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Cadmium in Drinking-water

Background document for development of
WHO *Guidelines for Drinking-water Quality*

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Preface

One of the primary goals of the World Health Organization (WHO) and its Member States is that "all people, whatever their stage of development and their social and economic conditions, have the right to have access to an adequate supply of safe drinking water." A major WHO function to achieve such goals is the responsibility "to propose ... regulations, and to make recommendations with respect to international health matters ...."

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as *International Standards for Drinking-water*. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO *Guidelines for Drinking-water Quality* (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects reviewing selected microorganisms was published in 2002. The third edition of the GDWQ was published in 2004, the first addendum to the third edition was published in 2006 and the second addendum to the third edition was published in 2008. The fourth edition will be published in 2011.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of public drinking-water quality is accordingly prepared and updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants of potential health concern in drinking-water. In the first and second editions, these constituted Volume 2 of the GDWQ. Since publication of the third edition, they comprise a series of free-standing monographs, including this one.

For each chemical contaminant or substance considered, a lead institution prepared a background document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Japan, the United Kingdom and the United States of America (USA) prepared the documents for the fourth edition.

Under the oversight of a group of coordinators, each of whom was responsible for a group of chemicals considered in the GDWQ, the draft health criteria documents were submitted to a number of scientific institutions and selected experts for peer review. Comments were taken into consideration by the coordinators and authors. The draft documents were also released to the public domain for comment and submitted for final evaluation by expert meetings.

During the preparation of background documents and at expert meetings, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health Criteria monographs and Concise International Chemical Assessment Documents, the International Agency for Research on Cancer, the Joint FAO/WHO Meetings on Pesticide Residues and the Joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite, in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO Internet site and in the current edition of the GDWQ.

Acknowledgements

The current version of Cadmium in Drinking-water, Background document for development of WHO *Guidelines for Drinking-water Quality*, is a revision of the background document prepared for the third edition of the Guidelines by Mr J. Fawell, United Kingdom.

The work of the following working group coordinators was crucial in the development of this document and others contributing to the fourth edition:

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The draft text was discussed at the Expert Consultation for the fourth edition of the GDWQ, held in December 2011. The final version of the document takes into consideration comments from both peer reviewers and the public. The input of those who provided comments and of participants at the meeting is gratefully acknowledged.

The WHO coordinators were Mr R. Bos and Mr B. Gordon, WHO Headquarters. Ms C. Vickers provided a liaison with the International Programme on Chemical Safety, WHO Headquarters. Mr M. Zaim, Public Health and the Environment Programme, WHO Headquarters, provided input on pesticides added to drinking-water for public health purposes.

Ms P. Ward provided invaluable administrative support at the Expert Consultation and throughout the review and publication process. Ms M. Sheffer of Ottawa, Canada, was responsible for the scientific editing of the document.

Many individuals from various countries contributed to the development of the GDWQ. The efforts of all who contributed to the preparation of this document and in particular those who provided peer or public domain review comments are greatly appreciated.

Acronyms and abbreviations used in the text

DNA	deoxyribonucleic acid
FAO	Food and Agriculture Organization of the United Nations
IARC	International Agency for Research on Cancer
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LD_{50}	median lethal dose
NOAEL	no-observed-adverse-effect level
PTWI	provisional tolerable weekly intake
USA	United States of America
WHO	World Health Organization

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1. GENERAL DESCRIPTION

1.1 Identity

Cadmium is a metal with an oxidation state of +2. It is chemically similar to zinc and occurs naturally with zinc and lead in sulfide ores.

1.2 Physicochemical properties (IARC, 1976; Ros & Slooff, 1987; Ware, 1989)

Property	*Value*
Physical state	Soft white solid
Density	8.64 g/cm^3
Melting point	320.9 °C
Boiling point	765 °C at 100 kPa
Solubility	Soluble in dilute nitric and concentrated sulfuric acids

1.3 Major uses

Cadmium metal is used mainly as an anticorrosive, electroplated onto steel. Cadmium sulfide and selenide are commonly used as pigments in plastics. Cadmium compounds are used in electric batteries, electronic components and nuclear reactors (Friberg et al., 1986; Ros & Slooff, 1987).

1.4 Environmental fate

Fertilizers produced from phosphate ores constitute a major source of diffuse cadmium pollution. The solubility of cadmium in water is influenced to a large degree by its acidity; suspended or sediment-bound cadmium may dissolve when there is an increase in acidity (Ros & Slooff, 1987). In natural waters, cadmium is found mainly in bottom sediments and suspended particles (Friberg et al., 1986).

2. ANALYTICAL METHODS

Cadmium can be determined by atomic absorption spectroscopy using either direct aspiration into a flame or a furnace spectrometric technique. The detection limit is 5 µg/l with the flame method and 0.1 µg/l with the furnace procedure (ISO, 1985, 1986; Ware, 1989).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Air

Cadmium is present in ambient air in the form of particles in which cadmium oxide is probably an important constituent (Friberg et al., 1986). Annual average concentrations in four cities in Germany in 1981–1982 were 1–3 ng/m^3. In the Netherlands, annual average concentrations in 1980–1983 were 0.7–2 ng/m^3. Levels are generally higher in the vicinity of metallurgical plants. In industrial areas in

Belgium, annual average levels in 1985–1986 were 10–60 ng/m^3 (Ros & Slooff, 1987). For the general population not living in such areas, cadmium intakes from air are unlikely to exceed 0.8 µg/day (JECFA, 1989).

Cigarette smoking increases cadmium concentrations inside houses. The average daily exposure from cigarette smoking (20 cigarettes a day) is 2–4 µg of cadmium (Ros & Slooff, 1987).

3.2 Water

Cadmium concentrations in unpolluted natural waters are usually below 1 µg/l (Friberg et al., 1986). Median concentrations of dissolved cadmium measured at 110 stations around the world were <1 µg/l, the maximum value recorded being 100 µg/l in the Rio Rimao in Peru (WHO/UNEP, 1989). Average levels in the Rhine and Danube in 1988 were 0.1 µg/l (range 0.02–0.3 µg/l) (ARW, 1988) and 0.025 µg/l (AWBR, 1988), respectively. In the sediments near Rotterdam harbour, levels in mud ranged from 1 to 10 mg/kg dry weight in 1985–1986, down from 5–19 mg/kg dry weight in 1981 (Ros & Slooff, 1987).

Contamination of drinking-water may occur as a result of the presence of cadmium as an impurity in the zinc of galvanized pipes or cadmium-containing solders in fittings, water heaters, water coolers and taps. Drinking-water from shallow wells of areas in Sweden where the soil had been acidified contained concentrations of cadmium approaching 5 µg/l (Friberg et al., 1986). In Saudi Arabia, mean concentrations of 1–26 µg/l were found in samples of potable water, some of which were taken from private wells or cold corroded pipes (Mustafa et al., 1988). Levels of cadmium could be higher in areas supplied with soft water of low pH, as this would tend to be more corrosive in plumbing systems containing cadmium. In the Netherlands, in a survey of 256 drinking-water plants in 1982, cadmium (0.1–0.2 µg/l) was detected in only 1% of the drinking-water samples (Ros & Slooff, 1987).

3.3 Food

Food is the main source of cadmium intake for non-occupationally exposed people. Crops grown in polluted soil or irrigated with polluted water may contain increased concentrations, as may meat from animals grazing on contaminated pastures (IARC, 1976). Animal kidneys and livers concentrate cadmium. Levels in fruit, meat and vegetables are usually below 10 µg/kg, in liver 10–100 µg/kg and in kidney 100–1000 µg/kg. In cereals, levels are about 25 µg/kg wet weight. In 1980–1988, average cadmium levels in fish were 20 µg/kg wet weight. High levels were found in shellfish (200–1000 µg/kg) (Galal-Gorchev, 1991).

Based on cadmium levels measured in 1977–1984, the estimated daily intake in food by the Netherlands population is 20 µg/person (IARC, 1976). The dietary daily intake of cadmium has also been estimated to be in the range 10–35 µg (Galal-Gorchev, 1991). In contaminated areas in Japan, daily intakes in 1980 were in the range 150–250 µg, based on measurements of cadmium in faeces (Friberg et al., 1986).

3.4 Estimated total exposure and relative contribution of drinking-water

Food is the main source of non-occupational exposure to cadmium, with dietary daily intakes, as stated above, in the range 10–35 μg. The intake from drinking-water is usually less than 2 μg/day (JECFA, 1989). Smoking will increase the daily intake of cadmium. In western Europe, the USA and Australia, the average daily oral intake of cadmium by non-smokers living in unpolluted areas is 10–25 μg (WHO, 1992).

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

The kinetics and absorption of cadmium have been reviewed in some detail (JECFA, 2000a). Absorption via the gastrointestinal tract is influenced by the solubility of the cadmium compound concerned. In healthy persons, 3–7% of the cadmium ingested is absorbed; in iron-deficient people, this figure can reach 15–20% (Krajnc et al., 1987). Absorbed cadmium enters the bloodstream and is transported to other parts of the body. After binding to metallothionein, it is filtered in the kidney through the glomerulus into the primary urine, then reabsorbed in the proximal tubular cells, where the cadmium–metallothionein bond is broken. The unbound cadmium stimulates the production of new metallothionein, which binds cadmium in the renal tubular cells, thereby preventing the toxic effects of free cadmium. If the metallothionein-producing capacity is exceeded, damage to proximal tubular cells occurs, the first sign of this effect being low-molecular-weight proteinuria (Friberg et al., 1986).

Tissue cadmium concentrations increase with age. Both kidney and liver act as cadmium stores; 50–85% of the body burden is stored in kidney and liver, 30–60% being stored in the kidney alone. The biological half-life in humans is in the range 10–35 years. Because of the considerable age-related accumulation of cadmium in the body, only a small part of the cadmium absorbed will be excreted in the urine. About 0.007% of the body burden is excreted daily by adults, but individual variation is large (Krajnc et al., 1987; JECFA, 1989; WHO, 1992).

5. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

5.1 Acute exposure

Cadmium compounds have a moderate acute oral toxicity; oral LD_{50} values for mice and rats range from 60 to over 5000 mg/kg of body weight. Major effects are desquamation of epithelium of the gastrointestinal tract, necrosis of the gastric and intestinal mucosa and dystrophic changes of liver, heart and kidneys (Krajnc et al., 1987).

5.2 Short-term exposure

After repeated oral administration, the critical effect in animals is a characteristic lesion of the proximal tubules in the kidneys, resulting in impaired tubular resorption and consequent urinary excretion of low-molecular-weight proteins. In rhesus monkeys, a NOAEL of 3 mg of cadmium per kg of diet (given as cadmium chloride) was found for these effects, which were also produced by repeated oral administration to rats of doses of 10 mg of cadmium per litre in drinking-water or 10 mg/kg of diet (given as cadmium chloride) and above. Effects on bone (osteoporosis) were also frequently seen at doses of 10–30 mg of cadmium per kg of diet or 10 mg/l and above in drinking-water. Effects on the liver, haematopoietic system and immune system have also been reported (Krajnc et al., 1987).

5.3 Reproductive and developmental toxicity

Studies on oral exposure have not provided evidence of teratogenic effects at dose levels below those that were toxic to maternal animals. Fetotoxic and embryotoxic effects were also observed only at toxic dose levels. In a multigeneration study in rats, dose levels up to 100 mg/kg of diet did not cause effects on reproduction. In four-generation studies, 1 mg of cadmium per litre in drinking-water and 0.125 mg of cadmium per kg in the diet caused effects on fertility in mice and rats, respectively. Mild testicular changes in rats were seen after oral administration of 50 mg of cadmium per kg of body weight for 15 months. No effects were seen at 5 mg/kg of body weight or when rats were exposed to 70 mg/l in their drinking-water for 70 days (Krajnc et al., 1987).

5.4 Mutagenicity and related end-points

Both negative and positive results have been noted with regard to DNA degradation, decreased fidelity of DNA synthesis, microbial DNA repair, gene mutations and chromosomal abnormalities in mammalian cell cultures, higher plants and intact animals. It should be noted that the positive results were often weak and seen at high concentrations that also caused cytotoxicity (Krajnc et al., 1987). However, cadmium does not appear to possess significant genotoxic potential via the oral route.

5.5 Carcinogenicity

Cadmium has been shown to induce carcinogenesis by both the inhalation and parenteral routes of exposure (Krajnc et al., 1987; Oldiges et al., 1989; JECFA, 2000a). An oral carcinogenicity study in rats with cadmium chloride (1–50 mg of cadmium per kg of diet) did not reveal significantly increased tumour incidences (Krajnc et al., 1987). However, in a study in which cadmium was given in the diet to rats, the authors concluded that cadmium given orally caused tumours of the prostate, testis and haematopoietic system (Waalkes & Rehm, 1994). The frequency of lesions of the prostate was increased in rats fed zinc-deficient diets, but the significance of the

prostate lesions for humans is uncertain due to anatomical differences in the organ (JECFA, 2000a).

6. EFFECTS ON HUMANS

The estimated lethal oral dose for humans is 350–3500 mg of cadmium; a dose of 3 mg of cadmium has no acute effects on adults (Krajnc et al., 1987).

With chronic oral exposure, the kidney appears to be the most sensitive organ. Cadmium affects the resorption function of the proximal tubules, the first symptom being an increase in the urinary excretion of low-molecular-weight proteins, known as tubular proteinuria (Krajnc et al., 1987) (see also section 4). Intakes of 140–255 µg of cadmium per day have been associated with low-molecular-weight proteinuria in the elderly; the minimum (critical) level of cadmium in the human renal cortex, related to the first sign of tubular dysfunction, ranged from 100 to 450 mg/kg wet weight (JECFA, 1989). The estimated critical concentration in the renal cortex at which the prevalence of low-molecular-weight proteinuria would reach 10% in the general population is about 200 mg/kg; this would be reached after a daily dietary intake of about 175 µg per person for 50 years, as calculated by regression analysis of cadmium intake and mean kidney cadmium concentration in various countries (JECFA, 1989). It was estimated that a daily intake of 100 µg of cadmium per person would lead to the critical cadmium concentration in the renal cortex being exceeded in 2% of the population (JECFA, 1989). More severe cadmium damage may also involve the glomeruli, detected by increased inulin clearance. Other possible effects include aminoaciduria, glucosuria and phosphaturia. Disturbances in renal handling of phosphorus and calcium may cause resorption of minerals from bone, which can result in the development of kidney stones and osteomalacia.

Many cases of itai-itai disease (osteomalacia with various grades of osteoporosis accompanied by severe renal tubular disease) and low-molecular-weight proteinuria have been reported among people living in contaminated areas in Japan and exposed to cadmium via food and drinking-water. The daily intake of cadmium in the most heavily contaminated areas amounted to 600–2000 µg/day; in other less heavily contaminated areas, daily intakes of 100–390 µg/day have been found (WHO, 1992). A relationship between chronic occupational exposure to cadmium or chronic oral exposure to cadmium via the diet in contaminated areas and hypertension could not be demonstrated (Krajnc et al., 1987).

Epidemiological studies of people chronically exposed to cadmium via the diet as a result of environmental contamination have not shown an increased cancer risk. The results of studies of chromosomal aberrations in the peripheral lymphocytes of patients with itai-itai disease exposed chronically to cadmium via the diet were contradictory. No reliable studies on reproductive, teratogenic or embryotoxic effects in humans are available. Epidemiological studies of humans exposed by inhalation to relatively high cadmium concentrations in the workplace revealed some evidence of an increased lung cancer risk, but a definite conclusion could not be reached (Krajnc et al., 1987).

A number of new studies of cadmium exposure and health impact in human populations have been carried out and reviewed by Jarup et al. (1998). These include studies of kidney dysfunction and osteoporosis. Some data indicate that adverse effects may occur at lower exposures than was previously thought. Although these data indicate that a proportion of the general population may be at increased risk for tubular dysfunction when exposed to cadmium at the PTWI, the risk estimates that can be made with current information are imprecise. JECFA (2000a,b) considered all of the new data but decided that, in view of the uncertainties, the existing PTWI of 7 µg/kg of body weight should be retained.

7. GUIDELINE VALUE

There is some evidence that cadmium is carcinogenic by the inhalation route, and IARC (1987) has classified cadmium and cadmium compounds in Group 2A. However, there is no evidence of carcinogenicity by the oral route and no clear evidence that cadmium is genotoxic.

On the assumption of an absorption rate for dietary cadmium of 5% and a daily excretion rate of 0.005% of body burden, JECFA concluded that, if levels of cadmium in the renal cortex are not to exceed 50 mg/kg, the total intake of cadmium should not exceed 1 µg/kg of body weight per day. The PTWI was therefore set at 7 µg/kg of body weight in 1989 (JECFA, 1989) and reconfirmed in 1993 (JECFA, 1993). This was maintained in 2000 (JECFA, 2000b). It was recognized that the margin between the PTWI and the actual weekly intake of cadmium by the general population was small, namely less than 10-fold, and that this margin may be even smaller in smokers. A guideline value for cadmium of 0.003 mg/l was retained in the third edition, based on an allocation of 10% of the PTWI to drinking-water.

In its most recent evaluation of cadmium, JECFA (2011) found that data relating excretion of the biomarker β_2-microglobulin in urine to cadmium excretion in urine for individuals who are 50 years of age and older provided the most reliable basis on which to determine a critical concentration of cadmium in the urine. Urinary excretion of less than 5.24 µg of cadmium per gram creatinine was not associated with an increased excretion of β_2-microglobulin, and the dietary exposure that would result in a urinary cadmium concentration at the breakpoint of 5.24 µg/g creatinine was estimated to be 0.8 µg/kg of body weight per day or about 25 µg/kg of body weight per month. Because of cadmium's exceptionally long half-life, the previous PTWI of 7 µg/kg of body weight was withdrawn, and a PTMI of 25 µg/kg of body weight was established.

The change from a PTWI to a PTMI has no effect on the guideline value calculation, and the guideline value of 0.003 mg/l is retained.

8. REFERENCES

ARW (1988) *45. Jahresbericht 1988.* [*45th annual report, 1988*.] Düsseldorf, Arbeitsgemeinschaft Rhein-Wasserwerke e.V.

AWBR (1988) *20. Jahresbericht 1988.* [*20th annual report, 1988*.] Karlsruhe, Arbeitsgemeinschaft Wasserwerke Bodensee-Rhein.

Friberg L, Nordberg GF, Vouk VB, eds. (1986) *Handbook of the toxicology of metals.* Vol. II. Amsterdam, Elsevier, pp. 130–184.

Galal-Gorchev H (1991) Dietary intake of pesticide residues, cadmium, mercury and lead. *Food Additives and Contaminants*, 8:793–806.

IARC (1976) *Cadmium, nickel, some epoxides, miscellaneous industrial chemicals and general considerations on volatile anaesthetics*. Lyon, International Agency for Research on Cancer, pp. 39–74 (IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man, Vol. 11).

IARC (1987) *Overall evaluations of carcinogenicity: an updating of IARC monographs volumes 1–42*. Lyon, International Agency for Research on Cancer, pp. 139–142 (IARC Monographs on the Evaluation of Carcinogenic Risk to Humans, Suppl. 7).

ISO (1985) *Water quality — determination of cadmium.* Geneva, International Organization for Standardization (ISO 5961:1985).

ISO (1986) *Water quality — determination of cadmium.* Geneva, International Organization for Standardization (ISO 8288:1986).

Jarup L et al. (1998) Health effects of cadmium exposure — a review of the literature and a risk estimate. *Scandinavian Journal of Work, Environment and Health*, 24(Suppl. 1):1–51.

JECFA (1989) *Toxicological evaluation of certain food additives and contaminants*. Geneva, World Health Organization, Joint FAO/WHO Expert Committee on Food Additives; Cambridge, Cambridge University Press, pp. 163–219 (WHO Food Additives Series No. 24).

JECFA (1993) *Evaluation of certain food additives and contaminants: forty-first report of the Joint FAO/WHO Expert Committee on Food Additives.* Geneva, World Health Organization, Joint FAO/WHO Expert Committee on Food Additives (WHO Technical Report Series No. 837).

JECFA (2000a) *Cadmium*. Geneva, World Health Organization, Joint FAO/WHO Expert Committee on Food Additives (WHO Food Additives Series No. 46).

JECFA (2000b) *Summary and conclusions of the fifty-fifth meeting, Geneva, 6–15 June 2000*. Geneva, World Health Organization, Joint FAO/WHO Expert Committee on Food Additives.

JECFA (2011) *Evaluation of certain food additives and contaminants: seventy-third report of the Joint FAO/WHO Expert Committee on Food Additives.* Geneva, World Health Organization, Joint FAO/WHO Expert Committee on Food Additives (WHO Technical Report Series No. 960).

Krajnc EI et al. (1987) *Integrated criteria document. Cadmium — Effects. Appendix*. Bilthoven, National Institute of Public Health and Environmental Protection (Report No. 758476004).

Mustafa HT et al. (1988) Cadmium and zinc concentrations in the potable water of the eastern provinces of Saudi Arabia. *Bulletin of Environmental Contamination and Toxicology*, 40:462–467.

Oldiges H, Hochrainer P, Glaser U (1989) Long-term inhalation study with Wistar rats and four cadmium compounds. *Toxicological and Environmental Chemistry*, 19:217–222.

Ros JPM, Slooff W, eds. (1987) *Integrated criteria document. Cadmium*. Bilthoven, National Institute of Public Health and Environmental Protection (Report No. 758476004).

Waalkes MP, Rehm S (1994) Cadmium and prostate cancer. *Journal of Toxicology and Environmental Health*, 43:251–269.

Ware GW, ed. (1989) Cadmium. US Environmental Protection Agency Office of Drinking Water health advisories. *Reviews of Environmental Contamination and Toxicology*, 107:25–37.

WHO (1992) *Cadmium.* Geneva, World Health Organization (Environmental Health Criteria 134).

WHO/UNEP (1989) *GEMS — Global fresh water quality*. Published on behalf of the World Health Organization/United Nations Environment Programme. Oxford, Blackwell Reference.