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## **Contaminants in soil: updated collation of toxicological data and intake values for humans Cadmium**

**Better Regulation Science Programme**  
Science report: SC050021 / TOX 3

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- 1) *Science Report SC050021/SR2: Human health toxicological assessment of contaminants in soil.*
- 2) *Science Report SC050021/SR3: Updated technical background to the CLEA model.*
- 3) *Science Report SC050021/SR4: CLEA Software (Version 1.04) Handbook.*
- 4) *CLEA Software version 1.04 (2009)*
- 5) *Toxicological reports and Soil Guideline Value briefings*

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Steve Killeen

**Head of Science**

# Executive summary

This report, one of a number on the assessment of risks to human health from contaminants in soil, presents key data and expert opinions on the toxicology and intake of cadmium. It provides an update to an earlier report by the Department for Environment, Food and Rural Affairs (Defra) and the Environment Agency published in March 2002.

The report is based on findings identified in a series of literature searches, the latest of which was undertaken in January 2009. These findings, together with evaluations of national, European and international expert groups, are used to recommend Health Criteria Values (HCVs) and to estimate mean daily intakes (MDIs) for cadmium in the UK.

## Chemical overview

Cadmium is a transition metallic element widely distributed at low levels in the Earth's crust. Some enters the general environment from the natural weathering of minerals, forest fires and volcanoes, but much larger amounts are released by human activities.

The soil chemistry of cadmium is based on the divalent cation. The hydrated free ion is the main species of cadmium in soil solution, although it also forms complexes with common anions including chloride and bicarbonate. Organic matter is more effective than inorganic constituents in reducing the mobility and bioavailability of cadmium.

## Pharmacokinetics

Ingested cadmium is generally assumed to be poorly absorbed from the gastrointestinal tract, with studies often finding less than 5% absorption, though higher levels have been reported. Absorptions of 3–10% have been used in expert group risk assessments. The absorption of inhaled cadmium is determined principally by the size and *in vivo* solubility of the particles, but values in the order of 30–50% have been described. Dermal absorption is very low.

Absorbed cadmium is widely distributed in the body, accumulating principally in the kidneys and liver. Exposure induces the production of the protein metallothionein in the tissues which is able to bind cadmium. This binding is generally considered to reduce toxicity. Cadmium has a very long biological half-life – risk assessments often assume values of around 14 years. The concentration of cadmium excreted in the urine correlates well with the concentration in the kidney.

## Toxicity

The principal toxicity targets of long-term exposure to cadmium are the kidney and bone. The dose–response of the renal effects are better characterised and so risk assessments of threshold toxicity are generally based on this. If the accumulated cadmium exceeds a critical concentration in the kidney, the tubule cells become damaged and renal function is impaired. Renal cadmium accumulation also affects vitamin D metabolism, which causes disturbances in calcium balance and can decrease the mineral content of bone resulting in osteoporosis and osteomalacia.

The International Agency for Research on Cancer has classified cadmium as “carcinogenic to humans” based on lung cancer seen in occupationally exposed workers following inhalation exposure. There is also weaker evidence of an association with other cancers. Cadmium exposure may result in damage to genetic material, particularly at the level of the chromosome, and this genotoxicity is expected to underlie the tumour formation. Most expert groups have generally assumed that there may be no threshold to the genotoxicity (and hence the carcinogenicity), although a

recent evaluation concluded that the mechanisms are indirect – production of reactive oxygen species and inhibition of DNA repair – and would thus demonstrate a threshold.

Other effects of cadmium, including toxicity to the respiratory tract and neurotoxicity, may be elicited at exposures above those causing renal and bone effects. Laboratory animal studies also indicate that cadmium may produce developmental toxicity; it is unclear from the data whether or not effects on the developing foetus may occur at exposures lower than those causing maternal toxicity.

### Health Criteria Values and risk assessment

An inhalation Tolerable Daily Intake (TDI<sub>inh</sub>) of 0.0014 µg kg<sup>-1</sup> bodyweight (bw) day<sup>-1</sup> (1.4 ng kg<sup>-1</sup> bw day<sup>-1</sup>) has been derived to protect against kidney toxicity. This HCV is also expected to protect against potential carcinogenic effects.

An oral Tolerable Daily Intake (TDI<sub>oral</sub>) of 0.36 µg kg<sup>-1</sup> bw day<sup>-1</sup> (360 ng kg<sup>-1</sup> bw day<sup>-1</sup>) is recommended, also to protect against kidney toxicity.

The effects of dermal exposure to cadmium are not expected to be significant in view of its limited absorption across this skin.

Kidney toxicity is a critical effect both of oral and of inhalation exposure; therefore, the potential for combined exposure to cause toxicity should be considered in a risk assessment where exposure is via more than one route.

The key determinant of cadmium's renal toxicity potential is its chronic accumulation in the kidney. Chronic exposure to levels in excess of either the TDI<sub>oral</sub> or the TDI<sub>inh</sub> might be associated with an increase in kidney disease in a proportion of those exposed, but (small) exceedances lasting for shorter periods are of less consequence. Therefore, derivation of SGVs using average lifetime exposure seems appropriate.

### Mean daily intakes from non-soil sources

The adult oral mean daily intake (MDI<sub>oral</sub>) of cadmium from its presence in food and drinking-water is estimated to be 13.4 µg day<sup>-1</sup>; the adult inhalation mean daily intake from ambient air (MDI<sub>inh</sub>) is estimated to be 0.02 µg day<sup>-1</sup>.

### HCV and MDI values for cadmium

Parameter	Units	Oral	Inhalation
MDI	µg day <sup>-1</sup>	13.4	0.02
MDI for 70-kg adult	µg kg <sup>-1</sup> bw day <sup>-1</sup>	0.19	0.0003
MDI for 20-kg child	µg kg <sup>-1</sup> bw day <sup>-1</sup>	0.50 <sup>a</sup>	0.0007 <sup>a</sup>
<b>TDI</b>	<b>µg kg<sup>-1</sup> bw day<sup>-1</sup></b>	<b>0.36</b>	<b>0.0014</b>

<sup>a</sup> See Environment Agency (2009) for details of MDI conversion factors.

### Summary of changes to recommendations

The 2002 TOX report recommended an oral TDI value of 1 µg kg<sup>-1</sup> bw day<sup>-1</sup> based on a TDI first set by the Joint FAO/WHO Expert Committee on Food Additives in 1972. More recent data and evaluations – in particular, the 2009 evaluation of the European Food Safety Authority – are the foundation of the TDI<sub>oral</sub> proposed herein. The ID<sub>inh</sub> of 0.001 µg kg<sup>-1</sup> bw day<sup>-1</sup> recommended in the 2002 TOX report has been removed from this report in view of the mechanisms of genotoxicity now believed to underlie the

observed cancers. The  $\text{TDI}_{\text{inh}}$  of  $0.0014 \mu\text{g kg}^{-1} \text{bw day}^{-1}$  recommended herein is based on the recommendations from a European Commission Working Group.

# Acknowledgements

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The Environment Agency is also grateful for the valuable inputs from various government agencies and departments, particularly the Department of Health, Health Protection Agency and Food Standards Agency. It would also like to thank the Medical Research Council Institute for Environment and Health for peer reviewing the 2002 document.

# Contents

<b>1</b>	<b>Introduction</b>	<b>1</b>
1.1	Update to R&D Publication TOX 3	1
1.2	Background	1
1.3	Advice on using this report	2
<b>2</b>	<b>Chemical overview</b>	<b>4</b>
<b>3</b>	<b>Toxicology</b>	<b>5</b>
3.1	Literature sources	5
3.2	Pharmacokinetics	5
3.3	Acute toxicity	8
3.4	Repeated dose toxicity	8
3.5	Reproductive and developmental toxicity	11
3.6	Genotoxicity	12
3.7	Carcinogenicity	12
3.8	Summary	14
<b>4</b>	<b>Derivation of Health Criteria Values</b>	<b>16</b>
4.1	Joint FAO/WHO Expert Committee on Food Additives	16
4.2	WHO guidelines for drinking-water quality	17
4.3	WHO air quality guidelines for Europe	17
4.4	European Food Safety Authority	17
4.5	EU Working Group on Arsenic, Cadmium and Nickel Compounds	19
4.6	EU Risk Assessment Report	19
4.7	EU Scientific Committee on Toxicity, Ecotoxicity and the Environment	21
4.8	Dutch National Institute for Public Health and the Environment	21
4.9	US Environmental Protection Agency	22
4.10	US Agency for Toxic Substances and Disease Registry	22
4.11	Discussion	24
<b>5</b>	<b>Background intake</b>	<b>27</b>
5.1	Food	27
5.2	Water	27
5.3	Air	27
5.4	Other sources	27
5.5	Estimation of mean daily intakes	28
<b>6</b>	<b>Conclusions</b>	<b>29</b>
	<b>References</b>	<b>30</b>

<b>List of abbreviations</b>	<b>40</b>
<b>Appendix – Literature search</b>	<b>42</b>



# 1 Introduction

## 1.1 Update to R&D Publication TOX 3

This report presents key data and expert opinion on the human toxicology and non-soil intakes of cadmium. It updates and replaces R&D Publication TOX 3 published in March 2002 (Defra and Environment Agency, 2002), taking into account:

- updates to the toxicological framework document which describes how the human toxicity of chemical soil contaminants is assessed (Environment Agency, 2009);
- further review of the scientific literature on the toxicology of cadmium and the findings and opinion of national, European, and international expert groups up to January 2009 (see Appendix).

## 1.2 Background

The main purpose of this report is to provide technical guidance to regulators and their advisors in support of the statutory regimes addressing land contamination, particularly Part 2A of the Environmental Protection Act 1990 and development control under the Town and Country Planning Acts.

Part 2A defines the term *contaminated land* according to whether or not it poses a significant risk to human health and/or the environment.

In relation to health effects not attributable to radioactivity, it considers land to be *contaminated land* where it:

“... appears to the local authority in whose area the land is situated to be in such a condition by reason of substances in, on or under the land that (a) significant harm [to human health] is being caused or there is a significant possibility of such harm being caused.”

Statutory guidance (Defra, 2006) explains that *significant harm* to a person would include such health effects as death, disease,<sup>1</sup> serious injury, genetic mutation, birth defects or the impairment of reproductive function. The definition of *significant harm* therefore encompasses a broad range of possible health outcomes from chemical exposure.

Land contamination is a material consideration within the planning regime. A planning authority has to consider the potential implications of contamination both when it is developing structure or local plans (or unitary development plans) and when it is considering applications for planning permission. *Planning Policy Statement 23* (England) (PPS 23) (ODPM, 2004) explains the relationship between planning and Part 2A. In the granting of planning permission for new development including permission to carry out remediation, PPS 23 states that remediation must remove unacceptable risk to human health and make the site suitable for its intended use. As a minimum, after carrying out a development and commencement of its use, the land should not be capable of being determined as *contaminated land* under Part 2A.

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<sup>1</sup> For the purpose of the Statutory Guidance, disease is taken to mean an unhealthy condition of the body or part of it and can include, for example, cancer, mental dysfunction, liver dysfunction or extensive skin ailments.

## 1.3 Advice on using this report

This report reviews the key toxicological literature and expert opinions on health effects arising from exposure to cadmium. It has been prepared by the Environment Agency with the support of the Health Protection Agency (HPA) and the Food Standards Agency (FSA).

This report recommends one or more Health Criteria Values (HCVs) for use in assessing the risks to health from long-term human exposure to cadmium in soil. HCVs are a critical part of the risk assessment process. They are used subsequently in the derivation of Soil Guideline Values (SGVs), which are scientifically-based generic assessment criteria used to simplify the screening of land contamination (Defra and Environment Agency, 2004). HCVs can also be used to derive site-specific assessment criteria for soil as part of any Detailed Quantitative Risk Assessment.

The HCVs set out in this report represent levels of minimal or tolerable risk from long-term human exposure to chemicals in soil. They represent a baseline and health protective position to minimise risks of *significant harm*. They do not represent thresholds above which there is an *unacceptable intake* or a *significant possibility of significant harm* in the context of Part 2A, but they can be a useful starting point for such an assessment (Defra, 2008). Science alone cannot answer the question of whether or not a given possibility of *significant harm* is significant, since what is either significant or unacceptable is a matter of socio-political judgment and the law entrusts decisions on this to the enforcing authorities (Defra, 2008).

In the context of Part 2A, an assessor using the HCVs in this report can conclude that (Defra, 2008):

- human exposure at or below the HCV is unlikely to represent a *significant possibility of significant harm*;
- human exposure above the HCV might represent a *significant possibility of significant harm*, with the significance linked to the margin of exceedance, the duration and frequency of exposure, and other factors that the enforcing authority may wish to take into account.

The information presented in this report is intended for technical professionals familiar with the assessment of the risks posed to human health by land contamination. It should be read in conjunction with Science Report SC050021/SR2 *Human Health Toxicological Assessment of Contaminants in Soil* (Environment Agency, 2009), which introduces and describes the terms and general technical approaches used in this review of cadmium.

Although HCVs are an important quantitative tool for judging the health risks associated with a particular level of human exposure, they should not be used in isolation from the rest of the information presented in this report. Further understanding of the mechanisms of toxicity and the range of potential health effects are important to assessing the risks posed by cadmium at any level of exposure, both individually and when combined with other chemicals present.

The remainder of this report is separated into the following sections.

Section 2 provides a short overview of the chemistry of cadmium, its main uses and its behaviour in the environment with particular reference to soils.

Section 3 presents information obtained from the literature search on the toxicity of cadmium (pharmacokinetics, acute toxicity, repeated dose toxicity, reproductive and developmental toxicity, genotoxicity and carcinogenicity).

Section 4 sets out the HCVs derived by various expert groups worldwide.

Section 5 gives estimates of exposure to background levels of cadmium in food and water, air and other sources.

Section 6 presents the conclusions drawn from the literature review including the recommendations for HCVs.

## 2 Chemical overview

Cadmium is a transition metallic element found in Group 2B of the periodic table. Although it has possible valencies of 0, +1 and +2, it forms almost all of its compounds in the +2 oxidation state.

Cadmium has a low crustal abundance but is widely distributed in rocks and soils. Some enters the general environment from the natural weathering of minerals, forest fires and volcanoes, but much larger amounts are released by human activities. These include production of non-ferrous metals and of iron and steel, combustion of fossil fuels, waste incineration, and application of phosphate fertiliser and sewage sludges to land (IPCS, 1992). In the UK, the major inputs of cadmium to arable land are from atmospheric deposition and the use of phosphate fertiliser (Hutton and Symon, 1986).

Cadmium is mainly used in the production of batteries, but also in metal coatings to improve resistance to corrosion by alkalis, salt water and the atmosphere. An important proportion of cadmium metal is subsequently converted to cadmium oxide powder, which constitutes the principal raw material in the production of other cadmium compounds, which have value as pigments or PVC stabilisers. Cadmium salts are also used in glassmaking, and the oxide improves the heat resistance or high temperature properties of nitrile rubbers or plastics (EC, 2007).

Cadmium metal is slowly oxidised in moist air and, when heated in air, rapidly forms cadmium oxide (USEPA, 1999). Cadmium may bind to proteins and other organic molecules, and form salts with organic acids; the resulting compounds are regarded as inorganic in character. The covalent binding of cadmium to carbon (to produce organo compounds) is not known to occur in nature (IPCS, 1992).

Cadmium sulphide, cadmium carbonate and cadmium oxide are almost insoluble in water, but can be converted to water-soluble salts by the action of acids or of light and oxygen. The sulphate, nitrate and halides are water-soluble (IPCS, 1992).

The soil chemistry of cadmium is based on the divalent cation. The hydrated free ion is the main species of cadmium in soil solution but it is also known to form complex ions with chloride, hydroxyl groups, and bicarbonate (Alloway, 1995). Soluble and insoluble complexes with organic matter can also be important although cadmium forms less stable complexes with humic and fulvic acids than those formed by copper and lead (Alloway, 1995; Kabata-Pendias and Mukherjee, 2007). Organic matter is more effective than inorganic constituents in reducing the mobility of cadmium. Adsorption is decreased, and mobility increased, with decreasing pH (ATSDR, 1999).

# 3 Toxicology

## 3.1 Literature sources

Major reviews of the literature on the toxicity of cadmium have been published by:

- Health and Safety Executive (HSE, 1983, 1991);
- Health Protection Agency (HPA, 2006);
- European Commission (EC, 2000, 2007);
- European Food Safety Authority (EFSA, 2009);
- World Health Organization (WHO, 1996, 2000);
- Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1972a, 1972b, 1989a, 2001, 2004a);
- International Programme on Chemical Safety (IPCS, 1992);
- International Agency for Research on Cancer (IARC, 1992; 1993);
- US Agency for Toxic Substances and Disease Registry (ATSDR, 1999, 2008);
- US Environmental Protection Agency (USEPA, 1985, 1992, 1994, 1999).

This section is based largely on the major conclusions of these reviews and proceedings; in general, the primary literature has not been consulted. Particular attention is given to those studies which have been used in the derivation of HCVs.

## 3.2 Pharmacokinetics

### 3.2.1 Absorption

No direct human data are available on the absorption of inhaled particulate cadmium or its compounds. As with any inhaled aerosol, absorption is determined principally by the size and *in vivo* solubility of the particles. The European Union (EU) Risk Assessment Report (RAR) for cadmium (EC, 2007) noted that the pulmonary absorption of a cadmium oxide dust would be in the range of 10–30%, whereas with cadmium oxide fume this could rise to 25–50%. The large differences in blood cadmium levels between smokers and non-smokers support the relevance of respiratory absorption of cadmium (EFSA, 2009).

Ingested cadmium is generally assumed to be poorly absorbed from the gastrointestinal tract. The presence of cations such as calcium, chromium, magnesium and zinc that may compete with cadmium for absorption may reduce cadmium uptake. Hence, the bioavailability of dietary cadmium may vary depending on the food within which it is ingested (EFSA, 2009).

Some studies in which humans were given radioactive cadmium (usually as the chloride) with food indicated that the fractional uptake was about 5% (IARC, 1993). Comparisons of the body burdens of cadmium in non-smokers with estimated daily intakes from diet give estimates of cadmium absorbed from food in the range 3–5% (Morgan and Sherlock, 1984).

Women with low body iron stores had on average a fractional uptake from the gut twice as high (about 10%) as a control group of women (Flanagan *et al.*, 1978). Women with multiple pregnancies will have an increased cadmium absorption (EFSA, 2009).

A Japanese study of 38 female volunteers reported an average gastrointestinal absorption of cadmium from the diet of around 6–7%, but absorption was found to vary greatly with age. When the study participants were divided into three age groups, the average absorption in the lowest tested age group (comprising eight 20–39 year olds) was 44% (Horiguchi *et al.*, 2004). The European Food Safety Authority (EFSA), however, has noted that a high bioavailability of cadmium in young women was not confirmed by European biomonitoring data, and that there was a very large variation in absorption rates between individuals in the Horiguchi *et al.* study suggestive of a methodological basis for the apparent discrepancy between this and other studies (EFSA, 2009).

The EU RAR (EC, 2007), which was essentially based on a 2001 view of the toxicological literature, concluded that the gastrointestinal absorption rate of cadmium metal and its salts is generally below 5% when iron stores are adequate but may increase up to 5–10% when iron stores are depleted (mainly in women). A risk assessment of cadmium in food published by EFSA in 2009 similarly concluded that absorption rates of 5% for men and 10% for women were reasonable estimates of gastrointestinal cadmium absorption in Western populations (EFSA, 2009). The US Agency for Toxic Substances and Disease Registry considered these same absorption rates appropriate for use in its 2008 draft risk assessment of cadmium (ATSDR, 2008).

Rodent studies have shown a much greater uptake of ingested cadmium in young animals and neonates than in adults (EC, 2007; EFSA, 2009), although it appears to decrease fairly rapidly with age – absorption in rats decreased from 12 to 5 to 0.5% at two hours, 24 hours, and six weeks after birth (Sasser and Jarboe, 1977).

A study in which radiolabelled cadmium was given in porridge to nine 12-month old infants in the UK (Crews *et al.* (2000) also suggests that cadmium uptake may be greater than in adults. Based on the difference between the cadmium content of the meals and the amount excreted in stools collected over four days, the apparent absorption of cadmium varied between 4 and 37%, with a mean of 18%. While a longer collection time might have been required for some individuals, the bioavailability of cadmium in infants may be higher than the 5% commonly quoted for adults (EFSA, 2009).

In eight-week old male rats, the bioavailability of gavage cadmium adsorbed to an artificial soil (intended to resemble a loam soil) at a dose of approximately 150 µg Cd (650 µg Cd kg<sup>-1</sup> bw) was about half that of cadmium chloride in saline (Schilderman *et al.*, 1997). The absolute bioavailabilities were not reported in this study; therefore, it is not possible to compare the uptake of soil-adsorbed cadmium in this study with the absorption of cadmium in food – the assumed exposure pathway on which most oral risk assessments are based.

The EU RAR noted that dermal absorption of soluble cadmium salts is low (EC, 2007). In an *in vitro* study using human cadaver skin, the bioavailability of cadmium mixed as the chloride salt with a sample of soil and applied to the skin for 16 hours was low; skin penetration was between 0.06 and 0.13% of the applied dose and amounts absorbed into plasma were 0.01–0.07%. When similarly applied but as a cadmium chloride solution, 10% of the applied dose had penetrated into the skin and 0.5% into the plasma; when applied for only 30 minutes (followed by a wash with soap and water to simulate having a bath), about 2% of the applied dose was measured in the skin and no cadmium was found in the plasma (Wester *et al.*, 1992).

### 3.2.2 Distribution and metabolism

Cadmium interacts with metallothionein in the body and this affects the toxicokinetics and toxicity of cadmium. Metallothionein is a family of low molecular weight (LMW) proteins capable of binding as many as seven cadmium ions per molecule. This binding is generally considered to reduce the toxicity of cadmium, although some laboratory animal data do not support this view (Groten *et al.*, 1994; Dorian *et al.*, 1995).

The synthesis of metallothionein is induced in most tissues by exposure to cadmium and other divalent metals (ATSDR, 1999). The rate of synthesis in the liver appears to be adequate to bind all the cadmium accumulated in this organ. Metallothionein-bound cadmium released from the liver into the blood reaches the kidney, where it is cleared by glomerular filtration and taken up by the renal tubules. Here, some of the metallothionein is degraded and the cadmium released. The rate of metallothionein synthesis in the kidney is lower than in the liver and thus the kidney is more susceptible than the liver to cadmium-induced toxicity (JECFA, 2001; EC, 2007).

Cadmium that reaches the systemic circulation is widely distributed in the body, with the major portion located in the liver and kidney (JECFA, 2001; CalEPA, 2006; ATSDR, 2008). For those people chronically exposed to environmental levels of cadmium (the principal sources of which are diet and smoking), the renal cortex shows the highest concentrations. Although knowledge of cadmium's kidney half-life is an important factor in the derivation of health-based guidelines, the value of 14 years that has been commonly used comes from a study of only eight male non-smokers (Ellis *et al.*, 1979) and is thus associated with a high degree of uncertainty (CalEPA, 2006). Nonetheless, it is similar to recent calculations of a half-life of approximately 12 years based on a study of 680 menopausal Swedish women (EFSA, 2009).

Kidney concentrations are close to zero at birth and, if exposure to cadmium throughout life remains constant and low in amount, rise roughly linearly with age to a peak between ages 50 and 60, after which they level off or decline (ATSDR, 1999). The concentrations reported in different national surveys vary considerably (IPCS, 1992). In the USA and Europe, the mean cadmium concentration in the renal cortex at age 40–50 has been shown to range from 10 to 50  $\mu\text{g g}^{-1}$  (CSTEE, 2004).

Liver cadmium concentrations also begin near zero at birth, increase to typical values of 1–2  $\mu\text{g g}^{-1}$  by age 20–25, and then increase only slightly thereafter (ATSDR, 1999).

In humans chronically exposed to high levels of cadmium, whole blood cadmium may be about 30-fold higher than plasma cadmium (EC, 2007).

Women tend to exhibit higher body burdens of cadmium than men, perhaps due to a higher level of oral absorption (EC, 2007). The placenta may act as a barrier to foetal exposure; cadmium concentrations in cord blood have been shown to be about half of those in maternal blood (ATSDR, 1999).

### 3.2.3 Excretion

Cadmium excretion has been studied in people occupationally exposed to cadmium. In workers with healthy kidneys, urinary cadmium excretion correlates well with the concentration of cadmium in the kidney and can be regarded as a measure of the accumulated cadmium content of the kidney. This relationship appears to hold for both active and retired workers (Roels *et al.*, 1981; Shaikh *et al.*, 1990). In workers with cadmium-induced kidney dysfunction, urinary cadmium excretion is higher. Urinary cadmium concentrations are also used as a biomarker of long-term environmental exposure within the general population (CSTEE, 2004). Although there are a number of

toxicokinetic models available (e.g. the Nordberg-Kjellström model) that have been used to estimate oral intakes and inhalation exposures from urinary cadmium concentrations, significant uncertainties remain over their validity, as they depend on assigned values for parameters such as the gastrointestinal absorption rate and kidney half-life (CSTEE, 2004; ATSDR, 2008).

### 3.3 Acute toxicity

Cadmium is toxic to a wide range of organs and tissues. Several fatal inhalation exposures have occurred in occupational accidents. Within a few days of exposure, severe pulmonary oedema and chemical pneumonitis develop, leading to respiratory failure and death. No reliable measurements of the cadmium concentrations in air during these accidents are available, but it has been estimated that an eight-hour exposure to  $5 \text{ mg m}^{-3}$  may well be fatal (Friberg *et al.*, 1974). Concentrations of  $1\text{--}5 \text{ mg m}^{-3}$  have been described as “immediately dangerous to health”, producing facial oedema, hypotension, confusion, oliguria, metabolic acidosis, pulmonary oedema, tracheobronchitis and pneumonitis (HPA, 2006). Cough, and irritation of the throat, resulted from a nine-hour exposure to  $0.01\text{--}0.15 \text{ mg m}^{-3}$  (HPA, 2006).

Intentional ingestion of cadmium salts has been used as a means of suicide. Death results from massive fluid loss, oedema and widespread organ destruction. The doses ingested in two known fatal cases were estimated to be  $25 \text{ mg kg}^{-1}$  bodyweight (bw) (for cadmium iodide) and  $1,840 \text{ mg kg}^{-1}$  bw (for cadmium chloride); the times to death were seven days and 33 hours respectively (ATSDR, 1999). Intake by humans of food or drink containing cadmium in concentrations in excess of about  $15 \text{ mg kg}^{-1}$  gives rise to acute gastrointestinal symptoms, with vomiting, abdominal cramps and diarrhoea (HPA, 2006). The emetic dose is probably about  $70 \text{ } \mu\text{g kg}^{-1}$  bw (ATSDR, 1999). The no-effect level of a single oral dose of cadmium is estimated at  $3 \text{ mg}$  (about  $40 \text{ } \mu\text{g kg}^{-1}$  bw) (EC, 2007).

### 3.4 Repeated dose toxicity

#### 3.4.1 Effects on the kidney

For chronic exposure, by either inhalation or ingestion, the primary target organ is the kidney. Cadmium accumulated in the kidney damages the proximal tubule cells and thus affects tubular function. The first sign of this is a decreased re-absorption of filtered LMW proteins such as  $\beta_2$ -microglobulin, retinol binding protein and  $\alpha_1$ -microglobulin; hence, increased levels of these proteins occur in the urine, which is described as “tubular proteinuria” (ATSDR, 2008). Most investigators consider a cadmium-associated 10% increase in the prevalence of abnormal levels of these proteins to be indicative of cadmium-induced kidney disease in a population, although there is a lower degree of consensus on the level of the LMW proteins that is regarded as elevated or abnormal (the cut-off point) (ATSDR, 2008).

The health significance of early kidney changes is difficult to assess. The decreased re-absorption of LMW proteins is not necessarily harmful in itself but may be indicative of increased excretion of other solutes (EC, 2007). As impairment of kidney function progresses, tubular proteinuria may be followed by other symptoms such as glomerular proteinuria, i.e. urinary excretion of high molecular weight (HMW) proteins. There is some debate as to whether this indicates glomerular damage or severe tubular

damage and it must be noted that there is some excretion of HMW proteins even in the early stages of the kidney dysfunction.

Cadmium-induced proteinuria is not readily reversible and continues to progress even after cadmium exposure ceases. There is some evidence of increased mortality rates from renal diseases among groups with a history of chronic occupational exposure (Kjellström *et al.*, 1979; Ellinder *et al.*, 1985a) or environmental exposure (Lauwerys and De Wals, 1981; Nishijo *et al.*, 1995, 2006; JECFA, 2001). Concern has also been expressed that individuals with diabetes may be especially sensitive to the renal toxicity of cadmium (Buchet *et al.*, 1990; Akesson *et al.*, 2005).

Tubular dysfunction usually develops only after the cadmium concentration in the renal cortex reaches a critical level. Studies on occupationally exposed men indicated that the critical concentration of cadmium in the renal cortex (measured *in vivo* by neutron activation analysis) corresponding to a 10% incidence of proteinuria was about 200  $\mu\text{g g}^{-1}$  (wet weight) (Ellis *et al.*, 1981; Roels *et al.*, 1981, 1983). At one time, this figure was widely accepted by regulators as a benchmark of acceptability. Roels *et al.* (1981) estimated that a critical level of 200  $\mu\text{g g}^{-1}$  corresponded to a concentration of cadmium in urine of about 10  $\mu\text{g g}^{-1}$  creatinine.<sup>2</sup> Nevertheless, there were several other reports of renal effects occurring in workers with values of urinary cadmium substantially below 10  $\mu\text{g g}^{-1}$  creatinine (Roels *et al.*, 1983, Thun *et al.*, 1991). These indicated that a reassessment of the critical concentration in renal cortex was required.

A number of epidemiological studies have been of particular value to expert groups in defining the dose–response of cadmium-induced effects on the kidney. Detailed studies of volunteers from polluted and non-polluted urban and rural areas in Belgium (the Cadmibel study) (Hotz *et al.*, 1989; Buchet *et al.*, 1990; Jung *et al.*, 1993; Staessen *et al.*, 1994), from an area of Sweden with past substantial environmental pollution (Järup *et al.*, 1995a, 2000; Suwazono *et al.*, 2006), and similarly exposed Japanese (Nogawa *et al.*, 1989; Nakadaira and Nishi, 2003; Uno *et al.*, 2005; Kobayashi *et al.*, 2006; Shiizu *et al.*, 2006), US (Noonan *et al.*, 2002), Chinese (Wu *et al.*, 2001; Jin *et al.*, 2004) and German (Fels *et al.*, 1994) populations have involved the measurement of a variety of biological markers in urine and blood (reflecting various aspects of kidney function) and examination of their relationship with cadmium exposure (generally expressed in terms of urinary cadmium as it reflects long-term exposure). Equivalent studies of cadmium-exposed workers in Belgium (Buchet *et al.*, 1980; Roels *et al.*, 1993), Sweden (Ellinder *et al.*, 1985a, 1985b; Järup and Ellinder, 1994; Järup *et al.*, 1995b), Germany (Fels *et al.*, 1994), China (Chen *et al.*, 2006a, 2006b) and Singapore (Chia *et al.*, 1992) have also added to the evidence-base for establishing the renal toxic potential.

On the basis of literature published up to mid-1997, Järup *et al.* (1998) estimated that a cadmium concentration of 200  $\mu\text{g g}^{-1}$  in the renal cortex would be associated with a 30% prevalence of tubular effects in a general population.

In 2000, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) noted that a mathematical synthesis (meta-analysis) of the epidemiological studies suggested that “the risk for renal dysfunction and progression to clinical disease could be lowered if exposure to cadmium were reduced such that the concentrations of cadmium in the kidney and urine were maintained below 50  $\mu\text{g g}^{-1}$  of renal cortex and 2.5  $\mu\text{g g}^{-1}$  of creatinine, respectively” (JECFA, 2001).

In 2004, the EU Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) felt that it was not possible to determine the dose threshold for kidney toxicity with any degree of precision. CSTEE suggested that risk assessments should explore

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<sup>2</sup> Cadmium concentrations in the urine are expressed relative to the concentration of creatinine, because in a healthy kidney the level of excretion of this protein is a more stable baseline than is urine volume.

the whole range of lowest-observed adverse effect level (LOAEL) values suggested by the scientific literature and recommended that values of 0.5, 2 and 2.6  $\mu\text{g g}^{-1}$  of creatinine for urinary cadmium be used in estimations of Margins of Exposure (MOE) (CSTEE, 2004). A LOAEL for kidney toxicity of 2  $\mu\text{g g}^{-1}$  creatinine was the critical data point in the EU RAR, which was finalised taking account of the CSTEE opinion (EC, 2007).

The California Environmental Protection Agency similarly concluded that proteinuria indicative of renal damage begins to occur when urinary cadmium levels exceed 2–5  $\mu\text{g g}^{-1}$  creatinine (CalEPA, 2006).

Studies of cadmium-exposed populations in Sweden (Akesson *et al.*, 2005; Suwazono *et al.*, 2006), Japan (Uno *et al.*, 2005; Kobayashi *et al.*, 2006; Shimizu *et al.*, 2006), China (Hong *et al.*, 2004; Jin *et al.*, 2004) and Thailand (Saturug *et al.*, 2004) published subsequently suggest there may be significant changes in biomarkers of kidney function at urinary cadmium concentrations of around 1  $\mu\text{g g}^{-1}$  creatinine or below. In its 2009 evaluation, EFSA used 1  $\mu\text{g g}^{-1}$  creatinine as the critical level, based on increases in  $\beta_2$ -microglobulin excretion (EFSA, 2009) (see Section 4.4). A meta-analysis in a draft 2008 assessment of ATSDR indicated that statistically detectable adverse effects on kidney function were present at urinary cadmium concentrations as low as 0.5  $\mu\text{g Cd g}^{-1}$  creatinine (ATSDR, 2008) (see Section 4.10).

### 3.4.2 Effects on the bone

The accumulation of cadmium in the kidney also affects renal vitamin D metabolism, with subsequent disturbances in calcium balance, which may lead to osteomalacia (softening of the bones as a result of inadequate mineralisation of bone matrix – the adult counterpart of rickets) and osteoporosis (an excessive but proportional reduction in the amounts of both the mineral and matrix phases of bone, resulting in bones that are brittle and liable to fracture) (Kjellström, 1986, 1992).

There are a number of reports of disorders of calcium metabolism and bone effects among men occupationally exposed to cadmium. Bone disease resulting from exposure to cadmium in the general environment has been noted in people from a heavily contaminated region in Japan. The main characteristics of this “itai-itai disease” are osteomalacia and osteoporosis, with a tendency to fractures, accompanied by severe pain and renal tubular dysfunction; people with low intakes of vitamin D are particularly at risk.

A cadmium-related increased risk of osteoporosis (in both sexes) (Staessen *et al.*, 1999; Alfven *et al.*, 2000, 2002) and an increased risk of fracture (in females) (Staessen *et al.*, 1999) have been observed in European populations. In one of these studies, the effect was reportedly observed above 3  $\mu\text{g g}^{-1}$  creatinine, while in the other, no quantitative relationships were given (CSTEE, 2004). Although there has been a great deal of discussion within the Member States of the European Community over the interpretation of these Belgian (Staessen *et al.*, 1999) and Swedish (Alfven *et al.*, 2002) studies, no consensus has been achieved and, in 2004, CSTEE concluded that it was not possible to conduct a reliable risk assessment on the basis of the bone effects (CSTEE, 2004). The 2008 ATSDR draft assessment, whilst accepting that studies of non-occupationally exposed populations supported the identification of the bone along with the kidney as the most sensitive targets of cadmium toxicity, also noted that the data base on the bone effects was not strong enough to support the derivation of an oral HCV (ATSDR, 2008).

### 3.4.3 Other toxic effects

Long-term occupational exposure to cadmium at levels of 50–66  $\mu\text{g m}^{-3}$  has resulted in bronchitis, obstructive lung disease and emphysema (HPA, 2006). Respiratory tract toxicity is generally considered to be a feature of exposures above those affecting the kidney (IPCS, 1992; USEPA, 1999).

There is some evidence of neurotoxicity in workers exposed to cadmium (JECFA, 2001). Subchronic oral studies in laboratory animals have shown that exposure to cadmium can cause aggressive behaviour, anxiety (as indicated by increased ethanol consumption and by increased passive avoidance behaviour) and alterations in the biochemical activity in the brain (ATSDR, 1999). The doses associated with these effects are somewhat higher than those for renal and bone effects. In 2004, CSTEE concluded that the neurotoxic potential of cadmium should be further investigated (CSTEE, 2004).

## 3.5 Reproductive and developmental toxicity

### 3.5.1 Effects on reproduction

No human data sufficient to determine whether or not exposure to cadmium has any reproductive effects have been found; however, a number of subchronic dietary or drinking-water studies on rodents have been reported. Although in general no reproductive effects were detectable at doses below about 5  $\text{mg kg}^{-1} \text{bw day}^{-1}$ , one study noted a decreased litter size and increased intervals between litters in rats ingesting 2.5  $\text{mg kg}^{-1} \text{bw day}^{-1}$  via drinking-water (Schroeder and Mitchener, 1971).

There is also a report of possible reproductive effects in dairy cows from a contaminated area in the Netherlands (Kreis *et al.*, 1993). Data on cadmium concentrations in the kidney had been recorded at slaughter over a three-year period and each cow was registered for fertility characteristics. The concentration of cadmium in the kidney was 2.5 times higher in the exposed group than in a control group grazing on uncontaminated fields and was associated with a significantly increased number of inseminations required for conception, significantly fewer twin births and an increased death rate among twins.

### 3.5.2 Effects on development

The few human data on possible developmental effects of cadmium are inconclusive (JECFA, 2004b). Several rodent studies indicate that cadmium can be foetotoxic. The most sensitive indicator appears to be neurobehavioural development. Offspring of female rats orally exposed to cadmium chloride at a dose of 0.04  $\text{mg Cd kg}^{-1} \text{bw day}^{-1}$  prior to and during gestation had reduced exploratory locomotor activity at age two months (Baranski *et al.*, 1983). The maternal no-observed adverse effect level (NOAEL) for this study was reported as 4  $\text{mg Cd kg}^{-1} \text{bw day}^{-1}$  (EC, 2007). A significant adverse impact both on the development of locomotor activity and on an aversion response was seen in the offspring of rats exposed to cadmium acetate in the drinking-water throughout gestation at a dose of 0.7  $\text{mg Cd kg}^{-1} \text{bw day}^{-1}$ . Lower doses were not tested (Ali *et al.*, 1986).

The offspring of female rats exposed to cadmium oxide at 0.02  $\text{mg m}^{-3}$  for five hours a day, five days a week for five months prior to mating and during the first 20 days of gestation showed delayed ossification, decreased locomotor activity and impaired

reflexes (Baranski, 1985). The EU RAR for cadmium (EC, 2007) reported the maternal NOAEL for this study as 0.16 mg Cd m<sup>-3</sup>, but also questioned the robustness of the study and the neurobehavioural findings. In the other inhalation study (NTP, 1995) reviewed in the RAR, maternal toxicity was more sensitive than developmental toxicity.

Under EU classification and labelling legislation, cadmium metal and a number of cadmium salts are designated as Category 3 developmental toxicants (substances which cause concern for humans owing to possible developmental toxic effects) that should be labelled with the risk phrase R63 (possible risk of harm to the unborn child) (EC, 2007).

### 3.6 Genotoxicity

Human cells treated with cadmium compounds *in vitro* have shown chromosomal changes – either greater damage or increases in chromosome number. DNA strand breaks, mutations and cell transformation have also been observed *in vitro*.

Cadmium salts do not appear to cause germ cell mutations following oral exposure in animals, but do so following subcutaneous exposure. An IARC Working Group in 1993 noted that cadmium appeared to have the capability to damage genetic material, particularly chromosomes in mammalian cells, but that germ cells seemed to be protected except at high parenteral doses (IARC, 1993). In making its overall evaluation of cadmium as a proven human carcinogen (Group 1), the Working Group “took into consideration the evidence that ionic cadmium causes genotoxic effects in a variety of eukaryotic cells, including human cells”.

The EU RAR (EC, 2007) noted that definitive conclusions on genotoxicity were not possible, but supported the health precautionary view that cadmium oxide and cadmium might be direct acting genotoxic substances. Under EU legislation, cadmium metal and a range of cadmium salts are classified as Category 3 mutagens<sup>3</sup> (“Possible risks of irreversible effects”) (EC, 2007). In 2009, however, EFSA concluded that cadmium is not directly genotoxic. Instead, it is able to cause genotoxic effects by two mechanisms that would be expected to demonstrate a threshold: the induction of reactive oxygen species and oxidative stress, and the inhibition of DNA repair (EFSA, 2009).

### 3.7 Carcinogenicity

IARC has assigned “cadmium and cadmium compounds” to its highest overall cancer category – Group 1, “carcinogenic to humans” (IARC, 1993). In 1993, an IARC Working Group noted that “early and recent studies provide consistent evidence that the risk for lung cancer is increased among workers exposed to cadmium” and concluded that there is “sufficient evidence” in humans for the carcinogenicity of inhaled cadmium and its compounds.

Studies on a group of about 600 workers from a cadmium recovery plant in the USA provide the best human data in support of the IARC classification (Thun *et al.*, 1985; Stayner *et al.*, 1992). The plant had processed cadmium metals and compounds since 1925 and was operated as an arsenic smelter from 1918 to 1925. The analysis was

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<sup>3</sup> Category 3 mutagens are substances which cause concern for man owing to possible mutagenic effects. There is evidence from appropriate mutagenicity studies, but this is insufficient to place the substance in category 2. Category 2 mutagens are substances which should be regarded as if they are mutagenic to man. There is sufficient evidence to provide a strong presumption that human exposure to the substance may result in the development of heritable genetic damage, generally on the basis of appropriate animal studies.

confined to men who had started work after 1925 when the plant ceased smelting arsenic – although some arsenic remained in the material being processed, decreasing with time. The investigators found a statistically significant excess risk of lung cancer in the highest exposure group and the exposure–response trend over the four exposure groups was highly significant. Confounding by cigarette smoking was minimised, if not eliminated. Regression analyses including the year of hire (as a surrogate for arsenic exposure) did not indicate any confounding by arsenic (Stayner *et al.*, 1992).

Support for a link between cadmium exposure in humans and prostate cancer is weaker. Some of the early occupational studies reported an increase in mortality from prostate cancer, but the increases were small and follow-up studies found either no increases or increases that were not statistically significant (IARC, 1993).

In a case-control study reported from the Netherlands (van der Gulden *et al.*, 1995), a significantly elevated excess risk of prostate cancer was found for subjects who reported frequent occupational exposure to cadmium; however, this association was based on only seven cases. A case-control study (40 cases and 58 controls) from Italy also found a relation between toenail cadmium concentration and prostate cancer risk (Vinceti *et al.*, 2007).

A study of cancer incidence rates among the residents of a cadmium-polluted area of England (Shipham) did report a slightly raised level of cancer of the prostate (Standardised Incidence Ratio (SIR) 235; 95% confidence interval (CI) 130–425) based on 11 cases and of the ovary (SIR 257; 95% CI 107–608) based on five cases. This part of the study was ecological in design and exposure status was inferred from area of residence and not from any direct measurements of the residents themselves (Elliott *et al.*, 2000).

A 2004 evaluation by the UK Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC, 2004) concluded that “there is no convincing evidence to associate occupational exposure to cadmium with cancer of the prostate”.

CSTEE (2004) has requested that the epidemiological studies exploring the link between cadmium exposure and kidney cancer be critically reviewed, noting that there have been a number of “recent” case-control studies reporting a significant association (citing Mandel *et al.*, 1995; Pesch *et al.*, 2000; Hu *et al.*, 2002).

Recent evidence suggests cadmium may also play a role in the development of other cancers, including cancers of the breast, testes, bladder, pancreas and gall bladder (EFSA, 2009).

Studies in laboratory animals provide strong evidence of the carcinogenic potential of inhaled cadmium (IARC, 1993; ATSDR, 1999). Exposure of male rats for 23 hours per day for 18 months to  $12.5 \mu\text{g m}^{-3}$  of cadmium (as a cadmium chloride aerosol) produced a 15% incidence of malignant lung tumours at month 31. None were seen in the controls (Takenaka *et al.*, 1983).

Rat studies involving the same exposure regimes have demonstrated the lung carcinogenicity of cadmium sulphate and cadmium chloride aerosols, cadmium oxide dust and cadmium oxide fume in both sexes. Exposure to the oxide dust at  $30 \mu\text{g Cd m}^{-3}$  resulted in primary lung tumours in over 70% of the exposed animals (Glaser *et al.*, 1990).

In female mice, repeated exposure (eight or 19 hours per day, five days per week for up to 69 weeks) to cadmium oxide dust or cadmium oxide fume was associated with a slightly increased incidence of lung tumours (in one instance in a group exposed to only  $10 \mu\text{g Cd m}^{-3}$  as a dust). The high and variable incidence of lung tumours in the

untreated mice, however, makes it difficult to confidently conclude that cadmium was tumourigenic in the mouse (Heinrich *et al.*, 1989; Heinrich, 1992).

Two studies in rats provide the best opportunity of elucidating the carcinogenic potential of orally administered cadmium. In an experiment involving four test groups and a control group (each of 100 males and 100 females) treated for up to two years, there was no treatment-related increase in tumour incidence. The maximum tested dietary concentration was 50 parts per million (ppm) cadmium – equivalent to about 2.5 mg kg<sup>-1</sup> bw day<sup>-1</sup> – administered as the chloride (Löser, 1980). Cadmium chloride was also tested in the other long-term dietary study in rats, in which the effects of zinc deficiency were also explored. Significant increases in the incidence of leukaemia, benign tumours of the testis and proliferative lesions of the prostate were observed (Waalkes and Rehm, 1992, 1994). The peak incidence of prostatic proliferative lesions occurred at the 50 ppm dietary level in both zinc-adequate and zinc-deficient rats (but not in the higher dose groups), and was statistically significantly increased relative to controls in both cases. The highest incidence of leukaemia occurred in rats receiving 200 ppm cadmium and a zinc-deficient diet (28% compared to a control incidence of 7.4%). Testis tumours were found at the highest level in the rats given 200 ppm cadmium and a zinc-adequate diet (22.2% compared to a control incidence of 3.6%).

The data of Waalkes and Rehm have encouraged several groups to call for further evaluation of cadmium's oral carcinogenicity (Vainio *et al.*, 1994; Waalkes and Rehm, 1994; Collins *et al.*, 1996). The California Environmental Protection Agency has noted that "there is little reason to believe that the carcinogenicity [of cadmium] is limited solely to inhalation exposure" (CalEPA, 2006). The EU CMR<sup>4</sup> Working Group – the expert group of the EU responsible for chemical classification and labelling – has also taken a cautious view on the oral carcinogenicity of cadmium compounds. Under the Classification, Packaging and Labelling regulations, cadmium and a number of its salts have been designated as Category 2 carcinogens (substances which should be regarded as if they are carcinogenic to man). Initially they had to be labelled with the risk phrase R49 (may cause cancer by inhalation); however, in 2002, the CMR Working Group agreed that the risk phrase should be changed to R45 (may cause cancer) – the implication being that there was a carcinogenic hazard irrespective of route of exposure (CSTEE, 2004; EC, 2007).

JECFA, however, considered the positive rat study of Waalkes and Rehm (1992, 1994) to be of questionable relevance to humans because of anatomical differences between the human and rodent prostate (the tumours in the rat involved the ventral lobe of the prostate, which was said to have no human analogue). JECFA concluded that "there was no evidence that cadmium is carcinogenic to humans exposed by the oral route" (JECFA, 2001).

In its 2009 evaluation, EFSA (2009) acknowledged the reported associations between cadmium exposure and cancers of the lung, endometrium, bladder and breast, but concluded that the data were insufficient for risk assessment and that human risk assessment of cadmium should be based on renal toxicity.

## 3.8 Summary

Lung damage is the main result of high acute inhalation exposures in man. Concentrations of 1–5 mg m<sup>-3</sup> have been described as immediately dangerous to health. Single oral doses of 15 mg kg<sup>-1</sup> bw produced severe effects on the gastrointestinal tract. An ingested dose of 70 µg kg<sup>-1</sup> bw can induce vomiting.

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<sup>4</sup> Carcinogenic, Mutagenic and/or Reprotoxic.

The kidney is considered to be a critical target of repeated exposure of humans to cadmium, either orally or by inhalation. Cadmium accumulates in the kidney and renal injury is thought to occur when the cadmium concentration reaches around  $50 \mu\text{g g}^{-1}$  tissue. Cadmium is excreted in the urine at levels reflecting the concentration in the kidney and effects on kidney function are thought to occur at urinary concentrations of  $1\text{--}2 \mu\text{g Cd g}^{-1}$  creatinine. There is some recent evidence suggesting exposures producing urinary concentrations as low as  $0.5 \mu\text{g Cd g}^{-1}$  creatinine might be toxic to the kidney.

The bone is also a sensitive target of systemically absorbed cadmium. Higher occupational inhalation exposures additionally produce effects on the respiratory tract and nervous system.

Cadmium compounds are proven human carcinogens, inducing lung tumours in workers following inhalation exposure. In rats, inhalation exposure to a range of cadmium compounds has also been shown to induce lung tumours. Of the two oral carcinogenicity studies in rats, one was negative and one produced equivocal results.

Cadmium's genotoxic potential has been assumed to play an important role in the development of the lung tumours and expert groups have generally assumed that there will be no threshold to the genotoxicity or carcinogenicity. The 2009 assessment of EFSA, however, concluded that cadmium's genotoxicity is due to the production of reactive oxygen species and the inhibition of DNA repair – mechanisms that would be expected to demonstrate a threshold.

There is some indication that cadmium may cause developmental toxicity in rats exposed either orally or by inhalation.

# 4 Derivation of Health Criteria Values

## 4.1 Joint FAO/WHO Expert Committee on Food Additives

Cadmium was evaluated at the 1972 meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1972a, 1972b). JECFA considered that renal damage may occur when the cadmium concentration in the renal cortex exceeds a critical value of  $200 \mu\text{g g}^{-1}$ . It estimated that, with the assumptions of 5% absorption from the gastrointestinal tract and a daily excretion rate of 0.005% of total body burden, a total oral intake of  $1 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$  would eventually lead to a concentration of cadmium in the renal cortex of  $50 \mu\text{g g}^{-1}$ . A provisional tolerable weekly intake (PTWI) of 400–500  $\mu\text{g}$  per person was recommended. No reason was given for the choice of  $50 \mu\text{g g}^{-1}$  (i.e. four-fold smaller than the value cited as the critical concentration) as the appropriate concentration on which to base the PTWI.

JECFA evaluated cadmium again at its 1988 meeting (JECFA, 1989a, 1989b) when it discussed the critical concentration of cadmium in the renal cortex in terms of the concentration that might produce an adverse effect on kidney function. JECFA noted that human studies had yielded estimates that a concentration (of cadmium in the renal cortex) of  $200 \mu\text{g g}^{-1}$  corresponded to a 10% prevalence rate of LMW proteinuria in the exposed population. Making the same assumptions as previously (a gastrointestinal absorption of 5% and a daily excretion rate of 0.005% of total body burden), JECFA concluded that the total oral intake should not exceed about  $1 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$  if levels of cadmium in the renal cortex (over a 50-year period) were not to exceed  $50 \mu\text{g g}^{-1}$ . JECFA therefore recommended a PTWI of  $7 \mu\text{g kg}^{-1} \text{ bw}$ , essentially the same as its 1972 recommendation.

JECFA noted at its 1993 meeting that, although the modelling assumptions on which its earlier PTWI recommendation was based were conservative, the PTWI did not include a safety factor. JECFA warned that there was only a relatively small safety margin between exposure in the normal diet and the exposure that would produce deleterious effects. There was an awareness also of the studies in Belgium (the Cadmibel study) and the Netherlands, which suggested that the PTWI might not be sufficient to prevent renal tubular dysfunction from cadmium. “The Committee maintained the current PTWI of  $7 \mu\text{g}$  per kg of body weight, pending further research” (JECFA, 1993).

JECFA reassessed cadmium again in 2000. Based on many epidemiological reports from Japan and the extensive recent Cadmibel studies from Belgium, it concluded that the critical concentration of cadmium in the kidney was  $50 \mu\text{g g}^{-1}$ , which would be associated with a level of urinary excretion of  $2.5 \mu\text{g g}^{-1}$  creatinine. A theoretical model was presented that predicted the dietary intake that would produce the critical level of urinary cadmium. With an assumed bioavailability of cadmium in the diet of 10%, a 100% excretion of absorbed cadmium in the urine and a ratio of dietary intake to urinary excretion of 12, all described as “reasonable values”, the  $2.5 \mu\text{g g}^{-1}$  threshold for urinary excretion would be produced by a daily cadmium intake of  $30 \mu\text{g}$ . Equally “reasonable” assumptions of a 5% bioavailability, a 50% urinary excretion of absorbed cadmium and a ratio of dietary intake to urinary excretion of 48, produced a figure of  $120 \mu\text{g day}^{-1}$ . The new data therefore indicated that a proportion of the general population might be at an increased risk for tubular dysfunction when exposed at the

previously assigned PTWI of  $7 \mu\text{g kg}^{-1}$  bw. However, JECFA maintained the  $7 \mu\text{g kg}^{-1}$  bw figure because “the risk estimates that can be made at present are imprecise” (JECFA, 2001).

The PTWI of  $7 \mu\text{g kg}^{-1}$  bw for cadmium was confirmed by JECFA at a 2003 meeting. An extensive amount of new information was available from epidemiological studies conducted in Japan, Europe and the USA. Although sensitive biomarkers indicated that changes in renal function and bone/calcium metabolism were observed at urinary cadmium concentrations of  $<2.5 \mu\text{g g}^{-1}$  creatinine, JECFA noted that “appreciable uncertainty remains regarding the long-term health significance of these changes” and reaffirmed its conclusion that “an excess prevalence of renal tubular dysfunction would not be expected to occur if urinary cadmium concentration remains  $<2.5 \mu\text{g g}^{-1}$  creatinine, even under a range of plausible assumptions about the relationship between the amount of bioavailable cadmium in the diet and the urinary excretion of cadmium”. JECFA’s opinion was that the new data “do not provide a sufficient basis for revising the PTWI” (JECFA, 2004a).

## 4.2 WHO guidelines for drinking-water quality

In 1993, WHO recommended a guideline concentration for cadmium in drinking-water of  $3 \mu\text{g L}^{-1}$  (WHO, 1993, 1996). An assessment in 2003 generated the same conclusion (WHO, 2006). This is based on the allocation to drinking-water of 10% of the PTWI of  $7 \mu\text{g kg}^{-1}$  bw recommended by JECFA for all oral exposures, and on the assumption that a 60-kg adult drinks two litres of water a day. WHO noted “that the margin between the PTWI and the actual weekly intake by the general population is small, namely less than 10-fold, and that this margin may be even smaller in smokers” (WHO, 2006).

## 4.3 WHO air quality guidelines for Europe

In 1994, a WHO Working Group attempted to evaluate the risk of kidney dysfunction and lung cancer in a general population hypothetically exposed to cadmium only by inhalation (WHO, 2000). On the basis of occupational epidemiology studies and extrapolation of the results to continuous exposure, the Working Group concluded that a “permissible concentration of about  $300 \text{ ng m}^{-3}$ ” would prevent kidney dysfunction. The study of cadmium-exposed workers by Thun *et al.* (1985, 1991) was described as the most reliable source of information of lung cancer risk, although the Working Group felt that the unit cancer risk of  $1.8 \times 10^{-3}$  per  $\mu\text{g m}^{-3}$  generated by the study “might be substantially overestimated owing to confounding by concomitant exposure to arsenic” (WHO, 2000).

“As no reliable unit risk can be derived to estimate the excess lifetime risk for lung cancer” (WHO, 2000), the WHO air quality guidelines were in the end driven by the need to prevent further increases in cadmium levels in the kidney, which in the middle age population of Europe were approaching the critical level of  $50 \mu\text{g g}^{-1}$  estimated by the Cadmibel study in Belgium. “To prevent any further increase of cadmium in agricultural soils likely to increase the dietary intake of future generations, a guideline of  $5 \text{ ng m}^{-3}$  is established” (WHO, 2000).

## 4.4 European Food Safety Authority

In 2009, the European Food Safety Authority (EFSA) published an evaluation of dietary cadmium (EFSA, 2009). As part of this, EFSA conducted a meta-analysis of selected

studies to evaluate the dose–response relationship between urinary cadmium and urinary  $\beta_2$ -microglobulin. A urinary  $\beta_2$ -microglobulin concentration of  $300 \mu\text{g g}^{-1}$  creatinine was selected as the threshold above which levels were considered ‘elevated’. A benchmark dose (BMD) analysis was conducted to determine the urinary cadmium concentration associated with a five per cent increase in the prevalence of elevated  $\beta_2$ -microglobulin (i.e. a  $\text{BMD}_5$ ). The lower confidence limit of this  $\text{BMD}_5$ , the  $\text{BMDL}_5$ , was  $4 \mu\text{g Cd g}^{-1}$  creatinine.

To allow for interindividual variation in urinary cadmium within the dose groups in the study populations (group mean data and associated ranges were used in the analysis rather than data points for individual subjects), a chemical-specific adjustment factor (CSAF) of 3.9 was applied,<sup>5</sup> producing a value of  $1 \mu\text{g Cd g}^{-1}$  creatinine.

Hence, EFSA concluded that a urinary cadmium concentration of  $1 \mu\text{g Cd g}^{-1}$  creatinine represents the internal dose below which 95% of the European population would not have ‘elevated’ urinary  $\beta_2$ -microglobulin greater than  $300 \mu\text{g g}^{-1}$  creatinine.

A one-compartment model was then used to estimate the dietary cadmium exposure that would correspond to this level of urinary cadmium after 50 years of exposure. The model was fitted to data from a population-based Swedish mammography cohort study within which 680 never smoker 56–70 year old women had urine sampled and completed dietary questionnaires to permit estimation of daily cadmium intake. On the basis of this data, the model suggested a mean cadmium half-life in the study population of about 11.6 years with a population variability of about 25% (Amzal *et al.*, 2009; EFSA, 2009). This value, along with gastrointestinal cadmium absorption rates of 1–10%, were used in Monte Carlo simulations to derive exposure levels for various percentiles of the population. A summary of the results is provided in Table 4.1.

**Table 4.1 Dietary cadmium exposures calculated by EFSA (2009) that would not exceed the concentration of cadmium in urine of  $1 \mu\text{g Cd g}^{-1}$  creatinine for certain proportions of the population (women)**

Percentage of population below $1 \mu\text{g Cd g}^{-1}$ creatinine	Dietary cadmium exposure	
	$\mu\text{g Cd kg}^{-1}$ bw day <sup>-1</sup>	$\mu\text{g Cd kg}^{-1}$ bw week <sup>-1</sup>
50%	0.78	5.46
90%	0.42	2.94
95%	0.36	2.52

It was concluded that the average daily dietary intake should not exceed  $0.36 \mu\text{g Cd kg}^{-1}$  bw, and that this should be expressed as a tolerable weekly intake (TWI) of  $2.5 \mu\text{g Cd kg}^{-1}$  bw (EFSA, 2009). Because the data related to both an early biological response and a sensitive population, EFSA considered no uncertainty factor for interindividual variability in susceptibility was necessary.

The EFSA TWI of  $2.5 \mu\text{g Cd kg}^{-1}$  bw was endorsed by the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) when it assessed UK dietary cadmium intake in 2009, though COT noted it considered the TWI to be conservative (COT, 2009).

<sup>5</sup> The CSAF of 3.9 was derived by dividing the 95<sup>th</sup> percentile benchmark dose (BMD) by the median BMD. Since concentrations were assumed to be lognormal, this CSAF was calculated using the standard formula for lognormal percentiles (EFSA, 2009).

## 4.5 EU Working Group on Arsenic, Cadmium and Nickel Compounds

An EU Working Group charged with the derivation of a Limit Value for cadmium (an atmospheric concentration that could assist the development of European Community regulations on air quality) issued its position paper in 2000 (EC, 2000).

Kidney toxicity was considered to be the critical feature of the non-cancer health assessment of long-term environmental exposure to cadmium. Occupational epidemiology was said to offer the best opportunity to define the dose–response. A previously published analysis of seven of these studies had concluded that increases in the prevalence of kidney dysfunction may occur at exposures (defined in terms of the product of an estimate of workplace atmospheric concentration and the average duration of employment) between 100 and 499  $\mu\text{g m}^{-3} \times \text{year}$  (Thun *et al.*, 1991). This lower figure of 100  $\mu\text{g m}^{-3} \times \text{year}$  was chosen by the Working Group as the starting point of its derivation of a non-cancer Limit Value. The majority of the Working Group considered that this value should be viewed as a minimal LOAEL for occupational exposure. After conversion to its continuous exposure equivalent<sup>6</sup> of 270  $\text{ng m}^{-3}$ , uncertainty factors (UFs) of 5 for the conversion of the minimal LOAEL to a NOAEL and 10 to take account of interindividual variations in susceptibility resulted (after rounding) in a Limit Value of 5  $\text{ng m}^{-3}$ .

The Working Group also attempted to develop a Limit Value based on cadmium's confirmed carcinogenicity in workers. This cancer risk assessment, which assumed cadmium's carcinogenic response would not exhibit a dose threshold, relied mainly on work undertaken to produce the WHO air quality guidelines (the Working Group had access to a 1997 draft report that was eventually published as WHO 2000 – see Section 4.3) and a 1999 USEPA draft document (see Section 4.9). The range of estimated inhalation Unit Risks<sup>7</sup> (of 1.8–4.15  $\times 10^{-3}$ ) indicated that a very conservative estimate (which in the opinion of the Working Group was likely to be an overestimate) of the lifetime cancer risks associated with the proposed Limit Value based on toxicity of 5  $\text{ng m}^{-3}$  was in the order of 1 in 100,000. “The majority of the Working Group believes that an annual mean concentration level of 5  $\text{ng m}^{-3}$  as derived from non-cancer effects provides also an appropriate level of protection from cancer risk due to exposure to cadmium” (EC, 2000).

## 4.6 EU Risk Assessment Report

The impact of cadmium on human health has been assessed at European Community level.<sup>8</sup> A Risk Assessment Report (RAR) written by a team from Université Catholique de Louvain in Belgium was presented in draft to the Commission in July 2003. It was peer-reviewed by CSTE (CSTE, 2004) (see Section 4.7) and issued as a final report<sup>9</sup> in 2007 (EC, 2007). The objective was to estimate the Margin of Safety (MOS)

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<sup>6</sup> The occupational LOAEL (in units of concentration  $\times$  time in years) was extrapolated from eight hours to 24 hours a day, and from 225 working days to 365 days, and distributed over a 75-year lifetime ( $100 \times 8/24 \times 225/365 \times 1/75$ ).

<sup>7</sup> An inhalation Unit Risk is an estimate of the excess lifetime cancer risk associated with continuous exposure to an atmospheric concentration of 1  $\mu\text{g m}^{-3}$ .

<sup>8</sup> Cadmium is a priority substance covered by Council Regulation (EEC) 793/93 on the evaluation and control of the risks of “existing” substances.

<sup>9</sup> The date of the “last literature search” is given in the final report as 2005. The reference list contains very few primary reports on toxicity published beyond 2000.

by comparing a toxic effect level (a LOAEL) with estimates of occupational exposure, consumer exposure and indirect human exposure via the environment. There was no explicit derivation of an oral HCV, but clear insights were offered on what was considered to constitute a tolerable oral intake of cadmium.

Based on epidemiological studies indicating both kidney<sup>10</sup> (Buchet *et al.*, 1990; Järup *et al.*, 2000) and bone<sup>11</sup> effects (Staessen *et al.*, 1999; Alfven *et al.*, 2000) in the general population at a body burden producing urinary cadmium levels below 5 µg Cd g<sup>-1</sup> creatinine, the selected chronic exposure LOAEL was 2 µg Cd g<sup>-1</sup> creatinine. In the light of the contrasting views on the health significance of the kidney effects occurring at this body burden (for example, the rapporteurs felt they most likely reflect “benign non-adverse responses”), the RAR suggested that the division of this LOAEL by an UF of 3 would be sufficient to convert it to a NOAEL. No additional factors were considered necessary to account for interindividual variations in susceptibility as these were implicitly included in the LOAEL value itself, which was derived from studies of large numbers of the general population.

A one-compartment pharmacokinetic model of cadmium metabolism was used to convert the derived urinary cadmium NOAEL of 0.66 µg Cd g<sup>-1</sup> creatinine to its equivalent chronic oral dose. Values were estimated for combinations of adult bodyweight (55 or 70 kg), half-life of cadmium in the kidney (10, 13.6 or 40 years) and level of gastrointestinal absorption (3, 5 or 10%) and an assumption of 53 years of exposure (see Table 4.1).

**Table 4.1 EU RAR modelled oral intakes (µg day<sup>-1</sup>) equivalent to the urinary cadmium NOAEL of 0.66 µg Cd g<sup>-1</sup> creatinine (EC, 2007)**

Gastrointestinal absorption (%)	Bodyweight (kg)	Half-life in kidney (years)		
		10	13.6	40
3	55	48	37	20
	70	62	47	25
5	55	29	22	12
	70	37	28	15
10	55	15	11	6
	70	19	14	8

Based on a gastrointestinal absorption of 3% and a half-life of 13.6 years, the oral intake was calculated as 37–47 µg day<sup>-1</sup> for adult non-smokers (equivalent to 0.53–0.67 µg kg<sup>-1</sup> bw day<sup>-1</sup> for a 70-kg adult). This intake range subsequently featured in the MOS calculations used to evaluate cadmium in the RAR. Using the same half-life, but a 10% gastrointestinal absorption, gave an intake range of 11–14 µg day<sup>-1</sup> (equivalent to 0.16–0.2 µg kg<sup>-1</sup> bw day<sup>-1</sup> for a 70-kg adult).

<sup>10</sup> A cadmium-related increase in calcuria was reported by Buchet *et al.* (1990), whereas Järup *et al.* (2000) reported a cadmium-related increase in the levels of urinary α<sub>1</sub>-microglobulin.

<sup>11</sup> Staessen *et al.* (1999) and Alfven *et al.* (2000) both reported decreased bone densities. Staessen *et al.* (1999) also recorded a cadmium-related increased incidence of fractures.

## 4.7 EU Scientific Committee on Toxicity, Ecotoxicity and the Environment

In a 2001 opinion on the previous year's position paper issued by the Commission Working Party (see Section 4.5), the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) developed its own inhalation Limit Value. This was based on a study of kidney function in a Belgian population (Buchet *et al.*, 1990) indicating that a urinary cadmium excretion of 2.7 µg per 24 hours was associated with a 5% increase in the baseline prevalence of N-acetyl-β-galactosidase – the most sensitive urinary protein marker in this population. Cadmium body burden is the result of both oral and inhalation exposure and a toxicokinetic model was therefore used by CSTEE to take account of intakes from both routes.

The operation of the model required a series of (conservative) assumptions to be made on the nature of the cadmium compound in the air (the oxide – a well-absorbed species), its fractional lung deposition (0.21 – halfway between values corresponding to ambient and occupational cadmium containing particles) and on systemic absorption (90% for the cadmium deposited in the lungs and 5% for that reaching the gastrointestinal tract). It was also assumed that members of this target population were at the time also ingesting 0.14 µg kg<sup>-1</sup> bw day<sup>-1</sup> of cadmium.

The end result was a value of 650 ng Cd m<sup>-3</sup>, which was the estimate of the atmospheric level of cadmium that would produce the urinary excretion of 2.7 µg per 24 hours. An overall UF of 100 was applied leading to a Limit Value of 6.5 ng m<sup>-3</sup>. The overall UF comprised a factor of 10 for the use of a LOAEL (as a significant fraction of the population were affected at the selected cut-off of 2.7 µg per 24 hours) and a factor of 10 to take account of the possible greater susceptibility of some population sub-groups, the possibility of higher oral intakes than had been assumed in the modelling, and the knowledge that cadmium kidney concentrations in the middle-aged general population were already close to the critical value of 50 µg g<sup>-1</sup> (CSTEE, 2001).

In its peer review of the draft RAR (see Section 4.6), CSTEE emphasised the significant uncertainties inherent in any cadmium assessment. Particular concern was expressed over the difficulties of defining what constituted a true control value for the very subtle biomarker of kidney injury used in the key studies and of converting a urinary cadmium concentration to its equivalent dietary intake.

CSTEE concluded it might be more appropriate to consider a range of possible LOAEL values and recommended that MOS values be calculated with LOAELs (in terms of µg Cd g<sup>-1</sup> creatinine in the urine) of 0.5, 2 and 2.6, which were said to be equivalent<sup>12</sup> to cadmium intakes of 10, 40 and 52 µg day<sup>-1</sup> respectively.

## 4.8 Dutch National Institute for Public Health and the Environment

A 1999 assessment by the Dutch National Institute for Public Health and the Environment (RIVM) concluded that the critical effect of long-term exposure to cadmium is renal tubular dysfunction, reflected initially in an increased excretion of low molecular weight proteins in the urine (RIVM, 2001). It was noted that “recent human datasets (including the study of Nogawa *et al.* (1989))” indicated adverse kidney effects can be detected in about 4% of the population when levels of cadmium in the kidney

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<sup>12</sup> These values arose from an assumption that 2.5 µg Cd g<sup>-1</sup> creatinine corresponded to a long-term intake of 50 µg Cd day<sup>-1</sup> and simple proportionality (i.e. 0.5 µg g<sup>-1</sup> creatinine = 50 x 0.5/2.5).

cortex reach  $50 \mu\text{g g}^{-1}$ , which corresponds to a urinary cadmium level of  $2.5 \mu\text{g g}^{-1}$  creatinine, and is likely to be reached after intake for 40–50 years of about  $1 \mu\text{g kg}^{-1} \text{bw day}^{-1}$ . As the objective was to develop a guideline level associated with a minimal degree of injury over a lifetime of 60–70 years, an UF of 2 was applied to this “population based adverse effect level” to produce a tolerable daily intake of  $0.5 \mu\text{g kg}^{-1} \text{bw}$ . Because of the bioaccumulation of cadmium, it was thought preferable to express this as a tolerable weekly intake of  $3.5 \mu\text{g kg}^{-1} \text{bw}$  (RIVM, 2001).

## 4.9 US Environmental Protection Agency

A 1994 derivation of an oral Reference Dose (RfD)<sup>13</sup> by the US Environmental Protection Agency (USEPA) was based on its 1985 review of the oral toxicity of cadmium as described in a Drinking Water Criteria Document. At that time, the highest concentration of cadmium in the renal cortex not to be associated with significant proteinuria was estimated to be  $200 \mu\text{g g}^{-1}$ . A pharmacokinetic model was used to estimate the dietary concentrations ingested over a lifetime that were unlikely to produce a kidney cadmium concentration above this critical value. Among the model’s assumptions were gastrointestinal absorptions of cadmium from food and water of 2.5 and 5% respectively, and a daily cadmium excretion rate of 0.01% of the total body burden. The model indicated that  $10 \mu\text{g kg}^{-1} \text{bw day}^{-1}$  in food and  $5 \mu\text{g kg}^{-1} \text{bw day}^{-1}$  in water were NOAELs (i.e. these levels ingested over the long term would not result in a cadmium kidney concentration of  $>200 \mu\text{g g}^{-1}$ ). An UF of 10 was used to take account of human variability and thus the RfDs for cadmium in food and in water were 1 and  $0.5 \mu\text{g kg}^{-1} \text{bw day}^{-1}$  respectively (USEPA, 1994).

The dose–response of the tumours of the respiratory tract seen in the workers studied by Thun *et al.* (1985) was the focus of a 1992 USEPA assessment of the carcinogenicity of cadmium. An inhalation unit risk of  $1.8 \times 10^{-3}$  per  $\mu\text{g m}^{-3}$  was estimated (USEPA, 1992). On this basis an exposure to  $6 \text{ ng m}^{-3}$  was said to pose a lifetime cancer risk of 1 in 100,000 ( $10^{-5}$ ).

An intention to update these 1992 and 1994 opinions produced a preliminary external review draft in 1999 (USEPA, 1999). The analysis of the occupational cancer epidemiology reported by Stayner *et al.* (1992) allowed USEPA to rework its earlier cancer risk assessment. Two estimates of unit cancer risk for continuous exposure were proposed:  $4.15 \times 10^{-3}$ , based on an ED<sub>10</sub> approach; and  $4.4 \times 10^{-4}$  using the Poisson regression model. Although this external review draft has not led to any formal final USEPA decision – and thus the current IRIS<sup>14</sup> record still only contains the 1992 and 1994 assessments – the 1999 draft was influential in the cancer risk assessment by the European Commission Working Group (see Section 4.5).

## 4.10 US Agency for Toxic Substances and Disease Registry

In 1999, the US Agency for Toxic Substances and Disease Registry (ATSDR) derived a guideline for oral exposure from an analysis of the dose–response of the effects on the kidney seen in a Japanese population exposed to high levels of cadmium in rice

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<sup>13</sup> A USEPA RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious non-cancer effects during a lifetime.

<sup>14</sup> IRIS is the USEPA’s Integrated Risk Information System, an online chemical toxicity database.

(Nogawa *et al.*, 1989). The indicator of kidney injury was an abnormal excretion of urinary  $\beta_2$ -microglobulinuria, defined as  $\geq 1,000 \mu\text{g L}^{-1}$  or  $1,000 \mu\text{g g}^{-1}$  creatinine, which was found in 5.3% of control males and 3.1% of control females (i.e. males and females resident in an equivalent non-polluted region). A total lifetime cadmium intake of 2,000 mg was estimated to be the threshold dose for any increase in the prevalence of  $\beta_2$ -microglobulinuria. Assuming an average bodyweight of 53 kg of the Japanese adult, this led to a NOAEL of  $2.1 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ . Application of an UF of 10 to take account of human variability generated a chronic oral Minimal Risk Level (MRL)<sup>15</sup> of  $0.2 \mu\text{g Cd kg}^{-1} \text{ bw day}^{-1}$  (ATSDR, 1999).

A draft re-assessment of cadmium was circulated by ATSDR for public comment in 2008. It was considered that there was strong support for the identification of both the bone and kidney as the most sensitive targets of chronic cadmium toxicity. Because the data base on kidney effects was stronger, it was used in the derivation of a chronic oral MRL. Epidemiological studies were selected that had reliable measures of urinary cadmium and indicators of low molecular weight proteinuria, that reported dose–responses amenable to independent analysis, that were of sufficient size to provide statistical power in the elucidation of the dose–response, and that allowed appropriate account to be taken of major co-variables. Seven studies qualified involving populations in Sweden (Järup *et al.*, 2000; Suwazono *et al.*, 2006), Belgium (Buchet *et al.*, 1990), Japan (Uno *et al.*, 2005; Kobayashi *et al.*, 2006; Shimizu *et al.*, 2006) and China (Jin *et al.*, 2004).

A meta-analysis of the various dose–responses (eleven data sets in all) allowed estimates of the internal cadmium doses, as indicated by the urinary cadmium concentration, which corresponded to probabilities of a 10% excess risk of low molecular weight proteinuria. The lowest  $\text{UCD}_{10}$  value of  $0.5 \mu\text{g Cd g}^{-1}$  creatinine, which was generated from the data of three European studies (Buchet *et al.*, 1990; Järup *et al.*, 2000; Suwazono *et al.*, 2006), was transformed into an estimate of chronic cadmium intake by the application of a toxicokinetic model. A 5% absorption of ingested cadmium was assumed for males and a 10% absorption for females. The resulting estimate of dietary cadmium intake in females of  $0.33 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$  (the corresponding value for males was  $0.7 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ ) was divided by an UF of 3 to account for possible “human variability” to generate, after rounding, the proposed chronic oral MRL of  $0.1 \mu\text{g Cd kg}^{-1} \text{ bw day}^{-1}$ . Even though the meta-analysis should have ensured that the  $\text{UCD}_{10}$  value applied to most of the usual sensitive sub-populations, the additional UF was considered necessary as a number of the selected critical epidemiological studies had excluded diabetics, and individuals with diabetes may be especially sensitive to cadmium’s kidney toxicity (ATSDR, 2008).

The draft assessment circulated for public comment in 2008 has also proposed a chronic inhalation MRL of  $0.01 \mu\text{g Cd m}^{-3}$ . It too was derived from a meta-analysis of studies that best elucidate the dose–response of cadmium’s impact on the kidney. For the inhalation MRL, the analysis included data from three occupational studies (Roels *et al.*, 1993; Järup and Elinder, 1994; Chen *et al.*, 2006a, 2006b), to add to those from the studies of general populations that featured in the oral MRL derivation. In fact, the  $\text{UCD}_{10}$  values from these additional occupation studies were each higher than the previously estimated value of  $0.5 \mu\text{g Cd g}^{-1}$  creatinine that was based solely on the three European general population studies, and therefore it was the latter that also provided the foundation for the inhalation MRL derivation. Modelling of the respiratory tract deposition and clearance of inhaled cadmium oxide and sulphide particles (ICRP, 1994) allowed estimates of cadmium transfer to the gastrointestinal tract and blood,

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<sup>15</sup> An ATSDR MRL is an estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse non-cancer health effects over a specified route and duration of exposure.

and thus the use of the same pharmacokinetic model that had been used in the oral MRL derivation.

On the assumption that air was the only source of cadmium, the pharmacokinetic model predicted that atmospheric concentrations of 1.8–2.4  $\mu\text{g Cd m}^{-3}$  as cadmium oxide or 1.2–1.4  $\mu\text{g Cd m}^{-3}$  as the sulphide would result in a urinary cadmium concentration of 0.5  $\mu\text{g Cd g}^{-1}$  creatinine. However, as the diet is also a significant contributor to the body burden of cadmium, it was assumed that the population would be ingesting 0.32  $\mu\text{g Cd kg}^{-1}$  bw day<sup>-1</sup> (the US estimate of cadmium oral intakes for non-smokers), and the tolerable atmospheric concentration was reduced accordingly to 0.1  $\mu\text{g Cd m}^{-3}$ . An UF of 3 to take account of the possible increased susceptibility of diabetics, and a Modifying Factor<sup>16</sup> of 3 (and rounding) produced the MRL of 0.01  $\mu\text{g Cd m}^{-3}$  (ATSDR, 2008).

## 4.11 Discussion

### 4.11.1 Inhalation

The kidney is the toxicity target of chronic exposure to cadmium in the air. The dose–response of kidney injury in workers described in the report of Thun *et al.* (1991) is the foundation of a guideline derived in 2000 by a European Commission Working Group (EC, 2000). An estimate of the occupational LOAEC, converted to its continuous and full lifetime equivalent, was divided by an UF of 100 to generate a Limit Value of 5  $\text{ng m}^{-3}$ . This atmospheric concentration provides the basis for an inhalation TDI derived to preclude kidney toxicity. Based on the default 70-kg adult inhaling 20  $\text{m}^3$  of air, this is equivalent to 1.43  $\text{ng kg}^{-1}$  bw day<sup>-1</sup>, which is recommended here as the  $\text{TDI}_{\text{inh}}$ .

CSTEE in 2001 used an epidemiological study of kidney changes in a Belgian population exposed both orally and via the atmosphere (Buchet *et al.*, 1990) for a further insight into the kidney toxicity dose–response. Toxicokinetic modelling was used to estimate the LOAEC of 650  $\text{ng m}^{-3}$ . The inhalation Limit Value of 6.5  $\text{ng m}^{-3}$ , which resulted from the division of this LOAEC by an overall UF of 100, therefore provided fairly good corroboration of the Working Group proposal.

Exposure to cadmium in the atmosphere also induces lung cancer in workers. Some expert groups have concluded that cadmium’s observed genotoxicity may play a central role in the tumourigenesis and have adopted the precautionary assumption that there may be no threshold to this effect. The most recent expert group evaluation of cadmium, that of EFSA in 2009, however, concluded that cadmium causes genotoxicity via oxidative stress and via inhibition of DNA repair – mechanisms which would demonstrate a threshold.

In 1992, on the basis of the epidemiological studies of Thun *et al.* (1985, 1991), USEPA estimated that the unit cancer risk was  $1.8 \times 10^{-3}$ . In 2000, the European Commission Working Group was essentially in agreement with this general approach to cadmium cancer risk assessment and suggested unit risk values of  $1.8\text{--}4.15 \times 10^{-3}$ .

WHO, also in 2000, was not as confident that the study by Thun *et al.* was a reliable source of data on the carcinogenicity of cadmium, noting that the risk estimate of  $1.8 \times 10^{-3}$  per  $\mu\text{g m}^{-3}$  might overestimate cancer risk. Instead, WHO proposed an air quality guideline level of 5  $\text{ng m}^{-3}$  to prevent further increases in cadmium in agricultural soils.

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<sup>16</sup> The Modifying Factor is to compensate for data base inadequacies, in particular “the lack of adequate human data that could be used to compare the relative sensitivities of the respiratory tract and kidneys”.

A unit cancer risk of  $1.8 \times 10^{-3}$  (the value recommended in 1992 by USEPA and the lower end of the range supported by a European Commission Working Group in 2000) indicates that a cadmium atmospheric concentration of  $5 \text{ ng m}^{-3}$  would pose an excess lifetime cancer risk in the order 1 in 100,000. Based on the default 70-kg adult inhaling  $20 \text{ m}^3$  of air per day, this concentration would be equivalent to a dose of  $1.43 \text{ ng kg}^{-1} \text{ bw day}^{-1}$ , i.e. the same as the  $\text{TDI}_{\text{inh}}$ .

It is therefore recommended that the  $\text{TDI}_{\text{inh}}$  of  $1.43 \text{ ng kg}^{-1} \text{ bw day}^{-1}$  based on kidney toxicity is used in the derivation of SGVs. Exposure at this level would be expected to pose only a minimal risk of lung cancer, even if the mechanism for carcinogenicity were to have no threshold.

#### 4.11.2 Oral

The oral HCVs proposed by the expert groups have been derived in a broadly similar way. In each case, a critical concentration of cadmium in the renal cortex for the onset of the early stages of kidney disease has been established (or assumed) and the corresponding average daily intake that over 50 years or so would produce such a kidney burden has then been estimated.

At one time, the critical kidney concentration was thought to be  $200 \text{ } \mu\text{g g}^{-1}$  (the RfD derived in 1992 by USEPA is based on this assumption, though an UF of 10 was applied in the derivation), but RIVM in 1999 and JECFA in 2000 concluded it was probably  $50 \text{ } \mu\text{g g}^{-1}$  (though earlier JECFA evaluations had also been based on this  $50 \text{ } \mu\text{g g}^{-1}$  value). Both JECFA and RIVM correlated  $50 \text{ } \mu\text{g g}^{-1}$  of cadmium in the kidney with a daily excretion of cadmium in the urine of  $2.5 \text{ } \mu\text{g g}^{-1}$  creatinine.

Conversion of a urinary cadmium concentration into an oral (or a mixed oral and inhalation exposure) requires the use of complex toxicokinetic modelling, which introduces the need for a number of assumptions on a variety of model inputs and expert groups have taken different views on these inputs. There are also differences of opinion on which of the number of indicators of kidney function should be classified as adverse and, for these very subtle changes, what constitutes the prevalence in a truly unexposed population.

In 1993, JECFA expressed doubts about its own PTWI of  $7 \text{ } \mu\text{g kg}^{-1} \text{ bw}$  (or TDI of  $1 \text{ } \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ ) first set in 1972, noting that it might not be totally effective in preventing kidney disease. In 2000, JECFA again concluded that a proportion of the general population might be at an increased risk of kidney dysfunction at this PTWI but did not set a lower figure because it considered that the risk estimates that could be made at the time were "imprecise". Conservative choices on the pharmacokinetic factors in JECFA's favoured model linking body burden and intake were said to produce a tolerable daily intake (TDI) of  $30 \text{ } \mu\text{g}$  (or  $0.5 \text{ } \mu\text{g kg}^{-1} \text{ bw}$  as JECFA assumed a 60-kg adult). JECFA noted that another set of "reasonable" choices on these same factors would have generated a TDI of  $120 \text{ } \mu\text{g}$  (or  $2 \text{ } \mu\text{g kg}^{-1} \text{ bw}$ ); thus, these values were not in conflict with the previously established PTWI. The availability of "extensive" new epidemiological data for the 2003 JECFA meeting also did not provide "a sufficient basis for revising the PTWI [of  $7 \text{ } \mu\text{g kg}^{-1} \text{ bw}$ ]".

In 1999, RIVM adopted a slightly more conservative position in converting the urinary cadmium concentration of  $2.5 \text{ } \mu\text{g g}^{-1}$  creatinine to an acceptable level for oral exposure, recommending a TDI of  $0.5 \text{ } \mu\text{g kg}^{-1} \text{ bw}$ .

ATSDR in 1999 derived an oral MRL of  $0.2 \text{ } \mu\text{g kg}^{-1} \text{ bw day}^{-1}$  on the basis of a single human study (albeit that an UF of 10 was introduced to take account of intra-population variations in susceptibility) and favoured a more direct assessment of exposure that precluded the need for toxicokinetic modelling.

In its review of the draft EU RAR issued in 2003, CSTE recommended that cadmium risk assessments should be conducted on the premise that the critical values for cadmium urinary excretion might be 0.5, 2 or 2.6  $\mu\text{g g}^{-1}$  creatinine, which it estimated would be equivalent to cadmium oral intakes of 10, 40 or 52  $\mu\text{g day}^{-1}$  (or 0.14, 0.57 and 0.74  $\mu\text{g kg}^{-1}$  bw  $\text{day}^{-1}$  based on a 70-kg adult). CSTE also noted that these values should be viewed as LOAELs not NOAELs.

The EU RAR finalised in 2007 focused on a LOAEL of 2  $\mu\text{g g}^{-1}$  creatinine and noted that the application of an UF of 3 would be sufficient to convert this to a NOAEL (of 0.66  $\mu\text{g g}^{-1}$  creatinine). On the assumption that the half-life of cadmium in the kidney was 13.6 years and the gastrointestinal absorption rate was 3%, the NOAEL of 0.66  $\mu\text{g g}^{-1}$  creatinine was said to be equivalent to a chronic cadmium intake by a 70-kg adult non-smoker of 47  $\mu\text{g day}^{-1}$  or 0.67  $\mu\text{g kg}^{-1}$  bw  $\text{day}^{-1}$ . However, it was noted that a longer half-life and higher levels of gastrointestinal absorption would lead to correspondingly lower tolerable daily intakes. A half-life of 13.6 years but a gastrointestinal absorption of 10%, for example, reduced the tolerable intake to 14  $\mu\text{g day}^{-1}$  (0.2  $\mu\text{g kg}^{-1}$  bw  $\text{day}^{-1}$ ).

The uncertainties associated with the conversion of urinary cadmium to chronic oral doses were increased by a 2004 study not considered in the RAR that indicated the oral absorption of cadmium in 20–39 year old female volunteers to be in excess of 40% (Horiguchi *et al.*, 2004). In addition, a number of recent epidemiological reports indicate that there may be adverse effects on the kidney at urinary cadmium concentrations even below 1  $\mu\text{g g}^{-1}$  creatinine (Hong *et al.*, 2004; Saturug *et al.*, 2004; Uno *et al.*, 2004; Akesson *et al.*, 2005; Suwazono *et al.*, 2006). Indeed, a 2008 draft reassessment of the cadmium epidemiology by ATSDR has proposed MRL values based on the premise that the first indications of kidney toxicity occur at urinary concentrations of 0.5  $\mu\text{g Cd g}^{-1}$  creatinine or possibly even below this in particularly sensitive population subgroups (ATSDR, 2008).

The most recent expert group evaluation, though – that of EFSA in 2009 – considered that use of a critical urinary cadmium level of 1  $\mu\text{g Cd g}^{-1}$  creatinine was appropriate. EFSA (2009) also commented that the discrepancy between the results of Horiguchi *et al.* (2004) and those of earlier studies of oral cadmium absorption are probably methodological and that absorption rates of 5% for men and 10% for women are reasonable estimates for Western populations (EFSA, 2009). In modelling the dietary intake corresponding to a urinary cadmium level of 1  $\mu\text{g Cd g}^{-1}$  creatinine, EFSA used oral absorption rates of 1–10% and various half-life values. An intake of 0.36  $\mu\text{g kg}^{-1}$  bw  $\text{day}^{-1}$  (2.5  $\mu\text{g kg}^{-1}$  bw  $\text{week}^{-1}$ ) was said to maintain 95% of the population beneath this critical urinary cadmium level.

The EFSA TWI of 2.5  $\mu\text{g kg}^{-1}$  bw was endorsed by the UK COT in May 2009 (COT, 2009) and is considered an appropriate basis for recommending an oral HCV for cadmium for use in deriving SGVs. The  $\text{TDI}_{\text{oral}}$  is thus 0.36  $\mu\text{g kg}^{-1}$  bw  $\text{day}^{-1}$ .

# 5 Background intake

## 5.1 Food

A survey of cadmium in food in the UK was carried out as part of the 2006 Total Diet Study (FSA, 2009). Toddlers (1.5–4.5 years of age) were estimated to have the highest dietary exposure to cadmium with a mean of about  $0.4 \mu\text{g kg}^{-1} \text{bw day}^{-1}$ . The mean daily intake (MDI) from food for the total population (across all age groups) was estimated to be  $11\text{--}13 \mu\text{g day}^{-1}$  (FSA, 2009). This was slightly higher than in 2000 when the average intake of cadmium was reported to be  $9 \mu\text{g day}^{-1}$  (COT, 2003), but lower than in most other previous surveys. In the period from 1981 to 1991, the average intake of cadmium was between  $17$  and  $19 \mu\text{g day}^{-1}$ ; by 1994 it had decreased to  $14 \mu\text{g day}^{-1}$  (MAFF, 1997; Ysart *et al.*, 1999) and by 1997 it was  $12 \mu\text{g day}^{-1}$  (MAFF, 1999; Ysart *et al.*, 2000; COT, 2003).

## 5.2 Water

The Drinking Water Inspectorate (DWI) collects data on cadmium concentrations in drinking-water, obtained from sampling at domestic taps in England and Wales (Table 5.1). Based on the mean concentrations and using the default adult drinking-water consumption rate of two litres per day, the MDI of cadmium from drinking-water is concluded to be about  $0.4 \mu\text{g day}^{-1}$ .

**Table 5.1 Summary of 2004–2007 levels of cadmium in samples of drinking-water in England and Wales (Marsden, 2009)**

Year	No. samples	Concentration ( $\mu\text{g L}^{-1}$ )			
		Min	Mean	Max	97.5%ile
2004	15,896	0.0002	0.2891	5.1	0.5
2005	13,201	0.01	0.2102	4.2	0.5
2006	13,220	0.01	0.1931	2.71	0.5
2007	14,352	0.0081	0.1604	1.63	0.5

## 5.3 Air

The average annual concentration of cadmium in urban air in the UK has been reported to be about  $1 \text{ ng m}^{-3}$  (DETR, 1997).

## 5.4 Other sources

Cigarettes are a significant source of cadmium. The cadmium content of one cigarette is often quoted as  $1\text{--}2 \mu\text{g}$ , and the estimated daily uptake of cadmium for someone

who smokes 20 cigarettes per day is usually given as within the range 1–4  $\mu\text{g}$  (IPCS, 1992; IARC, 1993).

## 5.5 Estimation of mean daily intakes

The adult oral mean daily intake ( $\text{MDI}_{\text{oral}}$ ) of cadmium from its presence in food ( $13 \mu\text{g day}^{-1}$ ) and drinking-water ( $0.4 \mu\text{g day}^{-1}$ ) combined is estimated to be  $13.4 \mu\text{g day}^{-1}$ , which is equivalent to  $0.19 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$  for a 70-kg adult. For a 20-kg six year old child ingesting 74% of the adult dietary intake (Environment Agency, 2009), this is equivalent to about  $9.9 \mu\text{g day}^{-1}$  or  $0.50 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ .

Based on the default 70-kg adult inhalation rate of  $20 \text{ m}^3$  of air per day and an average annual concentration of cadmium in urban air in the UK of about  $1 \text{ ng m}^{-3}$ , the adult inhalation mean daily intake ( $\text{MDI}_{\text{inh}}$ ) of cadmium is estimated to be  $0.02 \mu\text{g day}^{-1}$  or  $0.0003 \mu\text{g kg}^{-1} \text{ bw}$ . For a 20-kg six year old child inhaling 74% of the adult rate (Environment Agency, 2009), this is equivalent to about  $0.015 \mu\text{g day}^{-1}$  or  $0.0007 \mu\text{g kg}^{-1} \text{ bw day}^{-1}$ .

## 6 Conclusions

The key aspects of cadmium's toxicological profile in humans are its adverse effects on kidney and bone, arising from either oral or inhalation exposure, and its lung carcinogenicity demonstrated in exposed workers following inhalation. Although there is also evidence of toxicity to the respiratory tract and nervous system, it is currently accepted that any limits set to protect against kidney and bone toxicity will preclude damage at these other sites.

A  $\text{TDI}_{\text{oral}}$  of  $0.36 \mu\text{g kg}^{-1} \text{bw day}^{-1}$  is recommended based on the estimated dose threshold of cadmium's kidney toxicity in humans.

A  $\text{TDI}_{\text{inh}}$  of  $0.0014 \mu\text{g kg}^{-1} \text{bw day}^{-1}$  ( $1.4 \text{ ng kg}^{-1} \text{bw day}^{-1}$ ) has been derived also to preclude cadmium's kidney toxicity. Exposure at the  $\text{TDI}_{\text{inh}}$  is expected to pose at most only a minimal risk of lung cancer.

**Table 6.1 HCV and MDI values for cadmium**

Parameter	Units	Oral	Inhalation
MDI	$\mu\text{g day}^{-1}$	13.4	0.02
MDI for 70-kg adult	$\mu\text{g kg}^{-1} \text{bw day}^{-1}$	0.19	0.0003
MDI for 20-kg child	$\mu\text{g kg}^{-1} \text{bw day}^{-1}$	0.50 <sup>a</sup>	0.0007 <sup>a</sup>
<b>TDI</b>	$\mu\text{g kg}^{-1} \text{bw day}^{-1}$	<b>0.36</b>	<b>0.0014</b>

<sup>a</sup> See Environment Agency (2009) for details of MDI conversion factors.

Both oral and inhalation exposures contribute to the same systemic effects on the kidney (and bone); therefore, this should be considered in a risk assessment. The effects of dermal exposure to cadmium are not expected to be significant as the extent of dermal absorption appears to be low even compared with oral absorption. A conservative assessment of dermal exposure may, however, be achieved by comparison with the  $\text{TDI}_{\text{oral}}$ .

The key determinant of cadmium's renal toxicity potential is its chronic accumulation in the kidney. Therefore, it seems reasonable for SGVs to be derived based averaging exposure over a lifetime rather than the default modelling based on exposure of a young child. While adopting such an approach will mean that exposures of young children at soil concentrations equal to the SGV may exceed the HCVs by up to around two-fold (as exposures of young children to soil contaminants are, relative to bodyweight, greater than those of adults), this is not anticipated to be of significant toxicological concern. Long-term exposure to levels in excess of either the  $\text{TDI}_{\text{oral}}$  or the  $\text{TDI}_{\text{inh}}$ , however, might be associated with an increase in kidney disease in a proportion of those exposed.

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# List of abbreviations

ATSDR	Agency for Toxic Substances and Disease Registry [USA]
BMD	benchmark dose
BMDL	lower confidence limit of the benchmark dose
bw	bodyweight
CalEPA	California Environmental Protection Agency
CI	confidence interval
CMR	carcinogenic, mutagenic and/or reprotoxic
COC	Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment [UK]
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment [UK]
CSAF	chemical specific adjustment factor
CSTEE	Scientific Committee on Toxicity, Ecotoxicity and the Environment [EU]
Defra	Department for Environment, Food and Rural Affairs [UK]
DWI	Drinking Water Inspectorate [UK]
FAO	Food and Agriculture Organization of the United Nations
FSA	Food Standards Agency [UK]
HCV	Health Criteria Value
HMW	high molecular weight
HPA	Health Protection Agency [UK]
IARC	International Agency for Research on Cancer
IPCS	International Programme on Chemical Safety
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LMW	low molecular weight
LOAEC	lowest-observed adverse concentration
LOAEL	lowest-observed adverse effect level
MDI	mean daily intake
MOS	Margin of Safety
MRL	Minimal Risk Level
NOAEL	no-observed adverse effect level
NTP	National Toxicology Program [USA]
ppm	parts per million

PTWI	provisional tolerable weekly intake
RAR	Risk Assessment Report [EU]
RfD	Reference Dose
RIVM	National Institute for Public Health and the Environment [Netherlands]
SGV	Soil Guideline Value
TDI	tolerable daily intake
UF	uncertainty factor
USEPA	United States Environmental Protection Agency
WHO	World Health Organization

# Appendix – Literature search

The final main literature search forming the basis of this update report was undertaken in October 2008, using a proprietary database – the TRACE database developed and managed by bibra toxicology advice & consulting. The database was searched for comprehensive reviews and evaluations of cadmium. A search for primary literature published since the most recent expert group evaluation was also conducted (covering 2004–2008). Aware of the publication in January 2009 of EFSA's assessment of cadmium (EFSA, 2009), this document was specifically sought, but no further literature searching was conducted at this time.

TRACE includes information from peer-reviewed toxicology and nutrition journals as well as secondary sources (websites, official publications and evaluations by authoritative groups) including:

- UK government agency (Defra and the Environment Agency, FSA, HPA) and advisory committee (COT, COM, COC, ACAF, ACNFP and ACP) reports and evaluations
- EU Risk Assessment Reports
- EU expert committees (EU scientific committees, EFSA scientific panels)
- WHO/IPCS reports and evaluations (including CICADs and EHCs, and IARC, JECFA and JMPR monographs), and the WHO Air Quality and Drinking-Water Quality Guidelines
- US government agency reports and evaluations (EPA, ATSDR, FDA, NTP, OSHA, NCEA, CFSAN, CERHR, NIEHS and OEHHA)
- OECD SIDS dossiers/SIARS
- ECETOC, ACGIH, BG Chemie and DFG reports and monographs
- IUCLID data sets
- NICNAS Priority Existing Chemical Assessments

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