Cadmium Dietary Exposure Assessment in Adult Population and Preschool Children in the Republic of Serbia

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Research Article

Keywords: Cadmium dietary intake, worst-case risk assessment, probabilistic approach, Monte Carlo method

Posted Date: April 27th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1555277/v1

Abstract

Cadmium (Cd) is a toxic metal, present in all matrices of the environment. Cadmium is a common food contaminant and human exposure to it may elicit many diverse health impairments.

The aim of this study was to assess the dietary exposure to Cd for the adult population and preschool children in Serbia using the probabilistic methodology. We have measured Cd content in 11,227 food samples belonging to 50 food groups available on the Serbian market. Cadmium was detected in 90% of the tested food groups, and in 31% of the total samples. Food groups that contributed the most to total dietary Cd intake were potatoes in the adult population, and fruit and vegetable juices in children. Consumption data were taken from the GEMS/Food Consumption Cluster Diets database Calculated HI values showed that 54.4% of the adult population and 84.4% of the population of preschool children were under the unacceptable risk of Cd exposure.

The results of this study are based on a worst-case scenario. Thus, they are rather preliminary and should be considered as an indication of the need for further, more refined input data, particularly in terms of consumption database, which would altogether contribute to the more realistic risk assessment as a high priority approach, especially in the case of the vulnerable subpopulations such as children.

1. Introduction

Along with the great technological advances, there is an obvious increase in the number and the quantities of chemical substances that are used and released into the environment as products of human activity. All biological systems are exposed to a large number of different chemical substances primarily through air, water and food on daily basis. Today, pollution has taken on a global scale and exposure to hazardous chemicals released during production, use, or after disposal can cause significant risk to the health of humans and ecosystems. Human health is greatly affected by the hazardous substances that are linked to environmental, dietary, product or workplace exposures (1). The worldwide production of chemicals has the highest record in the European region, namely, 11 out of 30 highest chemical-manufacturing countries are European (2).

Many chemical substances with proven adverse health effects can be found as residues in everyday foods. Food contaminants frequently include environmental pollutants among which toxic metals are very significant. Cadmium (Cd) is a chemical element naturally found in small quantities in the earth's crust (0.1–0.5 mg/kg), mainly in zinc, lead and copper ores, as well as in ocean waters at a concentration of 5 to 110 ng/l. However, Cd can also be found in the environment as a result of human activity (3). The main anthropogenic sources of Cd in the environment are the processing of non-ferrous metals, the production of alkaline batteries and accumulators, the production and application of phosphate fertilizers, the combustion of fossil fuels and the incineration of municipal waste. Arriving in the environment, Cd pollutes water and soil, and then, mostly through plants, enters the human food chain (3). Cadmium concentration in the air of EU urban regions ranges from 1 to 10 ng/m^3, while the maximum measured daily content of Cd in PM_{10} in Serbia was 16 ng/m^3, which surpassed the target value of 6 ng/m^3 (4). European seas have the average Cd concentration between 5 and 20 ng/L in open seas, however, much higher content was reported in France and Norway coastline, up to 250 ng/L. European rivers have average Cd content in the range between 10 and 100 ng/L, while in surface soils, Cd level usually ranges from 0.01 to 2.7 mg/kg. Some reports have shown maximal values of Cd soil concentration of 50 mg/kg (5).

The adverse health effects of the lifelong human exposure to Cd, especially non-occupational exposure, have been a concern in the scientific community for a while now (6; 7; 8; 9). Many studies address the toxic effects of Cd followed by laboratory animal and human exposure. Matović et al. (10) reviewed the results of the animal studies that revealed the adverse influence of Cd exposure on kidneys, liver, lungs, bones, hematopoietic and pancreatic tissue, nervous, reproductive, and cardiovascular systems. One of the well known adverse effects of Cd toxicity is the induction of oxidative stress (10; 11; 12) while other mechanisms include an attachment to sulfhydryl groups of proteins which may result in enzyme inactivation, the displacement of bioelements from the metal-dependent enzymes, inhibition of apoptosis as well as the inhibition of the DNA repair (13; 3; 14; 15; 16; 12).

It has been evidenced that the target organ of long-term dietary Cd exposure is the kidney where Cd induces tissue impairment described by proximal tubule dysfunction in both animal and epidemiological studies (17; 18; 9). Even exposure to low and moderate Cd levels was related to renal dysfunction, which was proven by observing kidney biopsies done on the living donors in a healthy general Swedish population study (19). Besides the renal tissue, the liver is also sensitive to Cd exposure since it is involved in the detoxification and elimination of this metal. Liver damage induced by Cd includes endothelial cell damage followed by the production of reactive oxygen species, nitric oxide, and cytokines, which result in inflammatory injury of the hepatic tissue. Cadmium-induced hepatotoxicity additionally involves the disruption of homeostasis of essential metals such as Cu, Fe, and Zn and enzyme inactivation (14; 3; 15; 12). The environmental Cd exposure was associated with liver disease mortality in men and women of the US general population (20). Pancreatic impairment is also one of the well-recognized Cd toxic effects (17; 21; 22; 23; 24).

Exposure to Cd affects the human male reproductive system leading to declined spermatogenesis, semen quality, and hormonal synthesis and release. Furthermore, cadmium exposure disrupts human female reproductive hormonal balance, and may affect pregnancy outcome (25). Cadmium can cross the placental barrier leading to *in utero* exposure, which is linked to the adverse effects on the central nervous system during development stages resulting in behavioral and cognitive dysfunction. It is suggested that *in utero* and early life Cd exposure may have various adverse health outcomes later in life including cardiovascular, respiratory, kidney, and neurological issues as well as cancer, through various modes of action (26).

Some studies have revealed a probable relationship between chronic environmental Cd exposure and osteoporosis, which is likely to be related to kidney tubular damage (27; 17). Chinese farmers exposed to Cd from contaminated rice for more than 20 years had decreased bone mineral density as the Chinese study showed (28). The same study linked chronic Cd exposure to altered vitamin D metabolism and increased urinary excretion of calcium and phosphate (7). Exposure to Cd in Asia is usually higher than in Europe and in the USA due to the higher intake of locally grown rice on the industry-contaminated land (17). Several authors presented Cd potential to disrupt the endocrine system, especially the interference with the thyroid function and estrogen activity on the human adult population (29; 23; 30). Furthermore, occupational Cd exposure was proven to disturb serum insulin level (31). The International Agency for Research on Cancer (IARC), on the basis of relevant studies, places Cd in Group 1, a group of proven human carcinogens (32).

Food is the most important source of Cd exposure of the general non-smoking population. About 90% of the total Cd intake is through food, while the other 10% involves Cd intake through ambient air and drinking water (5; 33). Cereals, vegetables, and potatoes can account for more than 80% of dietary Cd intake, while the average dietary intake ranges from 8 to 25 μg/day (17). The smoker population inhales a significant amount of Cd via tobacco smoke so the blood concentration of Cd in smokers was proven to be 28% higher than in non-smokers (34).

In this study we have assessed dietary exposure to Cd for the adult population and the subpopulation of preschool children in the Republic of Serbia, considering their different dietary habits. With that aim, we have measured Cd content in a variety of foods available on the market in the Republic of Serbia. For the purpose of dietary exposure assessment probabilistic approach was used.

2. Material And Methods

2.1. Determination of cadmium concentration

Concentrations of Cd were determined in food items collected from the food contamination-monitoring program. A total of 11,227 food item samples were analyzed, belonging to 50 food items classified in accordance to World Health Organization Global Environment Monitoring System (GEMS)/Food Consumption Cluster Diets database (35). The number of samples for all individual food items is shown in Table 2. Measurements were done in National reference laboratory of the Institute for meat hygiene and technology, Belgrade, Serbia, in compliance with ISO standard 17025. Quantitatively and qualitatively, analyzed samples could be accepted as representative on the national level.

Each of a total of 11,227 samples of food items was homogenized and mineralized by microwave digestion (ETHOS Milestone, Italy). Depending on the type of food, 0.25 – 1 g (± 0.001 g) of homogenized sample was weighed into a Teflon bowl of the START D microwave apparatus (Milestone, Italy), followed by the addition of a digestion mixture (8 ml HNO_3 (Sigma, Germany) and 1.5 ml 30% H_2O_2 (Merck, Germany)). The mineralization conditions of the analyzed samples were set by adjusting the parameters of the digestion program, namely: achieving a temperature of 180°C for 5 minutes, maintained for the next 10 minutes, and ventilation cooling for 15 minutes. The prepared samples were quantitatively transferred with deionized water to the measuring vessels and used for the determination of Cd by atomic absorption spectrometry (AAS). Analyses were carried out on Varian “SpectrAA 220” (Australia) by the method of electrothermal atomization, using argon as an inert gas. The limit of quantification (LOQ) for Cd was 5 ng/g. Analytical quality control was achieved by using certified reference material BCR 186. In 69.2% of the total number of samples, Cd concentration was below the limit of detection.

2.2. Cadmium dietary exposure and risk assessment

Taking into consideration the impact of the variations in dietary habits in different subpopulations and age groups, the dietary exposure to Cd was evaluated in the typical adult population and in subpopulation of preschool children.

Typical adult population consisted of 808 volunteers, 395 women and 413 men, aged between 18 and 65 years, which were included in national survey from the Department of Endocrinology of Clinical Center Vojvodina, Novi Sad, Serbia and Faculty of Medicine, University of Novi Sad, Serbia (36). Their body weights ranged from 41 to 120 kg, with median of 70 kg. In the absence of the national food consumption database, these data were taken from the GEMS/Food Consumption Cluster Diets database (35) which is currently the only publicly availabe dataset with estimated average nutrition in the adult population of the Republic of Serbia (Table 1).

Data on body weights of preschool children were obtained from 119 healthy children, 57 girls and 62 boys, aged 4 to 7 years (37). Their body weights ranged from 15 to 32, with median of 21 kg. Average daily intakes of food groups in children were taken from preschool institution menus, including breakfast, snack and lunch (which make 75% of the total energy needs of children) (38) (Table 1). Cadmium concentrations were determined in 34 typically consumed food groups in this dietary pattern.

Median and maximal values of Cd intake were considered for all food groups.

The following formula was used for Cd dietary intake assessment expressed as weekly intake (WI) in µg/kg bw:

$$WI = \frac{7\ x\ \sum_{i=1}^{n}(Daily\ consumption\ (g)\ x\ Cd\ concentration\ (\mu g/g)i\ )}{Body\ weight\ (kg)i}$$

For the purpose of total dietary Cd exposure assessment, probabilistic methodology was used, with Monte Carlo simulations, to implement the variations in the Cd concentrations in food items and variations in body weights of individuals included in the study, to get a more accurate estimation of the exposure. Probability distributions were fitted to Cd concentrations (µg/g) for every food item and to body weights (kg) of the populations, while the food consumption had a fixed average value shown in Table 1. The number of iterations in the simulation required for accurate and stable results was 700, and it was based on monitoring convergence set to default values of convergence tolerance (3%) and confidence level to (95%).

Finally, for each population considered, hazard indexes (HI) were calculated based on the formula given below:

$$HI = \frac{Calculated\ weekly\ Cd\ intake}{Tolerable\ weekly\ intake\ (TWI)}$$

Tolerable Weekly Intake for Cd used for risk assessment is recommended by EFSA and amounts 2.5 µg/kg bw (39).

2.3. Statistical analysis

Test for normality (Kolmogorov-Smirnov test) of data on Cd concentratons and populations body weights, was done in IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA) with p value of 0.05 considered significant. Probabilistic exposure assessment was done in @RISK 5.5 software (Palisade corporation, ITHACA, NY, USA).

3. Results

3.1. Cadmium concentrations in food

Cadmium was detected in 90% of the tested food groups, and in a considerable number of tested samples (30.8%) (Table 2). The food group that contained the highest percentage of samples in which Cd was determined, was the group of mollusks and cephalopods (91.2% of tested samples). The maximal measured Cd concentration of 520 ng/g also belonged to the group of mollusks and cephalopods. Additionally, the median concentration of Cd was high in the mammal offal (56 ng/g), stalky vegetables (49 ng/g), potato products (45 ng/g), and in oilseeds (38 ng/g).

Cadmium was detected in over 50% of samples of oilseeds, potatoes and potato products, leafy, root and stalky vegetables, cereal products, cocoa products, mammal and poultry offal, crustaceans and fish products as well as in fruit and vegetable juices. It was not detected in the fat, teas and coffee-based beverages in any of the tested samples.

None of the tested food samples had Cd concentration values that exceeded the maximal permitted concentration given by the current Regulation in the Republic of Serbia (40).

3.2. Dietary Cd exposure and non-carcinogenic risk

Despite the fact that Cd concentration was the highest in mollusks and cephalopods, the relatively low intake of these foods has led to some other and more consumed food groups to be responsible for Cd intake in Serbian adult population, as well as in preschool children (Table 2).

The median intake value in the adult population was the highest through potato consumption (41% of total Cd intake), and through mammal offal (17% of total Cd intake). In addition to potatoes and mammal offal, potato products had a noteworthy contribution to the intake of Cd in the adult population of 13% of the total Cd intake, due to the high median concentration of Cd in this food group (Table 2).

For the subpopulation of preschool children, the highest median Cd intake was via consumption of fruit and vegetable juices, which accounted for 43.7% of the total Cd intake. A significant share of Cd intake in the same scenario was through consumption of cereal products (20.7%) and mammal offal (14.8%) (Table 2).

Distribution of total dietary Cd intake in the adult population ranged from 1.41 to 4.74 mg/kg bw per week, 5^{th} to 95^{th} percentile, respectively (Table 3). Slightly higher values of 5^{th} to 95^{th} percentile of Cd intake distribution were obtained in preschool children and amounted 2.07 to 4.93 mg/kg bw per week (Table 3). However, comparing the Cd intake distributions with tolerable weekly Cd intake has indicated that 54.4% of the adult population and even 84.4% of the preschool children were at unacceptable health risk of Cd adverse non-carcinogenic effects (Figure 1, Table 3).

4. Discussion

Type of food, conditions in which the food was grown, meteorological conditions and anthropogenic contamination of the environment are all very important factors affecting the concentration of Cd in food. As reports of regulatory bodies have shown, most foods have relatively low Cd content, lower than 20 ng/g (5; 41). Cadmium levels are typically low in meat, eggs, milk and fish. On the other hand, high Cd levels are frequently present in leafy vegetables, potatoes, cereals, shellfish, and cephalopods. EFSA made a survey on Cd dietary exposure in the European population in 22 EU member countries with data collected from 2003 to 2011 (42). The results revealed that the highest Cd content in food items sold in the EU market was found in algae, cocoa and cocoa products as well as in the edible offal, horse kidney as much as 61 µg/g. A Swedish study has shown that the highest average Cd content was found in spinach (104 ng/g), seafood (170 ng/g) and herring liver (660 ng/g) (43). Similar results of Cd concentrations in foods were obtained in our study. The median Cd concentrations in the tested foods were the highest in mollusks and cephalopods (89 ng/g). The median Cd content was also high in oilseeds, potato products, stalky vegetables and mammal offal, over 30 ng/g. Cadmium concentrations below 10 ng/g were measured in foods highly present in the diet such as fruits, milk and dairy products, eggs and egg products and meat and meat products. Cadmium concentrations in all tested samples were below the maximal permissible concentration given by the national rule book (40).

Despite the fact that the average content of Cd in mollusks and cephalopods is the highest, a very small intake of these foods in the Serbian adult population (on average 1.6 g/day) leads to a very low intake of Cd through this food group. On the other hand, a high intake of some staple foods like cereals and flour, milk or potatoes that have relatively low Cd concentration may possibly affect Cd exposure estimates. Potatoes have a relatively low Cd content compared to some other food groups, however, the daily average intake of 193.4 g caused their highest contribution to total dietary intake of Cd in the Serbian adult population. In addition to potatoes, mammal offal also had a noteworthy share in total Cd intake for the adult Serbian population, thanks to high values of the median concentration (56 ng/g).

The group of fruit and vegetable juices were the major source of dietary Cd in Serbian preschool children (43.7% of the total Cd intake) since the consumption of this foodstuff was fairly high (66.1 g) and the measured Cd concentration was noteworthy (19 ng/g). Mammal offal (14.8%) and potato products (9.9%) also had a significant share in the Cd intake in preschool children. Due to relatively low Cd concentration in cereal products, these foods were not the significant source of dietary Cd in preschool children even though cereal products were a significant dietary source with 20.7% of the total Cd intake.

A similar conclusion about Cd intake in adults derived in our study was provided by Sand and Becker (43), who found the share of potatoes and wheat flour in the total intake of Cd in the Swedish population of 40-50%. Further, the main sources of Cd exposure in Catalonia were legumes, potatoes and cereals (44). The US population consumes the most Cd through leafy vegetables, potatoes and cereals, while Cd intake was higher in people who had used larger amounts of shellfish and offal in their diet (3). In contrast to data relating to Europe, a Japanese study showed that in Japan Cd is mostly ingested through the rice (up to 40%) (6). Similarly, in China, vegetables, rice and flour were the food groups that contributed the most to Cd ingestion in the general population with 74.9% of the total Cd intake (45).

Tolerable weekly intake (TWI) of 2.5 μg/kg bw that was used as a reference dose for calculation of HI in this study was set by EFSA (39) based on an inquiry of numeral human studies regarding the relationship between urinary Cd levels and beta-2-microglobulin, a protein excreted in the urine, used as a biomarker for renal function. Taking these two markers and linking them to dietary Cd exposure, TWI was not established on the outcome of an actual renal injury, but on an initial indicator of alterations in kidney function implying likely damage of the renal function later in life. This way, even when the Cd intake exceeds the TWI, the risk of the immediate adverse health effect is relatively low.

In our study total weekly Cd intake in the adult population ranged from 1.41 mg/kg bw to 4.74 mg/kg bw, while in preschool children it ranged from 2.07 mg/kg bw to 4.93 mg/kg bw. These differences in total dietary Cd intake between the subpopulation of preschool children and the adult population were expected, given the differences in the diet and the differences in their body weights. These results are in line with the conclusion given by EFSA (39) that vegetarians, children, smokers and people living in extremely polluted regions, are likely to exceed weekly intake.

Acquired HI values in our study were lower than 1 in 45.5% of adults, and only in 15.6% of preschool children. Children population has a higher risk of Cd adverse influence, compared to the adult population.

Many studies have shown that dietary Cd intake is significant in other countries as well. Leblanc et al. (46) showed that the intake of Cd was 17 μg/day in France, which on a weekly basis and calculated on the average body weight of 60 kg is 2 μg/kg bw. Slightly lower values were registered in Spain (1.7 μg/kg bw Cd per week) (47). In Europe, the average Cd intake in children was 3.96 μg/kg bw per week, which is higher than TWI (42).

In comparison to Cd exposure calculated in our study, slightly lower values were acquired in Sweden where median dietary Cd exposure of 1 μg/kg bw was obtained for the average adult population, and 1.8 μg/kg bw for the 95th percentile of the adult population (43). Marti-Cid et al. (44) have estimated an average of 0.98 μg/kg bw for the population of Catalonia, calculated on a body weight of 70 kg.

The Dutch study found that the median daily intake of dietary Cd in the adult population was 0.14 μg/kg bw, and 0.32 μg/kg bw for the children aged 1-6 years (48). Translating daily Cd intake to weekly intake, 0.98 μg/kg bw was obtained for adults and 2.24 μg/kg bw for children, which is a 2.8 times lower intake in adults and 1.5 times lower intake in children compared to our assessment results, for the same calculation method.

Liu et al. in a 2010 paper (49) presented data on Cd intake in the population of the Jinhu area of China. The average weekly intake in adults was 1.49 μg/kg bw, while in children aged 1.9 to 7 years the intake was slightly higher (2.07 μg/kg bw). In both population groups, the intake was lower than the currently valid TWI.

In the United States, the estimated weekly intake of Cd in the adult non-smoking population was 2.45 μg/kg bw for men, and 2.1 μg/kg bw for women (3). These values correspond to the values obtained in our study for the adult population in the Republic of Serbia.

5. Conclusion

The possible non-carcinogenic health risk of dietary Cd was assessed in the typical adult population and in preschool children considering their different dietary habits. Analyzing the 11,227 samples, from 50 food groups, Cd was detected in 90% of food groups as well as in 30.8% of the tested samples found on the Serbian market, while the highest concentrations of Cd were in the group of mollusks and cephalopods. All samples of tested foods, in terms of concentrations of Cd were in accordance with the national regulations. Despite the actual measured concentrations of Cd in certain foods, when the amount of foods intake was taken into the account, the major contributors to total dietary Cd exposure turned out to be potatoes in the adult population, and fruit and vegetable juices in preschool children subpopulation.

The non-carcinogenic risk assessment of total dietary Cd in two populations with different dietary patterns was done using a probabilistic methodology. In this assessment, it has been shown that under specific circumstances weekly intake of total dietary Cd does surpass TWI value and consequently, HI values were above 1. Expectedly, this study indicated the higher health risk caused by total dietary Cd exposure of preschool children compared to the adult population.

However, the major uncertainty of this study arises from the use of previously determined consumption data on the average nutrition in the adult population in Serbia. According to our best knowledge, food intake based on individual data for the representative (sub)populations in Serbia still is not publicly available.

The results of this study are based on a worst-case scenario. Thus, they are rather preliminary and should be considered as an indication of the need for further, more refined input data, particularly in terms of consumption database, which would altogether contribute to the more realistic risk assessment as a high priority approach, especially in the case of the vulnerable subpopulations such as children.

Abbreviations

ATSDR, Agency for Toxic Substances and Disease Registry; EEA, European Environment Agency; EFSA, European Food Safety Authority; FAO/WHO, Food and Agriculture Organization/World Health Organization; HI, hazard index; IARC, International Agency for Research on Cancer; LOD, limit of detection; LOQ, limit of quantification; Cd, cadmium, TWI, tolerable weekly intake; UNEP, United Nations Environment Program; WI, weekly intake

Declarations

Acknowledgements

The authors kindly thank Đurđica Marić for the help on the one part of the statistical analysis.

Funding

This research was funded by the Ministry of Education, Science and Technological Development, Republic of Serbia through Grant Agreement with University of Belgrade-Faculty of Pharmacy No: 451-03-68/2022-14/200161.

Data Availability

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Ethical approval

All reported studies with human subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki Declaration and its amendments, institutional/ national research committee standards, and international/national/institutional guidelines).

Author contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Saša Janković. The first draft of the manuscript was written by Milena Stošić, Evica Antonijević Miljaković and Biljana Antonijević and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

References

1. European Environmental Agency. Consumption of Hazardous Chemicals (2019) https://www.eea.europa.eu/airs/2018/environment-and-health/production-of-hazardous-chemicals/ Accessed 12 October 2021.

2. WHO. Fact Sheet 5 – Chemical Safety. The importance of preventing early/life exposure to hazardous chemicals (2017) https://www.euro.who.int/en/media-centre/sections/fact-sheets/2017/fact-sheets-on-environment-and-health-priorities/fact-sheet-5-chemical-safety.-the-importance-of-preventing-early-life-exposure-to-hazardous-chemicals-2017. Accessed 12 October 2021.
3. Agency for Toxic Substances and Disease Registry. Toxicological profile for cadmium. Public Health Service (2012) https://www.atsdr.cdc.gov/toxprofiles/tp5-p.pdf. Accessed 12 October 2021.
4. Environmental Protection Agency. Annual report on the state of air quality in the Republic of Serbia in 2017. Belgrade, Serbia (2018) https://www1.undp.org/content/dam/serbia/Publications%20and%20reports/Aq%20report%20EN.pdf. Accessed 20 November 2021.
5. EFSA (2009) Scientific Opinion of the Panel on Contaminants in the Food Chain on a request from the European Commission on cadmium in food. EFSA J 980: 1–139
6. Ezaki T, Tsukahara T, Moriguchi J, Furuki K, Fukui Y, Ukai H, Okamoto S., Sakurai H., Honda S., Ikeda M (2003) Analysis for threshold levels of cadmium in urine that induce tubular dysfunction among women in non-polluted areas in Japan. Int Arch Occup Environ Health 76(3), 197–204. https://doi.org/10.1007/s00420-002-0390-9
7. Bernard A (2008) Cadmium and its adverse effects on human health. Indian J Med Res 128(4):557–564.
8. Trzcinka-Ochocka M, Jakubowski M, Szymczak W, Janasik B, Brodzka R (2010) The effects of low environmental cadmium exposure on bone density. Environ Res 110(3):286–93. https://doi.org/10.1016/j.envres.2009.12.003
9. Chunhabundit R (2106) Cadmium Exposure and Potential Health Risk from Foods in Contaminated Area, Thailand. Toxicol Res 32(1), 65–72. https://doi.org/10.5487/TR.2016.32.1.065
10. Matović V, Buha A, Bulat Z, Đukić-Ćosić D (2011) Cadmium toxicity revisited: focus on oxidative stress induction and interactions with zinc and magnesium. Arh Hig Rada Toksikol 62(1):65–76. https://doi.org/10.2478/10004-1254-62-2011-2075
11. Matović V, Buha A, Đukić-Ćosić D, Bulat Z (2015) Insight into the oxidative stress induced by lead and/or cadmium in blood, liver and kidneys. Food Chem Toxicol 78:130–40. https://doi.org/10.1016/j.fct.2015.02.011
12. Andjelković M, Buha Djordjević A, Antonijević Miljaković E, Antonijević B, Stanić M, Kotur-Stevuljević M, et al (2019) Toxic Effect of Acute Cadmium and Lead Exposure in Rat Blood, Liver, and Kidney. Int J Environ 16(2):274. https://doi.org/10.3390/ijerph16020274
13. Đukić-Ćosić D, Ninković M, Maličević Ž, Plamenac-Bulat Z, Matović V (2006) Effect of supplemental magnesium on the kidney levels of cadmium, zinc, and copper of mice exposed to toxic levels of cadmium. Biol Trace Elem Res 114: 281–291. https://doi.org/10.1385/BTER:114:1:281
14. Bulat Z, Djukić-Ćosić D, Maličević Ž, Bulat P, Matović V (2008) Zinc or Magnesium Supplementation Modulates Cd Intoxication in Blood, Kidney, Spleen, and Bone of Rabbits. Biol Trace Elem Res 124:110–117. https://doi.org/10.1007/s12011-008-8128-5
15. Bulat Z, Đukić-Ćosić D, Antonijević B, Buha A, Bulat P, Pavlović Z, et al (2017) Can zinc supplementation ameliorate cadmium-induced alterations in the bioelement content in rabbits? Arh Hig Rada Toksikol 68(1), 38–45. https://doi.org/10.1515/aiht-2017-68-2919
16. Rani A, Kumar A, Lal A, Pant M (2014) Cellular mechanisms of cadmium-induced toxicity: a review. Int J Environ Health Res 24(4):378–99. doi: https://doi.org/10.1080/09603123.2013.835032
17. Järup L, Akesson A (2009) Current status of cadmium as an environmental health problem. Toxicol Appl Pharmacol 238(3):201–8. https://doi.org/10.1016/j.taap.2009.04.020
18. Yuan X, Wang J, Shang Y, Sun B (2014) Health risk assessment of cadmium via dietary intake by adults in China. J. Sci. Food. Agric 94(2):373–380. https://doi.org/10.1002/jsfa.6394
19. Wallin M, Sallsten G, Lundh T, Barregard L (2014) Low – level cadmium exposure and effects on kidney function. Environment 71:848–854. https://doi.org/10.1136/oemed-2014-102279
20. Hyder O, Chung M, Cosgrove D, Herman JM, Li Z, Firoozmand A, et al (2013) Cadmium exposure and liver disease among US adults. J Gastrointest Surg 17(7): 1265–73. https://doi.org/10.1007/s11605-013-2210-9
21. Satarug S, Garrett SH, Sens MA, Sens DA (2010) Cadmium, environmental exposure, and health outcomes. Environ Health Perspect 118(2):182–90. https://doi.org/10.1289/ehp.0901234
22. Buha A, Wallace D, Matović V, Schweitzer A, Oluić B, Micic D, Djordjević V (2017) Cadmium Exposure as a Putative Risk Factor for the Development of Pancreatic Cancer: Three Different Lines of Evidence. Biomed Res Int Article ID 1981837. https://doi.org/10.1155/2017/1981837

23. Buha A, Matović V, Antonijević B, Bulat Z, Ćurčić M, Renieri EA., et al (2018) Overview of Cadmium Thyroid Disrupting Effects and Mechanisms. Int J Mol Sci 19(5):1501. https://doi.org/10.3390/ijms19051501
24. Buha A, Đukić-Ćosić D, Ćurčić M, Bulat Z, Antonijević B, Moulis JM, et al (2020) Emerging Links between Cadmium Exposure and Insulin Resistance: Human, Animal, and Cell Study Data. Toxics 8(3),63. https://doi.org/10.3390/toxics8030063
25. Kumar, S and Sharma, A (2019) Cadmium toxicity: effects on human reproduction and fertility. Rev Environ Health. 34 (4), 327–338. https://doi.org/10.1515/reveh-2019-0016
26. Chandravanshi L, Shiv K, Kumar S (2021) Developmental toxicity of cadmium in infants and children: a review. Environ Anal Health Toxicol 36(1):e2021003-0. https://doi.org/10.5620/eaht.2021003
27. Wang H, Zhu G, Shi Y, Weng S, Jin T, Kong Q, Nordberg GF (2003) Influence of environmental cadmium exposure on forearm bone density. J Bone Miner Res 18(3):553–60. https://doi.org/10.1359/jbmr.2003.18.3.553
28. Nordberg G, Jin T, Bernard A, Fierens S, Buchet JP, Ye T (2002) Low bone density and renal dysfunction following environmental cadmium exposure in China. Ambio 31(6):478–481. https://doi.org/10.1579/0044-7447-31.6.478
29. Silva N, Peiris-John R, Wickremasinghe R, Senanayake H, Sathiakumar N (2012) Cadmium a metalloestrogen: are we convinced? J. Appl. Toxicol 32(5):318–332. https://doi.org/10.1002/jat.1771
30. Buha A, Andjelković M, Kačavenda E, Javorac D, Antonijević Miljaković E, Marić Đ, et al (2021) Cadmium levels in human breast tissue and estradiol serum levels: Is there a connection? Arh farm 71(6):581–595. https://doi.org/10.1530/endoabs.73.AEP404
31. Lei L, Chen L, Jin T, Nordberg M, Chang X (2007) Estimation of benchmark dose for pancreatic damage in cadmium-exposed smelters. Toxicol Sci 97:189–95. https://doi.org/10.1093/toxsci/kfm016
32. IARC (2012) Cadmium and cadmium compounds. In: IARC monoraphs on the evaluation of carcinogenic risks to humans. Arsenic, metals, fibers, and dusts. IARC monographs, Vol. 100 C. Lyon, France: International Agency for Research on Cancer (IARC) https://publications.iarc.fr/120. Accessed 13 October 2021.
33. Schaefer HR, Dennis S, Fitzpatrick S (2020) Cadmium: Mitigation strategies to reduce dietary exposure. J Food Sci 85(2), 260–267. https://doi.org/10.1111/1750-3841.14997.
34. Kim H, Lee HJ, Hwang JY, Ha EH, Park H, Ha M, et al (2010) Blood Cadmium Concentrations of Male Cigarette Smokers Are Inversely Associated with Fruit Consumption, J. Nutr 140(6):1133–1138. https://doi.org/10.3945/jn.109.120659
35. FAO/WHO (Food and Agriculture Organization/World Health Organization) (2012) The GEMS/Food Consumption Cluster Diets database, Geneva, Switzerland.
36. Srdić B (2002) Examination of relationship between antropometric parameters and body weight in different types of obesity (Ispitivanje povezanosti antropometrijskih parametara i masne mase tela u različitim tipovima gojaznosti). Master thesis, Faculty of Medicine, University of Novi Sad
37. Janković S (2015) Risk Assessment On Exposure To Organohalogenous Contaminants And Heavy Metals Through Food (Procena rizika pri ekspoziciji organohalogenim kontaminantima i teškim metalima putem hrane). PhD thesis, Faculty of Pharmacy, University of Belgrade
38. Ružić P, Milosavljević R, Novičić S, Maković D, Krulj M, Andjelković M et al (1996) Nutrition in preschool institutions (Ishrana u predškolskim ustanovama). Zavod za ekonomiku domaćinstva Srbije, Beograd
39. EFSA (2011) Statement on tolerable weekly intake for cadmium. EFSA J 9(2), 1975. doi: https://doi.org/10.2903/j.efsa.2011.1975.
40. Official Gazette of RS, no. 132/2020 (2020) Regulation on maximum permitted quantities of residues of plant protection products in food and feed and on food and feed for which the maximum permitted quantities of residues of plant protection products are determined. https://www.paragraf.rs/propisi/pravilnik-o-maksimalnim-kolicinama-ostataka-za-zastitu-bilja-u-hrani-i-hrani-za-zivotinje.html Accessed 15 October 2021.
41. WHO (2011) Cadmium. Food Additives Series, 24. Geneva. http://www.inchem.org/documents/jecfa/jecmono/v024je09.htm Accessed 13 October 2021.
42. EFSA (2012) Cadmium dietary exposure in the European population. EFSA J 10(1), 2551. https://doi.org/10.2903/j.efsa.2012.2551
43. Sand S, Becker W (2012) Assessment of dietary cadmium exposure in Sweden and population health concern including scenario analysis. Food Chem Toxicol 50(3–4):536–44. https://doi.org/10.1016/j.fct.2011.12.034
44. Martí-Cid R, Llobet JM, Castell V, Domingo JL (2008) Dietary intake of arsenic, cadmium, mercury, and lead by the population of Catalonia, Spain. Biol Trace Elem Res 125(2):120–32. https://doi.org/10.1007/s12011-008-8162-3

45. Zhong MS, Jiang L, Han D, Xia TX, Yao JJ, Jia XY, et al (2015) Cadmium exposure via diet and its implication on the derivation of health-based soil screening values in China. J. Expo. Sci. Environ. Epidemiol 25:433–442. https://doi.org/10.1038/jes.2015.5
46. Leblanc JC, Malmauret L, Guérin T, Bordet F, Boursier B, Verger P (2000) Estimation of the dietary intake of pesticide residues, lead, cadmium, arsenic and radionuclides in France. Food. Addit. Contam 17(11):925–32. https://doi.org/10.1080/026520300750038108
47. Urieta I, Jalón M, Eguilero I (1996) 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(1):29–52. https://doi.org/10.1080/02652039609374379
48. de Winter-Sorkina R, Bakker MI, van Donkersgoed G, van Klaveren JD (2003) Dietary intake of heavy metals (cadmium, lead and mercury) by the Dutch population. RIVM report 320103001/2003. https://www.rivm.nl/bibliotheek/rapporten/320103001.html. Accessed 15 October 2021.
49. Liu P, Wang CN, Song XY, Wu YN (2010) Dietary intake of lead and cadmium by children and adults – Result calculated from dietary recall and availablelead/cadmium level in food in comparison to result from food duplicate diet method. Int J Hyg Envir Heal 213:450–7. https://doi.org/10.1016/j.ijheh.2010.07.002.

Tables

Table 1. Daily intake of the selected food items.

	Daily intake, g	
Food groups	**Adult population***	**Preschool children****
Berry fruit	22.1	-[a]
Citrus fruits	29	7.9
Apple fruit	64.6	28.6
Stone fruit	31.4	-
Tropical and subtropical fruits	30.6	17.1
Dried fruits	2.2	3.9
Fruit products, without juice	8.4	58.1
Legumes	20.9	23.6
Oilseeds	0.6	-
Nuts	4	1.4
Potato	193.4	23.6
Potato products	9.5	6.3
Cruciferous vegetables	58.7	17.7
Tubers	36.1	10.1
Cucumber	34.4	10.3
Tomatoes, watermelons, melons and mushrooms	73.9	19.2
Leafy vegetables	7.5	8.7
Root vegetables	25.3	17.4
Stalky vegetables	0.3	-
Other mixed vegetables	40.8	19.3
Spices and food additives	3.3	0.1
Sauces and vinegar	2.4	0.3
Cereals and flour	262.3	38.4
Cereal products	19.4	84.9
Sugar, honey, candy	87.4	15.7
Cocoa products	6.3	-
Milk fats	14.4	0.9
Other animal fats	14.1	-
Poultry fats	0.3	-
Vegetable fat	43.2	103
Milk	352.3	194.4
Milk products	35.8	48.1
Mammal meat	114.1	25
Poultry meat	55.6	-
Mammal offal	10	7.6

Poultry offal	0.9	-
Meat and offal products	7.5	8.3
Eggs	30	14.4
Egg products	1	1.1
Freshwater fish	2.1	-
Sea fish	0.1	8.6
Crabs	0.2	-
Molluscs and cephalopods	1.6	-
Fish products	21.7	1.1
Fruit and vegetable juices	13.5	66.1
Non-alcoholic beverages	55.7	-
Coffee based beverages	9.3	-
Teas	0.9	0.6
Beer	225.2	-
Other alcoholic beverages	61.4	-
Total	2145.7	891.8

*GEMS Food consumption cluster diets database (FAO/WHO. 2012); **Ružić et al. (1996); [a]dash is an indication that particular food group has not been taken into consideration in a given dietary pattern

Table 2. Cadmium daily intake in adults and preschool children

	Food group	Sample size	% of samples in which Cd concentration was below LOD*	Median, Cd concentration (ng/g)	Min/max Cd concentration (ng/g)	Median daily intake in adults (µg/g bw)	Maximal daily intake in adults (µg/g bw)	Median daily intake in preschool children (µg/g bw)	Maximal daily intake in preschool children (µg/g bw)
1.	Berry fruit	322	87.3	0	6/44	0	0.972	-	-
2.	Citrus fruits	902	94	0	6/45	0	1.305	0	0.355
3.	Apple fruit	478	91	0	6/50	0	3.230	0	1.430
4.	Stone fruit	84	78.6	0	6/32	0	1.004	-	-
5.	Tropical and subtropical fruits	142	90.1	0	6/17	0	0.520	0	0.290
6.	Dried fruits	58	79.3	0	6/56	0	0.123	0	0.218
7.	Fruit products, without juice	264	73.1	0	6/51	0	0.428	0	2.963
8.	Legumes	104	80.8	0	7/46	0	0.961	0	1.085
9.	Oilseeds	5	40	38	38/117	0.022	0.070	-	-
10.	Nuts	38	60.5	0	7/50	0	0.200	0	0.070
11.	Potato	107	36.4	7	6/102	1.353	19.725	0.165	2.407
12.	Potato products	12	25	45	15/50	0.427	0.475	0.283	0.315
13.	Cruciferous vegetables	227	82.4	0	6/49	0	2.876	0	0.867
14.	Tubers	131	66.4	0	6/98	0	3.537	0	0.989
15.	Cucumber	318	94.3	0	6/28	0	0.963	0	0.288
16.	Tomatoes, watermelons, melons and mushrooms	612	78.3	0	6/229	0	16.923	0	4.396
17.	Leafy vegetables	17	17.6	16	6/45	0.120	0.337	0.139	0.391
18.	Root vegetables	19	47.6	0	6/26	0	0.657	0	0.452
19.	Stalky vegetables	11	9.1	49	12/179	0.147	0.053	-	-
20.	Other mixed vegetables	554	73.1	0	6/42	0	1.713	0	0.810
21.	Spices and food additives	13	53.8	0	9/25	0	0.082	0	0.002
22.	Sauces and vinegar	72	53.8	0	6/43	0	0.103	0	0.012
23.	Cereals and flour	248	52	0	6/356	0	93.378	0	13.670
24.	Cereal products	1159	42	7	6/330	0.135	6.402	0.594	28.017

25.	Sugar, honey, candy	110	83.6	0	6/30	0	2.622	0	0.471
26.	Cocoa products	426	15.5	13	6/480	0.819	3.024	-	-
27.	Milk fats	7	71.4	0	9/10	0	0.144	0	0.009
28.	Other animal fats	6	100	0	0/0	0	0	-	-
29.	Poultry fats	3	100	0	0/0	0	0	-	-
30.	Vegetable fat	25	100	0	0/0	0	0	-	-
31.	Milk	725	90.5	0	6/19	0	6.693	0	3.693
32.	Milk products	204	93.1	0	6/10	0	0.358	0	0.481
33.	Mammal meat	612	93.6	0	6/45	0	5.134	0	1.125
34.	Poultry meat	214	81.8	0	6/31	0	1.723	-	-
35.	Mammal offal	133	12	56	7/501	0.560	5.010	0.425	3.807
36.	Poultry offal	93	24.7	6	6/78	0.005	0.070	-	-
37.	Meat and offal products	670	74.6	0	6/70	0	0.525	0	0.581
38.	Eggs	48	83.3	0	8/29	0	0.870	0	0.417
39.	Egg products	15	60	0	7/20	0	0.020	0	0.022
40.	Freshwater fish	68	88.2	0	6/38	0	0.079	-	-
41.	Marine fish	525	56.4	0	6/64	0	0.006	0	0.550
42.	Crabs	41	26.8	12	6/348	0.002	0.069	-	-
43.	Molluscs and cephalopods	68	8.8	89	9/520	0.142	0.832	-	-
44.	Fish products	927	40	8	6/150	0.173	3.255	0.008	0.165
45.	Fruit and vegetable juices	11	18.2	19	8/38	0.256	0.513	1.255	2.511
46.	Non-alcoholic beverages	134	89.6	0	6/25	0	1.392	-	-
47.	Coffee based beverages	18	100	0	0/0	0	0	-	-
48.	Teas	25	100	0	0/0	0	0	0	
49.	Beer	35	77.1	0	6/27	0	6.080	-	-
50.	Other alcoholic beverages	187	90.4	0	6/37	0	2.271	0	-
	Total	11,227	3,286.1	365	131/4,680	4.161	196.7	2.869	72.859

*LOD - limit of detection 5 ng/g

Table 3. Non-carcinogenic total dietary cadmium intake

Percentile	Intake of adult population (mg/kg bw)	Hazard index* adult population	Intake of preschool children (mg/kg bw)	Hazard index* preschool children
P 5	1.41	0.6	2.07	0.8
P 10	1.64	0.7	2.30	0.9
P 15	1.75	0.7	2.43	1.0
P 20	1.89	0.8	2.61	1.0
P 25	1.99	0.8	2.75	**1.1**
P 30	2.08	0.8	2.83	**1.1**
P 35	2.18	0.9	2.94	**1.2**
P 40	2.32	0.9	3.05	**1.2**
P 45	2.45	1.0	3.20	**1.3**
P 50	2.54	1.0	3.29	**1.3**
P 55	2.66	**1.1**	3.38	**1.4**
P 60	2.82	**1.1**	3.50	**1.4**
P 65	2.96	**1.2**	3.60	**1.4**
P 70	3.10	**1.2**	3.75	**1.5**
P 75	3.26	**1.3**	3.88	**1.6**
P 80	3.50	**1.4**	4.04	**1.6**
P 85	3.67	**1.5**	4.26	**1.7**
P 90	4.14	**1.7**	4.39	**1.8**
P 95	4.74	**1.9**	4.93	**2.0**

* Values higher than 1 are indicated in bold

Figures

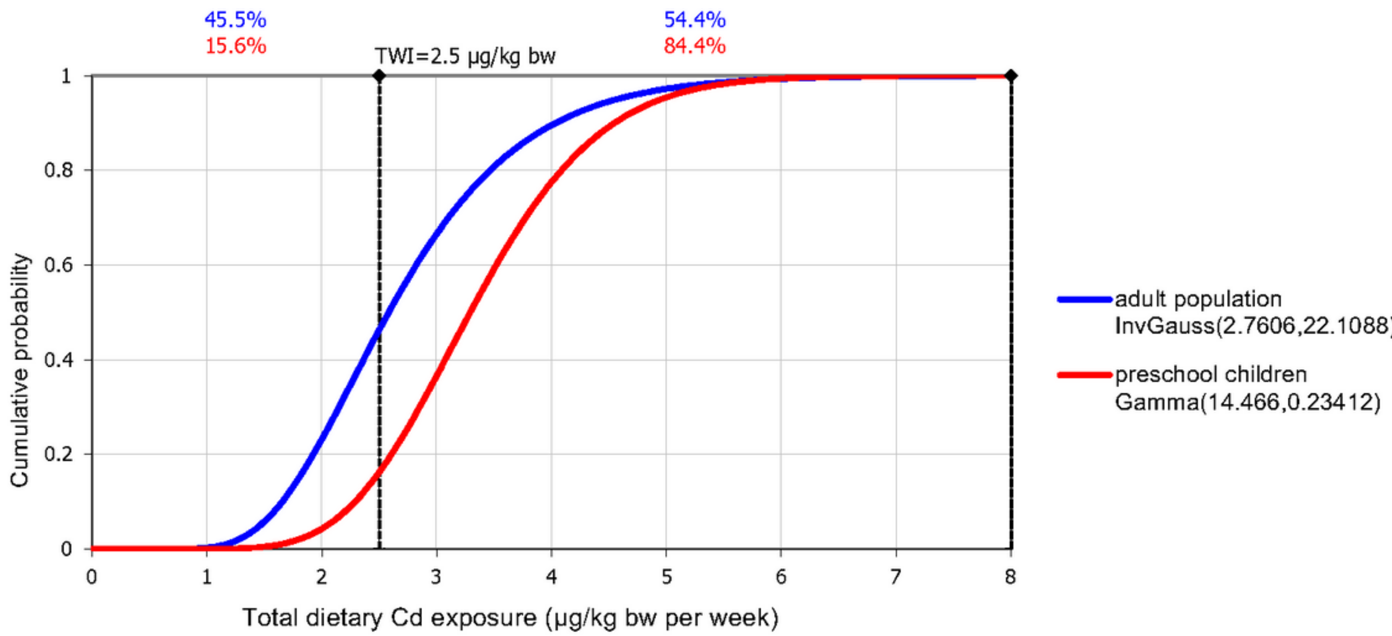

Figure 1

Total weekly dietary Cd exposure (µg/kg bw per week). Tolerable weekly Cd intake (TWI) of 2.5 µg/kg bw was given by EFSA (39). Distributions of exposures are presented as cumulative probability graphs with names and descriptors of the distributions given in the legend of the graphs.