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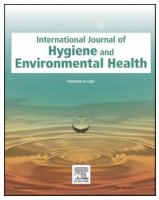

Cadmium exposure in adults across Europe: Results from the HBM4EU Aligned Studies survey 2014–2020

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ABSTRACT

The objectives of the study were to estimate the current exposure to cadmium (Cd) in Europe, potential differences between the countries and geographic regions, determinants of exposure and to derive European exposure levels. The basis for this work was provided by the European Human Biomonitoring Initiative (HBM4EU) which established a framework for alignment of national or regional HBM studies. For the purpose of Cd exposure assessment, studies from 9 European countries (Iceland, Denmark, Poland, Czech Republic, Croatia, Portugal, Germany, France, Luxembourg) were included and urine of 20–39 years old adults sampled in the years 2014–2021 (n = 2510). The measurements in urine were quality assured by the HBM4EU quality assurance/quality control scheme, study participants' questionnaire data were post-harmonized. Spatially resolved external data, namely Cd concentrations in soil, agricultural areas, phosphate fertilizer application, traffic density and point source Cd release were collected for the respective statistical territorial unit (NUTS). There were no distinct geographic patterns observed in Cd levels in urine, although the data revealed some differences between the specific study sites. The levels of exposure were otherwise similar between two time periods within the last decade (DEMOCOPHES - 2011–2012 vs. HBM4EU Aligned Studies, 2014–2020). The age-dependent alert values for Cd in urine were exceeded by 16% of the study participants. Exceedances in the different studies and locations ranged from 1.4% up to 42%. The studies with largest extent of exceedance were from France and Poland. Association analysis with individual food consumption data available from participants' questionnaires showed an important contribution of vegetarian diet to the overall exposure, with 35% higher levels in vegetarians as

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opposed to non-vegetarians. For comparison, increase in Cd levels due to smoking was 25%. Using NUTS2-level external data, positive associations between HBM data and percentage of cropland and consumption of Cd-containing mineral phosphate fertilizer were revealed, which indicates a significant contribution of mineral phosphate fertilizers to human Cd exposure through diet. In addition to diet, traffic and point source release were identified as significant sources of exposure in the study population. The findings of the study support the recommendation by EFSA to reduce Cd exposure as also the estimated mean dietary exposure of adults in the EU is close or slightly exceeding the tolerable weekly intake. It also indicates that regulations are not protecting the population sufficiently.

1. Introduction

Cadmium (Cd) is widespread in the environment and its presence is a consequence of both natural and anthropogenic sources. Anthropogenic sources include industrial emissions, urban pollution and pollution by cadmium-containing fertilizers and may result in elevated levels of Cd in soil (Nordberg et al., 2015, 2018). Most of agricultural soil contamination occurs by the use of Cd-containing phosphate fertilizers leading to elevated levels of Cd in crops and for example, in France, mineral phosphate fertilizers have been identified as the main source of Cd in agricultural soil in arable farming regions (Carne et al., 2021). Consistent with the very slow turnover of Cd in soils (Nordberg et al., 2018), several studies indicated gradual increases in Cd content in soil after long-term application of mineral phosphate fertilizers (summarized by Park et al., 2021). However, in addition to phosphate fertilizers, contributors to Cd deposition in agricultural soils are also atmospheric pollution, sewage sludge and compost material (EFSA, 2009; Park et al., 2021).

Depending on the Cd mobility in soils (speciation, pH, organic matter, etc.), Cd is taken up by plants which results in increased levels of Cd in food and feeds (EFSA, 2009), and the use of phosphate fertilizers and sewage sludge facilitates the mobilization of Cd in the environment and its accumulation in crops (Nordberg et al., 2018). The primary source of Cd exposure in humans is therefore through ingestion of food crops grown on soils that are either Cd-contaminated or are naturally rich in this metal (Park et al., 2021). In populations with high consumption of rice, the main source of Cd is rice; while cereal products, grains, and root vegetables are important sources in many populations worldwide (EFSA, 2012; Nordberg et al., 2018). Meat and fish normally contain lower Cd levels. Animal offal such as kidney and liver can exhibit high Cd concentrations, as these are the organs in animals in which Cd concentrates, but these are normally consumed in lower quantities (EFSA, 2009, 2012; Nordberg et al., 2018). In addition to diet, smoking is another major source of Cd exposure in the general population as tobacco plants tend to accumulate high levels of Cd in their leaves (Ganguly et al., 2018).

In humans, Cd is widely distributed in the body, where it accumulates over time, with a biological half-life ranging from 10 to 30 years. As Cd is mainly stored in the liver and kidneys (EFSA, 2009; ATSDR, 2012) it affects the kidneys in particular and can cause renal failure after long-term exposure, even at low exposure levels (Nordberg et al., 2018). In addition, Cd is classified as a human carcinogen, which is mainly based on occupational studies of lung cancer. Epidemiological studies in general populations have also reported significant associations with a number of adverse health effects at low exposures, but more evidence is needed in order to establish causality (Nordberg et al., 2018). A recent study showed that at low levels of exposure, Cd can contribute to the risk of osteoporosis, with 28% of cases of osteoporosis in women over 55 years of age being attributable to Cd exposure (Ougier et al., 2021a).

In order to ensure a high level of protection to all consumers, including exposed and vulnerable subgroups of the population, the Panel on Contaminants in the Food Chain within EFSA (2012) proposed a tolerable weekly intake (TWI) of 2.5 μg/kg body weight. Maximum levels of Cd in foodstuffs are set by the Regulation (EC) No. 1881/2006, and furthermore, the use of Cd is restricted in certain products (Annex XVII of REACH), among them recycled PVC, which is currently under review. There is also an ongoing discussion regarding the allowable maximum levels in mineral phosphate fertilizers with a link to maximum levels in food. In spite of improved regulations and guidelines it is not clear whether Cd exposures in human populations have increased, decreased, or stayed unchanged in the last decades, with varying trends being reported for different regions or countries (summarized by Nordberg et al., 2018).

The European Human Biomonitoring Initiative (HBM4EU) provided a framework for alignment of national and regional studies based on existing HBM capacity and the development of new capacities. Cd was included as one of the priority substances (Gilles et al., 2021, 2022) identified based on the needs of EU institutions, participating countries and stakeholders (Ougier et al., 2021b). In line with the identified knowledge gaps, the objective of the present study was to assess the current exposure to Cd in Europe, potential differences between the countries and/or regions in Europe and to evaluate whether the HBM values reflect environmental levels (Cd in soil) or not, particularly whether Cd variability in soil, and consequentially food, explains Cd variability in HBM data.

2. Methodology

2.1. Study design and sampling frame

The study is part of the European Human Biomonitoring Initiative (HBM4EU) conducted in 21 European countries, the so-called HBM4EU Aligned Studies. It builds on existing HBM capacity in Europe by aligning national or regional HBM studies targeting the general population (Gilles et al., 2021). The studies were aligned with respect to the sampling period (2014–2021), age groups (children, teenagers and young adults), sampling size (240–300 per study) with a 1:1 male to female ratio, biomarkers of interest, and questionnaire data available per age group. Residents in hotspots, patient groups, or specific occupational groups were excluded. Studies of all 4 geographical regions of Europe according to the United Nations geo-scheme (North, West, South, East) were included, with at least two countries per region. Key aspects of recruitment, sampling, questionnaire development and sample transport were quality assured following the standard operating procedures for each study phase, which were developed within the HBM4EU project. Details on the framework of the HBM4EU Aligned Studies and the approach that has been applied to align European HBM initiatives across Europe are provided by Gilles et al. (2021, 2022).

For the purpose of the present paper, data on adults (20–39 years of age) of the following studies were used: CPHMINIPUB (parents)/DYMS (Denmark, n = 292), Diet_HBM (Iceland, n = 203), (C)ELSPAC: YA (Czech Republic, n = 300), POALES (Poland, n = 228), HBM in Croatia (Croatia, n = 300), INSEF-ExpoQuim (Portugal, n = 295), ESTEBAN (France, n = 393), Oriscav-Lux2 (Luxembourg, n = 210), and ESB (Germany, n = 289). Detailed information for each study is provided by Gilles et al. (2022). Cadmium concentrations were available in first morning (n = 1288), random spot (n = 933) and 24 h urine samples (n = 289) (Table 1).

2.2. Chemical analysis

According to the framework of the HBM4EU Aligned Studies, determination of Cd in urine samples was performed in laboratories that successfully passed the HBM4EU quality assurance quality control (QA/QC) program (Esteban López et al., 2021; Nübler et al., 2021), except for the ESTEBAN study (France), for which measurements were performed before the establishment of the HBM4EU QA/QC program and were therefore not quality assured by HBM4EU. Seven laboratories were involved in the determination of Cd concentrations in urine samples for the presented study and all of them used Inductively Coupled Plasma Mass Spectrometry (ICP-MS) for the measurements. More details on the analytical procedures used by different laboratories are provided in Table 2. Limit of detection (LOD) ranged from 0.002 μg/L to 0.01 μg/L (not available for Luxembourg and Germany studies) and limit of quantification (LOQ) between 0.0016 μg/L and 0.1 μg/L.

Creatinine concentrations in urine were available for all data collections (n = 2500), however specific gravity was only available for one data collection (Czech study, n = 300), and the latter was therefore not considered for normalization of urinary Cd concentrations in the present study. All urine samples had creatinine levels above 5 mg/dL limit set by Lauwerys and Hoet (2001) for biomonitoring in the U.S. workplace to exclude too diluted samples for the screening of selected drugs of abuse. According to the WHO criteria for valid urine samples for occupational monitoring (WHO, 1996), the number of samples with creatinine levels below the lower limit of 30 mg/dL were 77 (3.5%), and the number of samples above the higher limit of 300 mg/dL were 92 (4.2%).

2.3. Questionnaire and ancillary data

Accompanying data were available from the questionnaires and spatially resolved data extracted from the available European databases. Since the HBM4EU Aligned Studies aligned both new, ongoing and recently conducted studies, a post-harmonization approach was applied to harmonize the collected questionnaire data.

Questionnaire data included personal information (sex, age, educational level, country of birth), socio-demographic information on the participant (socio-economic status - income, current occupation status, occupational sector and occupational activities), information on residential environment (country of residence, NUTS level 1, 2, and 3, type of residence/degree of urbanization, residential history, density of traffic in the residential area, farmlands, orchards or vineyards in vicinity, frequency of dusting and vacuuming), information on dietary habits (vegetarian diet, consumption of local food, seafood, fish, meat, poultry, vegetable and fruit, offal and cereals, type and source of drinking water), lifestyle information (smoking status, number of cigarettes smoked per day, passive smoking exposure), personal care and health (height, weight, body mass index, chronical illness, physical activity, and pregnancy status and parity if the subject was female). Educational level was used as a surrogate for socio-economic status. The classification was based on the International Standard Classification of Education (ISCED) (Gilles et al., 2021).

Additional supporting data for the statistical analyses were obtained from various data sources available at European level. Two sources with different spatial resolution were used for Cd distribution in soil. Distribution of Cd in topsoil mapped based on the FOREGS (Forum of European Geological Surveys) geochemical database with 5 km resolution (Lado et al., 2008), and a map of Cd concentration in the topsoil of the European Union produced based on the LUCAS (Land Use/Land Cover Area Frame Survey) data and available in 1 km resolution (Tóth et al., 2013, 2016). Moreover, the following ancillary data were extracted from the statistical office of the European Union (Eurostat): percentage of agricultural areas and cropland, respectively; annual application of phosphate fertiliser reported as consumption by countries or estimated in tonnes; and the density of motorways and other road network in km per km^2. The data were extracted for the year(s) most closely corresponding to the year of conduct of the respective study. Annual releases of Cd to air and water from industrial facilities located within the individual NUTS regions as reported in the European Pollutant Release and Transfer Register (E-PRTR) (https://prtr.ec.europa.eu/) in the period 2008–2015 were also considered. All data were extracted and assigned to the HBM data at NUTS unit level at the finest resolution possible, depending on the spatial resolution of the source data (EUROSTAT, 2018). Visualization of the acquired external data is provided in the Supplemental material (Fig. S1).

2.4. Statistical analysis

In case of Cd levels below LOD/LOQ, random values were imputed between 0 and LOD, between 0 and LOQ, or between LOD and LOQ (depending on the values reported by the data provider) using a truncated lognormal distribution. Urinary Cd concentrations were standardized by creatinine as estimator of urine density, as it was available for all studies. The descriptive statistics (N, geometric mean (GM) and 95% confidence intervals (CIs) and percentiles P05, P10, P25, P50, P75, P90, P95) were calculated using unadjusted data for each country. The levels are reported per volume (μg/L) and standardized for creatinine (μg/g creatinine). As the studies differed in the type of urine sample (Table 1), creatinine-standardized Cd concentrations were used in data interpretation. European exposure values were calculated using survey procedures to take into account the complex survey design when calculating variance estimates (Park and Lee, 2004), for the pooled population, and stratified by sex, educational level, smoking, degree of urbanization and geographic region (North, South, East, West). We calculated the GM and 95th percentile (P95), and their 95% confidence interval. The geometric mean and its confidence limits were obtained by

Table 1
Basic information for the participating studies.

Country	Study	N	Representativeness	Sample type	Reference
Denmark	CPHMINIPUB (parents)/DYMS	292	Regional	Spot random	Busch et al. (2021)
Iceland	Diet_HBM	203	National	Spot random	–
Czech Republic	(C)ELSPAC: YA	300	Regional	First morning	Piler et al. (2017)
Poland	POALES	228	Regional	Spot random	–
Croatia	HBM in Croatia	300	National	First morning	–
Portugal	INSEF-ExpoQuim	295	National	First morning	–
France	ESTEBAN	393	National	First morning	Balicco et al. (2017); Fillol et al. (2021)
Luxembourg	Oriscav-Lux2	210	National	Spot random	Alkerwi et al. (2019)
Germany	ESB	289	Regional	24 h	Kolossa-Gehring et al. (2012); Lemke et al. (2021); Lermen et al. (2014)

CPHMINIPUB(parents)/DYMS = Copenhagen Minipuberty study (parents)/Danish Young Men Study; Diet_HBM = Icelandic National Dietary Survey; (C)ELSPAC:YA = Central European Longitudinal Studies of Parents and Children: Young Adults; POALES = Polish Aligned Environmental Study; HBM in Croatia = Human biomonitoring survey in adults in Croatia; INSEF-ExpoQuim = Exposure of the Portuguese Population to Environmental Chemicals: a study nested in the 1st Portuguese National Health Examination Survey (INSEF) conducted in 2015; ESTEBAN = Etude de santé sur l'environnement, la biosurveillance, l'activité physique et la nutrition; Oriscav-Lux2 = Observation des Risques et de la Santé Cardiovasculaire au Luxembourg; ESB = Environmental Specimen Bank.

Table 2
Basic information on the chemical analytical procedures used in different laboratories.

Country of the study	Urine dilution ratio	Isotopes used for quantification	Analysis mode	LOD (μg/L)	LOQ (μg/L)
Denmark	1:9	^{111}Cd, ^{113}Cd, ^{114}Cd	Helium-mode	0.015	0.05
Iceland	1:9	^{111}Cd	Collision cell, Helium	0.01	0.03
Czech Republic	1:9	^{111}Cd	Collision cell, Helium	0.004	0.013
Poland	1:9	^{114}Cd	DRC, methane	0.004	0.008
Croatia	1:9	^{111}Cd	Collision cell, Helium	0.004	0.013
Portugal	1:4	^{111}Cd	Standard mode	0.0075	0.025
France	1:9	^{103}Rh, ^{202}Hg	Standard mode	0.002	0.005
Luxembourg	1:9	^{111}Cd	Collision cell, no gas and Helium	–	0.1
Germany	4:15	^{111}Cd, ^{113}Cd, ^{114}Cd	Collision cell, no gas and Helium	–	0.0016–0.0184

LOD = Limit of detection for cadmium in urine; LOQ = Limit of quantification for cadmium in urine; DRC = Dynamic Reaction Cell.

taking the antilog of the estimated mean and its upper and lower confidence limit of the log-transformed biomarker values. European exposure values for cadmium were calculated in μg/L and in μg/g creatinine.

With relevance to health risk, we calculated proportion of study population which exceeded the available health-based guidance levels (HBM GVs) for Cd in urine. We used HBM-I value (1 μg/L), which was derived by the German HBM Commission and presents the concentration below which there is no risk for adverse health effects, and consequently, no need for action (Apel et al., 2017). Because HBM-I is based on the kidney effects in women above 50 years of age, the HBM4EU produced age-dependent values which considered accumulation of Cd in the human body: 0.2 μg/g crt (11–20 years of age), 0.3 μg/g crt (21–30 years of age), 0.5 μg/g crt (31–40 years of age) and 0.8 μg/g crt (41–50 years of age) (Lamkarkach et al., 2021).

For geographic comparison survey procedures were used as well, with linear regression adjusting for main characteristics of the study population that could be of influence on the observed exposure values and differ between the countries. Namely these are creatinine, age, sex, smoking, educational level, sampling year and urine sample type (first morning, random spot or 24 h urine).

In order to identify determinants of cadmium exposure, Cd concentrations in urine were studied in relation with possible determining factors using analysis of variance (ANOVA), bivariate linear regression and multiple mixed linear regression models, with country as a random factor. For this purpose, ln-transformed imputed Cd data standardized for creatinine were used. Creatinine was additionally forced into the regression model. Sensitivity analysis was done for variables in a limited set of studies (e.g. applying the WHO creatinine exclusion criteria; exclusion of smokers; subsets of data with availability of specific dietary variables). The obtained linear regression coefficients were reverse log transformed and were therefore expressed as the fold change in Cd concentration for unit increase of the covariate. Regression diagnostics of the final models included linearity, normality, multicollinearity, and independence.

Biomarker data that did not successfully pass the HBM4EU QA/QC program (ESTEBAN, France), was excluded from the calculation of European exposure values and geographical comparison. However, it was included in the calculation of HBMGVs exceedance proportion and analysis of exposure determinants.

Statistical analysis was performed using STATA SE 12.0 and R software 4.1.2. Spatial analyses and visualizations were performed using the QGIS geographic information system application version 3.22.7.

3. Results

3.1. General characteristics of the study population

Studies selected for the present work were conducted between 2014 and 2021 (Table 3), with only four participants (from Iceland) sampled in 2021. The majority of the participants were sampled in 2017, 2018 and 2019 (n = 413, 449 and 787, respectively), followed by year 2020 (n = 309), 2015 (n = 259), 2014 (n = 145) and 2016 (n = 144). There were some differences according to the four geographic regions - the studies from the North covered the period 2017–2021, studies from the East years 2017 and 2019, South 2019–2020, and West 2014–2018. Overall, the sampling campaigns were more or less evenly distributed across different seasons, however, there were certain differences between the countries and regions (Table 3). Males and females were also more or less equally represented, with exception of the Polish study, where almost 70% of participants were women. The age of the participants ranged between 20 and 39 years and it was more or less evenly distributed between countries and regions. The lowest mean age was in the German study (24 years), and the highest in the Portuguese (almost 35 years) (Table 3).

Most of the participants lived in cities (overall 65%), which was the case in seven out of nine studies and in all four geographic regions. Among all study participants, 18% reported to be smokers. The percentage was lowest in Iceland (7%) and highest in Croatia (30%), and according to the regions lowest in the North and highest in the South. As usually experienced in HBM studies, the education of the study participants was skewed towards higher levels (level 5 or higher, according to the International Standard Classification of Education, ISCED). The skewness was less obvious in the Portuguese study (Table 3).

3.2. Cadmium levels in urine

The concentrations of Cd in urine samples in the pooled European population and in each participating country are presented in Table 4. Overall, there were 16 samples (0.6%) with Cd levels below the given limits of detection, and 85 (3.4%) below the given limits of quantification (both LOD and LOQ for the respective study are provided in Table 2). Among the latter, 54 values were reported to be between the LOD and LOQ. Although the measurements for the Luxembourg study showed markedly higher LOQ than other studies, they were not excluded from the data analysis as the number of participants below the LOQ was sufficiently low (7%) and lower than P50 of all participating studies.

Comparing unadjusted Cd levels in urine among the participating countries (Table 4), the lowest mean urinary Cd level was observed in the Portuguese study (GM 0.09 μg/g crt, 95% CI 0.09–0.10 μg/g crt), and did not differ statistically from the levels in the Danish (0.10 μg/g crt, 0.09–0.11 μg/g crt) and Czech studies (0.10 μg/g crt, 0.10–0.11 μg/g crt) ($p = 1.000$ for all comparisons, according to the ANOVA Bonferroni adjustment). The highest mean levels were observed in the Polish (0.36 μg/g crt, 0.34–0.39 μg/g crt) and French studies (0.39 μg/g crt, 0.36–0.42 μg/g crt), and the two did not differ statistically ($p = 1.000$, according to the ANOVA Bonferroni adjustment). The levels did not differ statistically also between Denmark, Czech and Iceland, and between Iceland and Croatia (all cross-comparisons $p = 1.000$, except Denmark vs. Iceland $p = 0.464$). All other differences were statistically significant ($p < 0.05$).

Mean concentrations of Cd in urine on the level of NUTS2 geographic units are presented in Fig. 1. The tendency toward higher urinary Cd levels in the studies from East and West can be seen from the raw

Table 3
General characteristics of the study population.

Country of the study	Sampling year	Sampling season (%)				Sex (%)		Age (years)		Degree of urbanization (%)			Smoking (%)		ISCED (%)		
		Spring	Summer	Autumn	Winter	Female	Male	Mean	Min-max	Cities	Towns/ suburbs	Rural	No	Yes	Low (ISCED 0–2)	Medium (ISCED 3–4)	High (ISCED ≥5)
ALL	2014–2021	16.3	22.8	38.3	22.6	53.8	46.2	30.7	20–39	64.9	17.45	17.6	82.0	18.0	5.0	27.7	67.3
Denmark	2017–2019	23.3	42.8	32.2	1.4	41.8	58.2	30.3	20–39	90.4	8.6	1.0	90.6	9.4	11.6	23.5	64.9
Iceland	2019–2021	0.0	35.0	52.7	12.3	56.2	43.8	30.8	20–39	76.4	11.6	12.1	93.0	7.0	6.0	29.5	64.5
Czech Republic	2019	39.7	29.7	26.7	4.0	51.7	48.3	27.3	20–37	74.7	10.4	14.9	87.9	12.1	0.7	23.4	75.9
Poland	2017	0.0	0.0	100.0	0.0	69.3	30.7	33.5	20–39	100.0	0.0	0.0	86.8	13.2	0.0	41.7	58.3
Croatia	2019–2020	0.0	0.0	59.7	40.3	53.0	47.0	30.6	20–39	58.0	13.7	28.3	69.7	30.3	0.3	36.0	63.7
Portugal	2019–2020	5.4	51.5	25.4	17.6	58.0	42.0	34.6	28–39	27.1	37.0	35.9	74.9	25.1	20.0	36.3	43.7
France	2014–2016	21.1	19.9	34.4	24.7	55.0	45.0	32.3	20–39	45.0	28.5	26.5	70.9	29.1	2.3	29.5	68.2
Luxembourg	2016–2018	20.5	27.1	30.0	22.4	52.9	47.1	33.6	25–39	19.1	45.2	35.7	82.9	17.1	4.8	32.9	62.4
Germany	2014–2018	27.7	0.0	0.0	72.3	49.8	50.2	24.1	20–29	100.0	0.0	0.0	90.0	10.0	0.0	0.0	100.0
Region																	
NORTH	2017–2021	13.9	39.6	40.6	5.9	47.7	52.3	30.5	20–39	84.7	9.8	5.5	91.6	8.4	9.3	26.0	64.7
EAST	2017–2019	22.5	16.9	58.3	2.3	59.3	40.7	30.0	20–39	85.9	5.8	8.3	87.4	12.6	0.4	31.3	68.3
SOUTH	2019–2020	2.7	25.5	42.7	29.1	55.5	44.5	32.6	20–39	42.7	25.2	32.1	72.2	27.8	10.1	36.1	53.8
WEST*	2014–2018	24.7	11.4	12.6	51.3	51.1	48.9	28.1	20–39	65.9	19.0	15.0	87.0	13.0	2.0	13.8	84.2

Remarks: NORTH: Denmark, Iceland; EAST: Czech Republic, Poland; SOUTH: Croatia, Portugal; WEST: Luxembourg, Germany; *ESTEBAN study (France) excluded for calculation European exposure values and geographical comparison.

(unadjusted) data, with some distinct regional differences within France (Fig. 1a). However, the concentrations adjusted for basic influencing factors (sample type, sex, age, smoking, education and sampling year) showed more unified concentrations across Europe, with smaller differences in GMs between the respective study areas (Fig. 1b). The adjusted GMs were 0.14 μg/g crt and 0.13 μg/g crt in Denmark and Iceland, respectively; 0.15 μg/g crt in Luxembourg; 0.22–0.24 μg/g crt in France; 0.19–0.22 μg/g crt in Germany; 0.149 μg/g crt in Poland and 0.168 μg/g crt in Czech; 0.16–0.17 μg/g crt in Croatia; and 0.20–0.21 μg/g crt for Portugal.

In accordance with the unadjusted mean Cd levels, the highest proportion of study participants exceeding the HBM-I value of 1 μg/L (Apel et al., 2017) was observed in the Polish and French studies (10.1% and 8.7%, respectively). In other countries, the percentage spanned between 0% and 2.4%, and the overall exceedance in the pooled population was 2.9% (Table 4). The age-dependent values (Lamkarkach et al., 2021) for relevant age groups of our study participants were exceeded by 16.4% participants of the total (pooled) population. The highest proportion of exceedances was again observed in Poland (33%) and France (43%), but also in Germany (36%). In one area in France, the percentage exceeded 50%. In other countries, the exceedance spanned between 1.4% (Denmark) and 8.7% (Czech Republic) (Fig. 2, Table 4).

If smokers were excluded from the study population (data not shown), the exceedance percentage was only slightly lower (15.3% in the pooled database), the highest was in France (39%), followed by Germany (35%) and Poland (33%). In the rest of the studies, the percentage of exceedances in non-smokers ranged from 0.4% in the Danish to 9.6% in the Czech study.

3.3. European exposure values

For derivation of European exposure values, we used survey design data analysis with country as a primary sampling unit (PSU). Because of the fact that the biomarker data in the French study was not quality assured by HBM4EU, this study was excluded from the calculation of European exposure values. The calculated levels are expressed per volume (μg/L) as well as per creatinine (μg/g creatinine) in order to make comparison with exposure values from other studies worldwide possible.

3.4. Geographic comparison

In order to compare the four geographic regions (North, South, West, East), survey data analysis was used as well (country = PSU), and additionally the models were adjusted for sample type, creatinine, sex, age, smoking, education and sampling year in order to take into account basic factors that could influence the difference in exposure levels between the countries/regions. According to linear regression, the difference between Western and Northern studies in adjusted estimated Cd levels in urine (μg/g crt) was 1.53-fold, and between Western and Southern studies 1.65-fold, however, the adjusted levels did not differ significantly between the regions ($p = 0.157$ and $p = 0.168$, respectively). Similarly, the estimated levels for the studies in Eastern Europe did not differ significantly from the Northern (1.42-fold difference, $p = 0.296$) and Southern studies (1.53-fold difference, $p = 0.265$). The difference between the West and East was 1.08-fold ($p = 0.832$), and the same between the North and South (1.08-fold, $p = 0.804$). The adjusted GMs with 95% CI are shown in Fig. 3.

3.5. Determinants of exposure

3.5.1. Basic determinants of exposure

The main influencing factors relevant for Cd exposure that were identified prior to the study were firstly checked for statistical significance and trends in the bivariate analysis (data not shown). In the second step, the influencing factors were included in the study-specific

Table 4
Cadmium concentration in urine in μg/L and μg/g creatinine in the pooled European database (All) and in each of the participating studies, indicated by the country names.

	N	N < LOD	N < LOQ	GM	95% CI	Min-Max	P5	P10	P25	P50	P75	P90	P95	N > HBMGV
Cd in urine (μg/L)														[a]**HBM-I**
Denmark	292	4	45	**0.123**	0.112–0.350	<LOD-1.39	0.033	0.041	0.075	0.127	0.217	0.325	0.433	3
Iceland	203	0	11	**0.135**	0.119–0.153	0.010–1.38	0.029	0.040	0.080	0.150	0.250	0.410	0.530	2
Czech R	300	0	0	**0.132**	0.122–0.142	0.019–0.801	0.046	0.053	0.087	0.138	0.205	0.303	0.336	0
Poland	228	0	0	**0.408**	0.369–0.450	0.021–2.67	0.115	0.158	0.261	0.435	0.705	1.01	1.16	23
Croatia	300	0	0	**0.175**	0.160–0.192	0.013–2.10	0.048	0.066	0.106	0.177	0.298	0.467	0.722	5
Portugal	295	12	14	**0.109**	0.098–0.120	<LOD-0.760	0.028	0.039	0.076	0.120	0.170	0.290	0.400	0
France	393	0	0	**0.365**	0.340–0.391	0.053–2.98	0.115	0.153	0.229	0.352	0.591	0.890	1.20	34
Luxembourg	210	–	15	**0.316**	0.288–0.347	<LOQ-1.30	<LOQ	0.120	0.210	0.350	0.520	0.675	0.890	5
Germany	289	–	0	**0.199**	0.186–0.213	0.053–1.11	0.077	0.096	0.131	0.200	0.285	0.451	0.593	2
Cd in urine (μg/g creatinine)														[b]**Age-dependent HBMGVs**
Denmark	282	4	45	**0.101**	0.094–0.109	<LOD-0.700	0.042	0.051	0.066	0.102	0.141	0.209	0.266	4
Iceland	203	0	11	**0.118**	0.109–0.128	0.026–0.758	0.051	0.059	0.075	0.116	0.172	0.231	0.316	7
Czech R	300	0	0	**0.104**	0.095–0.114	0.010–1.28	0.025	0.034	0.061	0.106	0.180	0.280	0.353	26
Poland	228	0	0	**0.364**	0.340–0.390	0.066–1.48	0.164	0.187	0.254	0.362	0.520	0.684	0.856	76
Croatia	300	0	0	**0.123**	0.114–0.133	0.017–0.785	0.042	0.050	0.080	0.125	0.189	0.277	0.361	9
Portugal	295	12	14	**0.094**	0.086–0.103	<LOD-0.771	0.023	0.041	0.064	0.104	0.147	0.218	0.280	4
France	393	0	0	**0.389**	0.360–0.420	0.055–8.86	0.123	0.155	0.241	0.369	0.598	1.08	1.71	168
Luxembourg	210	–	15	**0.183**	0.170–0.197	<LOQ-0.788	0.066	0.091	0.134	0.187	0.258	0.349	0.395	12
Germany	289	–	0	**0.267**	0.253–0.282	0.097–2.32	0.134	0.150	0.194	0.258	0.347	0.526	0.643	105

Remark: GM – geometric mean; CI – confidence interval; P5 – 5th percentile, P10 – 10th percentile, etc.; HBMGV – health-based guidance value.
[a] HBM-I value: concentration below which there is no risk for adverse health effects, and consequently, no need for action (Apel et al., 2017).
[b] Age-dependent alert values were derived by HBM4EU (Lamkarkach et al., 2021) to prevent exceeding the guidance value of 1 μg/g creatinine (crt) at later age (>50 years) and are based on kidney toxicity as critical target. Namely these are 0.2 μg/g crt for 11–20 years, 0.3 μg/g crt for 21–30 years and 0.5 μg/g crt for 31–40 years old adults.

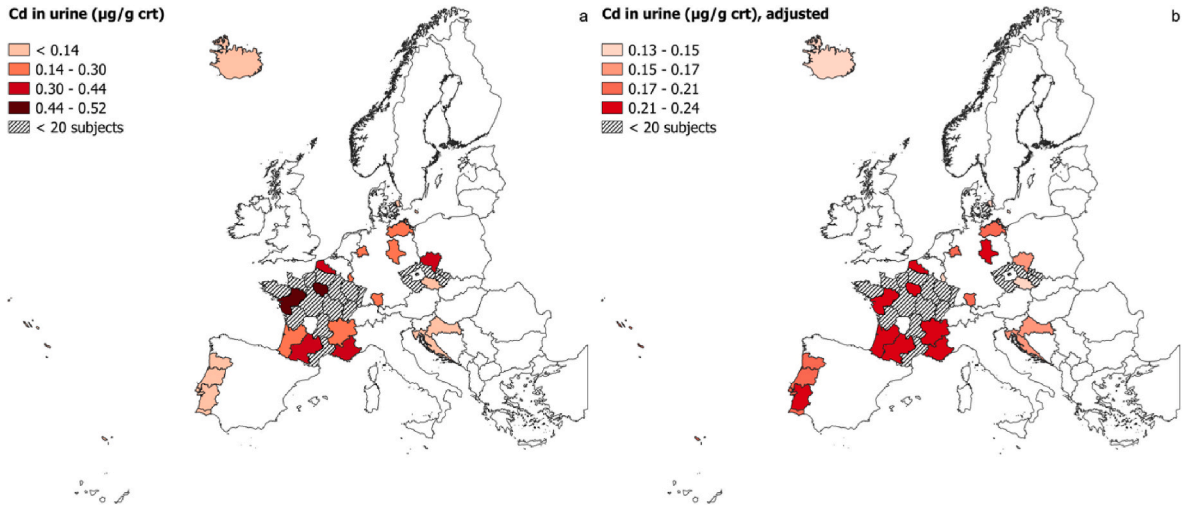

Fig. 1. Geometric means (GM) for Cd in urine (μg/g creatinine) per NUT2 area: (a) non-adjusted (n = 2500) and (b) adjusted for the main influencing factors (sample type, sex, age, smoking, education and sampling year) (n = 2088). GMs are given only for those NUTS2 with 20 or more participants.

multiple regression models (Table S2). The models revealed higher levels in women than in men and increasing Cd urinary levels with age in the majority of the studies. However, in the Polish study, association with sex and age was not significant (p = 0.119 and 0.178, respectively). Higher levels of urinary Cd in smokers than in non-smokers were observed only in three studies (Portugal, p < 0.001, France, p < 0.001, and Luxembourg, p = 0.022). Decrease in Cd levels with higher educational level was observed only in the Portuguese study, where the most obvious difference was between the low level of education and the other two levels (p = 0.009 and 0.059, respectively). With regard to the sampling year, the increasing trend in Luxembourg (p = 0.001) and decreasing trend in Germany (p = 0.002) were confirmed. In the other studies, no significant differences or trends were revealed with regard to the educational level or year of sampling, which might be due to unevenly distributed educational level and narrow sampling time range (Table 2). All study-specific models, except Polish, were highly statistically significant (p < 0.001) with 19%–34% of variability explained by the variables in the model. The model for the Polish study was insignificant (p = 0.103, R^2 = 0.04) (Table S2).

3.5.2. *Food-related determinants of exposure*

In addition to the basic influencing factors, some potential explanatory variables were checked for association with Cd levels in urine in a study-specific manner. They are summarized in Table S1. These variables were added to the basic models, presented in Table S2. Among the available variables, vegetarian food was observed as positively and at least marginally significantly associated with Cd levels in urine in the Czech and German studies (p = 0.071 and < 0.001, respectively).

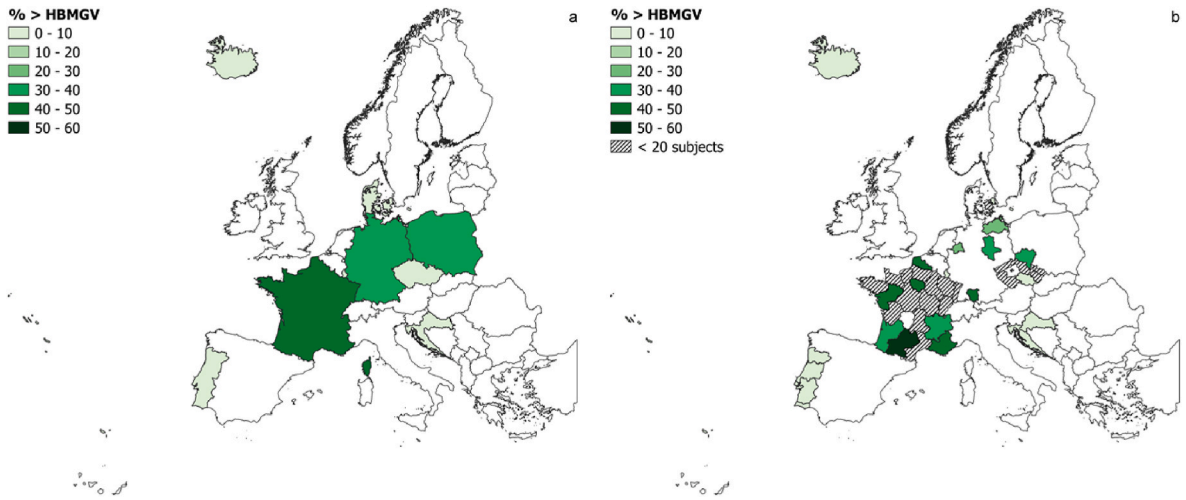

Fig. 2. Exceedance of age-dependent HBM-GVs in percentage of study population (a) per country and (b) per NUTS2. Percentages are given only for those NUTS2 with 20 or more participants.

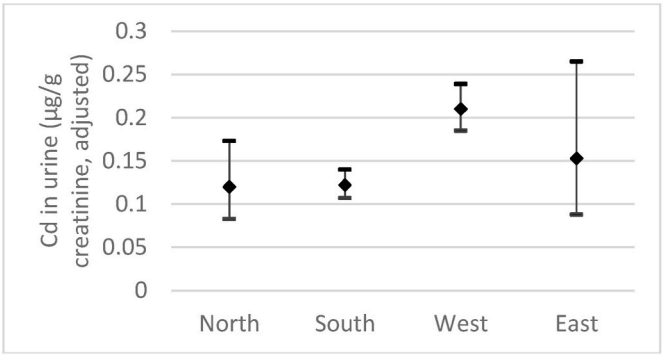

Fig. 3. Geographical comparison of adjusted Cd levels in urine (µg/g creatinine): GMs and 95% CI. The levels are adjusted for creatinine, sample type, sex, age, smoking, education and sampling year. Survey design was used (PSU = country). The French study (ESTEBAN) was excluded from the geographic comparison, because biomarker data was not assured by HBM4EU QA/QC.

Consumption of cereals was significantly associated with urine levels in the Polish study ($p = 0.028$). A significant trend was revealed also for organ meat consumption in the studies from Croatia and Luxembourg, but the trend was negative. However, it has to be noted, that there was limited availability of food-related data across different studies (Table S1). Frequency of local food consumption was available only for the Croatian study, and frequency of cereals consumption for the Icelandic, Czech, Polish, Croatian, and Luxembourg studies. Most covered was data for vegetarian diet, available in studies from Iceland, Czech Republic, Croatia, Portugal, France and Germany. Among these, very few participants reported to be vegetarians (3%), with the highest percentage in the German (7%), and the lowest in the Portuguese (0.7%) and French (1%). Organ meat consumption was available in studies from Czech Republic, Poland, Croatia, France, Luxembourg and Germany. Along with the dietary data, drinking water data was checked against Cd levels in urine, namely source (public, private well) and type of drinking water consumed by the subject (bottled, tap, ground or other type of drinking water). Marginal significance was found only in the French data, where the participants drinking water from 'other' sources had higher urinary Cd levels than those drinking bottled or tap water (Table S2).

3.5.3. Traffic-related determinants of exposure

As a potential traffic-related source of exposure, density of traffic in the residential area (no traffic, light traffic, intense traffic) was available from the questionnaire data for the Croatian and French studies. However, it was not found to be significantly associated with Cd levels in urine in none of the two studies (data not shown). Degree of urbanization was further checked in the models as a proxy for traffic density, and although available for all studies, it did not show any significance in relation to Cd levels in urine.

3.5.4. Pooled multilevel mixed model

In the last step, a multiple regression model was built for the pooled European population, which included all nine studies (Model 1, Table 6). Sex, age and smoking were confirmed to be highly statistically significantly associated with Cd levels in urine. The levels in women were 33% higher than in men, and they increased by 3% each year of life within the age range of the study participants. Smokers had 25% higher levels than non-smokers. Additionally, the levels were 14% lower in the participants with medium or high educational level in comparison to the ones with low level of education. With regard to the sampling year, a slight decreasing trend, 4% each year, was observed (Model 1, Table 6). As the participating studies differed in type of the urine sample collected, this factor was also included in the pooled model to control for potential influence of the sample type. Cadmium concentrations in daily and morning urine samples were somewhat higher than in spot urine samples, and concentrations in daily urine higher than the ones in morning urine, but none of the differences was statistically significant ($p = 0.214$, 0.126 and 0.260, respectively) (not shown).

Despite the fact that only 3% of the subjects declared themselves as vegetarians (among those that provided data on vegetarian food), vegetarians had 35% higher levels of Cd in urine than non-vegetarians with strong statistical significance (Model 2, Table 6). Other dietary variables were not found to be significant in the pooled model, which is partially also due to the above-mentioned fact that the data had very limited availability. However, organ meat consumption which had similar availability as vegetarian food (variable available in six studies, $n = 1976$) did not show any association with Cd levels in urine ($p = 0.906$). Traffic density was also not found to be significantly associated with Cd in urine in the pooled model ($p = 0.896$), and neither was the degree of urbanization ($p = 0.869$) (data not shown).

As part of sensitivity analysis, the model was applied on the subset of database with complete data on vegetarian diet ($n = 1631$) (not shown). The coefficients stayed exactly the same as shown in the Model 2 (Table 6). An additional model was checked applying the WHO creatinine criteria for urine levels exclusion based on creatinine levels (not shown). This model showed similar coefficients as shown in Model 2,

unless for vegetarian diet where the coefficient was even slightly higher (1.40, n = 1545). We also stratified the model based on the type of the urine sample - spot random sample and spot morning sample, while the model with daily urine sample type was not considered as it was only available for one country. The model with Cd concentrations measured in morning urine samples (n = 1264) showed the same trends and significance and also similar estimates of change (coefficients) as Model 1 (Table 6). The model with Cd concentrations measured in spot random samples (n = 922) showed somewhat different estimates of change, particularly for education and sampling year, where the trend was reversed in comparison with the Model 1 (Table 6) (not shown).

3.6. NUTS2 level-based variables

The variables collected at the NUTS2 level, namely Cd concentration in topsoil, percent cropland, application of phosphate fertilizer, Cd release to air and water, road density, and Cd point source release were added to the basic model. Step-wise inclusion of the listed variables was not possible, as they were not available for all studies and all NUTS2 areas. Therefore, the external (NUTS2) variables were checked for statistical significance by adding each one of them independently into the Model 1 shown in Table 6. As a result, five additional models were generated (Models 4–8, Table S3). The regression coefficients for associations between these variables and urinary Cd concentrations are presented in Fig. 4. Vegetarian diet is added to the figure for the sake of comparison of all potential sources of Cd exposure. All, except Cd concentrations in soil, were associated positively and significantly with the urinary Cd levels. Each 10 percent of cropland were associated with 3% increase in urinary Cd, but the association was marginally significant ($p = 0.060$), and 100 kg of phosphate fertilizer application per km^2 with 5.5% increase ($p < 0.001$). Road density and Cd release from point sources were also revealed significant for Cd exposure, with 27% increase for each km of roads per km^2 ($p < 0.001$), and 10% increase for each 1 kg Cd released per 100 km^2 ($p = 0.032$). Despite the substantial differences in sample size between the models, the models were robust with the main influencing factors having stable coefficients across the models (Table S3).

Finally, the external (NUTS2-based) variables were added to the Model 3 (Table 6). Unfortunately, among the statistically significant variables identified in Table S3, phosphate fertilizer data could not be used, as the sample size would be reduced to n = 215, with only two countries included. The estimated change due to the vegetarian diet was

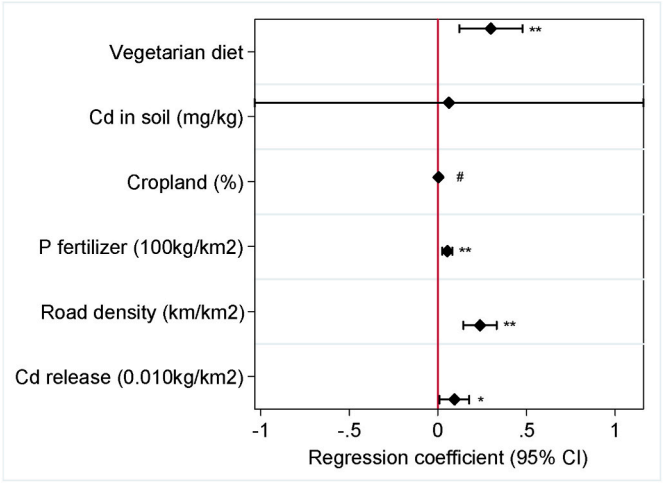

Fig. 4. Regression coefficients (95% CI) for association between potential explanatory variables and Cd concentrations in urine (ln μg/g crt) from the independent statistical models, each adjusted for creatinine, sample type, sex, age, smoking, education and sampling year. Level of significance marked as $^{\#}p<0.1$, $*p < 0.05$, $**p \leq 0.001$.

52%, and the coefficients for road density and Cd releases were 27% and 10%, respectively, the latter being marginally significant in the model. Coefficients for sex, age, smoking and sampling year were similar to the Models 1 and 2, while the educational level no longer showed significance with the urinary Cd levels in the Model 3. Without accounting for external information (Models 1 and 2), around 40% of variability explained by the variables in the model was between the countries, while in the Model 3, which included also external information, almost all variability was within the countries (Table 6).

4. Discussion

The paper deals with the assessment of current Cd exposure in the European population of adults and it is based on a study population which has been harmonized in terms of basic population characteristics: age (20–39 years), sex (female to male ratio 1:1), sample size (240–300), sampling period (2014–2021), exclusion of hotspots and patients, biomarkers of exposure (Cd concentration in urine), and partially also questionnaire data (socio-demographic characteristics, life style, health status, residential environment and diet). The harmonization process has been established within the HBM4EU project, which also coordinated the quality control procedure for measurement of Cd in urine to ensure comparability of analytical (biomarker) data. To ensure geographical comparability, two studies per region (North, East, South, West) were included. For identification of main sources and determinants of exposure, questionnaire data was used along with external data sources available at European level on the basis of the NUTS level (cropland percentage, phosphate fertilizer application, concentrations of Cd in soil, traffic density and point source release of Cd).

4.1. General characteristics of the study population

The study population of adults for assessment of Cd exposure (n = 2510) included 53.8% women and 46.2% men 20–39 years of age. According to the residential area 64.9% live in cities, 17.45% in towns/suburbs and only 17.65% in rural areas. The percentages are only slightly different from the percentages for the total HBM4EU Aligned Studies adult population (n = 3522) for which the characteristics were concluded to approach the characteristics of the general European population based on age matched EUROSTAT EU-28, 2017 data (Gilles et al., 2022). However, participants with no or low level of education (ISCED 0–2) were largely underrepresented (5%). The percentage of smokers in the study population was 18%, which is very similar to the percentage of every day smokers in the general European population in 2014 (19.9%) or 2019 (19.3%) (EUROSTAT EU-27). On a study level, some characteristics deviated from the country-level EUROSTAT statistics, namely level of urbanization, ISCED and particularly smoking. However, when comparing the characteristics on the regional level, the percentages better reflected the European situation (lower percentage of smokers in the northern countries and higher in some southern countries).

4.2. Exposure levels

The HBM4EU Aligned Studies is the second HBM survey that was harmonized on a European level in terms of performing comparable measurements of Cd in urine. The first pan-European HBM project - DEMOCOPHES produced harmonized measurements of Cd in urine in mother–child pairs from 16 European countries sampled in 2011–2012 (Berglund et al., 2015; den Hond et al., 2015). Results of the population group of women from the DEMOCOPHES study (n = 1632, 24–52 years) (den Hond et al., 2015) were compared to the results of women from the present study (n = 1350, 20–39 years) for those countries that participated in both studies (Table S4). The GMs for the overall group of women were the same in both surveys: being 0.20 μg/g crt. Comparing only non-smoking mothers, GM for the HBM4EU Aligned Studies was

0.20 μg/g crt and for DEMOCOPHES 0.18 μg/g crt (Berglund et al., 2015). In both surveys, the highest levels were observed for Poland and the lowest for Denmark.

The DEMOCOPHES Polish study reported a GM of 0.38 μg/g crt in all mothers and 0.36 μg/g crt in non-smoking mothers (Berglund et al., 2015; den Hond et al., 2015). Practically the same GM levels were observed in the HBM4EU Polish dataset (0.38 μg/g crt, both all and non-smoking women) (Table S4). On the lower exposure end, Denmark reported a GM of 0.12 μg/g crt for all mothers in DEMOCOPHES and 0.11 for non-smoking ones, while in HBM4EU the GM for all female participants was 0.14 μg/g crt and 0.13 μg/g crt for non-smoking ones (Berglund et al., 2015; den Hond et al., 2015) (Table S4). Similar to the Polish and Danish studies, also Luxembourg shows stagnating levels in comparison to the DEMOCOPHES assessment. In the latter, all participating mothers had exactly the same GM for Cd in urine as HBM4EU female participants from Luxembourg (0.22 μg/g crt), and the situation repeated for non-smoking women (both 0.21 μg/g crt) (Berglund et al., 2015; den Hond et al., 2015) (Table S4).

Another country that participated in both harmonized surveys was Czech Republic. Results for this country are consistent with the decreasing time trend reported from the observations of blood Cd concentrations in the period from 1996 to 2009 (Černá et al., 2012). The levels of 0.4 μg/g crt in women and 0.3 μg/g crt in men were reported for the period 2005–2009 (n = 1227), 0.21 μg/g crt in women in the DEMOCOPHES study (2011–12) (Berglund et al., 2015; den Hond et al., 2015) and in the present study 0.11 μg/g crt (in both studies GMs were equal in all and in the non-smoking women) (Table S4). A slight decreasing trend can be observed also for Portugal, where the GM for women was 0.16 μg/g crt in DEMOCOPHES and 0.11 μg/g crt in HBM4EU (Table S4).

The German DEMOCOPHES Cd data was re-analyzed later to achieve comparability with the DEMOCOPHES European study population, and reported lower levels for mothers (0.18 μg/g crt) (Schwedler et al., 2017) as were found in the HBM4EU Aligned Studies female participants of the German study (Table S4). The aligned studies population is part of the Environmental Specimen Bank (ESB) program active from 1980 and publicly available data of the ESB indicate that Cd in 24-h urine has generally decreased between 1990 and 2019 (UPB, 2022), but unchanged concentrations (expressed per volume) were observed for the last two decades, with slight increase in 2020 and 2021 (Becker et al., 2013; UPB, 2022). A similar situation was observed in a recent comparison of urinary Cd data for children in the German Environmental Survey (GerES), where overall, participants in GerES V (2014–2017) had about 15% lower Cd concentrations than GerES II (1990–92) children and adolescents, but not lower then GerES IV participants (2003–2006) (Vogel et al., 2021).

France was not part of the harmonized DEMOCOPHES survey, but as apparent from the literature data, the levels in this country seem to stagnate as well. Nisse et al. reported a GM of 0.39 μg/L Cd in urine of participants from Northern France for the period 2008–2010 (n = 1992), which is similar to the French study included in the aligned survey (0.37 μg/L, Table 3) (Nisse et al., 2017).

The above listed comparisons show somehow varying trends between the countries, but there is firm evidence indicating that overall Cd exposure levels in the general population are currently not decreasing markedly. The latter can be further observed from another HBM program, the Flemish Environment and Health study (FLEHS) representative for Flanders, the northern part of Belgium. Although in adults, urinary Cd levels decreased from the first (FLEHS I, 2002–06) to the third cycle (FLEHS III, 2012–15) (Schoeters et al., 2017), teenagers showed a decrease in blood Cd concentrations from FLEHS I to FLEHS II (2007–11) (Vrijens et al., 2014), but further comparison with succeeding cycles conducted up to year 2020 (FLEHS III and FLEHS IV) showed stable levels in blood with 40% teenagers exceeding the established health based HBM guidance values (HBM-GVs) for urinary concentrations and the corresponding age in the last sampling period, 2016–2020 (Schoeters et al., 2022). The authors refer to continuous efforts to reduce the sources and limit the exposures in humans (regulations) that were initially reflected in decreasing internal Cd levels (Schoeters et al., 2017, 2022), while stagnation or even increase in recent decade may be ascribed to unchanged nutritional habits and persisting Cd levels in soil, particularly in historically contaminated or industrial sites (Becker et al., 2013; Schoeters et al., 2022). Moreover, the data on phosphate fertilizer consumption per countries available for years from 2000 to 2018 (Eurostat) showed initial marked decrease in consumption from 2000 to 2009 for all countries except Poland, followed by somewhat varying trends from 2009 onwards (Fig. S2). Although the reason(s) for the observed trends could not be definitely explained, the observations provide firm evidence that the regulations are still required to protect humans from elevated exposure to Cd.

Moreover, the exceedance of HBM-GVs was evident in all studies of the HBM4EU Aligned Studies, in the total study population 16.4% of participants presented levels above the age-dependent HBM-GVs, recently derived by Lamkarkach et al. (2021) to protect from kidney dysfunction at later ages. The exceedance was particularly high in the Polish, French and German studies, with over one third of participants exceeding the value that is protective for risk of adverse kidney effects (Fig. 2a). According to the NUTS2 level information (Fig. 2b) we can see that in all areas (with n > 20) of these three countries, there is one third of the population or more at hypothetical risk for kidney effects: in the French study the exceedances ranged from 31% to 56%, in the German study from 28% to 43%, while the Polish study was represented only by one NUTS2 area (33%). According to the exceedances observed in the DEMOCOPHES (den Hond et al., 2015) and HBM4EU Aligned Studies (subgroup of women) based on the HBM-I values (1 μg Cd/L urine) the percentage has stayed at the same level in the last decade (2.9% and 3.0%, respectively).

These results are in line with the latest EFSA report, where a medium estimate for weekly intake for adults was 1.77 μg/kg b.w. (range 1.50–2.23 μg/kg b.w.) and P95 3.13 μg/kg b.w. (range 2.47–4.81 μg/kg b.w.). The latter is above the current tolerable weekly intake (TWI) of 2.5 μg/kg b.w. and confirms that adults at the 95th percentile exposure could exceed health-based guidance values on account of dietary intake of Cd (EFSA, 2012).

When the levels were adjusted for the main influencing factors (sample type, age, sex, smoking, education and sampling year) and compared geographically, smaller differences in mean levels were revealed between countries and/or regions (Fig. 1). Given that the 95% confidence intervals were sufficiently narrow, the results provide evidence of more or less uniform exposure across Europe, with somewhat lower levels in the North.

On a global scale, the HBM4EU population mean level for Cd in urine (0.15 μg/g crt, Table 5) was equal to the mean for the Canadian population group of 20–39 years old adults sampled in 2018–2019 (GM 0.15 μg/g crt, 95% CI 0.12–0.18 μg/g crt, n = 329), and somewhat higher than the mean for the adults of the same age sampled in 2016–17 (0.12 μg/g crt, 95% CI 0.10–0.14, n = 372) (Health Canada, 2021). Here, a similar situation can be observed as for Europe – initial decrease of concentrations from the beginning of the HBM program, but stagnation or even increase in the most recent campaigns as evidenced from the 6th survey cycle report (Health Canada, 2021). In the USA, the stagnating trend is evident for the last decade, with mean level in adults of 20 years or more being higher than in the HBM4EU population in the two latest sampling periods: 2015–2016 (0.190 μg/g crt, 95% CI 0.175–0.205, n = 1792) and 2017–2018 (0.189 μg/g crt, 95% CI 0.175–0.205, n = 1707) (CDC, n.d.). In the Korean National Environmental Health Survey, a downward trend since 2008 has been observed based on Cd concentrations in blood (Seo et al., 2015), however in the last cycle (2015–2017) the GM for spot urine was 0.36 μg/L (≥19 years of age) (Jung et al., 2022), which is considerably higher than in Europe or North America. The authors explain the levels with very frequent consumption of rice, which is a notable staple of the East Asian diet, and the Korean

Table 5
Exposure levels for the European population calculated using survey data analysis with country as primary sampling unit (PSU). The levels were **not** adjusted for basic influencing factors.

		n	Cd in urine (μg/L)		n	Cd in urine (μg/g creatinine)	
			GM (95% CI)	**P95 (95% CI)**		**GM (95% CI)**	**P95 (95% CI)**
Unstratified	All	2117	0.17 (0.12–0.25)	0.75 (0.69–0.81)	2107	0.15 (0.10–0.22)	0.53 (0.50–0.58)
Region	North	495	0.13 (0.12–0.14)	0.49 (0.43–0.57)	485	0.11 (0.09–0.12)	0.29 (0.26–0.33)
	South	595	0.14 (0.09–0.21)	0.52 (0.47–0.59)	595	0.11 (0.08–0.14)	0.33 (0.29–0.36)
	West	499	0.24 (0.16–0.36)	0.70 (0.62–0.78)	499	0.23 (0.16–0.32)	0.57 (0.51–0.64)
	East	528	0.21 (0.08–0.58)	0.94 (0.81–1.13)	528	0.18 (0.06–0.54)	0.69 (0.62–0.80)
Degree of urbanization	Cities	1441	0.18 (0.12–0.27)	0.77 (0.70–0.85)	1437	0.16 (0.10–0.27)	0.59 (0.54–0.65)
	Towns/suburbs	323	0.17 (0.10–0.30)	0.67 (0.56–0.80)	318	0.12 (0.09–0.17)	0.35 (0.31–0.40)
	Rural areas	336	0.16 (0.09–0.27)	0.60 (0.51–0.70)	336	0.12 (0.09–0.16)	0.36 (0.32–0.41)
ISCED	Low	117	0.15 (0.12–0.20)	0.74 (0.44–1.26)	113	0.11 (0.08–0.15)	0.39 (0.27–0.60)
	Medium	575	0.17 (0.10–0.29)	0.77 (0.67–0.89)	575	0.13 (0.08–0.22)	0.56 (0.47–0.67)
	High	1414	0.17 (0.13–0.24)	0.71 (0.65–0.78)	1408	0.16 (0.10–0.24)	0.54 (0.50–0.59)
Sex	Female	1134	0.18 (0.12–0.27)	0.79 (0.71–0.88)	1134	0.17 (0.11–0.27)	0.61 (0.56–0.67)
	Male	983	0.16 (0.12–0.22)	0.67 (0.60–0.76)	973	0.12 (0.08–0.18)	0.40 (0.37–0.44)
Smoking	No	1763	0.17 (0.11–0.24)	0.71 (0.65–0.78)	1756	0.14 (0.09–0.22)	0.53 (0.49–0.57)
	Yes	335	0.21 (0.15–0.30)	0.87 (0.72–1.06)	332	0.16 (0.11–0.22)	0.62 (0.50–0.77)

Remark: ESTEBAN data collection (France) excluded from calculations of European exposure values.

Table 6
Multilevel mixed regression model for the pooled European population with study as a random factor. The estimates are expressed as the fold change in Cd concentration for unit increase of the covariate.

Cd in urine (μg/g crt)	Estimate (95% CI), Model 1	Estimate (95% CI), Model 2	Estimate (95% CI), Model 3
N	*2475 (9 studies)*	*1631 (6 studies)*	*424 (3 studies)*
overall p-value	*<0.001*	*<0.001*	*<0.001*
var $_{BETWEEN}$	*43%*	*39%*	*<0.01%*
Age (years)	1.03 (1.02–1.04) **	1.04 (1.03–1.04) **	1.02 (1.00–1.03) **
Sex (F vs. M)	1.33 (1.26–1.40) **	1.32 (1.24–1.41) **	1.35 (1.21–1.50) **
Smoking (yes vs. no)	1.25 (1.17–1.33) **	1.26 (1.16–1.36) **	1.24 (1.09–1.41) **
ISCED - low	1.00	1.00	1.00
ISCED - medium	0.86 (0.76–0.97)*	0.75 (0.64–0.88) **	0.67 (0.30–1.45)
ISCED - high	0.86 (0.76–0.96)*	0.75 (0.64–0.87) **	0.55 (0.25–1.20)
Sampling year	0.96 (0.93–1.00)*	0.94 (0.91–0.98) **	0.93 (0.89–0.97) **
Vegetarian (yes vs. no)	–	1.35 (1.13–1.61) **	1.52 (1.19–1.93) **
Road density (km/km^2)	–	–	1.37 (1.22–1.54) **
Cd release (kg/ 100 km^2)	–	–	1.10 (1.00–1.20) #

#p < 0.10, *p < 0.05, **p < 0.01.
Model 1 = adjusted for creatinine, sample type, age, sex, smoking, education, and sampling year (all studies).
Model 2 = Model 1 + additionally adjusted for vegetarian diet (CZ, DE, FR, CRO, IS, PT).
Model 3 = Model 2 + additionally adjusted for road density and Cd release (CZ, DE, FR).

general population consuming even more frequently than populations from other Asian countries (Jung et al., 2022).

4.3. Determinants of exposure

The basic demographic and life-style factors of Cd exposure, namely sex, age, smoking and education are well recognized from previous HBM studies and (inter)national programs and were selected as the main potentially influencing factors of exposure. As such, they were included in the simple bivariate statistical analysis to check significance and trend for each study separately and further on in the basic regression models, both study-specific and pooled. They were also applied in the geographical comparison of exposure levels to better reflect dietary and environmental determinants of exposure, which might differ between the countries/regions in Europe. The type of urine sample (spot random urine, morning urine, daily urine) was also included in the statistical models and geographical comparison in order to control for potential influence of the sample type on Cd levels, but it was not our aim to explore the influence itself.

As expected, higher levels were observed in women than in men (33%), difference that is typically observed in adult healthy populations, and reflected by the urine as well as blood concentrations of Cd (CDC, n.d.; Černá et al., 2012; Health Canada, 2021; López-Herranz et al., 2016; Snoj Tratnik et al., 2019). The main reason are the lower iron stores (expressed as lower ferritin concentrations) in women in comparison to men, which enhances uptake of Cd as the two metals are known to have similar absorption mechanism (Lee and Kim, 2014). The sex-related difference was well established for all participating studies, with borderline significance in the Polish study, where women represented only one third of the study population.

Increasing levels of Cd in urine or blood with age are expected due to the accumulation throughout the lifetime (ATSDR, 2012) and have been observed in various national or regional HBM studies (Castaño et al., 2012; CDC, n.d.; Health Canada, 2021; Nisse et al., 2017; Snoj Tratnik et al., 2019), including the pan-European DEMOCOPHES survey (den Hond et al., 2015), as well as in the HBM4EU Aligned Studies (overall 3% increase per life year) where the age range was smaller (20–39 years) than in the DEMOCOPHES (20–49 years). Within the HBM4EU, only the Polish study did not show significant association between urinary Cd levels and age of participants.

Among the basic influencing factors, smoking was confirmed to be the major determinant with 25% higher urinary levels in smokers than in non-smokers (Table 6). This is consistent with the fact that tobacco plants hyperaccumulate Cd, resulting in high concentrations in their leaves independent of the soil Cd content and reports of many other

regional, national and international studies, including DEMOCOPHES where smoking mothers had 31% higher levels in urine than non-smoking mothers (den Hond et al., 2015). However, the significance on the study level was only evident in the studies with one of the highest proportion of smokers - Portugal, France and Luxembourg (Table 3), which were also the only studies with observed association between urinary Cd concentrations and number of cigarettes smoked per day (data not presented). The lack of significant associations in other participating studies could be explained by insufficient statistical power due to low percentage of smokers and/or the fact that urinary Cd concentrations reflect long-term accumulation of Cd in kidney cortex, while blood Cd concentrations better reflect current exposure (Nordberg et al., 2015) and as it was demonstrated on the basis of USA NHANES data (Adams and Newcomb, 2014), there is a noticeable overlap between the two. In fact, some previous studies reported the absence of difference in urinary Cd levels between smokers and non-smokers, while for blood levels the difference was significant (Baeyens et al., 2014; Snoj Tratnik et al., 2019). Moreover, while in the DEMOCOPHES study group of mothers, passive smoking at home was found to be associated with higher Cd levels in urine of non-smokers (Berglund et al., 2015), this was not reproduced in the present study, neither in the total population of non-smokers ($p = 0.608$), the group of non-smoking women ($p = 0.802$), nor in the study specific models (data not presented). This might be explained partially by the above-mentioned discrepancy between the two biomarkers of exposure, but also by the fact that data on passive smoking was available only for six studies and data on frequency of exposure to passive smoking only for three, and among them very few were exposed to passive smoking daily (2%). For example, Vogel et al. (2021) reported absence of association in case urinary Cd was used, but association was found with blood Cd levels in those who stayed daily in rooms at home where other people smoked. Clearly, blood Cd concentrations appear to be more reliable in relation to smoking and/or passive smoking, particularly in cases of limited statistical power or lack of fully harmonized questionnaire data.

Smoking has been discussed as a factor that might result in higher Cd exposure in people with lower educational level due to a higher proportion of smokers (Baeyens et al., 2014) and indeed significance of educational level did not persist after adjusting for smoking in the recent Flemish study including adolescents (Schoeters et al., 2022). However, at the same time increased Cd levels can be associated with high education due to increased consumption of vegetables (Vogel et al., 2021). In the present study, independently of smoking, lower levels of Cd in urine were associated with higher levels of education (Table 6). The effect of education was not evident on a study level, except in Portugal, which makes sense as in the latter the education was more equally distributed among the three levels than in the other participating studies (Table S2, Table 3). Similar results were reported in other studies (e.g. den Hond et al., 2015; Berglund et al., 2015) and could be that the variability in urinary levels is shared by both factors, but also some other factors related to diet might be part of the cause.

Among other potential explanatory variables relevant for Cd exposure that were checked for significance in the multiple regression models, vegetarian diet was the only dietary variable available from questionnaires that was revealed as strongly significantly associated with Cd in urine in the pooled population – vegetarians had 35% higher levels than non-vegetarians (Table 6). Vegetables are one of the main sources of Cd exposure in non-smokers (EFSA, 2009; Nordberg et al., 2018), which, together with presumption that vegetarians consume higher quantities of plant-based food than non-vegetarians, well explains our observation. However, there are only a few HBM studies reporting vegetarian-relevant results. Just recently, a similar observation was reported for children participating in the German GerES V program, with vegetarians having 35–41% higher levels of Cd in urine (Vogel et al., 2021). The authors stated that the participating children with a vegetarian diet had a significantly lower ferritin, which increases Cd absorption (EFSA, 2009). The most recent EFSA report on the cadmium dietary exposure in the European population (EFSA, 2012) provides estimates based on the Cd levels in food items and detailed frequencies of consumption and shows that food consumed in larger quantities had the greatest impact on dietary exposure to cadmium. The highest contribution to exposure across different age groups was on account of grains and grain products (27%), followed by vegetables and vegetable products (16%) and starchy roots and tubers (13%). For adults the respective percentages were 27%, 17% and 12%, whereas meat and edible offal accounted for 8.7% contribution to the overall exposure (EFSA, 2012). From these estimates it is clear that plant-based dietary items are by far the major exposure source, particularly if the diet is exclusively vegetarian and includes higher quantities of plant-based food as opposed to meat-including diet.

Among specific dietary sources available from the questionnaire data, only cereals in the Polish study were identified as significantly associated with the urinary Cd levels (Table S2). Cereals belong to the EFSA food category with largest contribution to exposure with bread and rolls identified as the major source (EFSA, 2012). Unfortunately, the reasons behind study-specific findings cannot be discussed further and with reference to country specifics/characteristics as the data were not available for all participating studies and also EFSA estimates are not provided for all countries.

In line with the hypothesis that application of mineral fertilizer based on phosphate may contribute to Cd exposure in the general population via diet, the association between urinary Cd concentrations and data on phosphate fertilizer application in kg/km^2 was confirmed, and with marginal significance also percentage of cropland in the area (Fig. 4). Direct association between soil and urine concentrations was not revealed, but it has to be noted that the range of mean Cd concentration in soil in the areas that were included in the present analysis was narrow, i.e. 0.05–0.20 mg/kg, and also that the levels are not given exclusively for agricultural land. Cropland and fertilizer data appear to be more relevant as they are directly linked with the exposure of consumers.

Fertilizers have been recognized as one of the main sources of Cd contamination through the food chain, and as demonstrated by some recent studies, plant-available Cd concentrations in soils amended with P fertilizer (and compost) gradually increase over decades of application (Park et al., 2021) and that the control of Cd input into the food chain is needed to stop the increase over time due to Cd accumulation in the part of the population likely to be overexposed to Cd through food (Carne et al., 2021). By the use of probabilistic mass-balance model, the authors simulated the transfer of Cd from agricultural soil to food consumed by the French population and account for variability in French soils, local specificities and agricultural practices and estimated that content of Cd in mineral phosphate fertilizers should not exceed 20 mg/kg P_2O_5 in order to achieve reduction of Cd content in agricultural soils and ensure the exposure of consumers does not exceed the health threshold values (Carne et al., 2021). The level is 3-times lower than the current concentration for phosphate fertilizers of 60 mg Cd/kg P_2O_5, adopted by the EC in view of a potential application of this regulation in 2022 (Regulation (EU) No 2019/1009).

Although the data analysis in the present paper does not exclusively deal with population groups consuming locally-grown crops and intake of crops imported from other regions cannot be excluded, the observed combined associations based on HBM and external data clearly indicate the importance of phosphate fertilizers contribution within the dietary exposure pathway in the general population. Together with the considerable share of population above the HBMGVs, these results support the findings from the probabilistic modelling (Carne et al., 2021) and confirm the need for control/reduction of Cd input into the food chain.

In addition to the diet-related intake, our results demonstrated traffic and industrial releases as significant contributors to Cd exposure in the general population. Traffic intensity close to home has been shown as a statistically significant determinant for blood Cd in children from six European countries, whose Cd measurements had also undergone strict

QA/QC procedures and were performed centrally and varied little between the countries (Hrubá et al., 2012). The authors explanation follows the fact that, although in small amounts, vehicle tires contain zinc contaminated by Cd. In the present study, traffic density in the participant's residential area was available through the post-harmonized questionnaire data with three categories (no traffic, light traffic, intense traffic) and through the Eurostat database (km roads/km^2). Statistically significant association with Cd concentrations in urine was observed for the latter, which demonstrates that NUTS2 level external information is superior to the data from questionnaires, reported by participants. Industrial point-source release of Cd to air and water is an additional potential source of Cd exposure, which is available from the E-PRTR database, and has been used as an external dataset for interpretation of HBM data before – in the DEMOCOPHES study (Smolders et al., 2015). There, the association between annual releases on a NUTS2 levels and mother's or child's urine Cd concentrations has not been observed. The association has been re-analyzed in the present study together with other potential sources of exposure, and it was revealed as significant (Fig. 4, Table 6). Furthermore, it showed that differences in exposure were mostly on account of variability within the countries/studies.

It is important to note that for a more realistic exposure characterization at environmentally-relevant levels of exposure as observed for Cd in Europe and also globally, it is crucial that all potential sources of exposure from different pathways are included in the assessment, as HBM data provides cumulative exposure (Knudsen et al., 2012; Smolders et al., 2009). Moreover, use of external data that was based on a NUTS2 spatial resolution rather than national (Fig. S1), provided data with higher precision on potential sources of exposure, and therefore enabled a refined association study also from a spatial perspective.

4.4. Strengths and limitations

Clearly, the most important strengths of the present study are comparable measurements of Cd in urine, which have undergone strict QA/QC procedures, harmonized study population characteristics across the participating studies, sample size and the fact that all four geographical regions (North, South, West, East) of Europe were covered. Another advantage is that we were able to perform refined analysis of exposure, by considering multiple sources of exposure (socio-demographic determinants, dietary and external environment-related determinants) simultaneously obtaining more realistic assessment of exposure.

Despite the achieved high degree of harmonization on a European level, there are still some important limitations which remain to be further addressed. The first is partial (post)harmonization of questionnaire data, resulting in limited availability of questionnaire data across studies, and the second is a lack of external data, which is not available at the same level of resolution and not for all NUTS areas. As a consequence, the statistical models were not entirely comparable between each other (each was built on a different dataset) and it was not possible to include all available potential sources of exposure into a single model. Another issue is related to urinary Cd concentrations and standardization of the levels for urine dilution and the risk of underestimating the exposure due to creatinine over-compensation (Hoet et al., 2016). We could overcome this issue by using standardization based on specific gravity, which appears to be a more reliable alternative in the context of environmental exposures, without the risk of over-adjustment and with fewer uncertainties associated with its use (Hoet et al., 2016; Stajnko et al., 2017). Unfortunately, measurements of specific gravity could not be used in the present study, as they were only available for one study. Availability of Cd concentrations in blood would allow further refinement of exposure assessment, with emphasis on recent exposures.

5. Conclusions

The HBM data of nine countries harmonized at the European level showed a small degree of variability in mean urinary Cd concentrations in adults across the four geographic regions of Europe, particularly when adjusted for the main influencing factors (sex, age, smoking, education and year of sampling). There was no clear time trend in exposure observed and the HBM-GVs for Cd in urine were exceeded by 16% of the study participants. Exceedances differed across the study areas, with the largest percentage of exceedance observed in the French and Polish studies, where approximately one third of the study population was above the age-dependent values.

To our knowledge, this study was the first to confirm, based on the HBM data, that the mineral phosphate fertilizers are a significant source of Cd exposure through the diet in Europe. Furthermore, vegetarian diet might increase exposure to Cd even more than smoking, which calls for attention in case of promoting vegetarian diet. In addition to EFSA's estimates on the food categories contributing the most to the exposure (EFSA, 2012), higher degree of traceability of plant-based dietary items is needed on a sub-national (regional) level. Besides the smoking and diet-related sources, traffic and Cd releases from industrial facilities remain a significant source of exposure to Cd in the general population.

The findings of the study support the recommendation by EFSA to reduce Cd exposure as also the estimated mean dietary exposure of adults in the EU is close or slightly exceeding the tolerable weekly intake. Results also indicate that current regulations are not protecting the general population sufficiently.

Author contributions

Conceptualization, J.S.T, D.K., M.H., L.G., E.G., O.S. and G.S.; data curation, L.R.M., L.G.; data analysis and visualization, J.S.T., D.K.; supervision, E.G., G.S., M.H.; writing—original draft, J.S.T, D.K.; writing—review and editing, S.N., M.R., A.V.N, M.K.-G., T.W., M.E.-L, L.G., G.S., E.G.; study PIs, A.-M.A., A.J., E.J., K. Ó., J.K., L.A., B.J., W.W., N.J. H., S.N., I.C., L.R., M.R., A.V.N, B.A., M.K-G., T.W. All authors have read and agreed to the published version of the manuscript.

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Informed consent statement

Informed consent was obtained from all subjects involved in the study. The detailed information on the ethics committees is provided by Gilles et al. (2022).

Declaration of competing interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2022.114050.

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