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Burden of osteoporosis and costs associated with human biomonitored cadmium exposure in three European countries: France, Spain and Belgium

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ABSTRACT

Cadmium (Cd) is a toxic heavy metal widespread in the environment leading to human exposure in particular through diet (when smoking is excluded), as documented by recent human biomonitoring (HBM) surveys. Exposure to Cd at environmental low-exposure levels has been associated with adverse effects such as renal toxicity and more recently bone effects. The implication, even if limited, of Cd in the etiology of osteoporosis can be of high importance at the population level given the significant prevalence of osteoporosis and the ubiquitous and life-long exposure to Cd. Therefore, the osteoporosis cases attributable to Cd exposure was estimated in three European countries (Belgium, France and Spain), based on measured urinary Cd levels from HBM studies conducted in these countries. The targeted population was women over 55 years old, for which risk levels associated with environmental Cd exposure were available. Around 23% of the cases were attributed to Cd exposure. Moreover, in a prospective simulation approach of lifelong urinary Cd concentrations assuming different intakes scenarios, future osteoporosis attributable cases were calculated, based on urinary Cd levels measured in women aged under 55. Between 6 and 34% of the considered populations under 55 years were at risk for osteoporosis. Finally, the costs associated to the burden of osteoporosis-related fractures attributable to Cd for each country targeted in this paper were assessed, standing for a major contributing role of Cd exposure in the overall social costs related to osteoporosis. Absolute costs ranged between 0.12 (low estimate in Belgium) and 2.6 billion Euros (high estimate in France) in women currently over 55 years old and at risk for fractures. Our results support the importance of reducing exposure of the general population to Cd.

1. Introduction

Cadmium (Cd) is a non-essential toxic metal widely distributed in the environment. It is naturally abundant but enriched through e.g. industrial and agricultural activities. Measured levels of Cd in agricultural products vary widely, depending on soil type, plant varieties, growing conditions, climate and agricultural methods. Anthropogenic sources, including smelter emissions and the application of fertilizers and sewage sludge to land, may contribute to the contamination of both soils and crops. Previous studies indicated that Cd-bearing fertilizers, especially manures, are an important source of Cd entering into the soil (Bergkvist et al., 2003; Grant and Sheppard, 2008; IPCS 1992). Cadmium occurs in the environment as a divalent cation and exhibits higher rates of soil-to-plant transfer than other toxic heavy metals (e.g. lead or mercury). Isotope dilution analysis shows that for most soils, indigenous Cd is equally available to plants as freshly added Cd. This makes Cd a food-chain contaminant of great concern. Next to foodstuff also cigarette smoke is a major source of Cd exposure for the general population (Satarug and Moore 2004). Cadmium is classified by the International Agency on Cancer (IARC) as carcinogenic to humans (Group 1) based on sufficient evidence that long-term occupational exposure to Cd contributes to the development of lung cancer (IARC 1993).

Safety limits of Cd in the environment and foodstuffs were established to safeguard population health. Concerning foodstuffs, Regulation

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No. 1881/2006 of the European Commission (EC) sets Cd maximum levels ranging from 0.05 mg/kg (some meat products and vegetables) to 1.0 mg/kg (kidney from some animals, bivalve molluscs and cephalopods) (EC, 2006). A safety limit of 3 mg Cd/kg dry matter is proposed since 2016 by the EC for Cd in inorganic fertilisers with a total phosphorus content of less than 5% phosphorus pentoxide (P_2O_5) equivalent by mass (EU 2016), while a limit of 5.0 μg/L is applied to drinking water (Council Directive 98/83/EC 1998).

In 2009, the European Food Safety Authority (EFSA) performed a risk assessment for dietary Cd exposure by comparing the calculated dietary Cd exposures of the EU general population with the recommended TWI (Tolerable Weekly Intake) of 2.5 μg/kg bw based on kidney function (EFSA 2009). Conclusions were that the mean Cd exposure for adults across Europe was close to, or slightly exceeding the TWI. The exposure of some subgroups of the population, such as vegetarians, children, smokers and people living in highly contaminated areas revealed the exceedance of the TWI by about 2-fold. As the TWI is based on an early indicator of changes in kidney function and not on actual kidney damage, the risk for adverse effects on kidney function at dietary exposure across Europe was considered low at the individual level. Nevertheless, EFSA concluded that the current human exposure to Cd at the population level should be reduced (EFSA 2009; EFSA 2012).

According to the scientific literature, exposure to Cd may not only cause toxic effects to kidneys but also to bones, which became evident with the outbreak of the Itai-Itai disease in a highly Cd-polluted area of Japan, after World War II (Buha et al., 2019; James and Meliker 2013; Nordberg 2004; Nordberg et al., 2018; Staessen et al., 1999). The Itai-Itai disease is characterised by osteomalacia, osteoporosis and multiple bone fractures besides renal dysfunction (WHO 1992). Since then, increasing evidence for the effect of Cd on bones at low-doses brought the scientific community to consider this effect as possibly occurring below the threshold value of urinary Cd (U–Cd) set by EFSA at 1.0 μg/g creatinine (crea) based on kidney effects (Alfven et al., 2000; Nordberg et al., 2018; Wallin et al., 2016).

Cadmium is a cumulative toxicant, of which the body burden increases with age because of the slow elimination rate (ATSDR 2012). While levels of Cd measured in blood are generally associated with Cd short-term exposure over the past 3–4 months (even though blood Cd can also partially reflect accumulated or long-term exposure as shown by e.g. Adams and Newcomb (2014) and Hecht et al. (2016)), U-Cd is considered the best biomarker to assess long-term Cd exposure (Akesson et al., 2014; Lauwerys et al., 1994). The high degree of temporal stability of the biomarker, regardless of spot samples or first morning voids, suggests that short-term variability in dietary Cd exposures does not contribute significantly to U–Cd levels (Vacchi-Suzzi et al., 2016).

The present paper focuses further on this effect on bones and intends to estimate the burden of osteoporosis attributable to Cd exposure among women from EU countries and its related costs. Therefore, the following stages were applied:

1) **Hazard characterisation**: Selection of an exposure-response relationship for the selected health event, i.e. osteoporosis, determined at environmental (low-level) exposure to Cd.
2) **Exposure assessment**: Selection of human biomonitoring (HBM) datasets reflecting the Cd aggregated chronic exposure of population subgroups having similar characteristics to the one for which an exposure-response relationship for osteoporosis was identified. As Cd can be taken up by the oral and inhalation routes of exposure, using HBM data is particularly valuable here, as it reflects the aggregate exposure (i.e. exposure coming from multiple sources) and thus the actual body burden of individuals.
3) **Estimation of the fraction of the population at risk for osteoporosis:** Estimation of the fractions of the HBM study populations at risk for osteoporosis (as a representative sample of the target population at the national level), considering the U–Cd levels at their age.
4) **Estimation of the Cd attributable burden of osteoporosis**: Estimation of the number of osteoporosis cases attributable to Cd exposure, among the population of each selected country.
5) **Costs assessment**: Evaluation of the costs associated to the burden of osteoporosis-related fractures attributable to Cd for each country targeted in this paper.

The present study was performed within the HBM4EU (Human Biomonitoring for Europe) project. This is a Horizon 2020 Framework Project for the development of a sustainable European wide HBM network (2017–2021). HBM4EU will provide better evidence of the actual exposure of citizens to chemicals and the possible health effects to support policy making (https://www.hbm4eu.eu/about-hbm4eu/).

2. Methods

2.1. Hazard characterisation

As part of the work performed by ANSES for the refinement of recommended health-based guidance values for Cd exposure in France, a review of the scientific literature regarding Cd toxicity was performed (ANSES, 2017). The effect of Cd exposure on bones was selected as the critical effect, based on the results of an epidemiological study indicating a relationship between Cd internal exposure in women and enhanced risk for osteoporosis or bone fractures.

Among the studies identified from the literature search, several epidemiological studies reported associations between low-level Cd exposure and bone demineralization and fracture risk (Akesson et al., 2006; Engström et al. 2011, 2012; Gallagher et al., 2008; Thomas et al., 2011; Wallin et al., 2016). The ANSES panel of experts considered bone effects as the most sensitive effect associated to long-term intake of Cd, based particularly on the findings of an epidemiological study by Engström et al. (2011; 2012). This study was conducted among 2680 women, aged 56–69 years, within the Swedish Mammography cohort. The study population was categorised into three groups of exposure (U–Cd concentrations from first morning voids at <0.50, 0.50–0.75 and ≥ 0.75 μg Cd/g of crea), with the lower exposed group being used as the reference group for calculating odds ratios (ORs) and 95% Confidence Intervals (95% CI). Results indicate that, starting from 0.50 μg/g crea, U–Cd is inversely associated with bone mineral density (BMD), and associated with elevated risk of osteoporosis and fracture. The calculated ORs, according to measured U–Cd levels, of hip or spine BMD-defined osteoporosis among 400 women aged between 56 and 69 years were 1.61 (1.20–2.16) for 0.50–0.75 μg U–Cd/g crea and 1.95 (1.30–2.93) for $\geq$0.75 μg U–Cd/g crea (cfr. Supplementary Data - Table S1) (Engström et al. 2011, 2012). These data were subsequently used to perform the calculations on the Cd attributable number of osteoporosis cases within similar study populations of women (>55–70 years).

In order to apply the ORs to women of younger age (<55 years), age-dependent U–Cd so-called "alert" values were derived, reflecting values not to be exceeded at various ages to avoid being at risk for osteoporosis at age over 55 years. Indeed, previous lifetime modelling of the U–Cd levels indicates that, when exposure to Cd remains constant, the body burden increases in a linear manner with age up until approximately 55 years, after which it reaches a plateau (or declines slightly) (ATSDR 2012). To predict the evolution of U–Cd levels assuming different lifetime constant intakes and considering the exposure levels referred by Engström et al. (2011; 2012) and their corresponding ORs, a PBPK modelling was considered. Therefore, the 8-compartments human PBPK model by (Kjellström and Nordberg 1978) for Cd, that was recently refined by the introduction of equations describing the French general population mean body weight and creatinine excretion evolutions according to age, was considered (Leconte et al., 2021). Two scenarios of intake were considered for derivation of the U–Cd alert values of at each age class, for the population groups aged <55 years:

- **Scenario 1** - Starting from age 0, lifetime constant Cd intakes (obtained from PBPK modelling) leading, at age over 55, to the two levels of exposure (U–Cd) for which ORs were calculated by Engström et al. (2011; 2012): 0.50 Cd μg/g crea (i.e. assumed threshold value for bone effects) and 0.75 μg Cd/g crea;
- **Scenario 2** - A constant Cd intake at 0.24 μg/kg bw/d (i.e. the middle bound mean lifetime average Cd exposure of European adults estimated by EFSA), from the average age of each selected age group of women in the HBM studies (EFSA 2012).

2.2. Exposure assessment: selection of HBM datasets reflecting Cd exposure at different ages

Available HBM datasets on U–Cd were identified from the HBM4EU data repository (a database where HBM data are gathered). A bibliographic search on Medline, Scopus and Web of Science was also carried out, in order to select HBM datasets complying with the following parameters:

- Study population: living in Europe, same gender, same smoking status and similar levels of Cd exposure as the population considered in the Engström studies, in which a significant relationship between osteoporosis and U–Cd levels was observed;
- HBM data: availability of measured U–Cd levels distribution (percentiles P10 to P95) and geometric mean (GM); availability of the number of samples, these being sufficient numerous for reconstructing the U–Cd levels distribution using a mathematical function in R version 3.5.1 (2018-07-02); availability of HBM datasets covering age categories over and below 55 years within selected EU countries, allowing for estimating respectively the current burden of osteoporosis attributable to Cd exposure, and prospective burden by including upcoming cases according to different hypothetical Cd intake scenarios (through the use of PBPK modelling).

2.3. Estimation of the fractions of the HBM study populations at risk for osteoporosis

The fractions of the HBM study populations from various age categories at risk for osteoporosis were estimated based on the relationship between the U–Cd levels and health effects on bone, as indicated by Engström et al. (2011; 2012).

The distribution of the U–Cd concentrations from the HBM studies were assumed to be log-normal. Based on available data (percentiles), distributions were fitted using the cumulative distribution function under the software R.

For the population groups aged >55 years, the risk fractions were determined from the U–Cd level distributions, by calculating the percentages included in the 0.50–0.75 μg/g crea range or exceeding 0.75 μg/g crea.

For the population groups aged <55 years, the risk fractions were estimated by the percentage of the U–Cd levels included or exceeding the exposure categories as determined by the alert values predicted by the PBPK model. These alerts values corresponds to the lowest U–Cd concentrations for which there is a risk of exceeding 0.50 or 0.75 μg/g crea at latter ages (>55 years) according to the U–Cd levels trajectories, as modelled for the two different Cd intake scenarios.

2.4. Estimation of the cadmium attributable burden of osteoporosis

The study population, among which the Cd attributable burden of osteoporosis (ABO) can be estimated, has to fit in terms of gender, age and exposure level to the study population in which a Cd exposure-response relationship for bone effects is determined. These conditions allow for estimating the ABO by directly applying the selected exposure-response relationship for osteoporosis to the corresponding population. The general methodology for the Cd ABO calculations follows the comparative risk assessment approach (Hänninen and Knol 2011; Prüss-Üstün et al., 2003). Data on the prevalence of osteoporosis in women aged 50 years or more was retrieved from the literature: 22.4%, 22.6% and 22.5% in Belgium (including Flanders), Spain and France, respectively (Hernlund et al., 2013).

Recognizing that osteoporosis is not rare and that application of the OR could lead to overestimation, we estimated relative risks (RRs) at different Cd levels based on ORs indicated in the epidemiological study of Engström et al. (2011) as well as the osteoporosis prevalence in the reference group (i.e. women having U–Cd level <0.5 μg/g crea) from the same study using the following formula of Zhang and Yu (1998):

$$\boldsymbol{RR} = \frac{\boldsymbol{OR}}{(1 - \boldsymbol{prev}) + (\boldsymbol{prev} \times \boldsymbol{OR})}$$

with $\boldsymbol{RR}$ *= relative risk;* $\boldsymbol{OR}$ *= odds ratio;* $\boldsymbol{prev}$ *= baseline prevalence of disease.*

Based on the estimated RRs for osteoporosis at specific U–Cd levels and the calculated fractions of the HBM studies population's at risk for osteoporosis, Cd attributable fractions (AFs) were calculated according to the following formula:

$$\boldsymbol{AF} = \frac{\boldsymbol{f}.(\boldsymbol{RR} - 1)}{\boldsymbol{f}.(\boldsymbol{RR} - 1) + 1}$$

with $\boldsymbol{AF}$ *= attributable fraction;* $\boldsymbol{RR}$ *= relative risk at a specific exposure level;* $\mathbf{f}$ *= fraction of the population exposed at a specific exposure level.*

Finally, the attributable number of cases (i.e. the ABO) in each country was obtained by multiplying the AF by the number of cases (C) among the target population (which was obtained by multiplying the national disease prevalence by the size of the target population), as with the following formula:

$$\boldsymbol{AC} = \boldsymbol{AF}\ .\boldsymbol{C}$$

with $\boldsymbol{AC}$ *= attributable number of cases;* $\boldsymbol{AF}$ *= attributable fraction;* $\boldsymbol{C}$ *= number of cases among the target population.*

For the sake of the inter-country comparison of the estimated Cd attributable number of osteoporosis cases, the number of women of the exact same age range was retrieved in each selected country from Eurostat (thereby deviating somewhat from the age range of female samples from the HBM studies). Thereby, it was assumed that the AFs calculated for the women study populations aged >55 years are representative of women aged between 55 and 70 years, given that Cd accumulation in the kidney cortex (and thus U–Cd) is reaching a plateau by around 55 years of age. For the population groups aged <55 years for which HBM data were available for France, Spain and Belgium, the attributable number of osteoporosis cases were calculated at country level for almost the same age range as observed in the HBM studies, i.e. 35-45 years.

2.5. Costs assessment

Based on the estimated attributable number of osteoporosis cases, the costs associated with the osteoporosis-related fractures were assessed for the population of women above 55 years old in the targeted countries. The assessment included three types of costs: direct costs, indirect costs and intangible costs. Direct and indirect costs were based on Borgström et al. (2006) and values were inflation adjusted to 2019. A range of costs per osteoporotic fracture, (wrist, hip and vertebrae), i.e. 2500€ to 17,000€, was applied. Intangible costs were based on reduction in quality of life (quality-adjusted life years (QALYs) lost) from Peasgood et al. (2009), Hernlund et al. (2013) and Ström et al. (2011) (between 0.04 and 0.41 for wrist, hip and vertebrae). The QALY value was set at 62,000€ (see further discussion). The range of costs per case (based on the range of direct, indirect and intangible costs) was set identical for all the countries and were expressed in 2019 Euros (i.e. 4980–42,420€).

The low and high values of this range were used to build two (low/high) scenarios for the costs assessment.

The attributable cases estimated in the female population groups aged >55 are assumed to be already at risk and are likely to incur osteoporosis-related fractures anytime. They stand for 'current' cases.

Regarding the estimated attributable cases in the female population groups aged <55 years (based on PBPK modelling), we assumed that those groups will keep on being at risk during their lifetime, assuming that they will keep on being exposed to Cd, and may incur osteoporosis-related fractures after the age of 55. They stand for 'future' cases. Population numbers used to assess current (2019) and future (2040, considered as the earliest year the youngest women in the sub-group <55 years old are likely to incur an osteoporosis-related fracture) costs are those for the year 2010. To both groups, we assigned values of lifetime risks of incurring a major osteoporosis fracture (MOF), based on literature: lifetime risks values in women at age 50 for France from the IOF Report (2018) and for Spain from Borgström et al. (2020); lifetime risks in women at age 60 from Hiligsmann et al. (2008) for Belgium (22% for France, 20% for Spain and 44.3% for Belgium) (Borgström et al., 2020; Hiligsmann et al., 2008; IOF 2018). The number of attributable cases were multiplied by these lifetime risks values to get the number of osteoporosis-related fractures. The costs for future cases were discounted at a rate of 2.5%. Using a discount rate of 4% is common practice to estimate present values for typical financial assessments. However, when dealing with health costs assessment, a decreasing discount rate of 4% the first 30 years, and then 2% (for health adverse effects occurring after 30 years) can be used in order to take into consideration intergenerational equity when human health effects occur over long-term beyond 30 years. This is common practice at European level, for example in ECHA's human health impact assessments for hazardous chemicals (ECHA 2016). Moreover, it is considered that the value of preventing a fatality has a constant utility value over time and it is therefore uprated in real terms each year by real GDP (gross domestic product) per capita growth. An uprating factor, usually based on GDP growth and income elasticity, estimated around 1.5%, based on OECD forecasts[1] was used in our assessment. Therefore, when combined with a 4% discount rate (2% for adverse effects occurring after 30 years), it gives an 'effective' discount rate of 2.5% for effects occurring over 2020–2050 and 0.5% beyond. Since the costs for future cases were assessed for 2040, they were discounted at 2.5%.

3. Results

3.1. Hazard characterisation

The Cd exposure-response relationship for bone effects from the Engström et al. (2011) study was selected. It relates to never- and ever-smoking women aged over 56 years. Based on the Engström et al. results, the U–Cd concentration of 0.50 μg/g crea was selected as the toxicological threshold value for bone effects due to Cd exposure.

According to the selected PBPK model, constant lifetime Cd dietary intakes of 0.36 and 0.54 μg/kg bw/d are the lowest doses that would lead to exceed the U–Cd values of 0.50 μg and 0.75 μg Cd/g crea at age around 55 years, respectively (starting from 0 μg Cd/g crea at birth, see Fig. 1). The estimated U–Cd alert values for each specific age (from 0 to 62 years) and age ranges of interest as well, are presented respectively in Supplementary Data - Table S2 and in the results section.

3.2. Exposure assessment: selection of HBM datasets reflecting cadmium exposure at different ages

HBM studies focussing on Cd concentrations in elderly women were reported in France, Flanders (Belgium), and Spain. The French National Nutrition and Health Survey (ENNS) ran from 2006 to 2007 and included 18-74-year-old adults. Distributions of U–Cd concentrations in 421 women aged 60–74 years are available (Fréry et al., 2011). The third Flemish Environment and Health Study (FLEHS) reported among others Cd levels in 111 women aged 50–65 (Schoeters et al., 2017). The Spanish BIOAMBIENT. ES study was conducted in 2009 among 119 women aged 50–65 years (López-Herranz et al., 2016).

HBM data for Cd in adult women under 55 years (on average) were also available for these three EU countries: the DEMOCOPHES (DEMOnstration of a study to COordinate and Perform Human biomonitoring on a European Scale) study ran from 2010 to 2012 and implied 17 European countries. Participating women were aged 18–45 years (Den Hond et al., 2015) and measured U–Cd levels are available according to the following age stratification: 18–35 years, 35–40 years and >40–45 years (Berglund et al., 2015). Results of U–Cd concentrations for Spanish and Belgian women were considered from this study. As France did not participated to DEMOCOPHES, the French ELFE (French Longitudinal Study since Childhood) cohort describing levels of U–Cd among 162 pregnant women aged 35–47 years having given birth in continental France in 2011 was considered (Dereumeaux et al., 2016; SPF 2017).

In summary, three EU countries for which distributions of urinary levels of Cd for adult women were available at comparable age ranges (on average) below and over 55 years were identified: Belgium, Spain and France. The characteristics of the selected studies and of the study populations are indicated in Table 1.

3.3. Estimation of the population's fraction at risk for osteoporosis

3.3.1. Risk of bone effects attributable to cadmium in the study population groups > 55 years

Table 2 presents the results for estimation of the percentage of the population exceeding the U–Cd threshold value for bone effects of 0.50 μg/g crea. Additionally, the fractions of studied populations presenting U–Cd concentrations between 0.50 and 0.75 μg/g crea and above 0.75 μg/g crea were estimated.

In the three countries, more than or equal to 40% of the women have a concentration > 0.50 μg Cd/g crea and are at risk for osteoporosis by Cd exposure. Largest exceedance was found for Flanders (48%), but 57% of these were situated in the U–Cd category 0.50–0.75 μg Cd/g crea. For Spain, 42% of the women exceeded 0.50 μg Cd/g crea but 61% of these were situated in the U–Cd category ≥0.75 μg Cd/g crea. For France, 40% exceeded 0.50 μg Cd/g crea with 56% of these in the category 0.50–0.75 μg Cd/g crea, similarly to Flanders.

3.3.2. Risk of bone effects attributable to cadmium in the study population groups <55 years and estimation of alert levels

Distributions of U–Cd levels measured in women aged under 55 years from the DEMOCOPHES Belgium, DEMOCOPHES Spain and ELFE studies are indicated in Table 3. Geometric mean values are close together, although age differences between the different groups.

Using the Cd lifetime biokinetic model, the evolution of U–Cd levels for these women was simulated assuming two different scenarios regarding their Cd intake until they reach approximately 55 years. Therefore, the estimation of the Cd attributable number of osteoporosis cases constitutes in these cases a prospective estimation.

Regarding the scenario 1, where constant Cd intakes of 0.36 μg/kg bw/d for those reaching 0.50 Cd μg/g crea and 0.54 μg/kg bw/d for those reaching 0.75 μg Cd/g crea starting from age 0 were considered, the U–Cd alert levels for the different age categories of women from the selected HBM studies were determined by using the alert value corresponding to the median of the age interval. The alert values differ by HBM campaign due to age interval differences (Table 4). For the DEMOCOPHES women from Spain and Belgium, the U–Cd alert values estimated to avoid exceedance of 0.50 μg Cd/g crea and 0.75 μg Cd/g

[1] https://knoema.fr/iuacek/euro-area-gdp-growth-forecast-2019-2024-and-up-to-2060-data-and-charts.

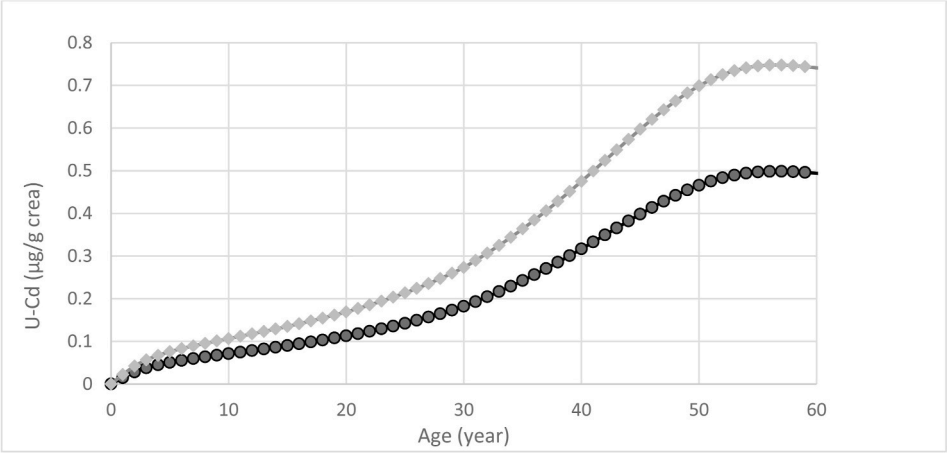

Fig. 1. Predicted urinary Cd (U–Cd) concentrations (µg/g crea) as a function of age (year), reaching or exceeding at age around 55 years the values of: 1) dotted curve - 0.50 µg U–Cd/g crea (constant dietary intake of 0.36 µg/kg bw/d estimated from PBPK modelling); 2) curve with squares - 0.75 µg U–Cd/g crea (constant dietary intake of 0.54 µg/kg bw/d estimated from PBPK modelling).

Table 1
Characteristics of the HBM datasets reporting the distribution of urinary Cd (U–Cd) concentrations (adjusted for crea) among women from EU countries. All women (smoking and non-smoking) in all studies were selected.

Country	Study	Timeframe	Age of selected study population in years (mean)	Number of individuals	Type of sampling
Belgium	DEMOCOPHES	2011	35-40 (37.5)	58	Morning urine
			>40–45 (43)	45	
	FLESHIII	2012–2015	50-65 (57.5)	111	Spot-urine
Spain	DEMOCOPHES	2011	35-40 (37.5)	49	Morning urine
			>40–45 (43)	57	
	BIOAMBIENT.ES	2009	50-65 (57.5)	119	Morning urine
France	ELFE	2011	35-47 (41)	162	Spot-urine
	ENNS	2006–2007	60-74 (67)	421	Spot-urine

Table 2
Percentages of women aged over 55 years from the FLESHIII, BIOAMBIENT and ENNS studies exceeding the urinary Cd (U–Cd) threshold value for bone effects (0.50 µg/g crea), either for U–Cd concentrations between 0.50 and 0.75 µg/g crea or ≥ 0.75 µg/g crea, according to the U–Cd concentration distributions.

Study	U–Cd concentrations (µg Cd/g crea)								% of the study population at risk		
	GM	95% CI GM	P10	P25	P50	P75	P90	P95	% > 0.50 µg Cd/g crea	% at 0.50–0.75 µg Cd/g crea	% ≥ 0.75 µg Cd/g crea
FLESH III	0.49	0.44–0.53	0.27	0.37	0.48	0.64	0.96	1.12	48.5	**27.8**	**20.7**
BIOAMBIENT.ES	0.42	0.34–0.52	–	0.29	0.46	0.69	1.27	1.82	42.3	**16.3**	**26.0**
ENNS	0.43	0.40–0.46	0.20	0.29	0.42	0.65	0.99	1.15	40.1	**22.4**	**17.7**

With **GM** = Geometric mean; **CI** = Confidence Intervals; **P10** = Percentile 10; **P25** = Percentile 25; **P50** = Percentile 50; **P75** = Percentile 75; **P95** = Percentile 95.

Table 3
Distributions of urinary Cd (U–Cd) levels in the selected HBM studies population of women aged under 55 years.

Study	Age (mean) in years	U–Cd concentrations (µg/g crea)							
		GM	95% CI GM	P10	P25	P50	P75	P90	P95
DEMOCOPHES - Belgium	**35–40** (37.5)	0.18	0.15–0.28	0.10	0.12	0.17	0.31	0.41	0.54
	41–45 (43.0)	0.19	0.15–0.23	0.09	0.14	0.21	0.27	0.37	0.46
DEMOCOPHES - Spain	**35–40** (37.5)	0.21	0.17–0.27	0.09	0.14	0.19	0.39	0.58	0.64
	41–45 (43.0)	0.22	0.19–0.27	0.09	0.14	0.21	0.32	0.57	0.75
ELFE - France	**35–47** (41.0)	0.21	0.19–0.24	<LOQ*	0.15	0.20	0.31	0.41	0.57

With **GM** = Geometric mean; **CI** = Confidence Intervals; **P10** = Percentile 10; **P25** = Percentile 25; **P50** = Percentile 50; **P75** = Percentile 75; **P95** = Percentile 95.

crea at latter age were respectively 0.28 µg/g crea and 0.42 µg/g crea for the 35–40 years age group and 0.33 µg/g crea and 0.50 µg/g crea for the 41–45 years age group). For the ELFE study women (35–47 years), the U–Cd alert values estimated to avoid exceedance of 0.50 µg Cd/g crea and 0.75 µg Cd/g crea at latter age were 0.33 µg/g crea and 0.50 µg/g crea, respectively. Overall, based on the modelling, between 10 and 34% of the women will have a concentration exceeding 0.50 µg Cd/g crea and thus are at risk for developing osteoporosis due to Cd exposure.

For the scenario 2, where an intake of Cd equivalent to the lifetime average Cd dietary intake of European adults was considered, it was assumed that the women younger than 55 years of the selected HBM studies would have a constant intake of Cd of 0.24 µg/kg bw/d from

Table 4
Percentage of the study populations at risk for osteoporosis considering their modelled urinary Cd (U–Cd) levels at age over 55 years, according to two different scenarios of Cd intake (Scenario 1: constant Cd intake of 0.36 μg/kg bw/d for those reaching 0.50 Cd μg/g crea and 0.54 μg/kg bw/d for those reaching 0.75 μg Cd/g crea, starting from age 0; Scenario 2: constant Cd intake at 0.24 μg/kg bw/d from their age on). Urinary Cd "alert" values estimated for each age group of each study are also presented.

Study	Age (mean) in years	Scenario 1				Scenario 2			
		% of the study population at risk for osteoporosis depending on their measured Cd exposure				% of the study population at risk for osteoporosis depending on their measured Cd exposure			
		U–Cd alert value	U–Cd ≥ 0.50 μg/g crea at age over 55y	U–Cd alert value	U–Cd ≥ 0.75 μg/g crea at age over 55y	U–Cd alert value	U–Cd ≥ 0.50 μg/g crea at age over 55y	U–Cd alert value	U–Cd ≥ 0.75 μg/g crea at age over 55y
DEMOCOPHES-Belgium	**35–40** (37.5)	0.28	**25.2%**	0.42	10.0%	0.32	**19.2%**	0.62	3.0%
	41–45 (43.0)	0.37	**10.4%**	0.55	2.20%	0.44	**5.6%**	0.68	0.8%
DEMOCOPHES-Spain	**35–40** (37.5)	0.28	**34.0%**	0.42	16.1%	0.32	**27.4%**	0.62	6.1%
	41–45 (43.0)	0.37	**24.4%**	0.55	11.1%	0.44	**17.8%**	0.68	6.6%
ELFE - France	**35–47** (41.0)	0.33	**22.6%**	0.50	7.40%	0.41	**13.2%**	0.66	2.8%

their age on. Fractions of the study populations likely to have U–Cd levels between >0.50 μg/g crea and ≥0.75 μg/g crea at later age (at 55 years) were calculated. Results are indicated in Table 4 under scenario 2. Based on the modelling, between 6 and 27% of the women will have a concentration >0.50 μg Cd/g crea and are thus at risk for developing osteoporosis by Cd. The fraction of the population at risk, i.e. exceeding 0.50 μg Cd/g crea in scenario 2, is on average a factor 1.5 lower than for scenario 1. In general (considering scenario 1 and 2), between 6 and 34% of the considered populations < 55 years were at risk for osteoporosis.

3.4. Cadmium attributable burden of osteoporosis

Based on the multivariable-adjusted ORs for hip or spine osteoporosis in women aged over 55 years calculated by Engström et al. (2011) according to specific U–Cd levels (OR of 1.61 [95% CI (1.20–2.16)] for U–Cd at 0.50–0.75 μg/g crea; OR of 1.95 [95% CI (1.30–2.93)] for U–Cd ≥ 0.75 μg/g crea) and considering the 13% prevalence of hip or spine osteoporosis in the 2067 women with a U–Cd level < 0.50 μg/g crea (i.e. the prevalence of the outcome in the reference group considered as non-exposed), following RRs were estimated: 1.49 [95% CI (1.17–1.88)] for U–Cd levels at 0.50–0.75 μg/g crea and 1.74 [95% CI (1.25–2.34)] for U–Cd levels ≥ 0.75 μg/g crea.

3.4.1. Cadmium attributable burden of osteoporosis in the study population over 55 years

The Cd attributable risks (i.e. the AFs) for osteoporosis in the target countries population of women over 55 years were calculated based on the fractions of the population at risk for osteoporosis according to their U–Cd levels as indicated in Table 2, and the U–Cd levels-depending estimated RRs as previously indicated.

Multiplying the AFs by the calculated number of osteoporosis cases (themselves obtained by multiplying the country-specific disease prevalence by the size of the target population in the corresponding country), the Cd ABO in women aged between 55 and 70 years depending on their U–Cd levels were obtained and are presented in Table 5. The number of osteoporosis cases in each country was finally obtained by summing these U–Cd levels-depending number of cases.

From Table 5, it becomes clear that around 23% (sum of the AFs) of the osteoporosis cases in women aged 55–70 years can be due to Cd exposure which is a relatively significant proportion. Largest burden per 1000 women is in Flanders followed by Spain and France, however confidence intervals overlap.

3.4.2. Cadmium attributable burden of osteoporosis in the study population at younger ages than 55 years

Attributable prospective number of cases is given in Table 6. For scenario 1, seeing the consistency of the prevalence of osteoporosis in the three countries (around 22% according to Hernlund et al., 2013) and the relatively larger U–Cd concentrations in the Spanish DEMOCOPHES data compared to the Belgian and French HBM data, the largest attributable number of cases is estimated for Spain. Confidence intervals overlap. Regarding scenario 2, as the fraction of the population exceeding 0.50 μg Cd/g crea is on average a factor 1.5 lower than for scenario 1 for all countries (see above), this is also reflected in the attributable number of cases which are somewhat lower for scenario 2

Table 5
Cd attributable burden of osteoporosis (ABO) for the female populations between 55 and 70 years in the target-countries.

Country (HBM Study)	U–Cd levels (μg/g crea)	AF (lower and upper limits)	Country-specific target population aged 55-70y in 2010	Cd ABO depending on U–Cd levels (lower and upper limits)	Total Cd ABO for women aged 55-70y (lower and upper limits)	Attributable number of cases per 1000 women 55-70y (lower and upper limits)
Belgium - FLESH III	0.50–0.75	**0.12** (0.05–0.2)	960942	25830 (10763–43050)	**54243** (19157–89760)	**56** (20–93)
	≥0.75	**0.13** (0.04–0.22)		28413 (8395–46709)		
Spain -BIOAMBIENT. ES	0.50–0.75	**0.07** (0.03–0.13)	3815137	63804 (23280–107778)	**202622** (75875–331093)	**53** (20–87)
	≥0.75	**0.16** (0.06–0.26)		138818 (52595–223315)		
France - ENNS	0.50–0.75	**0.10** (0.04–0.16)	5804897	129304 (48326–214201)	**279506** (104488–464972)	**48** (18–80)
	≥0.75	**0.12** 0.04–0.19)		156732 (56162–250772)		

Table 6
Cd attributable burden of osteoporosis (ABO) for the female populations at younger ages than 55 years in the target-countries, assuming in Scenario 1: lifetime constant Cd intake of 0.36 μg/kg bw/d, if reaching 0.50 μg Cd/g crea at age around 55 years or 0.54 μg/kg bw/d, if reaching 0.75 μg Cd/g crea around 55 years; in Scenario 2: constant intake of 0.24 μg/kg bw/d from the average women age at which the U–Cd levels were measured until about 55 years.

Country (HBM study)	Age range (mean) in years	U–Cd level (μg/g crea)	AF (lower and upper limits)	Age range considered for Cd ABO calculation (years)	Country-specific target population in 2010	Scenario 1				Scenario 2			
						Cd ABO depending on U–Cd level category	Total Cd ABO according to age (lower and upper limits)	Total Cd ABO for women aged 35-45y (lower and upper limits)	Attributable number of cases per 1000 women aged 35-45y (lower and upper limits)	Cd ABO depending on U–Cd level category	Total Cd ABO according to age (lower and upper limits)	Total Cd ABO for women aged 35-45y (lower and upper limits)	Attributable number of cases per 1000 women aged 35-45y (lower and upper limits)
Belgium - DEMOCOPHES	35-40 (37.5)	0.50–0.75	**0.07** (0.03–0.12)	35–40	446086	6995	**13889** (4996–23582)	**18770** (6682–32100)	**22** (8–38)	7394	**8105** (3397–16287)	**12166** (4285–20813)	**14** (5–25)
		≥0.75	**0.07** (0.03–0.12)			6895				2198			
	41-45 (43.0)	0.50–0.75	**0.04** (0.01–0.07)	41–45	396135	3461	**4880** (1686–8518)			2041	**2168** (887–4525)		
		≥0.75	**0.02** (0.01–0.03)			1420				532			
Spain - DEMOCOPHES	35-40 (37.5)	0.50–0.75	**0.08** (0.03–0.14)	35–40	2306223	42218	**97466** (35442–163659)	**157252** (56983–266526)	**37** (13–63)	49515	**60884** (26060–121441)	**115008** (41446–196174)	**27** (10–46)
		≥0.75	**0.11** (0,04–0.18)			55248				22412			
	41-45 (43)	0.50–0.75	**0.06** (0.02–0.10)	41–45	1945154	26816	**59786** (21541–102868)			22859	**36410** (15386–74733)		
		≥0.75	**0.08** (0.03–0.13)			32970				20222			
France - ELFE	35-47 (41)	0.50–0.75	**0.07** (0.03–0.12)	35–45	5020856	79078	**137822** (48577–234976)	**137822** (48577–234976)	**27** (10–47)	55355	**65682** (27113–135563)	**77949** (27113–135563)	**16** (5–27)
		≥0.75	**0.05** (0.02–0.09)			58744				22594			

Table 7
Number of major osteoporotic fractures (MOF) and costs related to Cd exposure in Belgium, Spain and France.

	Women aged >55 years (Current cases | Current costs)					Women aged < 55 years (Future cases | Future costs)	
						Scenario 1[a]	
	# Cd attributable cases likely to incur osteoporosis-related MOF (lower and upper limits)	Cost associated to burden of Cd osteoporosis-related MOF (not discounted, in million €) (lower and upper limits)		Cost associated to burden of Cd osteoporosis-related MOF (not discounted, in million € per 1000 women) (lower and upper limits)		# Cd attributable cases likely to incur osteoporosis-related MOF (lower and upper limits)	Cost associated to burden of Cd osteoporosis-related MOF (discounted at 2.5% in 2040, in million €) (lower and upper limits)
		Low cost	High cost	Low cost	High cost		Low cost
Belgium	24030 (8487–39764)	119.7 (42.3–198.0)	1019.3 (360.0–1686.8)	0.125 (0.044–0.206)	1.061 (0.375–1.755)	8315 (2960–14220)	25.3 (9.0–43.2)
Spain	40524 (15175–66219)	201.8 (75.6–329.8)	1719.0 (643.7–2809.0)	0.053 (0.020–0.086)	0.451 (0.169–0.736)	31450 (11397–53305)	95.6 (34.6–162.0)
France	61491 (22987–102294)	306.2 (114.5–509.4)	2608.5 (975.1–4339.3)	0.053 (0.020–0.088)	0.449 (0.168–0.748)	30321 (10687–51695)	92.1 (32.5–157.1)

aScenario 1: PBPK model used to derive alert values, starting from no internal Cd exposure at age 0 and assuming a lifetime constant dietary Cd intake of 0.36 μg Cd/kg bw/d, if reaching 0.50 μg Cd/g crea at age ~55 years and 0.54 μg Cd/kg bw/d if reaching 0.75 μg Cd/g crea at age ~55 years. Exceedance of the alert values means an increased risk of osteoporosis related to Cd exposure at latter age.

bScenario 2: PBPK model used to derive alert values, starting from observed internal Cd exposure (U–Cd levels in the selected HBM studies) at considered age and assuming from then on a constant dietary Cd intake of 0.24 μg/kg bw/d. Exceedance of the alert values means an increased risk of osteoporosis related to Cd exposure at latter age.

than 1.

In the women >55 years the largest burden is observed for Belgium (although results of different countries per 1000 women lay close together) (Table 5), whereas in the women < 55 years the number of cases per 1000 women stands out for Spain compared to the other countries (Table 6). Per 1000 women, the number of cases is lower in the two scenario calculations (Table 6) than in the female population > 55 years (Table 5).

3.5. Costs assessment

Based on the attributable cases estimated above, the costs for the first year after a major osteoporotic fracture (MOF) associated to Cd exposure for the three countries targeted in this paper were assessed and are presented in Table 7. The range of costs between the low/high scenarios reflects the range of severity of the different types of fractures (wrist, hip or vertebrae). The absolute first year (future) cost associated to Cd osteoporosis-related MOF in women aged < 55 years is lower for all scenarios for Belgium given that the attributable cases in Belgium are much lower than in Spain and France (factor of 3–4). Future costs for Spain and France are comparable for this same age category of population. Current absolute costs in women aged >55 years are significantly higher for France (factor of 1.5–2.5) proportionally to the higher attributable cases in this country (Table 7). In general, absolute costs ranged between 0.1 (low estimate Belgium) and 2.2 billion Euros (high estimate France). The relative first year (future) cost (per 1000 women) associated to Cd osteoporosis-related MOF in women aged < 55 years is the highest for Belgium (factor of 1.5 on average). Current costs in women aged >55 years are also significantly the highest for Belgium (factor of 2.3) and are identical for Spain and France (Table 7). Reasons may come from a larger probability for a MOF in Belgium (44% in Belgium versus around 20% in the other countries). Moreover, for women <55 years, the difference in costs per 1000 women between Belgium and the other countries becomes smaller when compared to women >55 years old. This is mainly because for women >55 years the number of osteoporotic cases per 1000 women was largest for Belgium (Table 5) compared to the other countries, whereas for women < 55 years this was the smallest (Table 6).

4. Discussion

This work, which focuses on the estimation of the effects of human Cd exposure on osteoporosis, suggests a significant societal impact. As also other health effects are known or suspected to be caused by Cd at low-level exposure, the associated costs are probably underestimated (Li et al., 2016; Satarug et al., 2010; Tellez-Plaza et al., 2013). The renal toxicity of Cd for example is well-known and most of the regulatory guidance or limit values derived for this substance are based on it (ATSDR 2012; EFSA 2009). An HBM-guidance value of 1 μg/g crea for U–Cd in adults, based on kidney effects, was recently proposed under the HBM4EU project (Lamkarkach et al., 2021). The literature review performed thereby underlined that studies' results released within the past ten years support also causal associations between Cd low-level exposure and bone or cardiovascular effects. However, for the time being, the weight of evidence relating to these effects was not considered sufficient within the HBM4EU project to select them as critical effects for the derivation of an internal reference value. Due to some missing information when interpreting epidemiological findings on bone effects (e.g. nutritional factors, toxicodynamics associated with Cd tissue levels that cause bone decalcification), the causal relationship between low-level exposure to Cd (i.e. low concentrations of U–Cd) and decreased BMD is debated by the scientific community. Despite this, multiple recent publications provide evidence of effects of Cd on bones at low-doses occurring below the U–Cd critical value of 1 μg/g crea set by EFSA, as well as associated exposure-response relationships (Buha et al., 2019; Engström et al. 2011, 2012; Wallin et al., 2016). Buha et al. (2019) showed that bone mineral health is significantly related to environmental Cd exposure based on experimental and human data. Human data, including direct bone analysis, i.e. measurement of Cd concentration in the bone, showed that bone health is extremely sensitive to even background levels of environmental Cd, supporting the epidemiological evidence. Besides human studies, toxicity studies in rats showed

Women aged < 55 years (Future cases | Future costs)							
Scenario 1[a]			Scenario 2[b]				
Cost associated to burden of Cd osteoporosis-related MOF (discounted at 2.5% in 2040, in million €) (lower and upper limits)	Cost associated to burden of Cd osteoporosis-related MOF (discounted at 2.5% in 2040, in million € per 1000 women) (lower and upper limits)		# Cd attributable cases likely to incur osteoporosis-related MOF (lower and upper limits)	Cost associated to burden of Cd osteoporosis-related MOF (discounted at 2.5% in 2040, in million €) (lower and upper limits)		Cost associated to burden of Cd osteoporosis-related MOF (discounted at 2.5% in 2040, in million € per 1000 women) (lower and upper limits)	
High cost	Low cost	High cost		Low cost	High cost	Low cost	High cost
215.3 (76.6–368.1)	0.030 (0.011–0.051)	0.256 (0.091–0.437)	5390 (1898–9220)	16.4 (5.8–28.0)	139.5 (49.1–238.7)	0.019 (0.007–0.033)	0.166 (0.058–0.283)
814.2 (295.0–1380.0)	0.022 (0.008–0.038)	0.192 (0.069–0.325)	23002 (8289–39235)	69.9 (25.2–119.2)	595.5 (214.6–1015.7)	0.016 (0.006–0.028)	0.140 (0.050–0.239)
784.9 (276.7–1338.3)	0.018 (0.006–0.031)	0.156 (0.055–0.267)	17149 (5965–29824)	52.1 (18.1–90.6)	443.9 (154.4–772.1)	0.010 (0.004–0.018)	0.088 (0.031–0.154)

that effects on femur phosphor and zinc levels were observed at lower dietary Cd levels than the corresponding safe intake level for Cd currently based on renal effects. In the year 2000, the EC categorised Cd as not having sufficient evidence for endocrine activity (BHK/TNO 2000). However, in recent decades, more and more evidence has shown that Cd has endocrine disrupting properties (Kortenkamp 2011). considered Cd as an estrogen mimic. Cadmium exposure has also been linked with prostate cancer although the associations are weak which would merit further work to confirm them (WHO/UNEP 2013). Cadmium is capable of disrupting osteoblasts homeostasis by altering the Wnt/β-catenin pathway thus influencing bone health (Papa et al., 2015). The Wnt/β-catenin pathway promotes bone formation and suppresses bone resorption (Baron and Kneissel 2013). This mechanism is worth considering in endocrine disrupting chemical action (Üstündağ and Emekli-Alturfan 2020). Noteworthy is that bone effects were recently selected by a panel of experts as endpoint for deriving an oral toxicological reference value of 0.35 μg/kg bw/d for conducting a health risk assessment of Cd dietary exposure in France (ANSES, 2017). Thereby, the threshold value of 0.50 μg Cd/g crea, based on the Engström et al. (2011; 2012) results, was considered in the present study. Women ≥50 years of age with U–Cd levels between 0.50 and 1.00 μg/g crea based on the US NHANES (National Health and Nutrition Examination Survey) results were also found to be at 43% greater risk for hip-BMD–defined osteoporosis, relative to those with levels ≤ 0.50 μg/g (OR = 1.43; 95% CI, 1.02–2.00; p = 0.04) (Gallagher et al., 2008), supporting this threshold value of 0.50 Cd μg/g crea in urine for bone effects. Ximenez et al. (2020) examined the association of heavy metals & metalloids with BMD loss based on data of three NHANES cycles using a data mining approach (Ximenez et al., 2020). The model was able to identify arsenic, Cd and tungsten as having critical importance on BMD loss. Cadmium concentrations in urine were below 0.50 μg/L. Stronger correlations between these elements and BMD loss were found as compared to smoking or diabetes, which are important predictors for bone loss and fracture risk. A low concentration of Cd is thus important for bone health, but there may be a complex interplay between metals and other elements influencing bones.

Efforts for estimating the Cd attributable disease burden already exists, but differences in approaches can be raised. As an example, Zang et al. (2019) estimated the global burden of late-stage chronic kidney disease resulting from dietary exposure to Cd, including in WHO regions (Belgium, France and Spain) (Zang et al., 2019). However, their estimation is based on PBPK simulated U–Cd levels arising from an assumed Cd dietary intake (0.31 μg/kg bw/d in Belgium and 0.30 μg/kg bw/d in France and Spain). Despite the fact that food is the most significant source of exposure to Cd, other sources contribute nevertheless to the total Cd human exposure as e.g. inhalation of tobacco smoke or particulate matter from ambient air (ATSDR 2012; Satarug et al., 2017). Therefore, using HBM data reflecting the aggregated exposure to Cd seems more reliable for calculating the Cd attributable disease burden.

Based on this knowledge and in the framework of the precautionary principle, a calculation of the ABO was merited. We further think that large scale human studies measuring Cd in urine together with Cd in bone and bone health are supportive for unravelling the effect of Cd on osteoporosis and setting safe biomarker concentrations.

Uncertainty in our estimation of the Cd ABO is related in particular to the assumptions and extrapolations underlying the calculations as well as the PBPK modelling, including the chemical-specific, human physiological and HBM scaling parameters, described in more detail below.

- Uncertainty related to the estimation of the Cd aggregated exposure in our target country populations: we relied on limited-sized female samples from HBM studies, which we considered as representative (in terms of sex and age) of our population of interest (the population for which exposure to Cd and associated osteoporosis was identified). Thereby, uncertainty may exist in the reconstruction of the U–Cd concentration distributions from the study samples based on the publicly available GMs and percentiles P10–P95, and to the subsequent extrapolation of these study samples distribution to the corresponding total population of the same age in the respective country. Predicting whether an under- or overestimation of the ABO cases may result from a possible difference in the U–Cd distributions between the HBM study samples and the total population is however not possible.
- Uncertainty related to the OR: the uncertainty on the OR and consequently the estimated RR is in general categorised as parameter uncertainty (Knol et al., 2009). The applied ORs from Engström et al. (2011) were significantly higher than 1 but the uncertainty is considerable (cfr. Table S1). This is reflected in the attributable cases

estimations, which are about 2.6 times lower when considering the lower limit of the 95% CI of the ORs and 1.6 times higher when considering the upper limit of the 95% CI of the ORs than the estimations using the OR central values. A detailed sensitivity analysis to estimate the impact of the uncertainty related to the ORs on the results would still be necessary.
- Uncertainty related to the threshold at which the effect of Cd on bones start: this is still debated in the scientific community (cfr. discussion above).
- Uncertainty related to the modelling of lifelong internal exposures to Cd: changes in body weight and in kidney function (urinary creatinine excretion) with age were considered in the biokinetic PBPK model. However, these two age-related physiological parameters were scaled on physiological datasets measured in the French population (Leconte et al., 2021). These physiological parameters may differ among the European populations, nonetheless we assume that the impact on the results is quite limited. As the PBPK model used is only integrating the oral route, Cd intake *via* smoking was not considered in the age-related U–Cd levels predictions. As U–Cd levels are raising more steeply in current/former smokers than in non-smokers with age (López-Herranz et al., 2016; Mortensen et al., 2011), an underestimation of the Cd attributable future burden (osteoporosis cases) is likely.

Regarding costs assessment, direct costs include medical care (hospitalization, outpatient care and pharmaceuticals) based on the study of Hernlund et al. (2013). They evaluated the first-year cost of fracture (hip, vertebral, forearm and others) for EU 27 countries including France, Spain and Belgium. For those countries, costs are comparable and range from about 1000€ to 12,000€ per fracture (therefore considered as "costs per case"). These values are consistent with other values available in the literature for France and Spain, such as the ones from (Ström et al., 2011). Regarding Belgium, there seems to be no study estimating cost per case to be compared with but only evaluations for the whole Belgian population (such as Svedbom et al., 2013). Indirect costs refer to the losses of labour and productivity that are incurred in addition to the direct costs of an illness. In the present case, the costs of fracture-related productivity losses were not included in the Hernlund et al. (2013) evaluation given that they are only incurred in patients below the retirement age —median age 60 years in Europe— and have previously been estimated to be limited in osteoporosis in literature (Hernlund et al., 2013; Ström et al., 2011). However, Borgström et al. (2007) estimated that below the age of 65 years the indirect costs were approximately 9% of the total costs for hip fractures and 23% for wrist fractures. We consider that although these costs may be not the most significant in the overall cost of osteoporosis burden, they should be included in the assessment. Borgström et al. (2007) estimated (direct and indirect) costs of osteoporosis for Sweden at 2000€-14,000€, standing for the cost the year after a hip, vertebral and wrist fracture. This range is slightly higher than the one from Hernlund et al. (2013), which only accounts for direct costs. We thus used Borgström et al. (2007) values (inflation-adjusted to 2019) in our assessment in order to account for both direct and indirect costs. Intangible costs are based on a monetary valuation of QALYs lost, due to the lower quality of life in patients suffering from osteoporosis. QALYs lost associated to osteoporosis-related fractures were taken from the literature Peasgood et al. (2009), Hernlund et al. (2013) and Ström et al. (2011) and estimated between 0.04 and 0.41. To value these QALYs lost, Borgström et al. (2007) suggested to assign a Willingness To Pay of 2 x GDP/capita for industrialised countries, such as the ones targeted in this paper, as a proxy to the societal value of a QALY (based on WHO's own recommendations, 2001) (Borgström et al., 2007; WHO 2001). In 2019, the GDP per capita in the EU27 was around 31,000€ (Eurostats[2]), therefore a value of 62,000€ per QALY was used.

Uncertainty in the costs assessment may be due to several elements: firstly, the lifetime risks of incurring a MOF for France and Spain is available in women at 50 years old whereas it is in women at 60 years old for Belgium. The HBM data sets used in the paper starts from 55 years old which does not entirely fit the lifetime risks. However, no other data on lifetime risks were available. Secondly, the years of reference used in the costs calculation may show some discrepancy: the HBM dataset is from 2010 and the disease burden costs are estimated for 2019 (current costs) and 2040 (future costs). The population numbers are assumed to stay steady regardless the period. Thirdly, one source of overestimation of the costs assessed may be due to differences in country-specific costs data: for example, Borgström et al. (2020) indicate lower (but only direct) costs for Spain. However, one source of underestimation of the costs assessed is due to the fact that we don't take into account costs of consecutive and multiple fractures (i.e. long term costs) but only the first year costs associated to the first fracture. Finally, Borgström et al. (2020) provide a loss of QALYs of 0.16 for forearm fracture which is higher than the lower bound used herein for QALYs lost (wrist). Using 0.16 as a sensitivity parameter in our assessment would increase the low cost scenarios results with a factor of 2.5.

Compared to total cost of osteoporosis such as reported in the IOF 2018 report (in 2017, annual cost associated to new fragility fractures in the EU6 were estimated at €37 billion), the costs assessed in this paper show that Cd exposure stands for a major contribution.

HBM datasets meeting the parameters for being relevant for our calculations were available only for three EU countries. Therefore, we refrained from extrapolating the estimated costs to whole Europe. Extrapolating our results to a larger scale may be of interest in the future, provided that comparable HBM data relating to a similar target population becomes available for more countries.

5. Conclusion

Current calculation on the ABO cases due to Cd exposure shows that in women aged 55 years or older, around 20% of the osteoporosis cases are associated with Cd aggregated exposure. PBPK modelling shows that for the future generation, between 6 and 34% of the women are at risk of osteoporosis due to Cd. Seeing the relatively large prevalence of osteoporosis and its associated costs, these results should be of great interest particularly to risk managers and policy makers, to define priorities and mitigation strategies to reduce Cd exposure and the subsequent health costs. In this regard, Schaefer et al. (2020) have reviewed current or new mitigation efforts that may reduce dietary exposure to Cd and therefore the global burden on human health (Schaefer et al., 2020).

Finally, more efforts are needed to reduce the uncertainty related with bone effects at low environmental Cd concentrations. Measurements of U–Cd in HBM studies coupled with assessment of indicators of bone status reflecting short-term and long-term effects can help in targeting this issue.

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[2] https://ec.europa.eu/eurostat/tgm/refreshTableAction.do?tab=table&plugin=1&init=1&pcode=tec00001&language=en; retrieved on June the 2nd 2020.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2021.113747.

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