein >338 µg day⁻¹, indicating that the possible effects on bone were not secondary to kidney effects of cadmium. The results of the Swedish [165] and the Belgian [167] studies also showed associations between cadmium exposure and biomarkers of bone resorption, i.e. increased calciuria and lower serum levels of parathyroid hormone in both studies.

In another study, children in Belgium were studied [168]. A statistically significant association was found between urinary cadmium and urinary deoxypyridinoline. It is unclear to what extent adjustment for urine flow was performed.

7.4.3 NHANES studies (USA)

A large study in the USA using National Health and Nutrition Examination Survey (NHANES) population-representative data measured urinary cadmium and BoneMD of the hip in 2826 women 50–90 years of age.

Osteoporosis was diagnosed in cases where the T-score < -2.5 . In a multivariable-adjusted model, including urinary cadmium as a continuous variable [also adjusted for age, race, income, ever-smoking and underweight], the odds ratio (OR) for osteoporosis in the hip was significantly associated with urinary cadmium. Based on categorized exposure, this NHANES study found a statistically significant increased risk of osteoporosis at the hip, OR of 1.43 (95 % CI, 1.02–2.00) for urinary cadmium in the range 0.50–1.0 nmol mmol⁻¹ creatinine and a close-to-significantly increased OR of 1.40 (95 % CI, 0.97–2.03) for urinary cadmium > 1.0 nmol mmol⁻¹ creatinine, compared to urinary cadmium ≤ 0.50 nmol mmol⁻¹ creatinine. Only 15 % of the women had urinary cadmium above 1.0 $\mu\text{g g}^{-1}$ creatinine [169], which might indicate a lack of power at the highest exposure level.

Similar results were obtained in an update of the NHANES-study, which included over 10 000 subjects 30–90 years of age, both men and women [170]. After adjustment for age, sex, ethnicity, body mass index, calcium intake, and physical inactivity, ORs for osteopenia and osteoporosis increased with urinary cadmium. OR values for osteopenia were 1.49 (95 % confidence interval (CI) 1.24–1.80) at urinary cadmium 1–1.99 $\mu\text{g g}^{-1}$ creatinine and 2.05 (95 % CI, 1.52–2.78) for those with > 2 $\mu\text{g g}^{-1}$ creatinine, compared to those with urinary cadmium less than 1 $\mu\text{g g}^{-1}$ creatinine. OR values for osteoporosis were 1.78 [95 % CI, 1.26–2.52] for 1–1.99 $\mu\text{g g}^{-1}$ creatinine and 3.80 (95 % CI, 2.36–6.14) for > 2 $\mu\text{g g}^{-1}$ creatinine. The association was consistent in all age, sex, race, and smoking status subgroups.

7.4.4 Belgian workers

An association between urinary cadmium and BoneMD was reported for Belgian workers exposed to high air concentrations of cadmium in the past [171]. In 83 male workers and ex-workers (mean age 45 years; range 24–64 years) in a radiator factory previously using cadmium-containing solder, BoneMD in distal forearm, hip and lumbar spine (by dual-energy photon absorptiometry), and urinary calcium excretion were assessed. The geometric mean urinary cadmium at the time of BoneMD measurement was 1.02 $\mu\text{g g}^{-1}$ creatinine (5th–95th percentile 0.17–5.51 $\mu\text{g g}^{-1}$ creatinine), *i.e.* only slightly higher than in the general population. However, in the past, 42 of the workers had a measured urinary cadmium > 2 $\mu\text{g g}^{-1}$ creatinine and many had much higher values.

BoneMD was negatively correlated with urinary cadmium, adjusted for age, BMI, and current smoking. Adjusted for the same covariates, the risk of osteoporosis increased with dose. Only four men (5 %) had evidence of renal tubular dysfunction (B2M concentration above 300 nmol mmol⁻¹ creatinine) and even when those men were excluded cadmium was associated with lower BoneMD, a higher risk of osteoporosis, and higher urinary calcium excretion [171]. Because of the higher exposures in the past, the dose-response relationships observed at the time of BoneMD measurements do not represent causal relationships.

7.4.5 Chinese studies

Several studies have investigated the effect of cadmium on bone in the same three cadmium exposure areas (low, moderate, and heavy) in China. Those published in 2004 and earlier have already been mentioned in the preceding text [83, 134, 162]. Jin *et al.*, 2004 [134] found clear associations between urinary cadmium or blood cadmium and decreased BoneMD. Osteoporosis was statistically significantly associated with urinary cadmium and the severity of renal tubular deficiency, but not with glomerular dysfunction as indicated by albuminuria. In a study published in 2009, the long-term effects of cadmium on forearm BoneMD were assessed after the cessation of the ingestion of cadmium-polluted rice. This was a follow-up study of 458 persons from the three areas [172]. Those living in the moderate and heavy exposure areas ceased ingesting cadmium-polluted rice (cadmium in rice: 0.51 mg kg⁻¹ and 3.7 mg kg⁻¹, respectively) in 1996, 10 years prior to the analysis by Chen *et al.*, 2009 [172]. BoneMD was measured by dual energy X-ray absorptiometry at the

proximal radius and ulna. Cadmium in blood or urine, analyzed in samples from 1998, was used as an exposure marker.

The absolute decrease and the per cent decrease in bone mineral density from 1998 to 2006 were more pronounced with increasing urinary and blood cadmium. These decreases were statistically significant at a urinary cadmium/creatinine ratio above $5 \mu\text{g g}^{-1}$ creatinine and at blood cadmium mass concentrations above $10 \mu\text{g L}^{-1}$, as compared to the low-exposure groups (urinary cadmium $<2 \mu\text{g g}^{-1}$ creatinine and blood cadmium $<2 \mu\text{g L}^{-1}$) in all subjects. After stratification by sex, these differences were significant only in the women, $p < 0.001$. The prevalence of osteoporosis (Z-score < -2) in 2006 was higher than that in 1998 and increased along with the level of urinary and blood cadmium in both men and women. Blood cadmium $>5 \mu\text{g L}^{-1}$ was associated with an OR = 3.45 (0.95–13.6); blood cadmium $>10 \mu\text{g L}^{-1}$, OR = 4.5 (1.6–13.5) in men and women and urinary cadmium $>10 \mu\text{g g}^{-1}$ creatinine with OR = 4.7 (1.8–12.8) in women. The authors concluded that decreasing dietary cadmium exposure at the population level is not associated with bone recovery at the individual level [172].

Chen *et al.*, 2013 [173] estimated different dose-response relationships when using the blood and urine cadmium values measured in 2006 simultaneously with the effect measurements. Because of the substantial decrease in exposure, the much lower blood cadmium values after 10 years of low exposure resulted in much lower estimates of blood cadmium concentrations associated with bone effects. The difference for urine cadmium was less pronounced. Because the maximum blood and urine cadmium values are more relevant than the lower values measured at the time of effect measurements, the dose-response values reported by Chen *et al.*, 2013 [173] are not included here.

See further discussion and explanation in Section 7.4.11.

7.4.6 Women in mid-Sweden [Mammography Cohort]

Based on data from the Swedish Mammography Cohort [174], the association between urinary cadmium and BoneMD and fractures were evaluated. From 2003 to 2009, all women in the cohort living in the town of Uppsala were invited to undergo total body BoneMD measurements (by DXA), to provide blood and urine samples, and to complete a detailed questionnaire on diet and lifestyle factors (participation rate 65 %). Register-based information on fractures was retrieved from 1997 to 2009. All women 56–69 years of age ($n = 2688$) were selected and urinary cadmium was measured. The regression models adjusted for factors associated with bone health: age, education, height, total fat mass, lean body mass, parity, use of postmenopausal hormones, ever use of corticosteroids, total physical activity (MET-hours day $^{-1}$), smoking status, alcohol intake, inflammatory joint disease, kidney diseases, liver diseases, and malabsorption. Osteoporosis was diagnosed in cases with T-score < -2.5 .

Urinary cadmium (median $0.35 \mu\text{g g}^{-1}$ creatinine) was statistically significantly associated with a decrease in BoneMD of the total body, femoral neck, and total hip, but not significantly associated with BoneMD of the lumbar spine. The adjusted mean BoneMD was lower in the highest exposure category, with urinary cadmium $\geq 0.75 \mu\text{g g}^{-1}$ creatinine, as compared to the lowest ($<0.5 \mu\text{g g}^{-1}$ creatinine). This difference in BoneMD between high and low exposure was similar to the decrease observed for a 5- to 11-year increase in age.

In comparison to women with urine cadmium $<0.50 \mu\text{g g}^{-1}$ creatinine, those with urine cadmium $\geq 0.75 \mu\text{g g}^{-1}$ creatinine had an OR for osteoporosis of 2.45 (95 % CI 1.5–4.0) at the femoral neck and an OR 2.0 (95 % CI 1.2–3.1) at the lumbar spine. The ORs among never-smokers were higher. This study was performed on a population-based female cohort with no occupational exposure to cadmium. In studies of the same cohort by Engstrom *et al.*, 2012 [175], relationships between dietary intake of cadmium, estimated by a food frequency questionnaire, and BoneMD were described. An OR of 1.31 (95 % CI 1.02–1.69) for decreased BoneMD was reported for dietary cadmium $>$ median ($13 \mu\text{g day}^{-1}$) compared to those with $<$ median intake. The study was stratified for smoking. There was a statistically significant, slightly higher OR in analyses restricted to never smokers.

7.4.7 Men and women in northern Sweden

A case-control study was nested within the prospective Northern Sweden Health and Disease Study [176]. Erythrocyte samples taken for a prospective cohort study were retrieved from freeze-storage and analyzed for Cd. Included in the study were 109 individuals, of which 88 were women, who later in life experienced a hip fracture, and two age- and sex-matched controls per case. The mean erythrocyte Cd mass concentration was $1.3 \mu\text{g L}^{-1}$ in cases vs. $0.9 \mu\text{g L}^{-1}$ in controls. These concentrations correspond to approximately half as much in whole blood. The odds ratio was 1.63 (95 % CI 1.10–2.42) for suffering a hip fracture for each microgram per liter increase in Ery-Cd. When adjusting for smoking, BMI and height, the odds ratio decreased to 1.52 and did not remain statistically significant (95 % CI 0.77–2.97). A separate analysis of women showed an increased risk (OR 1.94, 95 % CI 1.18–3.20) that also remained in a multiple analysis (OR 3.33, 95 % CI 1.28–8.56).

The authors concluded that fracture risk is associated with Cd, but that it is not possible to draw firm conclusions on whether Cd is the causal factor or whether other smoking-related factors cause this association.

7.4.8 Cohorts of Swedish men

Within a population-based prospective cohort of 22 000 Swedish men, the individual dietary cadmium exposure was estimated based on a food frequency questionnaire at baseline (1997) and was used to estimate the relationship to the risk of fractures [177]. During an average of 10 years of follow-up between the baseline and the end of 2007, 2183 incident cases of any fracture and 374 hip fractures were ascertained. The median estimated dietary cadmium intake was $19 \mu\text{g day}^{-1}$. In the multivariable adjusted model, dietary cadmium intake was associated with a 19 % increased risk of any fracture [$p = 0.01$; test for trend], comparing the highest tertile with the lowest. When the statistical analysis was restricted to never smokers, a statistically significant dose-dependent increased risk was observed only for hip fracture.

In another study in Sweden, evidence of associations between bone effects and low-level exposure to cadmium was provided by Wallin *et al.*, 2016 [178]. This study was based on a selected cohort of osteoporotic fractures in men. The study involved 936 men, aged 70–81 years, including 484 ex-smokers and 73 current smokers. At baseline, the participants were physically examined, answered a questionnaire, and underwent BoneMD measurements in the total body, as well as in the hip and in the lumbar spine. They also gave urine and blood samples for the determination of urinary cadmium and of serum total estradiol, total testosterone, free estradiol, free testosterone, sex hormone-binding globulin (SHBG), plasma osteocalcin, and N-terminal propeptide of type I procollagen (PINP). Subjects were followed for 8.9 years on average and all new, X-ray confirmed fractures occurring during that period were recorded.

At baseline, the mean urinary cadmium/creatinine ratio was 0.33 (range 0.01–6.98) $\mu\text{g g}^{-1}$ creatinine. The mean urinary cadmium of both current smokers ($0.67 \mu\text{g g}^{-1}$ creatinine) and former smokers ($0.36 \mu\text{g g}^{-1}$ creatinine) was significantly higher ($p < 0.001$) than that of never-smokers ($0.22 \mu\text{g g}^{-1}$ creatinine). A multiple linear regression model, adjusted for age, body mass index, pack-years, and physical activity, showed significantly lower total body BoneMD, and BoneMD for all sites, in the 4th quartile of urinary cadmium (mean $0.67 \mu\text{g g}^{-1}$ creatinine), using the 1st quartile as reference. In never-smokers ($n = 353$), BoneMD was lowest in the 3rd quartile but not in the fourth. The study also revealed positive associations between urinary cadmium and incident fractures, especially non-vertebral osteoporosis fractures, in the fourth quartile of urinary cadmium, with hazard ratios of 1.8–3.3 in the various models. There were, by contrast, no significant associations between urinary cadmium and plasma sex hormones, SHBG, osteocalcin, or N-terminal propeptide of type I procollagen. Of note, hazard ratios and confidence intervals were very similar whether or not BoneMD was included in the models. According to the authors, this could indicate that cadmium increases fracture risks by affecting bone fragility through factors other than the BoneMD or by mechanisms not involving the bones. The mechanisms underlying the strong associations of bone fractures with low-level urinary cadmium remain elusive.

A limitation of the study by Wallin *et al.*, (2016) [178] is that it did not address the risks of confounding and misclassification that may arise when using creatinine-adjusted urinary cadmium as the sole indicator of long-term cadmium exposure (see Section 6.1.2). Confounding by creatinine adjustment may also arise because of the parallel decrease of muscular mass and creatinine excretion with ageing. Further complicating the issue is the fact that urinary cadmium levels off or decreases in the general population after the age of 60. Thus, because all participants in the study by Wallin *et al.*, (2016) [178] were over 60, their urinary cadmium probably did not reflect their lifetime exposure to the metal.

7.4.9 Residents in an industrial complex in South Korea

The relationship between urinary cadmium values and BoneMD was studied by Shin *et al.*, 2011 [179] in 804 residents (men and women, all ages) in an industrial complex in South Korea. BoneMD was measured by dual X-ray absorptiometry in the heel and T-scores were calculated. Osteopenia was diagnosed when the T-score was -1 to -2.5 and osteoporosis when the T-score was <-2.5 . Osteopenia was associated with statistical significance to high urinary cadmium ($>1 \mu\text{g g}^{-1}$ creatinine) in men and women of older ages. A majority of the participants were non-smokers. In the univariate analysis, smoking was statistically significantly associated with low BoneMD, but in the multivariate analysis a statistically significant association was not found.

7.4.10 Four studies without obvious associations

Four studies have failed to establish any association between urinary cadmium levels and bone mineral density. Horiguchi *et al.*, 2005 [180] studied women farmers (age 41–75 yrs) from areas in Japan with varying levels of cadmium in rice. The authors found no statistically significant association in multivariate analysis between BoneMD and urinary cadmium [range 0.3 – $27 \mu\text{g cadmium g}^{-1}$ creatinine (0.3 – $27 \text{ nmol mmol}^{-1}$ creatinine)], highest exposure group $>5 \mu\text{g cadmium g}^{-1}$ creatinine (5 nmol mmol^{-1} creatinine)]. Wallin *et al.*, 2005 [181] studied Swedish fishermen and their wives, in total 380 persons. They found no associations with urine cadmium in the range 0.22 – $0.34 \mu\text{g cadmium g}^{-1}$ creatinine (0.22 – $0.34 \text{ nmol mmol}^{-1}$ creatinine). In a study, comprising 170 women and 100 men in Poland, urinary and blood cadmium concentrations and the markers of renal tubular dysfunction and forearm bone mineral density were measured. Geometric mean urinary cadmium was $1.1 \mu\text{g cadmium g}^{-1}$ creatinine ($1.1 \text{ nmol mmol}^{-1}$ creatinine) in women and $0.9 \mu\text{g cadmium g}^{-1}$ creatinine in men. The results of the multivariate analysis did not indicate an association between exposure to cadmium and a reduction in bone density [182]. Another study included 908 Swedish women with data on single photon absorptiometry in the non-dominant forearm. Cadmium mass concentration in blood (median $0.4 \mu\text{g cadmium L}^{-1}$), an indicator of recent exposure, was negatively associated with bone mineral density and parathyroid hormone level, and positively associated with the biochemical marker of bone resorption (CTx). However, this association disappeared after adjustment for smoking. The authors concluded that no convincing associations were observed between cadmium concentration in blood and bone mineral density [183].

7.4.11 Summary of bone effects

In summary, the present group of scientists scrutinized sixteen studies published after 2004 that investigated potential adverse effects of cadmium exposure on the skeleton. Six of these studies [32, 134, 169–172, 171, 174] were included in a meta-analysis by James and Meliker, 2013 [184]. Based on their analysis, the authors concluded that an association between cadmium exposure and occurrence of osteoporosis was detected. However, they considered that the inference of causation is ambiguous and more prospective studies with strong assessment of osteoporosis, major confounders, and effect modifiers are needed. In

our own assessment, we noted that statistically significant associations were reported between markers of cadmium exposure and decreased BoneMD [139, 165, 167, 172, 179, 181], risk of osteoporosis [169–172, 174], increased urinary deoxypyridinoline [168], or risk of fractures [174, 176, 177, 181]. In some of these studies, however, separate statistical analyses of non-smokers were not included and some of the observed relationships between cadmium-exposure biomarkers and bone effects were not statistically significant. Two of the studies described relationships after previous high exposures occupationally [171] or in the general environment [134, 172]. Only a few studies with clearly increased exposures above the general background had well documented exposure histories, and it is difficult to determine exactly what exposures preceded the observations of adverse bone effects. In four studies, a statistically significant association between cadmium exposure and BoneMD was not seen [180–183]. These studies included mostly low exposures, but, in the study by Horiguchi *et al.*, [180] higher exposures were included.

Studies published between 1999 and 2004 included some high exposures [83, 134, 162]. These studies, as well as later high exposure studies [171, 172], probably describe causal associations, even if only osteoporosis and no osteomalacia was observed (osteomalacia was a prominent feature of Itai-itai disease). Nutritional deficiencies may have contributed to Itai-itai disease. They are, however, difficult to define in retrospect. In the original studies of Itai-itai disease, and in the studies in China by Nordberg *et al.*, 2002 [83], and Chen *et al.*, 2009 [172], high dose dietary exposures gave rise to cadmium mass concentration in blood of $>20 \mu\text{g L}^{-1}$ or urinary cadmium/creatinine ratio of $>20 \mu\text{g cadmium g}^{-1} \text{ creatinine}$. These observations represent long term (decades) high exposure to cadmium. The study by Chen *et al.*, 2009 [172] also demonstrated that, despite substantially decreased exposures in the high and medium exposed groups after 1996, BoneMD continued to deteriorate after 10 years of lower exposures. These findings illustrate the long-term slow development of this disease and the fact that there seems to be no reversibility. Compared to the lowest exposed subgroup, Chen *et al.* [172] found a statistically significant decrease in BoneMD in all subgroups with urine-cadmium $>5 \mu\text{g g}^{-1} \text{ creatinine}$ (or blood-cadmium $>5 \mu\text{g L}^{-1}$) in women, but no statistically significant associations at lower exposures.

It is difficult to estimate the lowest exposures giving rise to bone effects. Based on available evidence, it seems reasonable to consider long term (decades) cadmium exposures with urinary cadmium of $5 \mu\text{g g}^{-1} \text{ creatinine}$ ($5 \text{ nmol mmol}^{-1} \text{ creatinine}$) or higher (or blood cadmium of $5 \mu\text{g L}^{-1}$ or higher) as related to an increased risk of adverse bone effects in terms of osteoporosis and (or) decreased BoneMD. The basis for this is the fact that there are consistent observations of such effects in several studies with such exposures. Studies with lower exposures display a complex picture. A majority of studies have reported a relationship between cadmium exposure and bone effects at urine cadmium lower than $5 \text{ nmol mmol}^{-1} \text{ creatinine}$, e.g. studies from Sweden by Akesson *et al.*, 2006 [165], Thomas *et al.*, 2011 [177], and Engstrom *et al.*, 2011 [174]. Akesson *et al.*, 2014 [185] reported decreased BoneMD and increased occurrence of fractures at urine cadmium in the range of $0.75\text{--}2 \mu\text{g g}^{-1} \text{ creatinine}$ ($0.75\text{--}2 \text{ nmol mmol}^{-1} \text{ creatinine}$). However, other studies have not found any statistically significant associations with urinary cadmium. There is a general understanding that, in addition to cadmium, nutritional deficiencies were important for the development of Itai-itai disease. However, there is incomplete documentation of these deficiencies. Also, in several studies published in the last two decades, described and discussed in some detail in the present document, nutritional conditions have not been well defined.

There are alternative interpretations of the observations by Akesson *et al.*, 2006 [165] and Shutte *et al.*, 2008 [167] on biomarkers of bone mineral metabolism in the low exposure range. One interpretation is that there is a direct effect of cadmium on bone, which seems to be intensified after menopause. Even in the absence of measurable cadmium-induced renal tubular dysfunction, low-level environmental cadmium exposure may mobilize bone minerals from the skeletal tissue, indicated by calciuria and reactive changes in calciotropic hormones, i.e. lower levels of parathyroid hormone in both studies. This interpretation was advanced by the authors and has been repeated by Akesson *et al.*, in 2014 [185]. Another interpretation is that the calciuria is due to a higher combined uptake of calcium and cadmium in the intestine due to nutritional imbalances. Such increased calcium uptake can also lead to a lowering of serum levels of parathyroid hormone and the nutritional imbalances may cause osteoporosis. A third possibility is that an unknown

factor causes osteoporosis with calciuria and lowering of parathyroid hormone and that this causes an up-regulation of cadmium absorption, accompanied by increased blood- and urine cadmium. A fourth possibility is that calciuria, cadmiuria, and parathyroid hormone levels are all age dependent and the data have not been fully adjusted for these effects. Confounding caused by the possibility that food with relatively high cadmium levels contains low levels of calcium and vitamin D, while food rich in vitamin D and calcium, like dairy products, contains very low levels of cadmium, is another possibility. High cadmium levels in biomarkers and intake measurements may just be a biomarker of long-term inadequate intakes of these nutrients that are crucial for bone health. It is interesting to note that in one of the cohorts referred to in Section 7.4.6, the “Swedish mammography cohort”, Snellman *et al.*, 2014 [186] found that higher vitamin D intakes were associated with higher bone density. It is possible that there exist population groups with particular susceptibility to the development of bone effects, for example those with suboptimal nutrition.

When interpreting epidemiological findings on bone effects, additional information is required. This includes information about nutritional factors, as well as the toxicodynamics associated with tissue levels of cadmium that cause decalcification of bone. It is also important to have a better understanding of the toxicokinetics of cadmium in bone and the relationship between bone effects and biomarkers of exposure. Without this information, while it is possible to conclude these effects are adverse, it is not possible to be certain that there is a causal relationship between urine cadmium in the range $0.5\text{--}5\text{ }\mu\text{g g}^{-1}$ creatinine ($0.5\text{--}5\text{ nmol mmol}^{-1}$ creatinine) and decreased BoneMD. Consequently, it is not possible to establish a satisfactory LOAEL/BMD for this effect.

7.5 Cancer

7.5.1 Studies in animals and *in vitro*

After cadmium administration to animals through injection, inhalation, or oral routes, tumor formation has been detected in the testes, lungs, prostate, hematopoietic system, and at sites of subcutaneous and intramuscular injections (IARC 1993 [187], 2012 [188], Nordberg *et al.*, 2015 [1]). Prostate carcinogenesis in animals depends on an intact testicular production of testosterone. Cadmium-induced changes in the expression of MT, p53, and proto-oncogenes, such as c-jun, may be important for the development of prostatic and testicular tumors in rats [189, 190]. A dose-related increase in lung cancer was reported in rats exposed to cadmium chloride through inhalation (Takenaka *et al.*, 1983 [191]). Molecular mechanisms of cadmium carcinogenesis in the animals tested are still not well established. Epigenetic mechanisms may be important. The available information from *in vivo* and *in vitro* studies has been reviewed by Laulicht *et al.*, 2015 [192], by Davidson *et al.*, 2015 [193], and by Hartwig 2013 [194]. The role of cadmium as an endocrine disruptive substance is reviewed in Section 7.6.5.

7.5.2 Cancer in humans

Human cancer-related mortality was not statistically significantly raised in surveys conducted into the causes of death in inhabitants of any of the cadmium-polluted regions in Japan [195, 196]. Similar findings were obtained with regard to the inhabitants of a cadmium-polluted region in England [197]. Because of the limited number of people studied, *e.g.* only 275 persons studied by Arisawa *et al.*, (2001) [195], no conclusions can be drawn from these studies.

Cohort studies are available with regard to the development of lung and prostate cancers in cadmium workers in England, Sweden, and the United States. In serial studies on English nickel-cadmium battery workers, cadmium exposure was found not to be significantly associated with lung or prostate cancers [198–200]. However, in the study by Sorahan and Esmen [199], the mortality from cancers of the pharynx was significantly higher than that in the general population of England and Wales. In a study of Swedish battery

workers that also considered smoking status [201], the incidence of lung cancer was significantly increased in male workers [standardized mortality rate (SMR) 176; 95 % confidence interval (CI), 101–287]. In a study of copper-cadmium alloy workers in England conducted between 1946 and 1992, no significant increase in SMR was found for lung cancer, but the SMR for chronic nonmalignant disease of the respiratory system was increased significantly, with a dose-response relationship found with respect to the amount of cumulative exposure to cadmium [124]. In a series of surveys focusing on cadmium workers in English factories, no clear association was noted between cadmium exposure and the development of lung or prostate cancers [202–206]. In investigations of an American cadmium recovery plant, Thun *et al.*, [207] and Stayner *et al.*, [208] reported that lung cancer SMRs were significantly increased, with a dose-response relationship between the exposure to cadmium and the development of lung cancer. On the other hand, Lamm *et al.*, 1992 [209] and Sorahan and Lancashire, 1997 [210], who surveyed the same population, found that the development of lung cancer in this plant was more closely associated with exposure to arsenic and smoking than with exposure to cadmium. Verougstraete *et al.* [211] reviewed the literature and pointed out that data for occupational exposure obtained before 2003 indicated a lower relative risk in groups exposed to cadmium in the absence of arsenic and nickel than in the presence of these agents; nevertheless, these authors considered these data indicative of a role for cadmium as a human carcinogen. All these data on humans concern occupational exposure; until 2006, there were no data from environmental cadmium exposure with individual-related exposure measurements. Nawrot *et al.*, 2006 [212] found an association between an increased risk of lung cancer and exposure to environmental cadmium in a prospective population-based cohort study in Belgium. These authors included information on urinary cadmium excretion in each person, as well as data on several potential confounding factors, such as smoking and concomitant arsenic exposure, in their analysis. Median urinary cadmium excretion was $1.1 \mu\text{g day}^{-1}$. As noted [213] in a commentary, arsenic exposure is of particular interest as a potential confounding factor because oral exposure to arsenic from drinking water has been demonstrated to increase the incidence of lung cancer [214]. The adjustments for arsenic made by Nawrot *et al.*, [212] need further comment. The investigators did not determine urinary arsenic for all participants, but they did calculate probable values using two different models. In those subjects who were exposed environmentally, urinary cadmium remained a significant predictor for lung cancer with only one of the models. Although these studies [212] give some support to cadmium as an environmental carcinogen, no other studies of general environmental population groups have so far reported a relationship between cadmium and lung cancer.

Early observations of an increased occurrence of prostate cancer in cadmium workers (Kipling and Waterhouse, 1967 [215]) were not confirmed in some later studies by Kazantzis *et al.*, 1988 [205]; other epidemiological studies have reported variable results [216, 217]. Cadmium has been demonstrated to induce the malignant transformation of human prostate epithelial cells *in vitro*. Achanzar *et al.*, 2001 [218] and Zeng *et al.*, 2004 [219] carried out epidemiological studies in a cadmium-polluted area in China (urine cadmium $>20 \text{ nmol mmol}^{-1}$ creatinine in the most exposed subgroup) and found a statistically significant relationship between high testosterone levels and urinary cadmium, but not blood cadmium. There were also indications of a possible increase in prostatic lesions and a statistically significant relationship between urinary cadmium and the presence of increased levels of prostate specific antigen [220]. Recent studies of prostate cancer and cadmium in non-polluted areas (see below) have reported both positive and negative findings.

A German case-control study of kidney cancer [221] reported an OR for renal cell carcinoma of 1.4 (CI 1.1–1.8) in men and 2.5 (CI 1.2–5.3) in women for high versus low occupational cadmium exposure. Another case-control study in Germany [222] found an OR of 1.7 (CI 0.7–4.2, *i.e.* not statistically significant) for those with increased cadmium exposure. Hu *et al.*, 2002 [223] performed a case-control study in Canada and found self-reported cadmium exposure to be a statistically significant risk factor. Transitional cell carcinoma of the bladder was studied with a case-control approach by Kellen *et al.*, 2007 [224]. They found that the highest exposure category of blood cadmium had an OR of 5.7 (CI 3.3–9.9), blood-cadmium $>1 \mu\text{g L}^{-1}$, as compared to those with low blood-cadmium ($<0.2 \mu\text{g L}^{-1}$).

Relationships between dietary cadmium exposure and cancer were studied in population groups in Sweden with low (background) exposures to cadmium [225–228]. Dietary intake of cadmium, estimated

based on a food frequency questionnaire (FFQ), was on average $15 \mu\text{g day}^{-1}$ in women and $19 \mu\text{g day}^{-1}$ in men. Those in the highest tertile of intake were compared with those in the lowest tertile. The RR for ovarian cancer was 0.90 (95 % CI 0.71–1.15), endometrial cancer 1.39 (95 % CI 1.04–1.86), breast cancer 1.21 (95 % CI 1.07–1.36), and prostate cancer 1.13 (95 % CI 1.03–1.24).

In a large Japanese study (90 000 men and women) of cancer and dietary cadmium intake (highest quartile $37.5 \mu\text{g day}^{-1}$ in men and $33.9 \mu\text{g day}^{-1}$ in women), no associations were found between cadmium intake and total, as well as specific, cancers [229]. In a hospital-based case-control study of 405 pairs of women, [36] there was no overall increase in breast cancer in relation to FFQ estimated daily cadmium intake, but when estrogen positive tumors among postmenopausal women were considered, an adjusted OR of 1.94 [CI 1.04–3.63] was found when the lowest tertile of intake was compared to the highest. Mean intake was $31.5 \mu\text{g}$ in the highest tertile and 21.4 in the lowest.

Adams *et al.*, 2012 [230] studied dietary cadmium intake and postmenopausal breast cancer in 30 000 women in the USA with dietary cadmium intakes varying between 0.5 and $55.7 \mu\text{g day}^{-1}$ (mean $10.9 \mu\text{g day}^{-1}$). They found no association between cadmium intake and breast cancer (OR 1.0 for highest versus lowest quartile). In a case-control study of breast cancer, McElroy *et al.*, 2006 [231] found an OR of 2.29 (CI 1.3–4.2) after adjustment for confounding variables when comparing the highest quartile of urinary cadmium ($>0.58 \text{ nmol mmol}^{-1}$ creatinine) with the lowest quartile ($<0.26 \mu\text{g g}^{-1}$ creatinine). Gallagher *et al.*, 2010 [232] performed two case-control studies of breast cancer in US women and found OR 2.69 (CI 1.07–6.78) and OR 2.5 (CI 1.11–5.63) when comparing highest and lowest quartiles of urinary cadmium. A positive association between mammographic density and urinary cadmium was reported by Adams *et al.* [233]. In most of these studies, adjustments for smoking have been made, but never-smokers have not been reported separately. A quantitative estimate of risks in relation to cadmium exposure and the role of cadmium from smoking is difficult to determine.

Because the International Agency for Research on Cancer (IARC), 1993 [187] concluded that there was sufficient evidence to classify cadmium as a human carcinogen, it belongs to group 1 of the IARC classification system. The evidence available at the time of the 1993 IARC evaluation was discussed in a preparatory IARC publication [234]; the difficulties in reaching clear conclusions were pointed out. Subsequent evaluations of the newer evidence confirmed the classification of cadmium as a human carcinogen [Group 1] [188]. The classification was based on animal data and on the previously cited epidemiology [207, 208] demonstrating that the presence of cadmium can lead to lung cancer in industrial workers. IARC also noted positive associations, also described in the foregoing text, between occupational or environmental exposure to cadmium and risk of cancer in the prostate, kidney, bladder, breast, and endometrium.

Cancer classification is also performed by authorities other than IARC. In the EU, cadmium is recognized as a carcinogen, classified in group 1B for cadmium and some cadmium compounds (*e.g.* oxide, fluoride, chloride *etc.*) according to Regulation (EC) No 1272/2008 (Classification, Labelling and Packaging regulation). In the US, the Environmental Protection Agency (EPA) has classified cadmium as a possible human carcinogen by inhalation (Group1B) based on its assessment of limited evidence of an increase in lung cancer in humans and sufficient evidence of lung cancer in rats.

This group of scientists agrees with the IARC classification, *i.e.* cadmium and its compounds are human carcinogens. This is a classification of the carcinogenic hazard arising from cadmium exposure. However, we are unable to assess the risk of cancer in numerical terms because of the lack of consistent relationships in epidemiological studies and the complex interactions with smoking and other competing or co-carcinogenic factors discussed in the foregoing text. This means that we are unable to derive a dose-frequency relationship from the data available and to set this against the dose frequency deemed sufficiently low to be considered tolerable.

7.6 Other effects

Cadmium exposure may give rise to other adverse health effects in humans. The following section deals with the three principal other effects, namely, anemia, diabetes, and cardiovascular disease.

7.6.1 Anemia

Slightly decreased hemoglobin concentrations were observed in cadmium workers, but were found to be reversible changes unrelated to renal injury [118, 235]. However, in Itai-itai disease patients who have the most severe form of cadmium poisoning, there is sometimes extremely severe anemia, with hemoglobin values as low as 4.2 g dL^{-1} (42 g L^{-1}). In a group of 10 Itai-itai disease patients in whom serum iron, ferritin, and erythropoietin levels and renal function were determined, as well as bone marrow aspiration performed, the anemia was noted to be normochromic, with no decreases in the iron or serum ferritin levels and no particular abnormalities noted from smears of bone marrow aspirates. Serum erythropoietin concentrations were markedly decreased, causing renal anemia [236]. In patients with Itai-itai disease, normal liver Fe concentrations are found [237]. In animal experiments, the administration of cadmium has been reported to result in the development of iron-deficiency anemia, renal anemia [238], and hemolytic anemia [239].

These forms of anemia are not found among persons exposed to low levels of cadmium in non-contaminated areas and thus are not key adverse effects for establishing risk estimates.

7.6.2 Diabetes

With an increasing incidence of diabetes in the general population, there is also an increasing interest in factors that may contribute to this increase and/or contribute to adverse health effects and disease occurring among diabetics. It is well known that the pancreas is one of the organs in the body with prominent accumulation of cadmium. Links between cadmium and diabetes have been shown in experimental studies on laboratory animals (see Edwards and Prozialek, 2009 [240]). Human cross-sectional studies have indicated higher cadmium levels in blood and urine among individuals with type 2 diabetes or impaired fasting glucose, as compared to referents [241, 242]. Lei *et al.*, 2007 [243] found decreased levels of insulin in the serum of cadmium workers and they calculated lower BMDL values of urine cadmium for this effect than for tubular proteinuria in the same workers. All the mentioned studies were of cross-sectional design. Barregard *et al.*, 2013 [244], in a prospective study of a general population group in Sweden with urine cadmium $<1 \mu\text{g cadmium L}^{-1}$, found no association between diabetes and urine cadmium or blood cadmium. Borné *et al.*, 2014 [245] similarly found no association between blood cadmium and diabetes.

Diabetic subjects, such as type-2 diabetics, are recognised as a group vulnerable to cadmium exposure because a higher prevalence of tubular dysfunction has been observed in relation to cadmium in their urine than that observed among non-diabetic subjects. Chen *et al.*, 2006 [131] reported that diabetics in the general population with high levels of antibodies against MT in serum were at higher risk of developing tubular proteinuria at similar levels of cadmium in urine than people with lower levels of MT antibodies. Similar findings were also reported by Nordberg *et al.*, 2012 [84] in people occupationally exposed to cadmium. Barregard *et al.*, 2014 [246] found a relationship between cadmium exposure and albumin excretion in type-2 diabetic women, but not in non-diabetics.

Animal studies have shown that an increased susceptibility for cadmium-related renal effects occurs in diabetic animals when compared to non-diabetic animals [247–249].

The studies cited above confirm that humans with diabetes should be regarded as a vulnerable group concerning cadmium exposure, but the data currently available are insufficient to permit a specific risk estimation for this population group.

7.6.3 Blood pressure and cardiovascular disease

The relationship between blood pressure and metal exposure has been debated over the last half-century. Schroeder and Vinton, 1962 [250] reported increased blood pressure in cadmium-exposed animals. In a study

on humans, Schroeder, 1965 [251] found increased cadmium concentrations at autopsy in hypertensive subjects, but no information of smoking habits was given and other studies have found no difference [1].

The concentration of cadmium in blood in an elderly population consisting of 804 subjects with a mean age of 87 years, both men and women, was studied in relation to several factors, *e.g.* blood pressure and smoking. Information about the usage of anti-hypertensive drugs used for treating high blood pressure was recorded, as well as cognitive function. Cadmium concentration was analyzed in whole blood from 763 subjects and recorded in relation to never-smokers [3.9 nmol cadmium L⁻¹], previous smokers (4.4 nmol cadmium L⁻¹), and current smokers (7.5 nmol cadmium L⁻¹). There were no statistically significant relationships between cadmium and age, blood pressure, or cognitive functions (Nordberg *et al.*, 2000 [252]).

The Public Health and Environmental Exposure to Cadmium (PheeCad) group reported on a random sample, consisting of 692 subjects from 20 to 83 years of age, in order to determine how environmental exposure to cadmium influenced the incidence of hypertension and blood pressure. It was concluded by Staessen *et al.*, 2000 [253] that environmental exposure to cadmium was not associated with higher casual blood pressure (CBP), with higher 24 h arterial blood pressure (ABP), or with an increased risk of hypertension. Several other studies with variable results were reviewed by Nordberg *et al.*, 2015 [1].

In a survey of inhabitants in a cadmium-polluted area in Japan, a tendency to low blood pressure was found. In Itai-itai patients and in persons requiring observation for this disease, low blood pressure has been noted. Nordberg *et al.*, 2015 [1], in reviewing available evidence, noted that decreased blood pressure occurs in persons with severe cadmium-induced renal injury, but that the issue of blood pressure and mild cadmium exposure still has to be resolved. Some studies on cardiovascular mortality and cadmium are reviewed in Section 7.6.8. Telez-Plaza *et al.*, 2013 [254] reviewed 12 studies on cardiovascular disease and cadmium exposure. The pooled relative risks were: for cardiovascular disease 1.36 (CI 1.11–1.66), coronary heart disease 1.30 (CI 1.12–1.52), stroke 1.18 (CI 0.86–1.59), and peripheral vascular disease 1.49 (95 % CI 1.15–1.92). The authors consider that their review supports an association between cadmium exposure and cardiovascular disease, but that more studies, especially studies evaluating incident endpoints, are needed. Such a study of incident disease was reported by Barregard *et al.*, 2016 [255]. This study was based on a cohort with 4819 Swedish participants and found consistently increased hazard ratios for all cardiovascular endpoints in the 4th blood cadmium quartile (median 0.99 µg L⁻¹) compared to the lowest quartile when considering sex, smoking, and a number of other relevant risk factors for cardiovascular disease. Sjogren *et al.*, 2015 [256] reviewed a number of studies on cardiovascular disease or coronary heart disease and cadmium exposure (including some of the studies mentioned), and concluded that the data support an association that is, however, less conclusive than for some other metallic elements. These authors noted that several occupational mortality studies showed no association between cadmium exposure and cardiovascular disease compared to the general population. Cardiovascular disease related to cadmium is potentially of great importance, but more evidence is needed in order to establish causality and dose-response relationships.

7.6.4 Neurodevelopmental effects

Cadmium may be transferred into primitive nervous tissue at early stages of gestation before the placental barrier is established [257]. It does not readily cross the fully developed placental barrier, as shown using radiotracer techniques in animals [258] and repeatedly confirmed in humans, *e.g.* Chen *et al.*, 2014 [259]. The blood–brain barrier usually offers considerable further protection of the central nervous system (CNS) from the effects of cadmium in the fetus at later stages of pregnancy and in adult animals as well as in humans. However, in the special case of nasal inhalation of airborne cadmium, the blood-brain barrier can be circumvented because there is a direct pathway from the nasal mucosa into the olfactory part of the brain [260].

Indirect effects can be caused by secondary mechanisms, such as interference by cadmium with zinc metabolism, or factors of importance for the development of the CNS, *e.g.* hormones. Neurotoxicity of cadmium has been reviewed [1, 6, 58, 261, 262] and it has been suggested that exposure to cadmium can give rise to adverse effects on the CNS. Oral exposure of pregnant or lactating rats to low levels of cadmium caused

alterations in the brain serotonin levels of their offspring [263, 264]. De Burbure *et al.*, (2006) [137] studied the dopaminergic biomarkers, serum prolactin and urinary homovanillic acid, in children and found statistically significant effects at blood cadmium lower than $0.5 \mu\text{g cadmium L}^{-1}$. The possible role of higher exposures that occurred earlier, before the study was performed, needs consideration. Kippler *et al.* [265, 266] found lower size at birth in girls and lower child intelligence at higher cadmium exposures. A possible interaction with arsenic and other metals needs further analysis. Ciesielski *et al.* [267] found statistically significant relationships between cadmium and neurocognitive test scores in a cross-sectional study in the US.

In summary, there is limited evidence of adverse cadmium-related neurological and neurodevelopmental effects. This limited evidence is insufficient for the purpose of relating incidence to dose.

7.6.5 Reproductive effects; endocrine disruption

Early studies on laboratory animals showed that after injection of cadmium salt in doses of one or a few milligrams per kg body mass, necrosis of the testes occurs. While this effect occurs in many animal species at such relatively high doses, some strains of inbred mice are resistant, probably because of the lack of zinc transporter ZIP8 [268], a probable target for cadmium. While testicular necrosis occurs after a single injection of cadmium salt, such effects do not occur if the dose is fractionated or even when larger total doses are given during longer periods of time [59], *i.e.* at exposures more similar to those occurring in humans under occupational or environmental circumstances. Long-term or short-term administration of cadmium results in changes in the levels of male sex hormones and related changes in accessory reproductive organs in animals [269, 270]. Zeng *et al.*, 2004 [219, 220] detected changes in the levels of male reproductive hormones in a cadmium-exposed population in China. There is no doubt, therefore, that relatively high doses of cadmium can act as an endocrine disruptor in males.

In female animals, relatively high doses of cadmium can cause changes in the ovaries, changes in ovarian hormonal production, and placental necrosis. Thus, cadmium is also an endocrine disruptor in females. It was believed that binding of cadmium to estrogen receptors might mediate these effects, as indicated by animal experiments with low injected doses [271]. However, Ali *et al.*, 2012 [272], based on injection experiments in animals, presented evidence in favor of a cadmium effect on mitogen-activated protein kinases at low doses, but the data are not conclusive. Epidemiological evidence concerning an effect of low-level cadmium from smoking, occupational, and environmental exposure on the birth weight of newborns is not conclusive either. The probable role of interactions was mentioned already in Section 7.6.6 (Review presented by Nordberg *et al.*, 2015 [1]). In a study by Ali *et al.*, 2014 [273], serum levels of androstenedione, testosterone, estradiol, and sex-hormone binding globulin (SHBG) were studied in 438 postmenopausal Swedish women without hormone replacement therapy. A statistically significant positive association between blood cadmium (median 3.4 nmol L^{-1} ; $0.38 \mu\text{g L}^{-1}$) and serum testosterone levels, as well as a significant inverse association between blood cadmium and both serum estradiol levels and the estradiol to testosterone ratio, were reported in multivariate models adjusted for age, education, BMI, parity, smoking, and alcohol consumption. No similar associations with urine cadmium were found. Separate analyses of never smokers were not reported. Additional evidence is required, including animal experiments with dosing schedules more similar to human exposures, before conclusions can be reached that low doses of cadmium, as they occur in human environments, influence estrogen receptors. Thus, there is still uncertainty concerning the classification of cadmium as an endocrine disruptor under such conditions, although it is well established that changes in reproductive hormones occur at high dose exposures in experimental animals. The classification of chemical compounds as endocrine disruptors includes consideration of hormones other than those affecting the reproductive system. For cadmium, the reproductive endocrine system is, as far as we know, the most sensitive system, and the considerations of endocrine disruption are therefore dealt with in this section. In summary, this review does not make it possible to state with certainty whether there are effects of cadmium on hormone levels at low (background) exposures. Thus, dose-response relationships cannot be established.

7.6.6 Mortality

Mortality owing to cadmium exposure has been related to the incidence of bronchitis and emphysema following occupational exposure to high concentrations of cadmium, or following long-term exposure, as seen in Swedish and English workers [55, 124]. Segments of the population in cadmium-polluted areas in Japan, with cadmium-induced renal tubular dysfunction, had a significantly increased mortality [8, 129, 274–276]. In addition, a statistically significant relationship between urinary cadmium and mortality was noted [277]. Cadmium exposures giving rise to tubular proteinuria above the normal range should therefore be considered as an important health problem. Nawrot *et al.*, 2008 [278] found, after adjustment for a number of factors including arsenic, a statistically significant higher risk for all cancer in the general population in an area of Belgium with elevated cadmium exposure. Menke *et al.*, 2009 [279] and Tellez-Plaza *et al.*, 2012 [280] found a slightly higher mortality from cardiovascular diseases or cancer associated with creatinine adjusted urine cadmium after multivariate adjustment, as reported in the NHANES III survey in the USA. The effects were, however, attenuated in never-smokers. Nordberg *et al.*, 2015 [1], in their review pointed out that possible confounding by, or interaction with, smoking had not been sufficiently clarified in these studies. It is unlikely that this is a key effect for low level cadmium toxicity.

8 Discussion of issues influencing the risk assessment of effects of cadmium on human health

8.1 Biomarkers of exposure and exposure assessment

In exposure assessment, and when using biomarkers of exposure, it is desirable to focus on assessments and biomarkers that are, as much as possible, related to the concentrations in critical organs (see Section 6.1).

Cadmium in blood is a good indicator of recent exposure (see Section 6.1.1). Its use as an indicator of long-term exposure and body burden is possible when long term constant exposures take place, but calculations of cumulative exposure based on several blood cadmium values are to be preferred (Section 6.1.1).

Both blood cadmium and urine cadmium are indicators of internal exposure and accumulation of cadmium in tissues. Both will be influenced by the fractional intestinal absorption of cadmium that is affected by the presence of essential elements such as iron, zinc, and calcium (see Section 5.1.2). Calcium status may confound the relationship between cadmium biomarkers and bone health. Most likely this is relevant to the Japanese Itai-itai outbreak, causing increased fractional cadmium absorption and, in combination with high dietary cadmium exposure, causing high concentrations of cadmium in blood and urine, as well as osteoporosis and/or osteomalacia. A possible confounding of the relationship between cadmium biomarkers and bone effects by low calcium intake and low vitamin D status at much lower cadmium exposures was discussed in Section 7.4.11 (Summary of bone effects). There is a need to examine the possibility that associations between biomarker levels of cadmium and adverse health outcomes may reflect the increased intestinal absorption of cadmium that results from the general upregulation of intestinal metal transporters in deficiency states; the deficiencies may be the true cause of the adverse health outcome.

Cadmium in urine is usually better than blood cadmium as an indicator of body burden or kidney burden of cadmium; however, uncertainties exist, particularly at low-level exposures (see Section 6.1.2). A diurnal variation exists with higher values in the morning than in the afternoon. Urinary cadmium excretion is dependent on urine flow even after adjustment by creatinine or specific gravity. Urinary concentrations of albumin and LMM proteins are also dependent on urine flow, and, even if adjusted by creatinine or specific gravity, a statistically significant dependence often remains because of incomplete adjustment. This means that there is often an apparent relationship between urine cadmium and urinary LMM proteins that is mediated by urine flow. It is important not to interpret such a relationship as a sign of cadmium toxicity. The problem is most prominent in low dose exposures near the normal range. At higher cadmium exposures,

increases in LMM protein excretion are far higher than the residual variation due to incomplete adjustment for urine flow by creatinine.

A possible source of confounding in relation to bone effects is that high cadmium levels in biomarkers may be associated with low intakes of nutrients crucial for bone health. In order to avoid such problems, it would be useful to calculate daily intakes of cadmium and nutrients in food, preferably at repeated intervals, when long-term exposures and related effects are considered. Such studies can be performed in small groups of persons by double portion methods. However, because of the considerable amount of work involved, such studies are not possible in large population groups. In such large groups, food frequency questionnaires have been used (see Section 7.4.8). Obtained dietary intake values have a low precision and reflect exposures at the time the investigation is performed. Repeated determinations are seldom performed. If cadmium and nutrients are not simultaneously examined, there is still a risk of confounding, as food, contributing a large proportion of the daily intake of cadmium, may provide a poor intake of vitamin D and essential metals such as calcium, iron, zinc, and copper.

8.2 Critical effects and dose-response relationships

8.2.1 General considerations on adverse effects of cadmium exposure

Preceding sections of this document have reviewed adverse effects of cadmium on the respiratory tract, kidneys, bone, induction of cancer, cardiovascular effects, and on a number of other effects.

In risk assessments by other organizations, such as EFSA 2009 [2] and WHO/JECFA 2011 [26], kidney dysfunction has been considered as the critical effect, *i.e.* the effect that occurs at the lowest exposure. Uncertainties concerning low dose kidney effects and the increasing evidence for low-dose bone effects make it necessary to consider bone effects as a possible critical effect. For inhalation exposure to cadmium dust and fumes, respiratory effects should also be considered as possible critical effects. Detailed considerations relating to these possibilities will be given later in this document.

This document also describes other effects that have been related to cadmium exposure: anemia, diabetes, neurological effects, reproductive effects, and endocrine disruption. Mortality has been reported to be associated with low-level cadmium exposure in a few studies. The conclusion was reached that the evidence available is insufficient to reach causal interpretations of the associations found between cadmium exposure and these effects when reported for low level exposures.

Cardiovascular effects and changes in blood pressure have been reviewed. Associations between cadmium exposure and cardiovascular disease have been reported in a number of recent epidemiological population studies, but more evidence is needed in order to establish causality and valid dose-response relationships.

In the latest IARC assessment [188], cadmium was classified as a human carcinogen. The classification was based on animal data and epidemiology, demonstrating that exposure to cadmium can lead to lung cancer in industrial workers. IARC also noted positive associations, described in the foregoing text, between occupational or environmental exposure to cadmium and risk of cancer in the prostate, kidney, bladder, breast, and endometrium. Although it is likely that low level exposures can give rise to cancer and cancer therefore should be considered a critical effect, present evidence concerning dose-response relationships is too uncertain for a quantitative assessment. Further, the likelihood of cancer is difficult to evaluate in relation to the other candidate critical effects.

Reasonably good dose-response data from epidemiological studies are available only for kidney effects and, to some extent, for bone effects. Most of the previously published risk assessments for human health effects of cadmium have used the adverse effects on kidneys as the critical effect, but recently the bone effects have been suggested as critical effects (Akesson *et al.*, 2014 [185]). As to the kidney effects, some uncertainty exists because of confounding factors operating at low-level exposures. For bone effects, there are also problems as to the interpretation of available data at low exposures. However, they seem (at least partly) to be independent of the kidney effects, they occur at approximately the same exposure as the kidney effects, and

their medical consequences are often serious for the osteoporotic individual and for society. Thus, the choice of a critical effect is not an easy one. The following discussion will focus on these effects, starting with the respiratory and kidney effects following occupational exposures.

8.2.2 Respiratory effects and kidney effects from occupational exposures

In occupational settings, long-term exposure to cadmium is usually by inhalation. Adverse effects on the lungs and kidneys are well established as a result of excessive exposures that were common in the past. Respiratory effects have been observed even after lower-level exposures to workroom air (approximately $20 \mu\text{g m}^{-3}$ of respirable cadmium 8 hours per day, 5 days per week) over long time periods (see Section 7.2). The limited evidence concerning effects on lung function and enhancement of smoking-related respiratory effects, reported in general population groups, is not considered sufficient for the present risk assessment. Respiratory effects have previously not been considered to occur at low occupational exposures (below $20 \mu\text{g m}^{-3}$). However, such exposures can still cause dysfunction of the kidneys, justifying the recognition of this as the critical effect, and therefore the focus for risk assessment and preventive action. Low occupational exposure levels have been recommended based on the estimated exposure level that causes kidney effects (see for example ACGIH 2016 [281], OSHA 2013 [282], AFS 2015 [283]). In the EU, the Scientific Committee on Occupational Exposure Limits (SCOEL) [122] recommended such levels in 2010 (see Section 9). SCOEL derived a LOAEL corresponding to a cumulative exposure to cadmium by inhalation (respiratory size particles) of $500 \mu\text{g years m}^{-3}$. This corresponds to a urinary cadmium/creatinine ratio of 3 nmol mmol^{-1} , based on the observations of respiratory effects in cadmium exposed workers by Cortona *et al.*, 1992 [123]. However, the Biological Limit Value recommended by SCOEL is based on adverse effects of cadmium on the kidneys. This effect was considered by SCOEL as the critical effect, and an exposure limit corresponding to even lower urinary cadmium was recommended (see Section 9).

8.2.3 Kidney effects

Risk assessments based on kidney effects use, as a starting point, cadmium concentrations in the kidney cortex causing LMM proteinuria. Such calculations have previously been presented for occupational exposures as well as for exposures in the general environment. Based on calculations (see Section 7.3.1) using TKTD models, a lower confidence limit for the most sensitive 10 % of the population in the US was defined as $84 \mu\text{g cadmium g}^{-1}$ kidney cortex. The high 99th percentile for levels in the kidney cortex derived from normal dietary exposure in the US population ($78 \mu\text{g g}^{-1}$ kidney cortex in females and lower in males) is below this value [70]. On this basis, cadmium related risks of kidney dysfunction were considered negligible in the US population, and hence acceptable, because dietary exposure from the general environment does not cause such kidney accumulation.

Risk assessments of dietary cadmium exposures based on epidemiological studies were presented by the European Food Safety Agency (EFSA), 2009 [2] and by the joint FAO/WHO Expert Committee on Food Additives (JECFA) [26], as will be described in Section 9. There is no doubt that tubular dysfunction of the kidneys with low molecular mass (LMM) proteinuria is a well-established effect, induced in both animals and in humans as a result of long term cadmium exposure. When the cadmium-induced LMM proteinuria exceeds the normal range in a population group, it is related to an increased mortality in renal and cardiovascular diseases. Tubular proteinuria, *i.e.* LMM proteinuria, is well documented at exposures giving rise to urinary cadmium/creatinine ratios of $4\text{--}5 \text{ nmol mmol}^{-1}$ and higher. Points of departure in this range were used by both EFSA, 2009 [2] and JECFA, 2011 [26] as starting points for their risk assessments (see Section 7.3). The present group of scientists agreed that an adverse effect on the kidneys is well documented from long-term cadmium exposures with such urine cadmium, but, in addition, there is evidence that such effects occur also at slightly lower exposures. A number of high quality epidemiological studies have found

changes in biomarkers of kidney dysfunction at a urinary cadmium/creatinine ratio of 2–4 nmol mmol⁻¹ (see Sections 7.3.2 and 7.3.3). While the increases in albumin excretion seem reversible, such is not the case for tubular biomarkers (Sections 7.3.2 and 7.3.3), and changes indicating tubular kidney dysfunction have been documented down to 2 nmol mmol⁻¹ creatinine. According to the present group of scientists, there is good reason to consider this level as the lowest level causally related to a low risk of LMM proteinuria *i.e.* this is the LOAEL.

A number of epidemiological studies (see Section 7.3.1) have reported statistically significant associations between urine cadmium and increased urinary excretion of LMM proteins at ratios of urine cadmium to creatinine lower than 2 nmol mmol⁻¹ creatinine, and in some studies even below 1 nmol mmol⁻¹ creatinine. These increases have sometimes been within the range of normal variation of LMM proteins in urine. An association between low-level blood cadmium and urinary albumin or LMM protein excretion has also been reported (see Section 7.3.2.). As mentioned previously, a statistical association between urinary cadmium and LMM protein excretion at urine cadmium ratios of 1 nmol mmol⁻¹ creatinine and lower has been shown to be the result of the variable diuresis among participants in an epidemiological study (see also Section 7.3.5). Although creatinine correction is helpful to some extent, there is a residual dependence on diuresis.

Urinary excretion of proteins influences the excretion of cadmium and this relationship can cause important confounding, especially when studying the effects of cadmium on the kidneys. As pointed out in sections 7.3.4 and 7.3.5, the relationship between kidney cadmium and urine cadmium may be confounded by proteinuria. The statistical associations between LMM protein excretion and low-level urinary cadmium reported in the general population are now considered to be due to physiological associations driven by the inter-individual variations in the tubular uptake of LMM proteins, and thus are without causal relation to cadmium exposure (see Section 7.3.4).

It has been shown (see Sections 6.1.2 and 7.3) that urinary cadmium, especially at low concentrations, is influenced by factors related to renal function. If these factors are influenced by the outcomes of the study, confounding is taking place. Most of the presently available studies are not corrected for the factors shown to cause confounding and the associations observed at low level exposures (particularly at urinary cadmium/creatinine ratios below 1 nmol mmol⁻¹) should not be interpreted as a sign of a toxic effect of cadmium until appropriate control of the confounding factors has been ascertained.

In summary, there is sufficient evidence from epidemiological studies supported by TKTD calculations that long-term cadmium exposures in humans cause kidney dysfunction with LMM proteinuria. Exposures with urinary cadmium/creatinine ratios of 2 nmol mmol⁻¹ and higher cause such effects in a susceptible subsection the population. Several epidemiological studies have reported statistically significant associations between urine cadmium below 2 nmol mmol⁻¹ creatinine and LMM proteinuria. The present group of scientists consider that these associations are likely to be a result of confounding, particularly at urine-cadmium below 1 nmol mmol⁻¹ creatinine. The possible causal relationships at 1–2 nmol mmol⁻¹ creatinine require further studies employing adequate measures to control for confounding.

The estimated lowest observed adverse effect level (LOAEL) of 2 nmol mmol⁻¹ creatinine of cadmium in urine is supported by TKTD calculations (see Section 5.4) showing that such a cadmium fraction in urine corresponds to an average cadmium mass fraction in kidney cortex of 120 µg g⁻¹. A mass fraction of 84 µg g⁻¹ of cadmium in kidney cortex is the estimated lower confidence limit associated with a 10 % probability of cadmium induced LMM proteinuria. The urinary cadmium/creatinine ratio corresponding to this kidney cortex mass fraction was estimated (see Section 5.4) to be 1.4 nmol mmol⁻¹ creatinine and the daily dietary intake per kg body mass 1 µg kg⁻¹ day⁻¹. At a dietary intake of 0.6 µg kg⁻¹ day⁻¹, 90 percent of the population is expected to have a urinary cadmium below 2 nmol mmol⁻¹ creatinine (see Section 5.4). Based on the combined evidence from TKTD modeling and epidemiological observations we estimate the probability at <5–10 percent for developing LMM proteinuria from long term dietary cadmium exposures of 0.6 – 1 µg kg⁻¹ day⁻¹. The lower percentage applies to the lower intake when the whole population is considered and the higher percentage applies when the higher intake and the most sensitive group are considered. These estimates are derived from the mathematical models and no additional safety factor or uncertainty factor has been added.

8.2.4 Bone effects

It is well known that excessive exposure to cadmium through the diet may cause a combination of kidney dysfunction and bone disease in the form of osteoporosis and osteomalacia. This disease occurs primarily in a limited cadmium-polluted area in Toyama prefecture, Japan, and is known as Itai-itai disease. This bone disease is to a large extent secondary to cadmium induced kidney injury, and Itai-itai disease is considered as a form of renal osteomalacia with classical biochemical changes. There is a lack of TKTD models for bone effects of cadmium and, thus, an evaluation of epidemiological studies in relation to risk calculations from such models is not possible. Studies in Belgium, Sweden, Japan, and China published 1999–2004 (see Section 7.4) show that bone effects related to cadmium exposure have also occurred in other countries, as well as in areas of Japan outside the area where Itai-itai disease was first identified.

Sixteen epidemiological studies published after 2004 examine adverse effects of cadmium on the skeleton at lower cadmium exposures (see Section 7.4). Statistically significant associations were found between markers of cadmium exposure and decreased BoneMD, risk of osteoporosis or risk of fractures. Two of the studies described relationships after previous high exposures occupationally or in the general environment and do not show risks in the low dose range. In the original studies of Itai-itai disease and in the later high dose studies, exposures gave rise to cadmium values in blood or urine of $20 \mu\text{g L}^{-1}$ or $20 \text{ nmol mmol}^{-1}$ creatinine and even higher. These exposures most probably are causally related to the observed adverse effects on bone tissue. Although it is difficult to determine the lowest cadmium levels related to a risk of adverse effects on bones, it seems reasonable to consider such a risk to be present for cadmium exposures leading to urinary cadmium of 5 nmol mmol^{-1} creatinine (or blood cadmium $5 \mu\text{g L}^{-1}$) and higher because of the consistent dose-response relationships at this and higher exposures. Among studies with lower exposures, although a majority have positive associations there are four studies (see Section 7.4.10) without statistically significant associations between cadmium exposure and BoneMD. Studies in Sweden and other countries (see Section 7.4.11) reported relationships between cadmium exposure and bone effects in terms of decreased BoneMD and increased occurrence of fractures at urine cadmium $0.75\text{--}2 \text{ nmol mmol}^{-1}$ creatinine.

It cannot be excluded that exposure giving rise to less than 5 nmol mmol^{-1} creatinine may give rise to bone effects, but evidence would be welcome that could rule out the possibility that the observed higher urinary cadmium levels in the studied populations are caused by nutritional deficiencies and that the bone effects are caused by factors unrelated to cadmium, possibly by low dietary vitamin D intakes which probably are related to high cadmium intakes. In addition to better information about nutritional factors, more knowledge is needed about toxicodynamics, such as tissue levels of cadmium causing decalcification of bone, and about the toxicokinetics of cadmium in bone, in order to enable a causal interpretation of the epidemiologic observations with urinary cadmium in the range $0.5\text{--}5 \text{ nmol mmol}^{-1}$ creatinine. Very few epidemiological studies include adequate information on nutritional factors like Vitamin D, calcium, and other essential nutrients. We therefore consider that there are problems with causation for the observations of bone effects at cadmium exposures below 5 nmol mmol^{-1} creatinine and we consider this level as the LOAEL. Because of the uncertainties at lower exposures, currently it is not possible to establish a satisfactory NOAEL for this effect.

9 Tolerable dietary intakes or occupational exposure limits for inhaled cadmium set by other organizations

The Joint FAO/WHO Expert Committee on Food Additives (JECFA), 2011 [26]) recommended a provisional tolerable monthly intake (PTMI) of cadmium through food of $25 \mu\text{g kg}^{-1}$ body weight (body mass). This recommendation corresponds to an intake of $0.8 \mu\text{g kg}^{-1}$ body mass per day. The previous recommendation by JECFA, 2004 [30] of $7 \mu\text{g kg}^{-1}$ body weight per week ($1 \mu\text{g kg}^{-1}$ body mass per day) was withdrawn and replaced by the new monthly recommendation. The change from a weekly to a monthly value is based on the very long

biological half-life of cadmium. The assessment by JECFA, 2011 took into consideration all previous evaluations by WHO including the IPCS Health Criteria Document/IPCS 1992 [6]). This JECFA [26] recommendation was based on a meta-analysis of epidemiological observations of the relationship between urinary cadmium and urinary excretion of beta-2-microglobulin (see Section 7.3.1, Fig. 1). WHO/JECFA used the BMDL value, $5.24 \mu\text{g cadmium g}^{-1} \text{ creatinine}$, as a point of departure in further calculations. The one-compartment model of Amzal *et al.*, 2009 [66] was used and the lower bound of the 5th percentile dietary cadmium exposure that equates to the breakpoint was estimated to be $0.8 \mu\text{g kg}^{-1} \text{ body mass per day}$ or $25 \mu\text{g kg}^{-1} \text{ body mass per month}$. According to JECFA, 2011 [26], estimated exposures to cadmium through the diet for all age groups including consumers with high exposure and subgroups with special dietary habits (e.g. vegetarians) are below the PTMI. The PTMI is set to allow a certain variation of intake during a month, provided the PTMI is not exceeded. This recommendation by JECFA is used worldwide.

In Europe, the recommendations by the European Food Safety Authority (EFSA) are of particular interest. For cadmium EFSA, 2009 [2] recommended a tolerable weekly intake (TWI) of $2.5 \mu\text{g kg}^{-1} \text{ body weight}$ (corresponding to a daily intake of $0.36 \mu\text{g kg}^{-1} \text{ body mass}$). EFSA used all available information including the extensive review by a European Union Risk Assessment Report (EU RAR) [284]. A meta-analysis of 54 epidemiological studies was performed by EFSA [5] and this meta-analysis was also used by WHO/JECFA, 2011 [26] (see above). Using this meta-analysis (see Section 7.3.1., Fig. 1) EFSA derived BMDL-05 values for urinary cadmium between 3.62 and $5.95 \text{ nmol mmol}^{-1} \text{ creatinine}$ depending on beta-2-microglobulin cut off values and subpopulation groups included, and used $4 \text{ nmol mmol}^{-1} \text{ creatinine}$ as a point of departure. An adjustment factor of 3.9 was applied to compensate for the use of group means instead of individual values in the meta-analysis, and urinary cadmium of $1.0 \text{ nmol mmol}^{-1} \text{ creatinine}$ was derived as a value where 95 percent of a population would not exceed a urinary excretion of $0.3 \text{ mg g}^{-1} \text{ creatinine}$ of beta-2-microglobulin (upper bound of normal range). Based on the toxicokinetic model of Amzal *et al.*, 2009 [66], the dietary intake was derived at which 95 percent of a population would be below $1 \text{ nmol mmol}^{-1} \text{ creatinine}$ of urinary cadmium. This intake is $2.5 \mu\text{g kg}^{-1} \text{ body mass per week}$ ($0.36 \mu\text{g kg}^{-1} \text{ body mass per day}$). Thus, a recommendation was issued of a TWI of $2.5 \mu\text{g kg}^{-1} \text{ body mass}$. The mean dietary exposures in European countries are close to or slightly exceed the TWI [2]. Subgroups such as vegetarians, children, and people living in contaminated areas may exceed the TWI about two-fold. EFSA further stated that dietary exposure to cadmium at the population level should be reduced.

In the United States, the Agency for Toxic Substances and Disease Registry (ATSDR) published an extensive literature review in their Toxicological Profile on cadmium in 2012 [71] and issued a Minimal Risk Level (MRL) for chronic duration oral exposure of $0.1 \mu\text{g day kg}^{-1}$. The corresponding urinary cadmium was given as $0.2 \mu\text{g g}^{-1} \text{ creatinine}$. ($0.2 \text{ nmol mmol}^{-1} \text{ creatinine}$). The MRL was derived based on an estimated urinary cadmium point of departure of $0.5 \mu\text{g g}^{-1} \text{ creatinine}$.

The Scientific Committee on Occupational Exposure Limits (SCOEL) of the European Union published a recommendation for Cadmium in 2010 [122]. Based on available evidence the committee estimated a LOAEL for respiratory effects in workers at urinary cadmium of $3 \text{ nmol mmol}^{-1} \text{ creatinine}$. A LOAEL for renal effects in workers was set at a urinary cadmium of $5 \text{ nmol mmol}^{-1} \text{ creatinine}$. For renal effects in the general population, a LOAEL of $2 \text{ nmol mmol}^{-1} \text{ creatinine}$ was set. The reason for a lower level in the general population compared to workers is that there are proportionately more people with diabetes in the general population and diabetics are more vulnerable to renal damage. A LOAEL for bone effects in the general population was set at $3 \text{ nmol mmol}^{-1} \text{ creatinine}$.

A biological limit value (BLV) was set at a urinary cadmium of $2 \text{ nmol mmol}^{-1} \text{ creatinine}$. A comment was given that cadmium does not seem to induce an excess of lung cancer at the lowest exposures causing renal and respiratory toxicity [199].

In Section 7.2, data was given supporting the opinion that the lowest exposures to cadmium oxide in air, giving rise to respiratory effects, are $500 \mu\text{g years m}^{-3}$ of cadmium in inhaled workroom air: for example, 40 years of exposure at $12.5 \mu\text{g m}^{-3}$. SCOEL used a default extrapolation factor of 3 (LOAEL to NOAEL) and $4 \mu\text{g m}^{-3}$ (respirable fraction) was recommended as an Occupational Exposure Limit (OEL), i.e. exposure for 8 h day⁻¹, 5 days week⁻¹.

10 Conclusions and recommendations

Cadmium is an element that everybody is exposed to at low variable concentrations in food. Smokers and some industrial workers have additional exposure. An increase in exposure through food may have occurred in many industrialized countries from the 1920s to 1970, but no further increase has been shown in the following four decades up to the present. Daily average intakes below 20 μg per day ($178 \text{ nmol day}^{-1}$) were reported in the United States of America and in most European countries in the 2000s. In Japan there has been a decrease of cadmium exposures in the general population from between 59 and 113 μg per day ($525\text{--}1005 \text{ nmol day}^{-1}$) in the 1960s to around 25 μg per day ($222 \text{ nmol day}^{-1}$) in the period 1991–1997. A large number of adverse effects have been shown in experimental animals and in workers exposed to high doses of cadmium. In addition, a large number of epidemiological studies have reported statistically significant relationships between exposure measurements and (or) exposure biomarkers and a number of adverse health effects. Cadmium is recognized as a human carcinogen, mainly based on occupational studies of lung cancer, but other cancers have also been reported (see Section 7.5). The carcinogenicity of cadmium should be considered in risk and hazard assessment, even though a quantitative description of dose-response relationships is not possible. The implication is that there is no risk level considered ‘safe’, and that extrapolation to a ‘virtually safe’ low level of exposure using mathematical models is not appropriate. Cardiovascular disease has been associated with cadmium exposure in a number of recent epidemiological studies, but more evidence is needed in order to establish causality and dose-response relationships.

Adequate evidence of dose-response relationships and critical effects is only available for kidney effects and, to some extent, bone effects. As to the kidney effects, some uncertainty exists because of confounding factors operating at low-level exposures. For bone effects there are also problems as to the interpretation of available data at low exposure. However, they seem (at least partly) to be independent of the kidney effects, they occur at approximately the same exposure as the kidney effects, and their medical consequences are often serious for the osteoporotic individual and for society. Thus, the choice of a critical effect is not an easy one. As in some previous risk assessments by others, the present group of scientists concludes that there is evidence showing dose-effect and dose-response relationships between cadmium exposure and kidney effects in terms of LMM proteinuria. Long term cadmium exposures with urine cadmium of 2 nmol mmol^{-1} creatinine cause such effects in a susceptible subsection of the population. Higher exposures cause LMM proteinuria in a larger proportion of the population in a dose related manner, and more pronounced LMM protein excretion occurs. This dose-effect and dose-response estimate is supported by TK/TD modelling. Statistically significant associations that have been reported between urinary cadmium lower than 2 nmol mmol^{-1} creatinine and LMM proteinuria are confounded by diuresis, particularly at urine cadmium below 1 nmol mmol^{-1} creatinine.

Bone effects in terms of osteomalacia and osteoporosis (Itai-itai disease) are well established as an adverse effect of high dose long-term exposures to cadmium through the diet. A considerable number of epidemiological studies have reported statistically significant associations between biomarkers of cadmium exposure and bone demineralization and (or) increased incidence of fractures, some at cadmium/creatinine ratios in urine as low as 0.75 $\mu\text{g g}^{-1}$ creatinine ($0.75 \text{ nmol mmol}^{-1}$ creatinine). It is difficult to determine the lowest cadmium exposures giving rise to such effects because of variable findings, potential confounding, and a lack of TKTD models for bone effects. Because of the consistent dose-response relationships at higher exposures, the present group of scientists found it reasonable to consider exposures leading to urinary cadmium of 5 $\mu\text{g g}^{-1}$ creatinine (5 nmol mmol^{-1} creatinine) and higher as related to a risk of bone effects. It may be that lower exposures give rise to bone effects, but possible problems of causation exist. We therefore cannot define a no-effect level for this effect.

The present group of scientists selected the kidney effects (LMM proteinuria) as critical effects and noted that bone effects may occur at exposure levels similar to those giving rise to kidney effects. LMM proteinuria is caused, in a susceptible subsection of the population, by long-term cadmium exposure giving rise to a urinary cadmium/creatinine ratio of 2 nmol mmol^{-1} creatinine. Population exposures thus should be kept sufficiently low to prevent higher urinary cadmium than this. Oral intakes of cadmium corresponding to a low probability of reaching such urine values in a susceptible subsection of the population (women) were

estimated from mathematical models in Section 5.4 as 0.6–1 $\mu\text{g kg}^{-1}$ body mass per day (see also Section 8.2.3). For inhalation of industrial air 2.7 $\mu\text{g m}^{-3}$ was estimated (see Section 5.4).

Because of the uncertainties concerning dose-response relationships for kidney effects, bone effects and cancer from long-term low-level exposure, a numerical value for a no effect level cannot be determined and we recommend that cadmium exposures be kept as low as possible. The margin of safety between current exposures in many countries and exposures giving rise to toxic effects is small or non-existent and cadmium pollution causes considerable public health problems. There is a need to restrict cadmium pollution as much as possible, particularly as it is known that cadmium disappears very slowly from agricultural soils.

List of abbreviations

Abbreviations, Acronyms and Initialisms

A1M	α_1 -microglobulin
AAS	Atomic absorption spectrometry
ADME	Absorption, distribution, metabolism and excretion
ATSDR	Agency for Toxic Substances and Disease Registry
B2M	β_2 -microglobulin
BMD	Benchmark dose
BMDL	Benchmark dose lower confidence limit
BoneMD	Bone mineral density
BMI	Body mass index
BMR	Benchmark response, <i>i.e.</i> additional risk above background.
CC16	Club Cell protein 16 also named Clara Cell protein 16
CI	95 percent confidence interval
CDC	Centers for Disease Control and Prevention (USA)
CVD	Cardiovascular disease
DXA	Dual-energy X-ray absorptiometry
EEA	European Environment Agency
ECB	European Chemicals Bureau
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
ESRD	End-stage renal disease
EU	European Union
FAO	Food and Agriculture Organization (United Nations)
FFQ	Food Frequency Questionnaire
eGFR	Estimated glomerular filtration rate
HR	Hazards ratio
IAEA	International Atomic Energy Agency
IARC	International Agency for Research on Cancer
ICOH	International Commission on Occupational Health
ICP-MS	Inductively coupled plasma mass spectrometry
ICRP	International Commission for Radiological Protection
ICSC	International Chemical Safety Cards (ILO)
ILO	International Labour Organization
IPCS	International Program on Chemical Safety (UNEP/ILO/WHO)
IUPAC	International Union of Pure and Applied Chemistry
JECFA	Joint (FAO/WHO) Expert Committee on Food Additives

LMM	Low molecular mass
LOAEL	Lowest observed adverse effect level
MT	Metallothionein
NAA	Neutron activation analysis
NAG	<i>N</i> -Acetyl- β -D-glucosaminidase
NAS	National Academy of Sciences (USA)
NHANES	National Health and Nutrition Examination Survey (USA)
NIOSH	National Institute of Occupational Safety and Health (USA)
NOAEL	No observed adverse effect level
OR	Odds ratio
PBTK	Physiologically based toxicokinetics
PEL	Permissible exposure limit
PHIME	Public health impact of long-term low-level mixed elements exposure in susceptible population strata
PK	Pharmacokinetic
PTMI	Provisional tolerable monthly intake
RBP	Retinol-binding protein
REACH	Registration, Evaluation, Authorization, and Restriction of Chemicals (EU)
ROS	Reactive oxygen species
RR	Relative risk
SCOEL	Scientific Committee on Occupational Exposure Limits (European Union)
SCTM	Scientific Committee on the Toxicology of Metals, ICOH
SMR	Standardized mortality rate
TEF	Toxic equivalency factor
TEQ	Toxic equivalent
TKTD	Toxicokinetic – toxicodynamic
T-score	Number of standard deviations above or below the mean of BoneMD for a healthy 30 years old adult of the same sex and ethnicity as the patient
Z-score	Number of standard deviations above or below the mean of BoneMD for the patient's age, sex and ethnicity
UNEP	United Nations Environment Programme
USEPA	United States Environmental Protection Agency
USFDA	United States Food and Drug Administration
WHO	World Health Organization

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