CADMIUM

Heavy metal

Contamination source

Elementary cadmium (Cd) (CAS N° 7440-43-9) is a not essential heavy metal. It is primarily an environmental contaminant, which firstly occurs naturally and also may come from industrial and agricultural sources. Cadmium is mainly found in association with zinc in the earth's crust at concentrations between 0.1 and 1 mg/kg (AFSSA, 2006). It can be naturally dispersed into the air by training particles from the soil and as a result of volcanic eruptions and exfoliation of rocks and minerals (INERIS, 2005). Anthropogenic sources of cadmium are mainly derivatives of Cd (Cd chloride CAS # 10108-64-2, Cd oxide CAS :1306-19-0, Cd sulfate CAS :10124-36-4 , Cd sulfide CAS # 1306-23-06) and include industrial and agricultural emissions: Non-ferrous metal foundries, metal surfaces, and manufacture of storage batteries, pigments, stabilizers for plastics or alloys, manufacture and use of phosphate fertilizers. The combustion of coal or oil (but also of wood or peat) and incineration household waste are other significant sources of air releases of Cd. In water, Cd was mainly due to natural erosion, leaching of soils and industrial discharges, and treatment of industrial effluents and mining (INERIS, 2005).

Foodstuffs are the main source of Cd exposure for the non-smoking general population (EFSA, 2009).

Analytical method

Analytical methods for the determination of cadmium in foodstuffs are well established. The performance criteria of analysis methods for official controls are laid down in Regulation (EC) No. 333/2007.

Technique of sample preparation involves microwave-assisted acid digestion, or other techniques such as ashing and slurry preparation.

Detection techniques include: Atomic absorption spectrometry (AAS), flame atomic absorption spectrometry (FAAS), electrothermal (graphite or Zeeman furnace) atomic absorption spectrometry (ETAAS), beam injection (thermospray) flame furnace atomic absorption spectrometry (BIFF-AAS), hydride generation atomic fluorescence spectrometry, inductively coupled plasma optical emission spectrometry (ICP-OES) and inductively coupled plasma mass spectrometry (ICP-MS).

AAS is the most common analytical method used for measuring trace elements in food samples (EFSA, 2009). ICP-MS could be considered as the method of choice, as it offers lower detection limit and wide dynamic range and allows the simultaneous determination of several elements. Additionally, this technique offers high specificity through spectral interpretation and isotope information (WHO, 2011).

Toxicity

Cadmium is a cumulative contaminant.

In humans, cadmium is poorly absorbed from the digestive tract after dietary exposure (3-5%) (Morgan and Sherlock, 1984, cited by EFSA, 2009). The absorption rate of cadmium through dust that settles in the respiratory tract is higher. The absorption of cadmium would be increased in iron deficient subjects, whereas the presence in food of di-or tri-valent cations such as calcium, zinc or magnesium reduces its absorption (ATSDR, 1999). Other factors, including age (Horiguchi et al., 2004) and gender, may also influence cadmium uptake or retention.
Whatever the route of exposure, cadmium is transported in blood attached to hemoglobin or metallothionein before being distributed throughout the body. It accumulates mainly in the liver and the kidneys (up to 75% of the absorbed dose) (AFSSA, 2006). It is also found in the pancreas, thyroid gland, testes and salivary glands. In the liver and kidney, cadmium stimulates the production of cadmium metallothionein fixing cadmium (AFSSA, 2006). Cadmium is stored in the body mainly in complexed forms with metallothionein. The toxicity of cadmium is mainly due to its free form. It is when the capacity of synthesis of metallothionein is exceeded that the toxicity of cadmium is revealed.
Cadmium is excreted in faeces, urine and dander (hair, nails, and teeth). In absence of kidney damage, urinary excretion of cadmium is proportional to the body burden, mainly liver and kidney. The half-life of cadmium in the human body is 10 to 30 years (Nawrot et al., 2006).

Cadmium has many toxic effects. Exposure to cadmium has been associated with nephrotoxicity, bone effects, neurotoxicity, carcinogenicity and genotoxicity, teratogenicity and respiratory effects, endocrine and reproductive effects (EFSA, 2009).

The kidney is the critical target organ for chronic cadmium toxicity. Environmental exposure to cadmium is associated with renal tubular dysfunction (Koçak et al., 2006). Prolonged and/or high exposure may lead to tubular damage and progress to renal impairment with decreased glomerular filtration rate, and eventually to renal failure (EFSA, 2009). The level of urinary β2MG is the most widely used marker of renal tubular dysfunction (WHO, 2011).
Chronic exposure to cadmium may promote urinary calcium losses and increase the risk of bone fractures (Staessen et al., 1999.). The bone toxicity of Cd is an aspect of the disease "Itai-Itai" in Japan observed in populations exposed to Cd during the consumption of contaminated rice (Sci Com, 2009).
Cadmium shows a powerful androgenic and estrogenic activity *in vivo* (Åkesson et al., 2008) and *in vitro* by direct binding to estrogen and androgen receptors (Takinguchi and Yoshihara, 2006).

Carcinogenicity
Cadmium does not interact directly with deoxyribonucleic acid (DNA). It is genotoxic by induction of oxidative stress and inhibition of DNA repair. Cadmium can cause lung cancer in rats after inhalation (EFSA, 2009).
The International Agency for Research on Cancer (IARC) (1993) has classified cadmium compounds in the group I as "human carcinogen" on the basis of sufficient evidence for carcinogenicity in both humans and experimental animals for lung cancer and limited evidence for kidney, liver and prostate cancer (WHO, 2011). Most of the evidence is derived from high cadmium exposure of exposed workers through inhalation (WHO, 2011).
A report of the JRC (EC, 2007) concluded that there is currently no evidence that cadmium acts as carcinogen following oral exposure, but that the weight of evidence collected in genotoxicity test, long-term animal experiments and epidemiological studies leads to consider cadmium oxide as a suspected human inhalation carcinogen.
Data for human exposure to cadmium by the population have been associated with an increased risk of cancer such as lung cancer (Nawrot et al., 2006), endometrial cancer (Åkesson et al., 2008) bladder cancer (Kellen et al., 2007), prostate cancer (Verougstraete et al., 2003) and breast (McElroy et al., 2006) or liver cancer (Campbell et al., 1990).

Establishment of Health Based Reference Values
The CONTAM Panel did not consider the dose-response data as a sufficient basis for quantitative risk assessment (EFSA, 2009).
To determine a dose-response relationship for the general population, available data from epidemiological studies were compiled and used in a meta-analysis to characterize the relationship between levels of beta-2-microglobulin (β2MG) and urinary cadmium (EFSA, 2011; WHO, 2011). The level of urinary β2MG was chosen as the most adequate biomarker for renal tubular effects in the meta-analysis (EFSA, 2011; WHO, 2011).
The evaluation of EFSA and JECFA are based on two main components, a model concentration - an effect that establishes a relationship between cadmium concentration in urine at the β2MG and a kinetic model which establishes a relationship between the concentration of urinary cadmium and cadmium intake (EFSA, 2011).
Based on the meta-analysis, the CONTAM Panel established a Tolerable Weekly Intake (TWI) of 2.5 µg/kg bw (EFSA, 2009) and the Committee of JECFA established a provisional tolerable monthly intake (PTMI) of 25 µg/kg bw (WHO, 2011).

Occurrence in food

Cadmium is principally present in cereals, potatoes, root vegetables and offal. The highest concentrations of cadmium were measured by FASFC in offal (liver and kidney) of game and horse (Sci Com, 2009; Vromman et al., 2010).
High levels of cadmium in European countries and reported by EFSA (2012) were found in algal formulations, cocoa-based products, crustaceans, edible offal, fungi, oilseeds, seaweeds and water mollusks

Area with elevated levels may show higher cadmium concentrations in locally produced food. In addition, usage of cadmium-containing fertilizers in agriculture increases cadmium concentrations in the crops and derived products (EFSA, 2009).

Dietary exposure assessment

Based on consumption data from the Belgian food survey (2004) and cadmium concentration in food items from the control program of the Belgian Federal Agency for the Safety of the Food Chain for the period 2006 - 2008, the mean, median and 95th percentile dietary exposure of the Belgian adult population was estimated at 0.98, 0.85 and 2.02 µg/kg bw/week, respectively (Vromman et al., 2010). Mean, median and 95th percentile dietary exposure of children was estimated at 4.09, 2.96 and 7.3 µg/kg bw/week, respectively (Sci Com, 2009).
Dietary exposure to cadmium of the Belgian adult population is comparable to data published in the literature for other European countries: Netherlands 0.98 µg/kg bw/week (de Winter-Sorkin et al., 2003), United kingdom 0.98 to 1.19 µg/kg bw/week (FSA, 2009), Germany 1.45 µg/kg bw/week (BfR, 2009), Denmark 1.87 µg/kg bw/week (Larsen et al., 2002).
Cadmium dietary intake of the Belgian population was estimated by SCOOP in 2004 to 1.9 µg/kg bw/week and in 1996 to 2.74 µg/kg bw/week.

Mean and the 95th percentile cadmium dietary exposure estimated recently by EFSA (2012) for different age group in the European Union are presented in table 1. Middle bound mean cadmium dietary exposure estimated recently by EFSA (2012) for the Belgian population are 6.77 µg/kg bw/week for toddlers in Flanders, 5.04 µg/kg bw/week for other children in Flanders, 2.03 µg/kg bw/week for adolescent, 1.88 µg/kg bw/week for adults, 1.73 µg/kg bw/week for elderly and 1.69 µg/kg bw/week for very elderly.

Table 1: Lower (LB), middle (MB) and upper (UB) bound mean and 95th percentile (P95) dietary cadmium exposure in µg/kg bw/week for each age groups and as a mean and 95th percentile average lifetime exposure calculated by weighting the contribution of each age group according to the number of years covered (different range of countries covered in the respective age group) (source EFSA, 2012)

	Mean			P95		
Age group	**LB**	**MB**	**UB**	**LB**	**MB**	**UB**
Infants	1.97	2.74	3.50	4.97	6.56	8.42
Toddlers	3.80	4.85	5.90	6.76	8.19	9.84
Other children	3.23	3.96	4.69	5.55	6.58	7.66
Adolescents	1.87	2.20	2.54	3.66	4.17	4.70
Adults	1.41	1.70	1.98	2.72	3.09	3.50
Elderly	1.30	1.56	1.82	2.47	2.82	3.18
Very elderly	1.38	1.63	1.89	2.56	2.87	3.21

Mean exposure to cadmium estimated by JECFA (WHO, 2011) for adults ranges from 2.2 to 12 µg/kg bw/month.

The estimation of the dietary Cd exposure of the adult Belgian population shows that cereals products have the highest contribution to dietary Cd intake, followed by potatoes, pasta and vegetables
The highest contributors as averaged across all age groups for the lower bound results (less influenced by left censored data and limits) reported by EFSA (2012) were grains and grain products (26.9%) followed by vegetables and vegetable products (16.0%), starchy roots and tubers (13.2%), meat and edible offal (7.7%) and fish and seafood (7.5%). Looking at the food categories in more detail, potatoes (13.2%), bread and rolls (11.7%), fine bakery wares (5.1%), chocolate products (4.3%), leafy vegetables (3.9%) and water molluscs (3.2%) contributed the most to cadmium dietary exposure across age groups. At the finest detail, wheat bread and rolls (6.4%), boiled potatoes (5.7%), pastries and cakes (4.0%), potatoes unspecified (3.1%), rice (3.0%) and carrots (2.2%) were important contributors (EFSA, 2012).

Risk characterisation

Mean, median and 95th percentile dietary exposure of the Belgian adult population was estimated by Vromman et al. (2010) at 0.98, 0.85 and 2.02 µg/kg bw/week, respectively (table 2). Two percent of the Belgian adult population has a dietary exposure above the recent TWI of 2.5 µg/kg bw/week established by EFSA in 2009 (Vromman et al., 2010). Mean, median and 95th percentile dietary exposure of children was estimated at 4.09, 2.96 and 7.3 µg/kg bw/week, respectively (table 1). About 63% of children have an exposure above the TWI of 2,5 µg/kg bw (Sci Com, 2009).

The average dietary exposure to cadmium for adults across European countries was estimated to be between 1.9 and 3.0 µg/kg bw/week, and the high exposure adults have estimates in the range of 2.5-3.9 µg/kg bw/week by the CONTAM Panel (EFSA, 2009). The CONTAM Panel noted that such average dietary exposure in European countries is close to or slightly exceeding the TWI of 2.5 µg/kg bw Furthermore it was noted that subgroups of the population, such as vegetarians, children, smokers and people living in highly contaminated areas may exceed the TWI by about 2-fold. Although adverse effects on kidney function are unlikely to occur for an individual exposed at this level, the CONTAM Panel concluded that exposure to Cd at the population level should be reduced (EFSA, 2009). The recent review of cadmium dietary exposure by EFSA (2012) confirmed that children on average and adults at the 95th percentile dietary exposure could exceed health-based guidance values.

The estimates of exposure to cadmium through the diet for all age groups, including consumers with high exposure and subgroups with special dietary habits (e.g. vegetarians), examined by the Committee of JECFA are below the PTMI (WHO, 2011).

Table 2: Cadmium dietary exposure for adult and children in Belgium and percentage of the TWI and PTMI.

Population	Dietary exposure (µg/kg bw/week)	% TWI (= 2,5 µg/kg bw/week) (EFSA, 2009)	%PTMI (= 25 µg/kg bw/month = 5,8 µg/kg bw/week) (WHO, 2011)
Adults – Mean exposure	0.98	39.2	16.9
Adults – Mediane exposure	0.85	34	14.7
Adults - P95 exposure	2.02	80.8	34.8
Children – Mean exposure	4.09	163.6	70.5
Children - Mediane exposure	2.96	118.4	51.0
Children - P95 exposure	7.3	292	125.9

Legislation

Regulation (EC) No 1881/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs. (Official Journal of the European Union L 364/5-24 (20.12.2006))

Recommendations

The Scientific Committee in his advice 35-2009 emits the following recommendations:

- The Scientific Committee estimated that efforts should be made to limit cadmium exposure of consumer of vegetables, potatoes and cereals, especially pasta.
- The Scientific Committee recommends to analyze cadmium in cereals and cereal products (bread, pasta, biscuits, pastries, breakfast cereals, ...), distinguishing the finer products (eg white bread) from products known as whole.
- The Scientific Committee also recommends to analyze other foods that may contain large amounts of cadmium such as a wild mushrooms, walnuts, including pine moth, and oil derivatives. These foods can contribute to exposure trough their heigh consumption and/or contain large amounts of cadmium.
- The Scientific Committee recommends continuing to monitor cadmium in other foods. The number of samples taken for analysis of dairy products and eggs could be reduced.
- The Scientific Committee recommends to further identify food matrices analyzed in the database Foodnet and to ensure that the crossing with the consumption data is facilitated. For example, specify the type of bread (white bread, wholemeal bread, ...) as is the case in the consumer database (available on the internet http://www.iph.fgov.be/epidemio/epifr/foodfr / food04fr/fooda32fr.pdf). It is also recommended to differentiate into Foodnet fish, shellfish, and depending on the source (farmed or wild).
- The Scientific Committee draws attention to the fact that existing methods for estimating exposure to contaminants show some limitations, especially for the most at risk groups. Therefore, the Scientific Committee recommends that a standardized method should be developed and validated.

Recommendations of the CONTAM panel of EFSA (2009):

- More detailed food consumption information should be obtained to allow calculation of the impact of individual foods or food groupings on overall exposure to cadmium.
- There is a need for representative occurrence data in food commodities, including total diet studies to reduce the uncertainty in the exposure assessment. In addition, it would be valuable to establish exposure based sampling procedures in the food monitoring and surveillance programs to reduce uncertainties due to sampling adjustment factors.
- More data are required to evaluate the effects of cadmium on reproduction and development as well as the possible effect on cancer incidence (especially hormone related cancers) and mortality.
- The vulnerability of diabetics and patients with kidney disease needs to be ascertained with regard to cadmium effects on kidney function.
- Collection of biomonitoring data from diverse European populations should be promoted.

Recommendations of the CONTAM panel of EFSA (2011a):

- The use of probabilistic approaches to model variability and uncertainties in risk characterization needs to be further developed.
- An internationally harmonized approach for the use of epidemiological data in dose-response assessment for the purposes of risk assessment is urgently required.
- Means to communicate non-standard statistical modelling techniques e.g. Bayesian methods or simulation methods need to be improved to allow risk assessors to judge the assumptions made and their limitations.
- A careful procedure should be followed when choosing the toxicodynamic variability function to be used before drawing final conclusion on the health-based guidance value (HBGV) to be established (EFSA, 2011b).

Recommendations of EFSA (2012):

- It would be valuable to have a better coverage of the European food market since sample results submitted to EFSA come from a limited number of countries. These might not be fully representative of the European situation.
- For a few food categories rather high limits of detection and quantification were reported. To increase precision and accuracy in calculating exposure, it would be important to lower such limits as much as possible.

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