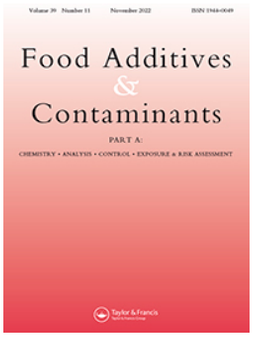

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Cadmium dietary exposure assessment in the adult population and pre-school children in the Republic of Serbia

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ABSTRACT

Cadmium (Cd) is a toxic metal, present in all matrices of the environment and a common food contaminant. 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 pre-school children in Serbia using probabilistic methodology. We measured Cd in 11,227 food samples belonging to 50 food items on the Serbian market. Cd was detected in 90% of the tested food items, and in 30.8% of the overall tested samples. The food item that contributed the most to total dietary Cd intake was potatoes (median Cd concentration of 7 ng/g) in adults, and fruit and vegetable juices in children (median Cd concentration of 19 ng/g). Weekly Cd intake shown as 50th and 95th percentiles were 2.54 and 4.74 μg/kg bw in the adult population, and 3.29 and 4.93 μg/kg bw in children. The results of this study are rather preliminary and should be considered as an indication of the need for further, more refined research, which would contribute to a more realistic risk assessment as a high-priority approach, especially in the case of vulnerable subpopulations such as children.

Abbreviations: AT SDR: 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; JECFA: Joint FAO/WHO Expert Committee on Food Additives; LOD: limit of detection; Cd: cadmium; TWI: tolerable weekly intake; UNEP: United Nations Environment Program; WI: weekly intake

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Cadmium dietary intake; risk assessment; probabilistic approach; Monte Carlo method

Introduction

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 and ocean waters, as well as in zinc, lead and copper ores. However, Cd can also be found in the environment as a result of human activity (UNEP 2010). 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 fertilisers, the combustion of fossil fuels and the incineration of municipal waste (UNEP 2010). Arriving in the environment, Cd pollutes water and soil, and then, mostly through plants, enters the human food chain (ATSDR 2012).

Since the biological half-life of Cd is approximately 20 years, 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 (Ezaki et al. 2003; Trzcinka-Ochocka et al. 2004;

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Bernard 2008; Trzcinka-Ochocka et al. 2010; Chunhabundit 2016; EEA 2019; Popov Aleksandrov et al. 2021). Numerous studies have addressed the toxic effects of Cd following laboratory animal and human exposure. Matović et al. (2011) reviewed the results of animal studies that revealed the adverse influence of Cd exposure on kidneys, liver, lungs, bones, hematopoietic and pancreatic tissue, nervous, reproductive and cardiovascular systems. Even though most of the molecular mechanisms that are responsible for the adverse effect of Cd are still not entirely understood, one of the well-known adverse effects of Cd toxicity is the induction of oxidative stress (Matović et al. 2011; Arroyo et al. 2012; Matović et al. 2015; Andjelković et al. 2019; Popov Aleksandrov et al. 2021). Other known 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 (Djukić-Cosić et al. 2006; Bulat et al. 2008, 2017; Joseph 2009; Rani et al. 2014; Andjelković et al. 2019; Genchi et al. 2020; Popov Aleksandrov et al. 2021). In addition, some studies identified mitochondria as the main intracellular targets of Cd (Branca et al. 2020; Genchi et al. 2020).

It has been evidenced that the target organ of long-term dietary Cd exposure is the kidney, even after exposure to low and moderate Cd levels, where Cd induces tissue impairment described by proximal tubule dysfunction in both animal and epidemiological studies (Järup et al. 2000; Järup and Akesson 2009; Yuan et al. 2014; Chunhabundit 2016). Besides the renal tissue, the liver is also sensitive to Cd exposure since it is involved in the detoxification and elimination of this metal (Bulat et al. 2008; ATSDR 2012; Arroyo et al. 2012; Bulat et al. 2017; Andjelković et al. 2019). Pancreatic impairment is also one of the well-recognised Cd toxic effects (Järup and Akesson 2009; Satarug et al. 2010; Buha et al. 2017, 2018, 2020). Epidemiological studies additionally indicate a moderate-certainty positive correlation between Cd and prediabetes, Types 1 and 2 diabetes (Guo et al. 2019; Liu et al. 2018; Filippini et al. 2022). Some studies have revealed a probable relationship between chronic environmental Cd exposure and osteoporosis, which is likely to be related to kidney tubular damage (Jin et al. 2004; Järup and Akesson 2009; Buha et al. 2019; Genchi et al. 2020).

Exposure to Cd affects the human male reproductive system leading to reduced spermatogenesis, semen qualit, and hormonal synthesis and release. Furthermore, Cd exposure disrupts human female reproductive hormonal balance, and may affect pregnancy outcome (Kumar and Sharma 2019; Genchi et al. 2020). Cd 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 behavioural and cognitive dysfunction (Chandravanshi et al. 2021).

Cd has the potential to disrupt the endocrine system (Silva et al. 2012; Buha et al. 2013, 2018, 2021) and has proven carcinogenic effect on humans which is why the International Agency for Research on Cancer (IARC) has placed Cd in Group 1 of carcinogens (IARC 2012). Beside the increased risk for cancer, Cd exposure has been linked with advanced risk of chronic diseases, in particular renal, bone and cardiovascular diseases (Filippini et al. 2022). Cd is also recognised as an immunotoxic agent since it can accumulate in immune cells, alter the immune function and trigger responses of the immune system, which can all lead to various health difficulties (Popov Aleksandrov et al. 2021; Wang et al. 2021).

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 (EFSA 2009; Schaefer et al. 2020). 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/d (Järup and Åkesson 2009). A study done on the Serbian population showed a level of daily dietary Cd intake of 11.51 µg/d (Škrbić et al. 2013). 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 (Kim et al. 2010).

The aims of this study were to measure the presence and levels of Cd in 50 available food groups on the Serbian market, and to assess dietary exposure to Cd for the adult population and the subpopulation of preschool children in the Republic of Serbia, considering their different dietary habits. For the purpose of dietary exposure assessment probabilistic approach was used.

Material and methods

Determination of cadmium concentration

Concentrations of Cd were determined in food items collected from the food contamination-monitoring programme. A total of 11,227 food item samples were analysed, belonging to 50 food items classified in accordance with World Health Organization Global Environment Monitoring System (GEMS)/Food Consumption Cluster Diets database (FAO/WHO 2012). The number of samples for all individual food items is shown in Table 1. Measurements were done in the National Reference Laboratory of the Institute for Meat Hygiene and Technology, Belgrade, Serbia, in compliance with ISO standard 17025.

Edible parts of each of a total of 11,227 samples of food samples were homogenised and mineralised by microwave digestion (ETHOS Milestone, Milan, Italy). Depending on the type of food, 0.25–1 g (± 0.001 g) of homogenised 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, Neustadt, Germany) and 1.5 ml 30% H_2O_2 (Merck, Darmstadt, Germany)). The mineralisation conditions of the analysed samples were set by adjusting the parameters of the digestion programme, namely: achieving a temperature of 180 °C for 5 min, maintained for the next 10 min and ventilated cooling for 15 min. The prepared samples were quantitatively transferred with deionised 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 (Artarmon, Australia) by the method of electrothermal atomisation, using argon as an inert gas. The limit of detection (LOD) 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 LOD.

Samples, all available on the Serbian market, were collected randomly in all districts of the Republic of Serbia in the period 2005–2012 (lines 141–142). Quantitatively and qualitatively, analysed samples could be accepted as representative on the national level. Region-specific nutritional differences were not considered.

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.

The typical adult population consisted of 808 healthy volunteers, 395 women and 413 men, aged between 18 and 65 years, who were included in the national survey done by the Department of Endocrinology of Clinical Center Vojvodina, Novi Sad, Serbia and Faculty of Medicine, University of Novi Sad, Serbia (Srdić 2002). Volunteers' body weights were the only data from the National survey we took into consideration, and they ranged from 41 to 120 kg, with median of 70 kg, and are representative on the national level. Due to the absence of a Serbian National Food Consumption Database, the information on dietary habits of the typical Serbian adult population was taken from the GEMS/Food Consumption Cluster Diets database (FAO/WHO 2012) which is currently the only publicly available dataset with estimated average nutrition in the adult population of the Republic of Serbia (Table 1). Cd concentrations were determined in 50 typically consumed food items in this dietary pattern (Table 1).

Data on body weights of preschool children were obtained from 119 healthy children, 57 girls and 62 boys, aged 4–7 years (Janković 2015). Their body weights ranged from 15 to 32, with median of 21 kg. Average daily intakes of food items in children were taken from preschool

Table 1. Daily intake of the selected food items with cadmium daily intake in adults and pre-school children.

	Food item	Sample size	Samples with Cd conc. <LOD[1]	Median, Cd conc. (ng/g)[2]	Min/max Cd conc. (ng/g)[3]	Daily intake for adults* (g)	Median daily intake for adults (μg/day)	Maximal daily intake in adults (μg/day)	Daily intake for pre-school children**(g)	Median daily intake for pre-school children (μg/day)	Maximal daily intake for pre-school children (μg/day)
1.	Berry fruit	322	87.3	0	6/44	22.1	0	0.972	–[a]	–	–
2.	Citrus fruits	902	94	0	6/45	29	0	1.305	7.9	0	0.355
3.	Apple fruit	478	91	0	6/50	64.6	0	3.230	28.6	0	1.430
4.	Stone fruit	84	78.6	0	6/32	31.4	0	1.004	–	–	–
5.	Tropical and subtropical fruits	142	90.1	0	6/17	30.6	0	0.520	17.1	0	0.290
6.	Dried fruits	58	79.3	0	6/56	2.2	0	0.123	3.9	0	0.218
7.	Fruit products, without juice	264	73.1	0	6/51	8.4	0	0.428	58.1	0	2.963
8.	Legumes	104	80.8	0	7/46	20.9	0	0.961	23.6	0	1.085
9.	Oilseeds	5	40	38	38/117	0.6	0.022	0.070	–	–	–
10.	Nuts	38	60.5	0	7/50	4	0	0.200	1.4	0	0.070
11.	Potato	107	36.4	7	6/102	193.4	1.353	19.725	23.6	0.165	2.407
12.	Potato products	12	25	45	15/50	9.5	0.427	0.475	6.3	0.283	0.315
13.	Cruciferous vegetables	227	82.4	0	6/49	58.7	0	2.876	17.7	0	0.867
14.	Tubers	131	66.4	0	6/98	36.1	0	3.537	10.1	0	0.989
15.	Cucumber	318	94.3	0	6/28	34.4	0	0.963	10.3	0	0.288
16.	Tomatoes, watermelons, melons and mushrooms	612	78.3	0	6/229	73.9	0	16.923	19.2	0	4.396
17.	Leafy vegetables	17	17.6	16	6/45	7.5	0.120	0.337	8.7	0.139	0.391
18.	Root vegetables	19	52.6	0	6/26	25.3	0	0.657	17.4	0	0.452
19.	Stalky vegetables	11	9.1	49	12/179	0.3	0.147	0.053	–	–	–
20.	Other mixed vegetables	554	73.1	0	6/42	40.8	0	1.713	19.3	0	0.810
21.	Spices and food additives	13	53.8	0	9/25	3.3	0	0.082	0.1	0	0.002
22.	Sauces and vinegar	72	53.8	0	6/43	2.4	0	0.103	0.3	0	0.012
23.	Cereals and flour	248	52	0	6/356	262.3	0	93.378	38.4	0	13.670
24.	Cereal products	1159	42	7	6/330	19.4	0.135	6.402	84.9	0.594	28.017
25.	Sugar, honey, candy	110	83.6	0	6/30	87.4	0	2.622	15.7	0	0.471
26.	Cocoa products	426	15.5	13	6/480	6.3	0.819	3.024	–	–	–
27.	Milk fats	7	71.4	0	9/10	14.4	0	0.144	0.9	0	0.009
28.	Other animal fats	6	100	0	0/0	14.1	0	0	–	–	–
29.	Poultry fats	5	100	0	0/0	0.3	0	0	–	–	–
30.	Vegetable fat	25	100	0	0/0	43.2	0	0	103	–	–
31.	Milk	725	90.5	0	6/19	352.3	0	6.693	194.4	0	3.693
32.	Milk products	204	93.1	0	6/10	35.8	0	0.358	48.1	0	0.481
33.	Mammal meat	612	93.6	0	6/45	114.1	0	5.134	25	0	1.125
34.	Poultry meat	214	81.8	0	6/31	55.6	0	1.723	–	–	–
35.	Mammal offal	133	12	56	7/501	10	0.560	5.010	7.6	0.425	3.807
36.	Poultry offal	93	24.7	6	6/78	0.9	0.005	0.070	–	–	–
37.	Meat and offal products	670	74.6	0	6/70	7.5	0	0.525	8.3	0	0.581
38.	Eggs	48	83.3	0	8/29	30	0	0.870	14.4	0	0.417
39.	Egg products	15	60	0	7/20	1	0	0.020	1.1	0	0.022
40.	Freshwater fish	68	88.2	0	6/38	2.1	0	0.079	–	–	–
41.	Marine fish	525	56.4	0	6/64	0.1	0	0.006	8.6	0	0.550
42.	Crabs	41	26.8	12	6/348	0.2	0.002	0.069	–	–	–
43.	Molluscs and cephalopods	68	8.8	89	9/520	1.6	0.142	0.832	–	–	–
44.	Fish products	927	40	8	6/150	21.7	0.173	3.255	1.1	0.008	0.165
45.	Fruit and vegetable juices	11	18.2	19	8/38	13.5	0.256	0.513	66.1	1.255	2.511
46.	Non-alcoholic beverages	134	89.6	0	6/25	55.7	0	1.392	–	–	–
47.	Coffee based beverages	18	100	0	0/0	9.3	0	0	–	–	–

(*continued*)

Table 1. Continued.

	Food item	Sample size	Samples with Cd conc. <LOD[1]	Median, Cd conc. (ng/g)[2]	Min/max Cd conc. (ng/g)[3]	Daily intake for adults* (g)	Median daily intake for adults (μg/day)	Maximal daily intake in adults (μg/day)	Daily intake for pre-school children** (g)	Median daily intake for pre-school children (μg/day)	Maximal daily intake for pre-school children (μg/day)
48.	Teas	25	100	0	0/0	0.9	0	0	0.6	0	
49.	Beer	35	77.1	0	6/27	225.2	0	6.080	–	–	–
50.	Other alcoholic beverages	187	90.4	0	6/37	61.4	0	2.271	–	0	–
	Total	11,227	3286.1	365	131/4680	2145.7	4.161	196.7	891.8	2.869	72.859

*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.
[1]LOD: limit of detection 5 ng/g.
[2]Median value was used because the normality test done on Cd concentration results for food samples of every food item tested did not show normal distribution.
[3]Minimal and maximal values shown are measured values that were above the LOD.

institution menus, including breakfast, snacks and lunch (which provide 75% of the total energy needs of children). The preschool menus were constituted according to guidelines offered by Ružić et al. (1996; Table 1). These guidelines are still valid. Cd concentrations were determined in 34 typically consumed food items in this dietary pattern.

Cd concentrations were shown as median value with minimum and maximum. When Cd intake was taken into account, median and maximal values of Cd intake were considered for all food items.

All reported studies with human subjects performed by the authors have been previously published and complied with all applicable ethical standards (Srdić 2002; Janković 2015).

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

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

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 (95%).

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

$$\mathrm{HI} = \frac{\text{Calculated weekly Cd intake}}{\text{Tolerable weekly intake (TWI)}} \quad (2)$$

Tolerable weekly intake (TWI) for Cd used for risk assessment is recommended by EFSA and amounts 2.5 μg/kg bw (EFSA 2011).

Statistical and probabilistic analysis

Test for normality (Kolmogorov–Smirnov test) of data on Cd concentrations and populations body weights, was done in IBM SPSS Statistics for Windows version 25.0 (IBM Corp., Armonk, NY) with p value of 0.05 considered significant.

For 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. Probabilistic exposure assessment was done in @RISK 5.5 software (Palisade Corporation, Ithaca, NY). 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. Software @RISK enabled fitting probability distributions to continuous sample data, that were Cd concentration and individuals body weight in our analysis. Fitting the probability distributions resulted in ranks of all the fitted distributions using chi-squared statistic, being the best-known goodness-of-fit statistic. The best-ranked fitted distribution for each input data was used for further simulation analysis: for adults and children body weights that were *pearson5* (Supplementary Figure 1); and *gamma* (Supplementary Figure 2), respectively; for Cd concentrations in different food items that were dominantly *Gamma*, *triangular* and *exponential* (Supplementary 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 (95%) (Palisade Corporation 2010).

Results

Cadmium concentrations in food

Cd was detected in 90% of the tested food items, and in a considerable number of tested samples (30.8%) (Table 1). The food item that contained the highest percentage of samples in which Cd was determined, were the molluscs and cephalopods (91.2% of tested samples). The maximal measured Cd concentration of 520 ng/g also belonged to the molluscs and cephalopods. Additionally, the median concentration of Cd was high in mammalian offal (56 ng/g), stalky vegetables (49 ng/g), potato products (45 ng/g) and in oilseeds (38 ng/g).

Cd 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

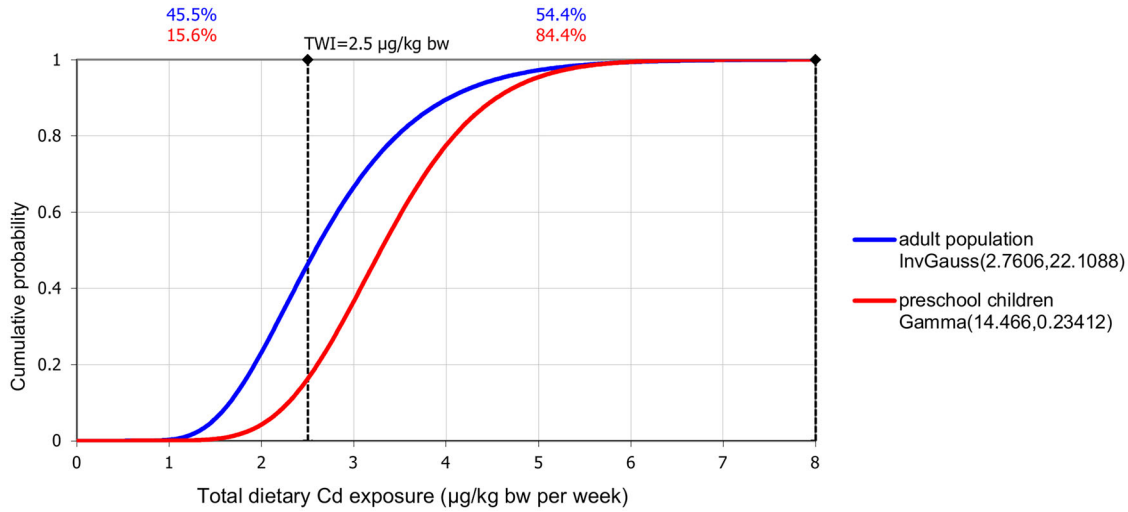

Figure 1. Total weekly dietary Cd exposure (µg/kg bw per week). Tolerable weekly Cd intake (TWI) of 2.5 µg/kg bw was given by EFSA (2011). Distributions of exposures are presented as cumulative probability graphs with names and descriptors of the distributions given in the legend of the graphs.

Table 2. Non-carcinogenic total dietary cadmium intake.

Percentile	Intake of adult population (μg/kg bw)	Hazard index* adult population	Intake of preschool children (μg/kg bw)	Hazard index* preschool children
P 50	2.54	1.0	3.29	**1.3**
P 95	4.74	**1.9**	4.93	**2.0**

*Values higher than 1 are indicated in bold.

juices. It was not detected in the fat, teas and coffee-based beverages in any of the tested samples.

Official maximal permitted doses of Cd vastly differ for different food items. Permitted levels can range from 0.05 to 1 mg/kg, depending on food group. None of the tested food samples had Cd concentration values that exceeded the maximal permitted concentration for corresponding food item given by the current Regulation in the Republic of Serbia (Official Gazette of RS no.132/2020 2020).

Dietary cd exposure and non-carcinogenic risk

Cd concentration was the highest in molluscs and cephalopods; however, the relatively low intake of these foods has led to other more-consumed food items to be responsible for Cd intake in Serbian adult population, as well as in preschool children (Table 1).

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 with 13% of the total Cd intake, due to the high median concentration of Cd in this food item (Table 1).

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 dietary scenario was through consumption of cereal products (20.7%) and mammal offal (14.8%) (Table 1).

Distribution of total weekly dietary Cd intake in the adult population ranged from 2.54 (50th percentile) to 4.74 μg/kg bw per week (95th percentile) (Table 2). Slightly higher values of 50th and 95th percentile of Cd intake were obtained in preschool children and amounted 3.29–4.93 μg/kg bw per week (Figure 1, Table 2).

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 (UNEP 2010; EFSA 2009; WHO 2011). Cd 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 (EFSA 2012). 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) (Sand and Becker 2012). Similar results of Cd concentrations in foods were obtained in our study. The median Cd concentrations in the tested foods were the highest in molluscs 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. Cd concentrations below 10 ng/g were measured in foods frequently present in the diet, such as fruits, milk and dairy products, eggs and egg products and meat and meat products. Cd concentrations in all tested samples were below the maximal permissible concentration given by the national regulations (Official Gazette of RS no.132/2020 2020).

Despite the fact that the average content of Cd in molluscs and cephalopods is the highest, a

very small intake of these foods in the Serbian adult population (on average 1.6 g/d) leads to a very low intake of Cd through this food item. 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 items, however, the daily average intake of 193.4 g caused potatoes to become the highest contributor 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).

Food items that contributed the most to Cd exposure in preschool children differed from food items that provided highest exposure in adults. That was expected due to differences in diets among these populations. While potatoes are very common in the adult everyday diet, preschool children have 8.2 times lesser intake of this food item on a daily basis, so potatoes did not contribute significantly to the Cd exposure in preschool children. The 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 food item was fairly high (66.1 g) and the measured Cd concentration was noteworthy (19 ng/g). Even though cereal products had relatively low Cd concentration, these foods were the second most significant source of dietary Cd in preschool children with 20.7% of the total Cd intake due to its high daily intake (84.9 g). Mammal offal (14.8%) and potato products (9.9%) also had a significant share in the Cd intake in preschool children.

A similar conclusion about Cd intake in adults as derived in our study was provided by Sand and Becker (2012), 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 (Martí-Cid et al. 2008). 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 (ATSDR 2012). In contrast to data relating to Europe, a Japanese study showed that in Japan Cd is mostly ingested through rice (up to 40%) (Ezaki et al. 2003). Similarly, in China, vegetables, rice and flour were the food items that contributed the most to Cd ingestion in the general population with 74.9% of the total Cd intake (Zhong et al. 2015).

The 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 (2011) 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.

The same toxicokinetic model that correlates Cd concentration in urine to dietary Cd intake, and the same biomarker (beta-2-microglobulin) for renal function were used by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in their evaluation of health-based guidance value (HBGV) for Cd. In this report, JECFA (2010) provided a different provisional tolerable monthly intake (PTMI) for Cd than the one EFSA reported one year earlier (EFSA 2009). While EFSA's CONTAM Panel established a TWI for Cd of 2.5 μg/kg bw, JECFA reported a PTMI of 25 μg/kg bw taking into account the long half-life of Cd in humans (JECFA 2011). National assessments given by JECFA on mean dietary Cd intake from all food items ranged from 2.2 to 12 μg/kg bw per month in adults. For population of children (<12 years old), this assessment was 11.9 μg/kg bw per month in Europe and from 20.4 to 22.0 μg/kg bw per month in children from the same age groups from Australia and the USA (JECFA 2021). When exposure values from our study were compared to JECFA's HBGV of 25 μg/kg bw, we got a different result than after using EFSA's guidance value. Namely, in our study total weekly Cd intake in the adult population was 2.54 µg/kg bw (50th

Table 3. Dietary Cd intake in different countries.

Country	Dietary Cd intake (adults)	Dietary Cd intake (children)	Reference
European union	2.27 μg/kg bw (mean weekly intake), 3.02 μg/kg bw (95th percentile weekly intake)	3.26 μg/kg bw (mean weekly intake)	EFSA (2009)
European union	1.70 μg/kg bw (mean weekly intake), 3.09 μg/kg bw (95th percentile weekly intake)	3.96 μg/kg bw (mean weekly intake), 6.58 μg/kg bw (95th percentile weekly intake)	EFSA (2012)
China	3.6 μg/kg bw (mean weekly intake), 10.25 μg/kg bw (95th percentile weekly intake)	/	Zhang et al. (2018)
China (Jinhu area)	1.49 μg/kg bw (mean weekly intake)	2.07 μg/kg bw (mean weekly intake)	Liu et al. (2010)
China	3.9 μg/kg bw (male mean weekly intake), 4.1 μg/kg bw (female mean weekly intake)	6.9 μg/kg bw (mean weekly intake in 2–3-year-old children), 6.4 μg/kg bw (mean weekly intake in 4–17-year-old children)	Yu et al. (2017)
Sweden	1 μg/kg bw (mean weekly intake), 1.8 μg/kg bw (95th percentile weekly intake)	/	Sand and Becker (2012)
Spain	1.7 μg/kg bw (mean weekly intake)	/	Urieta et al. (1996)
Spain	0.98 μg/kg bw	/	Martí-Cid et al. (2008)
France	2 μg/kg bw (mean weekly intake on the average body weight of 60 kg)	/	Leblanc et al. (2000)
Netherlands	0.98 μg/kg bw (mean weekly intake)	2.24 μg/kg bw (mean weekly intake)	de Winter-Sorkina et al. (2003)
USA	2.45 μg/kg bw (male mean weekly intake) 2.1 μg/kg bw (female mean weekly intake)	/	ATSDR (2012)
Nigeria	0.003 mg/kg (5th percentile weekly intake), 0.208 mg/kg (95th percentile weekly intake)	/	Amadi et al. (2022)
Italy	3.8 μg/kg bw (mean weekly intake)	/	Beccaloni et al. (2013)
Japan	7.2 μg/kg bw (mean weekly intake in polluted area A), 6.0 μg/kg bw (mean weekly intake in polluted area B)	/	Horiguchi et al. (2020)
Germany	1.46 μg/kg bw (mean weekly intake), 2.35 (95th percentile weekly intake)	/	Schwarz et al. (2014)
Portugal	2.3 μg/kg bw (median weekly intake)	/	Coelho et al. (2017)
Chile	1.81 μg/kg bw (mean weekly intake)	/	Muñoz et al. (2005)

percentile) and 4.74 μg/kg bw (95th percentile), while in preschool children it was 3.29 μg/kg bw (50th percentile) and 4.93 μg/kg bw (95th percentile). Displayed as a monthly intake, these values would amount to 10.16 and 13.16 μg/kg bw for 50th percentile (40.64 and 52.64% of PTMI), and 18.96 and 19.72 μg/kg bw for 95th percentile (75.84 and 78.88% of PTMI) in adult and children population, respectively. Also, according to articles by Leconte et al. (2021) and Qing et al. (2021) HBGVs for Cd can vary significantly. In the article by Qing et al., HBGV for Cd was estimated to be 0.64 μg/kg bw/d, while in the article by Leconte et al. (2021) the newly estimated HBGV for Cd was 0.35 μg/kg bw/d, which only means that HBGVs can fluctuate considerably depending on the observed population. 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 (2011) that vegetarians, children, smokers and people living in extremely polluted regions, are likely to exceed the desirable maximum weekly intake.

Acquired HI values in our study were less than one in 45.5% of adults, but only in 15.6% of preschool children. The child 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. (2000) showed that the intake of Cd was 17 μg/d in France, which on a weekly basis and calculated on the average body weight of 60 kg is 2 μg/kg bw (Table 3). Slightly lower values were registered in Spain (1.7 μg/kg bw Cd per week) (Urieta et al. 1996). In Europe, the average Cd intake in children was 3.96 μg/kg bw per week, which is higher than TWI (EFSA 2012). Horiguchi et al. (2020) showed a considerable mean intake of Cd in two polluted areas in Japan, 6.0 μg/kg bw, and 7.2 μg/kg bw. Weekly mean Cd intake in Germany was found to be 1.46 μg/kg bw while 95th percentile of weekly intake was 2.35 μg/kg bw (Schwarz et al. 2014).

In comparison to Cd exposure calculated in our study, slightly lower values were acquired in Sweden where a 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 (Sand and Becker 2012). Martí-Cid et al. (2008) have estimated an average of 0.98 µg/kg bw for the population of Catalonia, calculated on a body weight of 70 kg. Beccaloni et al. (2013) showed high weekly dietary exposure to Cd of 3.8 µg/kg bw.

The previous study done on the Serbian population (Škrbić et al. 2013) showed daily dietary Cd intake of 11.51 µg/d, which, calculated on weekly level for the average body weight of 70 kg, is 1.15 µg/kg bw which is in line with the 5th percentile exposure of this study. Škrbić et al. (2013) found that the highest Cd level was in paprika (0.118 mg/kg), but the highest contribution to the total intake of Cd was through bread owing to its greatest consumption rate. However, our assessments differ in the fact that Škrbić et al. (2013) assumed the value of LOD/2 for every sample that was below the detection limit, while in that case we assumed zero value which is one of the possible reasons why potatoes are the biggest contributor to dietary Cd intake in this study. Also, Serbian food consumption surveys on children and adults have been published (Zekovic, Milešević et al. 2022; Zekovic, Gurinović et al. 2022). In these studies, food description codes were harmonised with food codes used in EU, and FoodEx2 codes were used. Unfortunately, GEMS Food consumption database used in our study and FoodEx2 database are not comparable and food items that we used in study do not conform with the FoodEx2 database. Nevertheless, these new studies will have a positive impact on all future dietary exposure and risk assessment studies done on Serbian population so our present results can be put in the perspective and viewed in the light of new results obtained using more precise values of food intake.

The Dutch study found that the median daily intake of dietary Cd in the adult population was 0.14 and 0.32 µg/kg bw for the children aged 1–6 years (de Winter-Sorkina et al. 2003). 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.

In Chile, food items that participated with 47% in a dietary Cd intake were bread, cereals and potatoes, making average weekly Cd intake of 1.81 µg/kg bw (Muñoz et al. 2005). Coelho et al. (2017) reported a 2.3 µg/kg bw mean weekly intake of Cd *via* diet in Portugal where 35% of the participants demonstrated Cd dietary intake which was above the TWI.

A Nigerian study done by Amadi et al. (2022) exhibited high dietary exposure to Cd through vegetable oils, palm oils, butter and shea butter with 0.003 mg/kg for the 5th percentile of weekly intake, and 0.208 mg/kg for high consumer group at the 95th percentile weekly intake.

Liu et al. (2010) reported 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 1.9–7 years the intake was slightly higher (2.07 µg/kg bw). In both population groups, the intake was lower than the currently valid TWI. Yu et al. (2017) also reported 3.9 and 4.1 µg/kg bw of Cd intake in males and females, respectively, while Zhang et al. (2018) demonstrated the 95th percentile intake in China as high as 10.25 µg/kg bw.

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 (ATSDR 2012). These values correspond to the values obtained in our study for the adult population in the Republic of Serbia.

Limitations to the study

There are certainly some limitations of the reported study. First, in the absence of Serbian National Food Consumption Database, the information on dietary habits of the typical Serbian adult population was taken from the GEMS/Food Consumption Cluster Diets database (FAO/WHO 2012) which only gives the estimated average nutrition in the adult population of the Republic of Serbia. Since we did not conduct our survey by interviewing volunteers about their nutrition,

this may not reflect the eating habits of some groups with special diet regimes in the general population which, since using average intake values for all food items leaves room for an error in the estimated Cd exposure. Nevertheless, to alleviate and mitigate this error we used probabilistic estimation of exposure varying Cd concentrations (μg/g) for every food item sample and body weights (kg) of the included volunteers. Second, the LOD for Cd was 5 ng/g leaving a lot of food samples (69.2%) with an undetermined Cd level, i.e. below the LOD. While treating the left censored data, we assumed all concentrations that were below LOD to be zero (EFSA 2010). That also left a possibility for biased data since we cannot be sure that all of the samples that were found below the LOD in fact did not have Cd in them. Also, it should be noted that in this study we did not use the cooking processing factor in our calculations which can affect the final result related to dietary Cd intake and introduce additional inaccuracy in the final assessment.

Conclusions

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. Analysing 11,227 samples from 50 food items, Cd was detected in 90% of food items as well as in 30.8% of the tested samples found on the Serbian market, while the highest concentrations of Cd were in samples of molluscs 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 pre-school 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 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.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, [MS], upon reasonable request.

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