Zeitschrift: Mitteilungen aus Lebensmitteluntersuchungen und Hygiene = Travaux de chimie alimentaire et d'hygiène

Herausgeber: Bundesamt für Gesundheit

Band: 90 (1999)

Heft: 6

Artikel: Toxicity of dietary cadmium : a review

Autor: Daniel, Otto / Schlatter, Josef

DOI: https://doi.org/10.5169/seals-981805

Toxicity of Dietary Cadmium: a Review

Otto Daniel and Josef Schlatter, Swiss Federal Office of Public Health, Toxicology, Zürich

Received 1st September 1999, accepted 15 October 1999

Introduction

Cadmium was first described by *Hermann* in the year 1818 (1). It is widely but sparsely distributed over the Earth's surface, comprising about 0.1–0.5 mg/kg of the earth's crust (2), where it is found most commonly as cadmium sulfide and cadmium carbonate. In ancient times, with the onset of large-scale oxygen production on earth, insoluble metalsulfides were oxidized to soluble sulfates and might have become available to organisms in low concentrations (3). Human industrial activities in the past centuries changed again the distribution of cadmium in the environment. Cadmium emitted from incinerators and other sources is deposited on plants and soils as dry dust or wet precipitation (4). In Switzerland the use and emission of cadmium decreased since 1970 (5). Analyses of sediment cores in a meromictic alpine lake, where anoxic conditions have prevented the remobilization of metals precipitated as sulfide indicate that also cadmium deposition has decreased (6). Cadmium concentrations in soils do not generally decrease, because cadmium is relatively immobile. The mobility in soils and the availability to plants depend on pH, humus and clay content. Long-term trends of cadmium concentrations in soils are difficult to measure, because soil properties affecting cadmium retention are highly variable and soil material is continually redistributed by biological and physical soil processes. Since most cadmium taken up by humans stems from plants, background levels in the environment and the accumulation capacity of plants, which varies between species and subspecies, determine the dietary exposure of humans to cadmium.

Cadmium is not an essential element. It competes with calcium for transport into cells, binds to various enzymes and can replace zinc in many zinc-dependent enzymes and change their functionality (7). Health effects due to cadmium were not known until the late 1950ties, when the itai-itai disease, a degenerative bone disease related to renal damage, occurred in a limited area of about 1500 ha along the Jinzu

River in Japan. Past mining and smelting activities in the Kamioka region had caused persistent water-born cadmium contamination of soils, leading to elevated cadmium levels in locally grown rice (8–11). In the sixties, an increased incidence of prostatic tumors was suspected to be related to cadmium exposure in workers employed in a plant manufacturing nickel-cadmium batteries in the United Kingdom (2). Workers were mainly exposed to cadmium by inhalation of dust with cadmiumoxides and -hydroxides. A series of epidemiologic studies did not confirm an excess prostatic cancers among exposed workers, but found an increase in mortality from lung cancer (2). At the beginning of the 90^{ties}, the International Agency for Research on Cancer of the WHO concluded that there was sufficient evidence for the carcinogenic potential of cadmium compounds in animals and humans (2). However, the implications of these findings for the risk caused by dietary cadmium remained unclear, and it is difficult to quantify the risk of exposure to background levels of cadmium. In our review we provide basic information on the toxicity of dietary cadmium.

Dietary exposure

Typical cadmium concentrations in food items reported worldwide are 5 µg/kg in milk and eggs, 10 µg/kg in fruits, 15 µg/kg in meat, 25 µg/kg in vegetables, 30 µg/kg in cereals and cereal products, 35 µg/kg in fish, 350 µg/kg in molluscs and crustaceans and 500 µg/kg in kidneys (12). An extensive recent review of cadmium levels in different foods in various countries was published by *Tahvonen* (13). Except for populations with special dietary habits (exceptionally high intake of kidneys, liver, molluscs and crustaceans), the items contributing most to the human cadmium exposure are cereals and vegetables (14, 15). The cadmium content in cereals is substantially reduced during grinding, because the outer layers of the grains, which contain the highest contents of cadmium, are discarded. Cadmium in the food exists in both inorganic and organic forms. Part of the inorganic cadmium in plants is bound to heavy-metal binding peptides of the general structure poly-(γ-glutamyl-cysteinyl)-glycine, which are called phytochelatins (16–18). Another part is bound to phytate, a storage compound for phosphorous in plants, which can chelate metals. Cadmium in meat is partly bound to metallothionein (MT), a cystein-rich protein (19).

In Switzerland duplicate diet studies performed on whole dishes in the eighties revealed an average weekly cadmium intake of 85 µg/person (n = 40, range 35–168 µg/person) (20). In Korea the dietary intake of cadmium, also determined by a duplicate diet study, was 148 µg/person; about 23 % of the cadmium intake was from boiled rice (21). A total diet (market basket) study in the Netherlands showed that the weekly cadmium intake was age dependent and increased from 42 ± 14 (age 1–4 years) to 133: ± 42 (age 16–22 years) µg/person (22). A total diet study in the Basque country (Spain) estimated an average weekly cadmium intake of 77 µg/person (23). Another study in Spain (Valencia) using the duplicate diet method with students

gave also an average weekly intake of cadmium of 77 µg/person (24). In England, the national average weekly intake of cadmium was 100 µg/person (range: 50–170 µg/person); in Shipham, a village with high levels of cadmium in the soil because of its zinc mining history, the average weekly intake of cadmium was 180 µg/person (25).

The individual variability of the cadmium intake within human populations may be large. It has been observed in the Netherlands that cadmium intake of a population can be described by a lognormal distribution (26). This statistical model was used to calculate the 99th percentile of weekly cadmium intake at the age of 20 years and was found to be about 260 µg/person; the median was about 160 µg/person (26). In Shipham, the maximum weekly cadmium intake of one person was 1060 µg, which is about six times above the average (25). Minimum and maximum cadmium exposure of a population of more than 110 000 persons in the USA differed by a factor of about 40 (18–729 µg/person) (27).

Compounds and kinetics

Metallothioneins

The biological functions of MT seem to be the storage of essential and the detoxification of non-essential metals. It was hypothesized that during evolution oxygen levels in the atmosphere and soluble metal concentrations in the seas raised simultaneously and organisms had to develop protective mechanisms against both oxygen and metals (3). Many of the organisms made use of oxygen as electron acceptor (aerobes) and of metals as cofactors of enzymes (essential metals). Essential metals such as zinc and copper, but also the non-essential cadmium can bind to MT. Exposure to environmental factors such as metals, alkylating agents and radiation induces the production of MT. Inflammatory processes and hormonal changes following radiation also induce MT (28) (29). In the liver, cadmium and zinc induce an up to 100-fold increase of hepatic MT (29).

In many cells of vertebrates and invertebrates, cadmium is primarily bound to metallothioneins (MT) (30) and can therefore not interact with other macromolecules. MT from hepatocytes of mice and rats have molecular weights between 5600 and 6300 Da. There are four isoforms, called MT1, MT2, MT3 and MT4 (29). MT1 and MT2 are abundant in almost every tissue, whereas MT3 has only been detected in squamous differentiating epithelium and MT4 in the brain (29). The detection and quantification of MT can be performed with molecular probes (31–33) or immunological techniques (34).

Absorption

An average of 5 % of the cadmium in the diet is absorbed during gut passage (4). The interindividual variability of cadmium absorption is high; absorption ranges from < 1% to 20 %. In the stomach cadmium is poorly absorbed; the main location

of absorption is the duodenum (35). In the upper duodenum, where the pH of the content is low, inorganic cadmium tends to be present in the ionic form, which is preferentially taken up. Distal to the pancreatic duct, the pH increases and cadmium will be chelated by various dietary components (35). Cadmium bound to MT is presumably absorbed after passing the duodenum, but to a smaller extent than ionic cadmium.

MT in the mucosa of the small intestine was believed to be important for the regulation of the cadmium absorption, either because cadmium in desquamated mucosa cells can be excreted in the feces (19), or because the cadmium binding capacity of the intestinal cells may become saturated (36). However, studies with transgenic mice, which carried 56 copies of the MT1 gene and constitutively overexpressed MT1 by a factor of 4–15 in stomach, small intestine and other organs, did not support a relation between MT in the mucosa cells and the absorption of cadmium (37).

A MT-cadmium enriched diet resulted in a lower concentration of cadmium in the tissue of small intestine and liver of rats as compared to a cadmium chloride enriched diet (14, 38). In mice absorption of cadmium was lower from crab hepatopankreas than from mushrooms or when given as inorganic cadmium (39). Inuits in the Arctic were believed to accumulate high amounts of cadmium due to consumption of liver and kidneys of caribous and sea mammals, containing high cadmium contents. However, cadmium levels in the blood of nonsmoking inuits have been reported to be comparable to those of nonsmokers elswhere in the world (40). Also, in nonsmoking women in Sweden, the proportion of shellfish in mixed diets did not affect concentration of cadmium in blood and urine (41).

Not only MT in both human cells and food, but also calcium and protein content of the diet and iron status of the body (women with low ferritin content in the serum) affect cadmium absorption during gut passage (4). Animal experiments indicated that fiber content, phytate, GSH, α-tocopherol and selenium in the diet reduce the gastrointestinal absorption of cadmium (42, 43).

Distribution

After gastrointestinal absorption in mice, cadmium was mainly bound to plasma proteins with a molecular weight of 40–60 kDa, which was probably albumin, and transported to the liver. Because MT production has to be induced (37, 44), there was a lag-phase of several hours before the onset of MT-activity (19). In this lag-phase cadmium was bound to other proteins such as alcohol dehydrogenase (34). The distribution to other organs occurred mainly bound to MT in both blood plasma and erythrocytes.

The production of MT varied between and within organs. Transcription of MT1 and MT2 in interstitial cells of the testes of rats increased after exposure to cadmium, but the translation of the mRNA's remained minimal (45–47). In the prostate of rats, expression of MT does not occur in the ventral, but in the dorso-lateral lobe (31, 32). The production of MT in the dorso-lateral lobe was presumably affected by

testosterone (48). The elimination of cadmium in wildtype mice was significantly slower than in MT-null mice (44). The kidney is the major organ (besides the liver) accumulating cadmium. Both cadmium and cadmium-MT (both < 70 kD) pass the glomeruli and are partly reabsorbed in the proximal tubules.

Accumulation and toxicity in different organs

Kidney

In the cells of the proximal tubules cadmium-MT is degraded to amino acids and ionic cadmium. The released cadmium is believed to be the toxic principle in the cells. Early effects of ionic cadmium are an induction of a 70-kDa stress protein (49) and an increased urinary calcium excretion (50). Ionic cadmium may be bound to MT synthesized in renal cells or other low molecular weight proteins. In plasma membranes and lysosomal fractions of cells from the renal cortex of rats, cadmium was also found to bind to high molecular weight proteins (50). It was hypothesized that these were membrane proteins which might be important targets for cadmium induced nephrotoxicity. It was also hypothesized that cadmium in the non-MT fraction is capable of interfering with the formation of lysosomes, which results in a decreased reabsorption and degradation of low molecular weight proteins from the urinary filtrate (51).

β_2-microglobulin, retinol binding protein and other low molecular weight proteins in the blood (11.8 kD) are usually almost completely reabsorbed in the proximal tubules (52), where thy are degraded to amino acids in the lysosmes. Therefore, excretion of these proteins in the urine can be used as a sensitive indicator of a damage to proximal tubules and as a biomarker for cadmium exposure (52). The concentration of high molecular weight proteins such as albumin and transferrin may also increase in the urine after chronic cadmium exposure (53). Depressed glomerular filtration rates, indicating a damage of glomeruli, was observed (9, 53), but the damage to proximal tubules is assumed to be the primary chronic effect of cadmium in the kidney.

Cadmium levels in kidneys of newborns are low (< 0.1 mg/kg fresh weight) and rise steadily with age, reaching a maximum around the age of 45–50 years (4, 54, 55). Observed concentrations in the kidney in different countries (with different exposure) were correlated with dietary cadmium intake (55). Cadmium contents in the cortex of preserved kidneys from 1897–1938 in Germany were 0.86 mg/kg wet weight (56). In kidneys from 1980 and later, contents had increased to 40.7 mg/kg. In Swedish autopsy samples from the 19th century and samples from 1973/1974 cadmium contents were 15.1 and 57.1 mg/kg, respectively (57). The cadmium concentration in the kidney cortex being critical for proper renal tubular functioning, lies between 100 and 300 mg/kg wet weight (4, 8, 58, 59). When this critical concentration is reached, cadmium excretion increases and the concentration of cadmium in the kidney decreases. To accumulate a critical concentration of cadmium in the renal

cortex within 50 years, 1225 µg/person have to be consumed weekly with the diet (55). This corresponds to a life-time cadmium exposure of about 3 µg/kg bw per day.

Vitamin D is hydroxylated in the kidneys to the active 1,25-dihydroxycholecalciferol (DHCC). DHCC stimulates absorption of calcium from the intestine and incorporation into the bones. The regulation of the vitamin D hydroxylation in the kidneys by the parathyroid hormone may be impaired by cadmium (60). Persons suffering from Itai-Itai-disease in Japan in the late fifties, showed an altered metabolism of calcium, phosphate and vitamin D (60). Poor basic nutrition and low calcium and vitamin D intake might have increased the susceptibility of these persons to cadmium.

Liver

Cadmium bound to MT was either stored in the liver tissue or transported to other organs. Acute exposure to high doses of cadmium lead to functional and structural changes of the liver. Ionic cadmium lowered the pH within cells, possibly by an activation of the HCO_3^-/Cl^- antiport system (61). Acidic pH caused mitochondrial dysfunction with an increased H_2O_2 production and a subsequent permeability change and breakage of membranes (61). In mice (wildtype), alanine aminotransferase in the serum was increased by a factor of about 70 after i.v. cadmium application of 3.1 mg/kg bw (62). Transgenic mice overexpressing MT had only a seven fold increased alanine aminotransferase and fewer necrotic hepatocytes. Rabbits, fed food containing 300 mg/kg cadmium, i.e. about 7.5 mg/kg bw/d assuming a daily food consumption of 40 g/kg bw, showed amyloid depositions in the liver after 54 weeks (4).

Placenta

The placenta is a key organ with respect to the potential toxicity of cadmium to the unborn. Effects of cadmium at high doses (4.5 mg/kg bw, s.c., Wistar rats) in the cells of the trophoblast included lysosomal vesiculation and calcification of the mitochondria, subsequent necrosis and ischaemic effects, and fetal death (63). A dose of 1.1 mg/kg bw, s.c. seemed to be without effect on the conceptuses in Wiston-Porton rats (64). In rodents, cadmium accumulated in the embryo during early gestation. With ongoing development, the placenta acted as a barrier for cadmium. Therefore, contents of cadmium and MT became higher in the placenta than in the embryo or fetus. If mice blastocystes have been isolated from transgenic mice overexpressing MT1, they were nine times more likely to develop to midterm in foster mother mice after in vitro exposure to cadmium at 5.6 mg/l (33). Thus, MT reduced placental mediated toxicity of cadmium to the embryo.

Testes

Single s.c. cadmium injections of 3.372 mg/kg bw induced hemorrhagies, and an increase of lipidperoxydation, iron content and H_2O_2 concentration in the Leydig cells of rats (65). Testicular toxicity was reduced by zinc or by low-dose cadmium pretreatment (47). However, the testicular MT gene did not appear to play a major role in the tolerance induced by zinc to cadmium toxicity. In adult male Wistar rats no changes occurred in testicular MT expression when assessed either at the transcriptional or translational level (47). Testicular interstitial cells of adult male Fischer rats receiving a s.c. cadmium injection of 0.45 mg/kg bw had increased levels of MT1- and MT2-mRNA, but contained less total MT than cells from wildtype animals (45). In both wildtype and transgenic CD1 mice, which overexpressed MT1, histological damages in testes occurred after s.c. cadmium injection of 1.12, but not after 0.84 mg/kg bw (66). Possibly, cadmium in the testes was not bound at all to MT (46).

Carcinogenicity in different organs

Cadmium-induced carcinogenesis was observed in testes and prostate of rodents (67–69). An increase in tumor incidence of interstitial cells of the testes of Wistar rats under zinc-adequate nutrition occurred after 77 weeks at cadmium levels of 200 mg/kg in the food (67). Assuming a feeding rate of 18 g/d per rat and a bw of 400 g, the cadmium intake corresponded to 9 mg/kg bw/d.

In the prostate of rats, carcinogenic effects of cadmium were uniformly confined to the ventral lobe and have not been detected in the dorso-lateral lobe. An increase in hyperplastic foci and adenomas in the prostate of Wistar rats occurred after 77 weeks of feeding cadmium at concentrations of 50 mg/kg, i.e. at a dose of 2.3 mg/kg bw/d (67).

Leukemia of large granular lymphocytes (natural killer cells) in rats fed cadmium during 77 weeks was increased. The incidence of leukemia was 5.4, 7.4, 3.9, 11.5, 20 and 28 % for rats fed zinc-deficient diet, and 5.4, 3.6, 14.8, 20.8 and 3.7 % for rats fed zinc-adequate diet at 0, 25, 50, 100, 150 and 200 mg/kg (i.e. at 0, 1.1, 2.3, 4.5, 6.8, 9 mg/kg bw/d) (67). Interestingly, leukemia at the highest dose in rats fed zinc-adequate diet was not increased. The reasons for this phenomenon are unclear.

Genotoxicity and tumor promotion

Genotoxic effects

Cadmium was found to bind *in vitro* to bases, phosphate groups (70) and chromatin, and to cause conformational changes of the DNA at concentrations of 112 mg/l and higher (71). Incubation of bare DNA *in vitro* with cadmium did not show damages such as strand breaks or DNA-adducts. This finding suggested that the DNA-damage was caused by indirect mechanisms (72).

Susceptibility of different cells to genotoxic effects of cadmium is highly variable. Cadmium at cytotoxic concentrations induced DNA strand breaks (71, 73–75) and sister chromatid exchanges (76). At 56 mg/l, cadmium exposure for 1 h resulted in significant single strand damage in rat hepatocytes (TRL-1215) (74). Pretreatment of cells with zinc acetate, which increased the production of MTs, reduced strand damage. Other cells, such as the Leydig cells from male Wistar rats, did not show DNA damage at cadmium concentrations of 5.6–45 mg/l. In CHO (Chinese hamster ovary) cells cadmium at 0.034 mg/l increased the number of sister chromatid exchanges per cell from 7.5 to 16.4; 0.112 and 0.336 mg/l induced chromatid strand breaks (76). The viability of these cells was decreased at concentrations higher than 0.034–0.112 mg/l.

Metals can lead to redox-cycling and induce oxydative stress (30). It has been postulated that DNA damage by oxydative stress mainly occurs due to the formation of hydrogen peroxides and a decrease of the cellular GSH concentration (65, 72, 73). Scavengers of reactive oxygen species like katalase for hydrogen peroxide and D-mannitol for hydroxyl radicals reduced the number of chromosomal aberrations, whereas superoxide dismutase detoxifying singlet oxygen had no effect (72). Cadmium induced lipid peroxidation in the liver and kidney of Charles Foster rats. This process was inhibited by co-administration of antioxidants like GSH, α-tocopherol and selenium (42). Cadmium administered s.c. to male rats (3.4 mg/kg bw) increased the activities of selenium-dependent GSH peroxidase and reductase (28).

Heat shock proteins, which may be considered as indicators of cellular stress, were induced in Wistar rats after s.c. cadmium injection of 11.2 mg/kg bw. One example of a heat schock protein induced by cadmium with a known function is heme oxygenase. It converts heme into biliverdin, which is a precursor of bilirubin. Because heme oxygenase acts as an antioxidant, its induction by cadmium is presumably a mechanism to reduce oxydative stress in cells. It was not induced, if prior to the cadmium exposure bilirubin or α-tocopherol was administered (77). The induction of heme oxygenase in the rat liver occurred only after a decrease of GSH and an increase of H_2O_2 (77). Most stress proteins were only induced at doses of cadmium which were close to cytotoxic levels (71).

Below cytotoxic levels, interference of cadmium with DNA repair may be the predominant genotoxic effect (78). Cadmium inhibited DNA polymerases, including polymerase β, at non-cytotoxic concentrations, decreasing the fidelity of DNA polymerization (72, 78). Furthermore, it affected expression of several proteins, including gadd153, a protein involved in the recognition of DNA-damages (30). DNA-adducts induced by methylating agents and benzo(a)pyrene were more persistent in human fibroblasts and blood cells, if the cells were post-treated with cadmium sulfate (79). The enzyme O^6-methylguanin DNA alkyltransferase (MGTase) has a cysteine rich region, which binds and removes methyl groups from guanin. The repair of alkylated bases was inhibited by cadmium, possibly because both transcriptional activation and enzymatic activity of MGTase were inhibited

(72, 78). This coincided with synergistic interactions between alkylating agents and cadmium found in the tumor development of rats (72).

Tumor promotion

Induction of various genes was observed at cadmium concentrations of 0.056–2.2480 mg/l (71). Early-response genes such as the protooncogenes *fos, jun* and *myc* were induced by cadmium within 15 minutes. When these genes are overexpressed they become oncogenes, because they can drive cells beyond the G2 checkpoint and cause uncontrolled cell proliferation. Cadmium induced protooncogenes by activating certain protein kinases (80). MT induced by pretreatment with zinc reduced the induction of *myc* and *fos* in myoblasts of rats by cadmium exposure (81). In normal (C57BL/6J) and MT-null mice it was shown that *jun* was only induced when cadmium was given at doses which were hepatotoxic (82). Contrarily, it has been reported that exposure of L6 cells (rat skeletal muscle myoblasts) to cadmium *in vitro* led to a down-regulation of *myc* and *jun,* and to a reduced growth and malignancy (progression) of tumors originating from these cells after injection into athymic nude mice (Ncr-nu) (81). Nitric oxide reduced the expression of *myc* by a factor of 2–3 in Chinese hamster ovary cells (83). Generally, effects on *fos, jun* and *myc* occurred at cytotoxic concentrations.

The p53 protein is found in very small concentrations in normal cells. It can bind to DNA and block at elevated concentrations the cell cycle at the G1 checkpoint, allowing DNA-repair before the beginning of DNA-synthesis. Cells lacking the *p53* suppressor gene or having mutations in this gene can not slow down the cell cycle and may either die by the induction of apoptosis, or worse, pass the G2 checkpoint and proliferate with a corrupted genome. In contrast to the protooncogenes, levels of the *p53*-mRNA were already increased at doses of cadmium (0.56 and 1.12 mg/kg bw, s.c.), which did not elicit an obvious cytotoxic response (82).

Evaluation

Toxic effects of cadmium were observed at lower doses in the kidneys than in liver, placenta, testes or prostate. To assess a critical concentration for nephrotoxicity of cadmium, target organ concentration or the excretion of biomarkers can be used. A cadmium concentration of 200 mg/kg fresh weight in the renal cortex was considered to be the critical concentration for 10 % of a population (84). Cadmium concentrations in kidneys showed a log-normal distribution (8) and a high coefficient of variation of up to 83 % (26). Using a model on cadmium kinetics, it was estimated that in the Swedish population the critical steady-state concentration in the kidney cortex was reached in 1 and 0.1 % of a population, if cadmium intakes were 420 and 192 µg/week, respectively (8).

Urinary β_2-microglobulin, used as biomarker of renal damage, gave sigmoid dose response curves for cadmium exposure (9). Probit analysis showed that a cad-

mium intake of 175 µg/week during 50 years would increase levels of β_2-microglobulin in 0.1 % of the European population (70 kg body weight). At 385 µg/week the increase of β_2-microglobulin would be observable in 1%, at 553 µg/week in 2.5 % and at 756 µg/week in 5 % of the population. However, the 95 % confidence limits of cadmium intake were high, e.g. 175 and 861 µg/week for an average intake of 385 µg/week, and the background incidence of increased β_2-microglobulin was 2.5 %.

The JECFA proposed 1972 a provisional tolerable weekly intake (PTWI) of 400–500 µg per person (85), based on a threshold concentration in the renal cortex of 50 mg/kg wet weight. The committee recognised that there were many uncertainties involved in the estimation of this PTWI and suggested that the PTWI should be revised when better evidence becomes available. The JECFA confirmed the PTWI in the year 1989 based on dose-response relationships with β_2-microglobulin (84). In both approaches, safety margins were small and the high interindividual variability was not explicitely considered in the risk assessment.

The assessment of the cancer risk of dietary cadmium for humans is based on the extrapolation of cancer incidences of laboratory animals. Currently, there are two approaches used for extrapolations. One, the virtual safe dose (VSD) approach, assumes a linear dose/response curve and calculates the dose for a tumor incidence of 10^{-6} from the incidence observed in animals experiments. Using prostatic hyperplasia and adenoma in rats as endpoint (19 % incidence at 2.3 mg/kg bw/d) the VSD at a risk of 10^{-6} would be 12 ng/kg bw/d; with leukemia of large granular lymphocytes as endpoint (11.2 % incidence at 1.2 mg/kg bw/d), the VSD would be 10 ng/kg bw/d, i.e. about 5 µg/week.

Another approach, the threshold approach, assumes a negligible effect at low doses, i.e. a sublinear dose/response curve (as defined in (86)) for carcinogens not acting directly on the DNA (87). In this case uncertainty factors are applied to no observable adverse effect levels (NOAEL). Because results of experiments on genotoxicity and tumor promotion did not support direct interactions with DNA or a linear dose/response curve, a threshold approach seems to be more adequate for assessing safe cadmium intakes. In Wistar rats, no significant increases of the incidence of tumors in the prostate occurred at dietary cadmium levels of 25, but at 50 mg/kg or more (67). Based on a food consumption of 18 g/d and a bw of 400 g, the NOAEL for the rats was 1.13 mg/kg/d. Applying an uncertainty factor of 1000 and assuming a human body weight of 70 kg, a tolerable weekly cadmium intake of 550 µg per person can be calculated. This is close to the PTWI established by the JECFA for kidney damage as endpoint.

In many countries the average weekly intake of cadmium is usually below 100 µg/person and remained more or less constant over the last decades, because effective measures were taken to reduce cadmium emission. This is a factor of 4–5 below the PTWI. Therefore, most persons eating food produced at average background levels in the environment are not at risk from dietary cadmium. However, the variability at different levels of measurement, i.e. concentration in soils and food, gastroin-

testinal absorption, tissue distribution and excretion rates, as well as eating habit and genetic background of the human population, is high. Risks of sensitive populations, especially at the upper end of exposure, might be higher than previously anticipated. On the other hand, elevated short-term exposure to cadmium may be negligible compared to the long-term integrated background intake. Nevertheless, efforts to reduce cadmium use and emission in the environment, as well as the monitoring of cadmium contents in food, have to be maintained.

Acknowledgements

The authors express their appreciation to *Jürg Zarn* for his thoughtful review of the manuscript.

Summary

Dietary uptake of cadmium is the most important route of uptake in humans. Uptake and retention of cadmium depend on its chemical form, certain constituents of the diet, and detoxification by metallothioneins. Cadmium in high doses can lead to renal damage and bone demineralization in humans. In rats, cadmium induced prostatic tumors and large granular lymphocyte leukemia. In vitro, cytotoxic concentrations of cadmium lead to DNA strand breaks, and induced heat shock proteins and protooncogenes. At non-cytotoxic concentrations transcription of p53 was elevated and the DNA repair system was impaired.

Based on the NOAEL for prostatic tumors in rats of 1.13 mg/kg bw/d, an uncertainty factor of 1000 and a bw of 70 kg, a weekly cadmium intake of 550 µg per person is acceptable. The JECFA established a PTWI of 7 µg/kg bw, i.e. 400–500 µg per person, based on studies with biomarkers of renal damage and renal cadmium concentrations. Thus, this PTWI protects humans from both nephrotoxic and carcinogenic risks.

Intake of dietary cadmium is usually below 100 µg/person/week. Since this corresponds to about $^1/_5$ of the PTWI, average human populations are not at risk. Nevertheless, efforts to reduce cadmium use and emission in the environment, and the monitoring of cadmium in environment and food, have to be maintained.

Zusammenfassung

Der Mensch nimmt Cadmium vor allem mit der Nahrung auf. Aufnahme und Speicherung hängen von der chemischen Form, der Zusammensetzung der Nahrung und der Detoxifizierung durch Metallothioneine ab. Cadmium in hohen Mengen kann Nierenschäden und eine Demineralisierung der Knochen verursachen. In Ratten induzierte Cadmium Tumoren der Prostata und Leukämie der grossen granulären Lymphozyten. Zytotoxische Konzentrationen führten zu DNA-Strangbrüchen und induzierten Hitzeschockproteine und Protoonkogene. Bei nichtzytotoxischen Konzentrationen war die Transkription von p53 erhöht und die DNA-Reparatur beeinträchtigt.

Basierend auf einem NOAEL von 1,13 mg/kg KG/Tag für Prostatatumoren in Ratten, einem Unsicherheitsfaktor von 1000 und einem KG von 70 kg ergibt sich eine tolerierbare Cadmiumaufnahme von 550 µg/Person/Woche. Das JECFA legte, basierend auf Studien mit Biomarkern und der Akkumulation in der Niere, einen PTWI von 7 µg/kg KG, d. h. eine tolerierbare Aufnahme von 400–500 µg/Person/Woche fest. Somit schützt der PTWI sowohl vor nierentoxischen als auch kanzerogenen Risiken.

Die Aufnahme von Cadmium mit der Nahrung ist kleiner als 100 µg/Person/Woche. Da dies etwa $^1/_5$ des PTWI ist, sind durchschnittliche menschliche Populationen keinem Risiko ausgesetzt. Trotzdem sollte die Emission von Cadmium reduziert und das Monitoring in Umwelt und Nahrung fortgeführt werden.

Résumé

La plupart du cadmium absorbé par l'homme provient de son alimentation. L'absorption et l'accumulation de cadmium dépendent de sa forme chimique, de la composition de l'alimentation et de la détoxification par les métalliothionéines. Des doses élevées de cadmium peuvent endommager les reins et provoquer une déminéralisation des os. Des expériences sur les rats ont démontré que le cadmium induisait des tumeurs de la prostate et une leucémie des lymphocites granulaires. In vitro, des concentrations cytotoxiques de cadmium ont induit une rupture des filaments d'ADN, des protéines de choc thermique et des proto-oncogènes. Des concentrations non-cytotoxiques ont provoqué une augmentation de la transcription du p53 et un déréglement du système de réparation de l'ADN.

Basé sur un NOAEL pour les tumeurs de la prostate sur des rats de 1,13 mg/kg pc/j, un facteur de sécurité de 1000 et un pc de 70 kg, un apport de 550 mg par personne et par semaine est acceptable. En fonction des études réalisées avec des biomarkers de l'accumulation rénale du cadmium, le JECFA a établi un PTWI de 7 µg/kg pc, soit une absorption acceptable de 400–500 mg par personne et par semaine. La PTWI protège donc contre les risques nephrotoxiques et cancérogènes.

L'absorption du cadmium par l'alimentation se situe en dessous de 100 mg par personne et par semaine, soit environ $^1/_5$ du PTWI. Même si ces valeurs démontrent que le cadmium n'est pas un facteur de risque pour la moyenne de la population, il est nécessaire que le monitoring de l'environnement et des denrées alimentaires continue et que les efforts de réduction des émissions se poursuivent.

Abbreviations

bw = body weight
GSH = Glutathion
JECFA = Joint FAO/WHO Expert Committee on Food Additives
MT = Metallothionein
NOAEL = No observable adverse effect level

PTWI = Provisional tolerable weekly intake
VSD = Virtually safe dose

Key words

Bioavailability, Cadmium, Carcinogenicity, Exposure, Risk assessment, Toxicity

References

1 *Thiele, K.-H., Märtens, C.* und *Schönburg, T.:* Über die Entdeckung des Cadmiums vor 150 Jahren. Z. Chem. **9**, 55–57 (1969).

2 *Anonymous:* Cadmium and cadmium compounds. IARC monographs on the evaluation of carcinogenic risks to humans: Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry p. 119–237. WHO, Geneva 1993.

3 *Clarkson, T.:* Health effects of metals: a role of evolution? Environ. Health Perspect. **103 Supl. 1**, 9–12 (1995).

4 *Anonymous:* Cadmium. Environmental Health Criteria **134**, WHO, Geneva 1992.

5 *Anonymous:* Vom Menschen verursachte Luftschadstoff-Emissionen in der Schweiz von 1900 bis 2010. Bundesamt für Umwelt, Wald und Landschaft (BUWAL), Bern 1995.

6 *Birch, L., Hanselmann, K.W.* and *Bachofen, R.:* Heavy metal conservation in lake Cadagno sediments: historical records of anthropogenic emissions in a meromictic alpine lake. Water Res. **30**, 679–687 (1996).

7 *Beyersmann, D.:* Interactions in metal carcinogenicity. Toxicol. Lett. **72**, 33–38 (1994).

8 *Kjellstroem, T.:* Epidemiological aspects of the dose-response relationship of cadmium-induced renal damage. Cadmium 79 p. 118–122. Metal Bulletin Limited, London 1980.

9 *Hutton, M.:* Evaluation of the relationships between cadmium exposure and indicators of kidney function. A Technical Report (MARC Report) 16–13 (1983).

10 *Nogawa, K., Honda, R., Kido, T., Tsuritani, I., Yamada, Y., Ishizaki, M.* and *Yamaya, H.:* A dose-response analysis of cadmium in the general environment with special reference to total cadmium intake limit. Environ. Res. **48**, 42–52 (1989).

11 *Kido, T.* and *Nogawa, K.:* Dose-response relationship between total cadmium intake and β2-microglobulinuria using logistic regression analysis. Toxicology Letters **69**, 113–120 (1993).

12 *Clarke, H.:* The contamination of food. UNEP/GEMS Environmental Library UNEP, Nairobi 1992.

13 *Tahvonen, R.:* Contents of lead and cadmium in foods and diets. Food Rev. Int. **12**, 25–69 (1996).

14 *Anderson, O., Nielson, J.B.* and *Nordberg, G.F.:* Factors affecting the intestinal uptake of cadmium from the diet. Cadmium in the human environment: toxicity and carcinogenicity p. 173–187. IARC, Lyon 1992.

15 *Knutti, R., Andrey, D., Beuggert, H., Erard, M., Guggisberg, H., Wirz, E.* und *Zimmerli, B.:* Monitoring-Programm «Schwermetalle in Lebensmitteln». III. Blei, Cadmium, Kupfer und Zink in Mahlprodukten (Mehl und Kleie). Mitt. Gebiete Lebensm. Hyg. **80**, 363–386 (1989).

16 *Galli, U., Schüepp, H.* and *Brunold, C.:* Thiols in cadmium- and copper-treated maize (Zea mays L.). Planta **198**, 139–143 (1996).

17 *Vögeli-Lange, R.* and *Wagner, G.J.:* Relationship between cadmium, glutathione and cadmium-binding peptides (phytochelatins) in leaves of intact tobacco seedlings. Plant Sci. **114**, 11–18 (1996).

18 *Rauser, W.E.:* Phytochelatins and related peptides – Structure, biosynthesis, and function. Plant Physiol. **109**, 1141–1149 (1995).

19 *Altmann, H.J.:* Toxikologische Bedeutung der Metallothioneine. Bundesgesundheitsblatt. **21**, 317–324 (1978).

20 *Knutti, R.* und *Zimmerli, B.:* Untersuchung von Tagesrationen aus schweizerischen Verpflegungsbetrieben. III. Blei, Cadmium, Quecksilber, Nickel und Aluminium. Mitt. Gebiete Lebensm. Hyg. **76,** 206–232 (1985).
21 *Moon, C.-S., Zhang, Z.-W., Shimbo, S., Watanabe, T., Moon, D.-H., Lee, C.-U., Lee, B.-K., Ahn, K.-D., Lee, S.-H.* and *Ikeda, M.:* Dietary intake of cadmium and lead among the general population in Korea. Environ. Res. **71,** 46–54 (1995).
22 *Brussaard, J.H., Van Dokkum, W., Van der Paauw, C.G., De Vos, R.H., De Kort, W.L.* and *Lowik, M.R.:* Dietary intake of food contaminants in The Netherlands (Dutch Nutrition Surveillance System). Food Addit. Contam. **13,** 561–573 (1996).
23 *Urieta, I., Jalon, M.* and *Eguilero, I.:* Food surveillance in the Basque Country (Spain). II. Estimation of the dietary intake of organochlorine pesticides, heavy metals, arsenic, aflatoxin M1, iron and zinc through the total diet study, 1990/91. Food Addit. Contam. **13,** 29–52 (1996).
24 *Barbera, R., Farre, R.* and *Mesado, D.:* Oral intake of cadmium, cobalt, copper, iron, lead, nickel, manganese and zinc in the university student's diet. Nahrung. **37,** 241–245 (1993).
25 *Morgan, H.:* Intakes of metal. Sci. Total Environ. **75,** 71–71 (1988).
26 *Slob, W.* and *Krajnc, El:* Interindividual variability in modeling exposure and toxicokinetics: A case study on cadmium. Environ. Health Perspect. **102,** 78–81 (1994).
27 *MacIntosh, D.L., Spengler, J.D., Ozkaynak, H., Tsai, L.* and *Ryan, P.B.:* Dietary exposures to selected metals and pesticides. Environ. Health Perspect. **104,** 202–209 (1996).
28 *Iszard, M.B., Liu, J.* and *Klaassen, C.D.:* Effect of several metallothionein inducers on oxidative stress defense mechanisms in rats. Toxicology **104,** 25–33 (1995).
29 *Borghesi, L.A.* and *Lynes, M.A.:* Stress proteins as agents of immunological change: some lessons from metallothionein. Cell Stress & Chaperones **1,** 99–108 (1996).
30 *Snow, E.T.:* Metal carcinogenesis: mechanistic implications. Pharmacol. Ther. **53,** 31–65 (1992).
31 *Coogan, T.P., Shiraishi, N.* and *Waalkes, M.P.:* Minimal basal activity and lack of metal-induced activation of the metallothionein gene correlates with lobe-specific sensitivity to the carcinogenic effects of cadmium in the rat prostate. Toxicol. Appl. Pharmacol. **132,** 16–73 (1995).
32 *Coogan, T.P., Shiraishi, N.* and *Waalkes, M.P.:* Apparent quiescence of the metallothionein gene in the rat ventral prostate: association with cadmium-induced prostate tumors in rats. Environ. Health Perspect. **102 Suppl. 3,** 13–19 (1994).
33 *Lee, D.K., Fu, K., Liang, L.C., Dalton, T., Palmiter, R.D.* and *Andrews, G.K.:* Transgenic mouse blastocysts that overexpress metallothionein-I resist cadmium toxicity in vitro. Mol. Reprod. Dev. **43,** 158–166 (1996).
34 *Suzuki, K.T.:* Metallothionein: analysis in tissues and toxicological significance. IARC. Sci. Publ. **118,** 21–27 (1992).
35 *Andersen, O., Nielson, J.B., Sorensen, J.A.* and *Scherrebeck, L.:* Experimental localization of intestinal uptake sites for metals (Cd, Hg, Zn, Se) in vivo in mice. Environ. Health Perspect. **102 Suppl. 3,** 199–206 (1994).
36 *Lind, Y.* and *Glynn, A.W.:* The involvement of metallothionein in the intestinal absorption of cadmium in mice. Toxicol. Lett. **91,** 179–187 (1997).
37 *Liu, J.* and *Klaassen, C.D.:* Absorption and distribution of cadmium in metallothionein-I transgenic mice. Fundam. Appl. Toxicol. **29,** 294–300 (1996).
38 *Groten, J.P., Sinkeldam, E.J., Luten, J.B.* and *van Bladeren, P.J.:* Cadmium accumulation and metallothionein concentrations after 4-week dietary exposure to cadmium chloride or cadmium- metallothionein in rats. Toxicol. Appl. Pharmacol. **111,** 504–513 (1991).
39 *Lind, Y., Wicklund Glynn, A., Engman, J.* and *Jorhem, L.:* Bioavailability of cadmium from crab hepatopancreas and mushroom in relation to inorganic cadmium: A 9-week feeding study in mice. Food Chem. Toxicol. **33,** 667–673 (1995).
40 *Rey, M., Turcotte, F., Lapointe, C.* and *Dewailly, E.:* High blood cadmium levels are not associated with consumption of traditional food among the Inuit of Nunavik. J. Toxicol. Environ. Health **51,** 5–14 (1997).

41 *Vahter, M., Berglund, M., Nermell, B.* and *Akesson, A.:* Bioavailability of cadmium from shellfish and mixed diet in women. Toxicol. Appl. Pharmacol. **136,** 332–341 (1996).
42 *Rana, S.V.S.* and *Verma, S.:* Protective effects of GSH, vitamin E, and selenium on lipid peroxidation in cadmium-fed wats. Biol. Trace Elem. Res. **51,** 161–168 (1996).
43 *Rimbach, G.* and *Pallauf, J.:* Cadmium accumulation, zinc status, and mineral bioavailability of growing rats fed diets high in zinc with increasing amounts of phytic acid. Biol. Trace Elem. Res. **57,** 59–70 (1997).
44 *Liu, J., Liu, Y.P., Michalska, A.E., Choo, K.H.A.* and *Klaassen, C.D.:* Distribution and retention of cadmium in metallothionein I and II null mice. Toxicol. Appl. Pharmacol. **136,** 260–268 (1996).
45 *McKenna, I.M., Bare, R.M.* and *Waalkes, M.P.:* Metallothionein gene expression in testicular interstitial cells and liver of rats treated with cadmium. Toxicology **107,** 121–130 (1996).
46 *Shiraishi, N., Hochadel, J.F., Coogan, T.P., Koropatnick, J.* and *Waalkes, M.P.:* Sensitivity to cadmium-induced genotoxicity in rat testicular cells is associated with minimal expression of the metallothionein gene. Toxicol. Appl. Pharmacol. **130,** 22–36 (1995).
47 *Wahba, Z.Z., Miller, M.S.* and *Waalkes, M.P.:* Absence of changes in metallothionein RNA in the rat testes made refractory to cadmium toxicity by zinc pretreatment. Hum. Exp. Toxicol. **13,** 6–7 (1994).
48 *Tohyama, C., Suzuki, J.S., Homma, S., Karasawa, M., Kuroki, T., Nishimura, H.* and *Nishimura, N.:* Testosterone-dependent induction of metallothionein in genital organs of male rats. Biochem. J. **317,** 92–97 (1996).
49 *Liu, J., Squibb, K.S., Akkerman, M., Nordberg, G.F., Lipsky, M.* and *Fowler, B.A.:* Cytotoxicity, zinc protection, and stress protein induction in rat proximal tubule cells exposed to cadmium chloride in primary cell culture. Ren. Fail. **18,** 867–882 (1996).
50 *Nordberg, G.F., Jin, T.* and *Nordberg, M.:* Subcellular targets of cadmium nephrotoxicity: cadmium binding to renal membrane proteins in animals with or without protective metallothionein synthesis. Environ. Health Perspect. **102,** 191–194 (1994).
51 *Fowler, B.A.:* Mechanisms of kidney cell injury from metals. Environ. Health Perspect. **100,** 57–63 (1993).
52 *Piscator, M.:* Renale Wirkungen von Cadmium. Spurenelemente, p. 81–97. Georg Thieme, Stuttgart 1983.
53 *Nomiyama, K.:* Renal effects of cadmium. Environmental science and technology, p. 645–689. John Wiley & Sons, USA 1981.
54 *Kjellstroem, T.:* Exposure and accumulation of cadmium in populations from Japan, the United States, and Sweden. Environ. Health Perspect. **28,** 169–197 (1979).
55 *Morgan, H.* and *Sherlock, J.C.:* Cadmium intake and cadmium in the human kidney. Food Addit. Contam. **1,** 45–51 (1984).
56 *Drasch, G.A.:* An Increase of cadmium body burden for this century – an investigation on human tissues. Toxicol. Appl. Pharmacol. **26,** 111–119 (1983).
57 *Elinder, C.G.* and *Kjellstroem, T.:* Cadmium concentration in samples of human kidney cortex from the 19 century. AMBIO **6,** 270–272 (1977).
58 *Nogawa, K., Honda, R., Yamada, Y., Kido, T., Tsuritani, I.I.s.M.* and *Yamaya, H.:* Critical concentration of cadmium in kidney cortex of human exposed to environmental cadmium. Environ. Res. **40,** 251–260 (1986).
59 *Roels, H., Lauwerys, R.* and *Dardenne, A.N.:* The critical level of cadmium in human renal corte: A reevaluation. Toxicol. Lett. **15,** 357–360 (1983).
60 *Kjellstroem, T.:* Mechanism and epidemiology of bone effects of cadmium. In: Norberg, G.F., Herber, R.F.M. and Alessio, L. (eds.), Cadmium in the environment. Toxicity and carcinogenity, p. 301–310. IARC, Lyon 1992.

61 *Koizumi, T., Shirakura, H., Kumagai, H., Tatsumoto, H.* and *Suzuki, K.T.:* Mechanism of cadmium-induced cytotoxicity in rat hepatocytes: Cadmium-induced active oxygen-related permeability changes of the plasma membrane. Toxicology **114,** 125–134 (1996).
62 *Liu, Y.P., Liu, J., Iszard, M.B., Andrews, G.K., Palmiter, R.D.* and *Klaassen, C.D.:* Transgenic mice that overexpress metallothionein-I are protected from cadmium lethality and hepatotoxicity. Toxicol. Appl. Pharmacol. **135,** 222–228 (1995).
63 *SantAgnese, P.A.Di., Jensen, K.D., Levin, A.* and *Miller, R.K.:* Placental toxicity of cadmium in the rat: an ultrastructural study. Placenta **4,** 149–164 (1983).
64 *Samarawickrama, G.P.* and *Webb, M.:* The acute toxicity and teratogenicity of cadmium and the pregnant rat. J. Appl. Toxicol. **1,** 264–269 (1981).
65 *Koizumi, T.* and *Li, Z.G.:* Role of oxidative stress in single-dose, cadmium-induced testicular cancer. J. Toxicol. Environ. Health **37,** 25–36 (1992).
66 *Dalton, T., Fu, K., Enders, G.C., Palmiter, R.D.* and *Andrews, G.K.:* Analysis of the effects of overexpression of metallothionein-I in transgenic mice on the reproductive toxicology of cadmium. Environ. Health Perspect. **104,** 68–76 (1996).
67 *Waalkes, M.P.* and *Rehm, S.:* Carcinogenicity of oral cadmium in the male Wistar (WF/NCr) rat: effect of chronic dietary zinc deficiency. Fundam. Appl. Toxicol. **19,** 512–520 (1992).
68 *Piscator, M.:* Role of cadmium in carcinogenesis with special reference to cancer of prostate. Environ. Health Perspect. **40,** 107–120 (1981).
69 *Waalkes, M.* and *Rehm, S.:* Cadmium and prostate cancer. J. Toxicol. Environ. Health **43,** 251–269 (1994).
70 *Jacobson, K.B.* and *Turner, J.E.:* The interaction of cadmium and certain other metal ions with proteins and nucleic acids. Toxicology **16,** 1–37 (1980).
71 *Beyersmann, D.* and *Hechtenberg, S.:* Cadmium, gene regulation, and cellular signalling in mammalian cells. Toxicol. Appl. Pharmacol. **144,** 247–261 (1997).
72 *Rossman, T.G., Roy, N.K.* and *Lin, W.C.:* Is cadmium genotoxic? IARC. Sci. Publ. **118,** 37–75 (1992).
73 *Koizumi, T., Li, Z.G.* and *Tatsumoto, H.:* DNA damaging activity of cadmium in Leydig cells, a target cell population for cadmium carcinogenesis in the rat testis. Toxicol. Lett. **63,** 20–21 (1992).
74 *Coogan, T.P., Bare, R.M.* and *Waalkes, M.P.:* Cadmium-induced DNA strand damage in cultured liver cells: reduction in cadmium genotoxicity following zinc pretreatment. Toxicol. Appl. Pharmacol. **113,** 22–33 (1992).
75 *Latinwo, L.M., Ikediobi, C.O., Singh, N.P., Sponholtz, G., Fasanya, C.* and *Riley, L.:* Comparative studies of in vivo genotoxic effects of cadmium chloride in rat brain, kidney and liver cells. Cell. Molec. Biol. **43,** 203–210 (1997).
76 *Lin, R.H., Lee, C.H., Chen, W.K.* and *Lin-Shiau, S.Y.:* Studies on cytotoxic and genotoxic effects of cadmium nitrate and lead nitrate in Chinese hamster ovary cells. Environ. Mol. Mutagen. **23,** 9–14 (1994).
77 *Ossola, J.O.* and *Tomaro, M.L.:* Heme oxygenase induction by cadmium chloride: Evidence for oxidative stress involvement. Toxicology **104,** 141–147 (1995).
78 *Hartwig, A.:* Role of DNA repair Inhibition in lead- and cadmium-induced genotoxicity: A Review. Environ. Health Perspect. **102 S3,** 45–50 (1994).
79 *Hartmann, A.* and *Speit, G.:* Effect of arsenic and cadmium on the persistence of mutagen-induced DNA lesions in human cells. Environ. Mol. Mutag. **27,** 94–98 (1996).
80 *Smith, J.B., M'Smith, L., Pijuan, V., Zhuang, Y.* and *Chen, Y.C.:* Transmembrane signals and protooncogene induction evoked y carcinogenic metals and prevented by zinc. Environ. Health Perspect. **102 Suppl. 3,** 181–189 (1994).
81 *Abshire, M.K., Devor, D.E., Diwan, A., Shaughnessy, J.D.* and *Waalkes, M.P.:* In vitro exposure to cadmium in rat L6 myoblasts can result in both enhancement and suppression of malignant progression in vivo. Carcinogenesis (Oxford) **17,** 1349–1356 (1996).

82 *Zheng, H., Liu, J., Choo, K.H.A., Michalska, A.E.* and *Klaassen, C.D.:* Metallothionein-I and -II knock-out mice are sensitive to cadmium-induced liver mRNA expression of c-jun and p53. Toxicol. Appl. Pharmacol. **136,** 229–235 (1996).
83 *Misra, R.R., Hochadel, J.F., Smith, G.T., Cook, J.C., Waalkes, M.P.* and *Wink, D.A.:* Evidence that nitric oxide enhances cadmium toxicity by displacing the metal from metallothionein. Chem. Res. Toxicol. **9,** 326–332 (1996).
84 *Anonymous:* Evaluation of certain food additives and contaminants. WHO Technical Report Series **776,** 1989.
85 *Anonymous:* Evaluation of certain food additives. WHO Technical Report Series **505,** 1972.
86 *Lutz, W.K.:* Dose-response relationship and low dose extrapolation in chemical carcinogenesis. Carcinogenesis (Oxford) **11,** 1243–1247 (1990).
87 *Becking, G.C.:* Use of mechanistic information in risk assessment for toxic chemicals. Toxicol. Lett. (Shannon) **77,** 15–24 (1995).

Korrespondenzadresse: Dr. Otto Daniel, Swiss Federal Office of Public Health, Toxicology, c/o Institute of Veterinary Pharmacology and Toxicology, Winterthurerstrasse 260, CH-8057 Zürich