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KEYWORDS

Cadmium, PB-PK model, TRV.

Abbreviations: PB-PK, Physiologically based pharmacokinetic; TRV, toxicological reference value; EFSA, European Food Safety Agency; TDS2, Second French Total Diet Study; iTDS, French infant Total Diet Study; TWI, tolerable weekly intake; TDI, tolerable daily intake; Creat, creatinine.

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ABSTRACT

In France, part of the population is overexposed to cadmium by the diet.

In our work, we first revised the tolerable daily intake (TDI) of 0.36 µg Cd.kg bw.d.$^{-1}$ proposed by the European Food Safety Authority (EFSA), derived from effects on kidneys and based on the critical urinary Cd concentration of 1.0 µg Cd.g^{-1} creatinine for humans.

After reviewing the epidemiological data on Cd toxicity published after 2011, bone effects were selected as the critical effects. Body burden data of 0.5 µg.g^{-1} creatinine was chosen for the critical threshold for human urinary cadmium concentrations.

To be used for the derivation of the new oral toxicological reference value, we used a modified physiologically based pharmacokinetic model (PBPK). The reverse calculation on the PBPK model gave a TDI of 0.35 µg Cd.kg bw^{-1}.day^{-1}.

This TDI is compatible with a urinary Cd concentrations not exceeding 0.5 µg Cd.g^{-1} creatinine, in a 60 year-old adult, assuming that ingestion is the only source of exposure to Cd at 60 years. After implementing the PBPK model with French physiological data, Cd biological reference values as a function of age were modelled so as to remain below the revised health-based guidance values.

1. INTRODUCTION

Cadmium is a ubiquitous, non-essential heavy metal that is toxic for humans. It is found in various compartments of the environment (soil, water, air). This element is naturally present in the Earth's crust; additional sources include anthropogenic inputs related to industrial activities and agricultural practices. Plants easily take up cadmium through their roots, after which cadmium can enter the food chain.

Except the tobacco use, diet is the main source of exposure of the general population to cadmium (EFSA, 2009 a and b; ANSES, 2011). In France, a significant part of the population, and in particular children, are exposed to levels that may pose a health risk (ANSES, 2011a and b, 2016).

In humans, cadmium is a cumulative toxic element having a biological half-life of 10 to 30 years. It is retained in the liver and kidneys and is also known to accumulate in bones. Cadmium induces renal tubular dysfunction, leading to micro-proteinuria in humans after prolonged oral exposure (EFSA, 2009b; JECFA, 2010). Bone fragility and reproductive disorders have also been reported (ATSDR, 2012), as well as an increased risk of cancer after exposure by inhalation, resulting in the classification of cadmium as "carcinogenic to humans" (group 1) by the International Agency for Research on Cancer in 2012 (IARC, 2012). Cadmium is also classified as a Category 1B carcinogenic, a Category 2 germ cell mutagen and a Category 2 toxic for reproduction substance according to the European CLP Regulation (Regulation (EC) No 1272/2008).

Cadmium concentrations in blood and in urine are considered as good biomarkers of exposure for the general and occupational populations. Blood cadmium levels are representative of the cumulative body burden consecutive to recent exposure, whereas urinary cadmium mainly reflects the lifetime accumulation of cadmium in the body. Based on urinary cadmium concentrations, modelling tools linked to physiologically based pharmacokinetic models (PBPK) can estimate cadmium intake in humans (Fransson et al., 2014; EPA, 2016; RIVM, 2017).

Because cadmium is a contaminant of concern, monitoring actions involving this toxic element whose body burden has increased over time must be appropriate and feasible. However, no age-based benchmark health values have been set for screened biological fluids for comparison with monitoring data.

International and European scientific expert committees (EFSA, 2009; JECFA, 2010; ATSDR, 2012) have recommended health-based guidance values for cadmium, especially *via* ingestion, the main route of human exposure. These values were established from a relationship between urinary cadmium and renal biomarkers (beta-2-microglobulin) of cadmium toxicity, based on the conclusions that kidneys are the most sensitive organ to cadmium exposure, especially following dietary exposure. Renal damage is characterised by cadmium accumulation in convoluted proximal tubules and also an increase of elimination of low-molecular-weight urinary proteins such as beta-2-microglobulin, thereby causing cell dysfunction and damage.

Up to now, critical concentrations of urinary cadmium derived by various international agencies and varying from 0.5 to 5.24 µg $Cd.g^{-1}$ (ATSDR, 2012, EFSA, 2009b; JECFA 2010) creatinine (creat) have been used as the point of departure (POD) to set toxicological reference values (TRVs).

Specifically, in 2009, the European Food Safety Authority (EFSA) estimated that the effect levels for cumulative lifetime exposure to cadmium linked to renal dysfunction corresponded to a urinary cadmium level of 1.0 µg $Cd.g^{-1}$ creat. This POD is based on a meta-analysis of 35 studies showing a relationship between urinary excretion of cadmium and beta-2-microglobulin. For urine cadmium concentrations to remain below this critical threshold, EFSA used a one-compartment toxicokinetic model (Amzal *et al*., 2009) to estimate that dietary cadmium intake should not exceed 2.52 µg Cd.kg $bw^{-1}.wk^{-1}$. Hence, the tolerable daily intake (TDI) for cadmium should not exceed 0.36 µg Cd.kg $bw^{-1}.d.^{-1}$.

84 Nevertheless, the literature contains reports that other effects, such as bone effects, due to cadmium
85 exposure *via* the oral route can also be a marker of cadmium toxicity at low doses (IPCS 1992;
86 WHO 2001; EC, 2007; EFSA, 2009b).

87 Here, our objective was to revise the health-based guidance values for cadmium in order to
88 recommend benchmark values for monitoring populations exposed to this contaminant of public
89 health concern. Our first goal was to check critical toxicological effects against new scientific data.
90 Then, using a physiologically based pharmacokinetic model for cadmium, we derived reference
91 biological cadmium concentrations for different age groups in the French population.

92 ## 2. MATERIALS AND METHODS

93 ### 2.1. Toxicological review: selection of the critical effects

94 The first step of our work consisted in updating our knowledge on cadmium toxicity. We
95 reviewed the scientific literature from 2011 to 2017. We consider that studies on cadmium toxicity
96 by ingestion published before 2011 have already been assessed by international agencies (EFSA,
97 2009; JECFA, 2010; ATSDR, 2012). Our literature review thus includes the opinions published by
98 the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (FAO/WHO 2010 and 2011),
99 EFSA and the Agency for Toxic Substances and Disease Registry (ATSDR) up to 2012 on the
100 establishment of reference values for cadmium. All previous assessments selected kidney effects as
101 critical effects, with thresholds from 0.5 to 1.0 µg $Cd.g^{-1}$ creat.

102 For data published after 2011, seven experts from the ANSES Expert Committees on
103 "Assessment of physical and chemical risks in foods" (ERCA Committee) and "Characterisation of
104 substance hazards and toxicity reference values" (Substance Committee) independently performed
105 the literature search.

106 The bibliographic research was carried out on Medline and Science Direct. For more specific
107 publications, PubMed and Toxnet websites were also consulted.

108 The keywords used were cadmium and [toxicity or ingestion or cancer or chronic toxicity or
109 kidney effect or bone effect or critical effect or neurotoxicity or development or cardiovascular
110 effect or reprotoxicity or toxicological reference value or epidemiological studies or urine or blood
111 or low level or biomarker].

112 We only selected original studies published from 2011 to 2017, in health-related fields. Only studies
113 on the general population with cadmium exposure by ingestion were assessed. The following
114 inclusion criteria were used for the detailed analysis of the studies:

115 - studies showing an effect other than bone and kidney effects;

116 - and all studies (including those on bone and kidney effects) with body burden data lower
117 than the EFSA (2009) critical threshold for human urinary cadmium concentrations of 1.0
118 µg $Cd.g^{-1}$ creat.

119 As an example, Appendix 1 shows the bibliographic search performed using the Science Direct
120 website, which gave us the most results (Supplementary Material, Appendix 1).

121 For each case report, the bibliographic analysis was based on an ANSES in-house grid of evaluation
122 criteria for epidemiological studies. The following information was collected: age, sex, symptoms,
123 urinary cadmium or blood cadmium. Case reports were excluded if urinary cadmium was greater
124 than 1.0 µg $Cd.g^{-1}$ creat. We gave precedence to large cohort studies over small studies.

125

2.2. Refinement of the cadmium PBPK model

We first selected the Kjellstrom and Nordberg (KN) PBPK model to simulate the oral ingestion of cadmium (Kjellstrom and Norberg, 1978; Dede et al., 2018). This model describes cadmium absorption, transport, and excretion using differential equations.

This KN PBPK model was implemented with parameter values from Ruiz et al. (Ruiz et al., 2010) to interpret urinary cadmium concentrations in the US biomonitoring NHANES study. This model considers amount and flow between eight compartments: lungs, intestines, three blood compartments (plasma (B1), erythrocytes (B2) and metallothionine (B3)), liver, kidney and other tissues and two excretion routes: faeces and urine. Two exposure routes were included: inhalation and oral routes. The original PBPK model had been validated in Ruiz et al. (2010) by comparing simulations to other published model simulations and to human data sets (Choudhury et al., 2001; Diamond et al., 2003; Hays et al., 2008). Human physiological and chemical-specific parameters describing the absorption, distribution, and blood and tissue partitioning were taken from Kjellstrom and Norberg (1978) and Ruiz et al. (2010). This model has already used by ANSES to derive a TRV for cadmium by inhalation (ANSES, 2012).

2.3. Modelling urinary cadmium concentrations by age group for the French population

Because cadmium is a bioaccumulating substance, we set out to estimate the evolution of the total cadmium body burden over a lifetime in the French population.

Variability related to changes in body weight and renal function with age was included in the Ruiz et al. (2010) model. However, data were calibrated for the US population, which may differ from the French population. Therefore, we modified the PBPK model with French physiological data (body weight and urinary excretion).

In the modified PBPK model, we propose a new equation for the change in mean body weight based on French data commonly used for health risk assessments. Body weight values of the French

population were taken from the Second French Total Diet Study (TDS2), including 1918 adults aged 18–79 years old and 1444 children aged 3–17 years old (Arnich et al., 2012). Moreover, data from the French infant total diet study (iTDS) (ANSES, 2016; Jean et al., 2018) were considered for the characteristics of body weight of children under 3 years old. In the French iTDS, the distribution of weight by age and gender came from the French national survey on eating behaviour and food consumption in infants and young children (Nutri-Bébé SFAE, 2013; Chouraqui et al., 2018). This study, led by the Secteur Français des Aliments de l'Enfance (SFAE), included 705 children under 3 years of age.From these data, we built a specific algorithm that describes the change in body weight with age for the French population.

For the change in renal excretion with age, French anthropometric data and reference values for 24 h urinary creatinine excretion in a healthy population were taken from the French Nutrition and Health Survey (ENNS, Castetbon et al., 2009; SPF, 2006) for adults (3115 18–74 year-olds) and anthropometry-based creatinine reference values recommended from Remer et al. (2012) for children (225 boys and 229 girls aged 3–18 years old). From these data, we also built a second algorithm.

The two previous algorithms were combined with the cadmium PBPK model from Kjellström and Nordberg (1978), and applied to the French population.

The evolution of urinary cadmium during the lifetime was simulated in order to estimate the level not to exceed the health based guidance values of cadmium.

170 ## 3. RESULTS

171 ### 3.1. Choice of critical effect, key studies and critical concentration

172 Based on our bibliographic search, we selected 30 epidemiological studies published between
173 2011 and 2017. The list of these epidemiological studies is presented in Appendix 2
174 (Supplementary Material). These epidemiological studies have investigated the effects of cadmium,
175 other than nephrotoxicity, on various diseases. Bone effects, cardiovascular diseases, pregnancy
176 outcomes and neurodevelopmental behavioural disorders in children were identified. The
177 description of these studies and the effects observed are presented in Appendix 3 (Supplementary
178 Material).

179 Some of these studies are large prospective cohort studies in men or women from different parts of
180 the world (Sweden, USA, Spain, Bangladesh, etc.), and a few are transversal studies with fewer
181 people included. Exposure to cadmium was measured in urine, in blood from pregnant women, in
182 cord blood or in the hair of children. Cadmium in blood reveals recent exposure status, whereas
183 cadmium in urine and hair reflects the body burden and is an indicator for cumulative long-term
184 exposure (Adams 2014). However, because hair grows approximately 1 cm per month, hair levels
185 usually reflect exposure over the last few weeks. In contrast, urinary cadmium levels may reflect
186 several years of exposure (Adams 2014). Most of the assessed studies report an association between
187 the environmental level of cadmium exposure and health outcomes. Some studies in pregnant
188 women (Lin et al., 2011; Kippler et al., 2012; Gardner et al., 2013; Sun et al., 2014) report a
189 decrease in head circumference in new-borns following maternal exposure to cadmium. These
190 studies also suggest a decrease in the children's height and weight, recorded during medical check-
191 ups until the age of three or five years.

192 Some epidemiological studies have suggested that environmental and/or dietary exposure to
193 cadmium induces discrete neurocognitive disorders (Supplementary Material, Appendices 2&3).
194 However, the variability in the type and quality of measures used (different scales or different

versions of cognitive developmental scales) highlight the need for additional research using more rigorous methodologies (see also Liu et al. 2019).

New studies (post-2011) undertaken in adult populations of men and women have analysed the link between cadmium exposure and the development of atherosclerosis on the one hand, and an increase in the prevalence of vascular diseases associated with atherosclerosis on the other hand (Tellez-Plaza et al., 2012; Tellez-Plaza et al., 2013a and b; Borné et al., 2015; Barregard et al., 2016). Due to their heterogeneous study designs in terms of population, the ratio of men to women, choice of effect marker, etc., these studies could not be included for selecting the critical effect.

Several studies analyzed the link between increasing cadmium levels and decreasing bone mineral density (BMD) and increased fracture risk (Åkesson et al., 2014; Cheng et al., 2016).

Åkesson et al. (2014) supported the hypothesis that cadmium is associated with decreased BMD and that an increased fracture risk would occur at urinary cadmium concentrations as low as 0.5–2 µg/ g creatinine which is equivalent to blood cadmium levels of approximately 0.5–2 µg/L.

Engström et al. (2011 and 2012) have analysed the association between urinary cadmium and bone mineral density (BMD) in the body, and the association with BMD in the lumbar spine in the general population. Within the population-based Swedish Mammography Cohort, the authors assessed urinary cadmium as a marker of lifetime exposure and BMD using dual-energy X-ray absorptiometry (DXA). Register-based information on fractures was retrieved from 1997 to 2009. The studies have been driven in Swedish women aged 56 to 69 years old (2688 individuals). Relationships were evaluated by multivariable regression analyses. In these studies, Engström et al. (2011 and 2012) showed a modest, but significant correlation (odds ratio >1) between low-level cadmium exposure (<0.5 µg $Cd.g^{-1}$ creat) and BMD, associated with a risk of osteoporosis and fracture among women through diet, especially in never-smokers.

The bone effects are appeared at lower cadmium levels than those leading to renal dysfunction (0.5 µg $Cd.g^{-1}$ creat vs 1.0 µg $Cd.g^{-1}$ creat) for the Swedish woman population.

Previously to the Engström studies (2011, 2012), a few studies for men workers assessed the association between urinary cadmium and BMD in the lumbar spine: Järup et al. (1998) reported no association (n=43), but Nawrot et al. (2010) observed a non-significant inverse relationship (p=0.14; n=83). These critical effects are corroborated by two other studies identified in our study dataset. Firstly, Thomas et al. (2011) observed that relatively low levels of exposure to cadmium by diet increases the risk of fracture in a cohort of more than 20,000 Swedish men from 45 to 79 years old. This relationship was independent of smoking and more pronounced among low-level consumers of fruits and vegetables. Secondly, in 2017, Moberg et al. reported that high levels of blood cadmium (> 0.51 µg $Cd.L^{-1}$) do not increase the risk of bone fractures in middle-aged women (52–63 years), but appear to double the overall mortality rate (Moberg et al., 2017).

The association between urinary cadmium and BMD in the body has also been demonstrated in men (age > 69 years) according to Wallin study (2016): a cohort of Swedish men aged 70 to 81 showed an increased risk of osteoporosis and decreased bone density associated with relatively low urinary cadmium (mean: 0.67 µg $Cd.g^{-1}$ creat, range: 0.37-6.98 µg $Cd.g^{-1}$ creat). The results of these studies in men are consistent with those reported in women (Engström *et al.,* 2011), allowing us to include the risk of osteoporosis or bone fractures as critical effects. We considered the epidemiological studies by Engström et al. (2011 and 2012) as key studies.

The urinary cadmium concentration as reported by Engström et al. (2011 and 2012) of 0.5 µg $Cd.g^{-1}$ creat corresponds to a level with no observable adverse effect. It was selected in our study as the critical concentration.

3.2. Calculation of the tolerable daily intake (TDI) for cadmium

Based on the revised critical effect and critical concentration, an oral TRV was established using KN PBPK modelling with only the oral route and excluding the inhalation route by tobacco exposure. The KN PBPK model makes it possible to use reverse dosimetry to calculate an external critical dose, not exceeding the critical concentration of urinary cadmium of 0.5 µg $Cd.g^{-1}$ of creat at 60 years of age.

Results gave an oral tolerable weekly intake (TWI) of 2.45 µg $Cd.kg\ bw^{-1}.week^{-1}$ corresponding to an oral TDI of 0.35 µg $Cd.kg\ bw^{-1}.day^{-1}$. This TWI is compatible with urinary cadmium concentrations not exceeding 0.5 $\mu g.g^{-1}$ creat, in a 60 year-old adult, assuming that ingestion has been the only source of exposure to cadmium for 60 years. (Table 1).

Table 1. Chronic oral toxicological reference value (TRV) based on bone effects

Critical effect	**Critical concentration**	**TRV**
Risk of osteoporosis or bone fractures Engström et al. (2011 and 2012)	Urinary cadmium = 0.5 $\mu g.g^{-1}$ creatinine at the age of 60 years	TRV = 0.35 µg $Cd.kg^{-1}.day^{-1}$ (TWI = 2.45 µg $Cd.kg\ bw^{-1}.week^{-1}$) PBPK modelling

This TRV is based on the Engström et al. (2011 and 2012) epidemiological studies. Because these studies were conducted on the general population and based on clinical data, an additional uncertainty factor was not applied to the derivation of the TRV.

3.3. Implemented PBPK model with the change in urinary excretion of creatinine as a function of weight and age

3.3.1. Change in body weight with age

The two French datasets (from TDS2 and iTDS) were combined and polynomial regression was applied using R software (version 3.4.0, 21-04-2017) to determine the equation that describes the change in mean body weight with age. The following equation describes the change in body weight expressed in kg with age expressed in years:

$$\text{Mean body weight} = 3.68+4.47\ \text{years}-0.093*\text{years}^2+0.00061*\text{years}^3 \quad (1)$$

Equation 1: Change in body weight (kg) as a function of age (years) for the French population

3.3.2. Change in urinary excretion of creatinine as a function of weight and age

In the same way, the change in renal excretion for the French population aged 3–74 years was modelled combining data from ENNS (Castetbon et al. 2009; SPF 2006) and Remer et al. (2012). A theoretical set of creatinine excretion data was constructed from these two different studies and is shown in Figure 1.

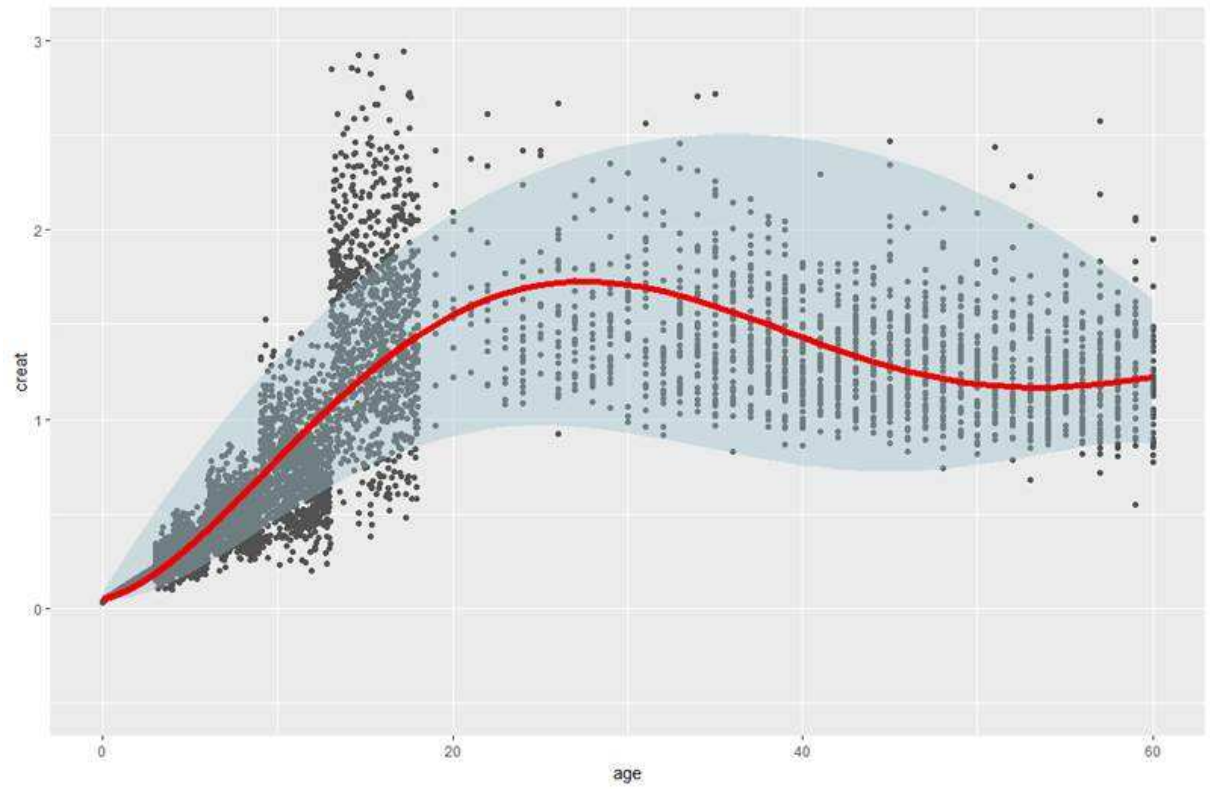

Figure 1: Change in creatinine excretion with age based on the observed data from French Nutrition and Health Survey (ENNS, Castetbon et al., 2009) for adults (>18 years) and data from Remer et al. (Remer et al.,2012) for children.

The following equations describe the change in urinary creatinine excretion expressed in $ug.g^{-1}$ with age in years (for the 50^{th}, 5^{th} and 95^{th} percentiles, respectively):

Ucreat_p50=0.05+0.0221* year+8.962e-03* year^2-4.486e-04* year^3+7.476e-06* year^4-4.168e-08* year^5

Ucreat_p5=0.04+0.000012* year+7.6e-03* year^2-4e-04* year^3+7.35e-06*year^4-4.55e-08* year^5

Ucreat_p95=0.08+1.5e-01* year-2.802e-03* year^2+1.7e-05* year^3-8e-8*year^4+8.489e-12* year^5

Equation 2: Change in urinary creatinine excretion (expressed in $ug.g^{-1}$) with age in years (for the 50^{th}, 5^{th} and 95^{th} percentiles, respectively)

3.4. Estimation of age-based benchmark biological values for cadmium

Using the implemented PBPK model simulating urinary cadmium concentrations over a human lifetime, predicted cadmium urinary concentrations (µg $Cd.g^{-1}$ creat) as a function of age (years) were modelled so as to not exceed the new threshold of 0.5 µg $Cd.g^{-1}$ creat for critical bone effects.

Reconstruction of urinary cadmium concentrations was also applied with the intention of remaining below the critical threshold of 1.0 µg $Cd.g^{-1}$ creat defined by EFSA (2009) based on critical kidney effects. This threshold is usually applied as an endpoint in the risk assessment for human health by EFSA (2012) and ANSES (2011, 2016).

Curves of predicted urinary cadmium concentrations (µg $Cd.g^{-1}$ creat) as a function of age (years) not exceeding either 0.5 µg $Cd.g^{-1}$ creat or 1.0 µg $Cd.g^{-1}$ creat are plotted together in Figure 2. The corresponding values are described and provided for each age in Table 1-SI together with the mean body weight used in the model.

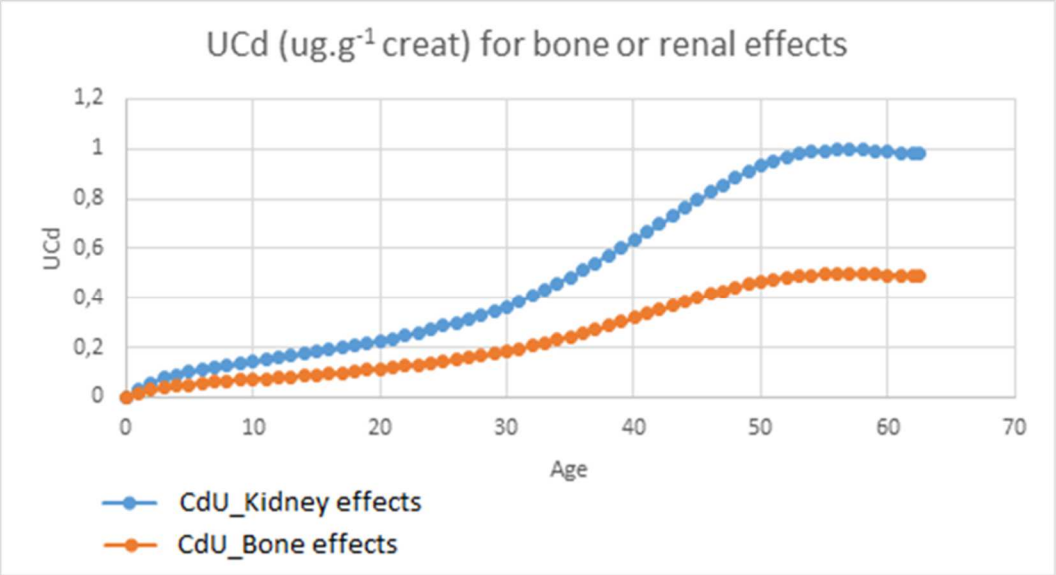

Figure 2: Predicted urinary cadmium (UCd) concentrations (µg $Cd.g^{-1}$ creat) as a function of age (years)
to reach the critical concentrations:
Bone effect: 0.5 µg $Cd.g^{-1}$ creat (orange)
Kidney effect: 1.0 µg $Cd.g^{-1}$ creat (blue)

In Supplementary Material (Table 1-SI, Appendix 4), all changes in urinary cadmium concentrations as a function of age from constant oral exposure (0.35 µg $Cd.kg\ bw^{-1}.day^{-1}$) clearly show a cumulative effect. This is fully consistent with the long half-life of cadmium in kidneys (25-30 years in the PBPK model).

Regardless of the cadmium concentration not to be exceeded at the age of 60 years (0.5 or 1.0 µg $Cd.g^{-1}$ creat), the shape of the change in urinary concentration is globally the same (Figure 2).

Thus, assuming constant oral exposure, a urinary concentration of 0.11 µg $Cd.g^{-1}$ creat at 20 years leads to a concentration of 0.18 µg $Cd.g^{-1}$ creat at 30 years, 0.32 µg $Cd.g^{-1}$ creat at 40 years and finally reaches 0.5 µg $Cd.g^{-1}$ creat at 60 years, which corresponds to the critical value related to the bone effect. Similarly, a urinary concentration of 0.21 µg $Cd.g^{-1}$ creat at 20 years leads to a concentration of 0.36 µg $Cd.g^{-1}$ creat at 30 years, 0.63 µg $Cd.g^{-1}$ creat at 40 years and finally reach 1.00 µg $Cd.g^{-1}$ creat at 60 years, which corresponds to the critical value related to the kidney effect.

4. DISCUSSION

Due to its ubiquity in natural and anthropogenic sources combined with its toxicity for humans, cadmium is a contaminant of concern for human health (EFSA, 2009; JECFA, 2010, ATSDR, 2012, IARC, 2012). It is also of concern that a part of population is over-exposed to this chemical contaminant through diet, the main exposure route. Specifically, in France, according to the ANSES opinion and report on the TDS2 (ANSES, 2011b), the dietary exposure of the French population to

cadmium appeared to be increasing compared to the previous TDS published in 2004. The TWI defined by EFSA in 2009 was exceeded in 0.6% of adults and 15% of children. More recently, the iTDS (ANSES, 2016) drew the same conclusion as the TDS2, i.e. that the health risk associated with cadmium cannot be ruled out for children under three years of age. Human overexposure to cadmium, calls for management measures to limit exposure, such as controlling environmental discharges, limiting mineral phosphate fertilizers identified as a major source of cadmium contamination in the food chain (Carne et al., 2020) or a review of regulatory thresholds in food. Complementarily, exposure of the population to cadmium should be controlled using biomonitoring. To ensure this protection, it is of interest to refine the health-based guidance values based on the implementation of available modelling tools and the revision of potential new existing data.

Up to now, the toxicity of cadmium had been addressed in several scientific reviews (WHO/IPCS, 1992; EC, 2007; EFSA 2009 a, b and 2011 a, b; ATSDR 2012; ANSES 2019). Their conclusions include the following: the critical effects of cadmium exposure primarily involve kidney function and bone tissue and can exceed the threshold values for urinary cadmium of 1 µg.g-^{1} creat for renal effects and 0.5 µg.g-^{1} creat for bone effects. The threshold for the occurrence of cardiovascular effects has been estimated at 2 µg Cd.g-^{1} creatinine. Available data in neurodevelopmental, reproductive and developmental studies are not currently sufficient to determine the thresholds for the occurrence of reprotoxic or neurodevelopmental effects (ATSDR, 2012). Similarly, carcinogenic effects (hormone-dependent, testicular, prostatic, renal, etc.) can affect individuals who are not occupationally exposed (IARC, 2012).

Our work made it possible to check if new toxicological or epidemiological data published recently on cadmium may justify a revision of the health-based guidance values used in Europe, which also correspond to the critical concentration and TWI from EFSA. Our study started with a review of the scientific literature on cadmium. This review of the new data available in the literature

consolidated the link between the onset of an adverse effect and the long-term oral exposure to cadmium. Moreover, emerging health outcomes have recently been published (Supplementary Material, Appendix 3), including pulmonary disorders, anaemia, cardiovascular diseases, diabetes, neurodevelopmental effects, endocrine disruption, abnormal sperm, hepatotoxicity, cancer and effects on the gastrointestinal tract. In these studies, some effects were similar to effects observed in kidneys by EFSA (2009) at the threshold for human urinary cadmium concentrations of 1.0 µg Cd.g^{-1} creat (see Supplementary Material, Appendix 3).

The previous cadmium risk assessments (EFSA, 2012; ANSES, 2011 and 2016) were based on the fact that urinary cadmium reflects the lifetime accumulation of cadmium in the body, but recent studies have questioned the validity of this assumption, specifically for low-level urinary cadmium (Chaumont et al., 2013; Haddam et al. 2011; Wang et al., 2017). Bernard (2016) indicated that low-level urinary cadmium varies widely within and between individuals depending on urinary flow, the urine collection protocol and recent exposure (Bernard, 2016). He reported that low-level urinary cadmium increases with proteinuria and essential element deficiencies, two potential confounders that might explain the multiple associations of urinary cadmium with common degenerative diseases.

Other authors have also suggested that effect of diuresis, variations in normal physiology, smoking, methodological uncertainties, etc. may also be confounding factors that hamper a causal relationship interpretation (Nordberg et al., 2015; Nordberg et al., 2018; Tang et al., 2016). Arguments for and against these alternative interpretations have been considered by EFSA (2009a). A causal relationship is, however, supported by the observed dose-response associations, in particular because cadmium in blood is also associated with the tubular effect markers, thus implying that cumulative cadmium exposure and not only cadmium excretion – is associated with the tubular effects.

374 Cadmium-related bone effects are also often combined with kidney dysfunction (Nordberg et al.,
375 2015; Nordberg et al., 2018). Some studies consider that observed associations of low cadmium
376 levels with bone effects (0.5 - 5 µg Cd. g^{-1} creat) are inconclusive and therefore impossible to
377 interpret as a causal relationship (Nordberg et al., 2018; Cheng et al., 2016).

378 Three hypothesis to explain the impact of cadmium on bone metabolism are proposed by authors:
379 - inhibited renal activation of vitamin D; - decreased absorption of calcium in the intestines due to
380 competing action of cadmium, and direct effects of Cd on collagen metabolism affecting bone
381 structure (Norberg et al., 2015). Bhattacharyya based on animal study has also indicated a direct
382 effect of cadmium on bone cells (2009).

383 Based on our analysis of the available data (Engstrom et al., 2011 and 2012, Wallin, 2016), we
384 consider that effects of cadmium on bones have also been well established and that the evidence is
385 sufficient to identify effects on bones as critical effects of cadmium to be used for the derivation of
386 health-based reference values. At similar low levels (0.5 µg $Cd.g^{-1}$ creat), cadmium is also
387 considered in some studies as a cardiovascular risk factor (Tellez-Plaza, 2013b). However, owing to
388 the inconsistency between studies, the causal relationships are less conclusive than for kidney or
389 bone effects. .

390 The implemented PBPK model was used to simulate the change in urinary cadmium concentrations
391 with age, so as to remain below the critical thresholds based on bone effects of 0.5 µg $Cd.g^{-1}$ creat
392 or the critical thresholds based on renal effects of 1.0 µg $Cd.g^{-1}$ creat (Table 1-SI, Appendix 4). It
393 was applied to the French population.

394 The comparison of modelling results with the body burden data observed in ENNS and Esteban
395 Survey for the general French population (SPF, 2006; Fréry et al, 2011) allowed us to check the
396 robustness of our modified PBPK model. The mean and median urinary cadmium concentrations
397 observed for the total adult population aged from 18 to 74 years are of the same order of magnitude

398 as the modelled urinary cadmium concentrations. They were 0.29 µg.g^{-1} creat (0.27 µg.g^{-1} creat in
399 non-smokers), and the 95th percentile was 0.91 µg.g^{-1} creat.

400 The values reported (Table 1-SI, Appendix 4) must be interpreted in light of the estimated body
401 weight and estimates of urinary creatinine for 24 h.

402 Due to the bioaccumulative behaviour of cadmium in the human body (long biological half-life
403 ranging from 10 to 30 years), health-based guidance values for cadmium linked to critical internal
404 concentrations or biological reference values are more realistic for monitoring cadmium exposure in
405 humans than external exposure.

406 From the PBPK model, by reverse calculation, we derived an oral TDI of 0.35 µg Cd.kg bw^{-1}.day^{-1}
407 or an oral TWI of 2.45 µg Cd.kg bw^{-1}.week^{-1}. This new TWI is similar to the EFSA TWI (2.5 µg.kg
408 bw^{-1}) established in 2009. Both TRVs were obtained using two different approaches. We did not
409 use the same critical effect (bones vs kidney), nor the same construction method to establish each
410 TRV. This health-based guidance value is of interest for interpreting the risk of humans exposed *via*
411 the diet, knowing that food is the main route of cadmium exposure for non-smokers.

412 The proposed kinetic modelling was used to simulate lifelong exposure to cadmium. However,
413 the PBPK model was originally built and validated for an adult population. The parameters related
414 to the volume of the compartments were scaled to the body weight following allometric
415 assumptions. The only age-related changes that have been taken into account are variations in body
416 weight and urinary creatinine excretion. Nevertheless other changes in the kinetics of cadmium with
417 age may occur. In particular, absorption may differ in children and adults, because iron status seems
418 to be related to cadmium absorption (Choudhury et al., 2001). Distribution may also vary between
419 an adult and a child in association with metallothionein or bone remodelling. In this respect, the
420 PBPK model applied in this study does not have a specific bone compartment; bones are included in
421 the slowly perfused tissues. This does not affect our use of the model: the compartment of interest

422 was the kidneys because even the bone effect is connected to a urinary concentration. However, the
423 inclusion of a bone compartment would be of interest to add bone-specific remodelling effects on
424 cadmium kinetics. Finally, the kidney function in children can be very different from that of adults,
425 which may influence the kinetics of cadmium. Even if the model has been validated in a lifelong
426 exposure context, predictions for childhood periods (<18 years old) have never been validated by
427 biomonitoring data. For all these reasons, the uncertainty associated with the benchmark urinary
428 concentration for children is high. It is recommended to use these values with great caution.

429 In 2020, one study developed a method to assess lifetime dietary risk due to cadmium exposure
430 for the French population (Pruvost-Couvreur et al., 2020). In this study, exceedances of the critical
431 concentration of 1 µg $Cd.g^{-1}$ creat were studied, depending on the method used to simulate exposure
432 trajectories. According to the methodology used in this study, from 2.9% to 5.3% of the virtual
433 population had a urinary concentration higher than 1 µg $Cd.g^{-1}$ creat at least one week during their
434 lifetime. Including sociodemographic parameters in the methodology, the study also indicated that
435 3.7% of the simulated population had a body burden trajectory exceeding 1.0 µg $Cd.g^{-1}$ creat.

436 To date, the median and the mean of urinary cadmium concentrations in the adult French
437 population were 0.29 µg.g^{-1} creat according to the French biosurveillance study (INVS, 2011). At
438 the 95th percentile, this study reported a urine cadmium concentration of 0.91 µg.g^{-1} creat for the
439 French population. It recorded that 3.6% of French adults exceeded the threshold of 1.0 µg $Cd.g^{-1}$
440 creat defined by EFSA (2009).

441 Based on our work, the threshold of 0.5 µg $Cd.g^{-1}$ creat should be considered as the critical
442 concentration in biological fluids for a French 60 year-old adult, assuming that ingestion is the only
443 source of exposure to cadmium (excluding exposure from smoking). Refining the critical cadmium
444 threshold decreasing by a factor of 2 and according to urinary cadmium concentration biomonitored
445 in INVS (2011), 25% of women and 10% of men in France now exceed the critical level of 0.5

446 µg.g^{-1} creat. These results are consistent with the observations in the Pruvost-Couvreur et al. (2020)
447 study, which reported that the critical threshold of 0.5 µg Cd.g^{-1} creat had been exceeded in up to
448 36.5% of their virtual population.

449 If risk is interpreted by ingestion only as used in food risk assessments, the refinement of the
450 health-based guidance values of cadmium confirms the need to implement actions to reduce
451 exposure to cadmium. According to ANSES (2018), the comparison of dietary exposure with
452 cadmium estimated in adults and children from the TDS2 (ANSES, 2011a) with the newly derived
453 TDI of 0.35 µg Cd.kg bw^{-1}.day^{-1} (ANSES, 2019) enhances the fact that the risk has not been ruled
454 out for a part of the population. The exceedance of the revised TDI is now increased with up to
455 1.1% of adults and 18.5% of children overexposed by diet.

456

457 ## 5. CONCLUSION

458 In this work, we updated the current state of knowledge on the toxicological effects of cadmium
459 on human health. Using a modified KN PBPK model, we derived a new oral TRV. It is based on
460 the most sensitive effect observed in humans following low-level cadmium exposure, e.g. effects on
461 bones. This new TRV constitutes a health-protective reference value for future health risk
462 assessments for consumers exposed to food contaminated with cadmium resulting from natural and
463 anthropogenic sources and transferred along the food chain.

464 By the implementation of a PBPK model taking account the change in urinary excretion of
465 cadmium as a function of weight and age for the French population, we were able to predict urinary
466 cadmium concentrations (µg Cd.g^{-1} creatinine) in order to remain below the refined health-based
467 guidance value for cadmium. These results may be used under certain conditions by risk managers.
468 For example, in a risk assessment for people living on sites or soils polluted with cadmium, current

urinary dosages can be compared with the estimated concentrations of cadmium in urine depending on age. Because the estimated data come from modelling the concentration of cadmium in urine, parameterized so that it remains below a critical threshold at the age of 60, a risk manager can estimate the future (adulthood) urinary cadmium concentrations of children, assuming that they are exposed throughout their life to the same level of cadmium. Other exposure scenarios can be considered. Depending on the contamination conditions (site / soil / food contamination) and urinary cadmium estimated at age 60, risk managers can make local decisions (e.g., reducing the consumption of contaminated food by cadmium) or take drastic measures (e.g., displacement of the population to less contaminated areas).

In the future, this work could be refined by integrating the two exposure routes (inhalation and oral) in the construction of the oral TRV. To do so, it would be necessary to include cadmium data from tobacco exposure in the PBPK model.

Acknowledgements

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FIGURES.

Figure 1: Change in creatinine excretion with age, based on data from the French Nutrition and Health Survey (Castetbon et al., 2009) for adults (>18 years of age) and data from Remer et al. (2012) for children.

Figure 2: Predicted urinary cadmium concentrations (µg $Cd.g^{-1}$ creatinine) as a function of age (years)

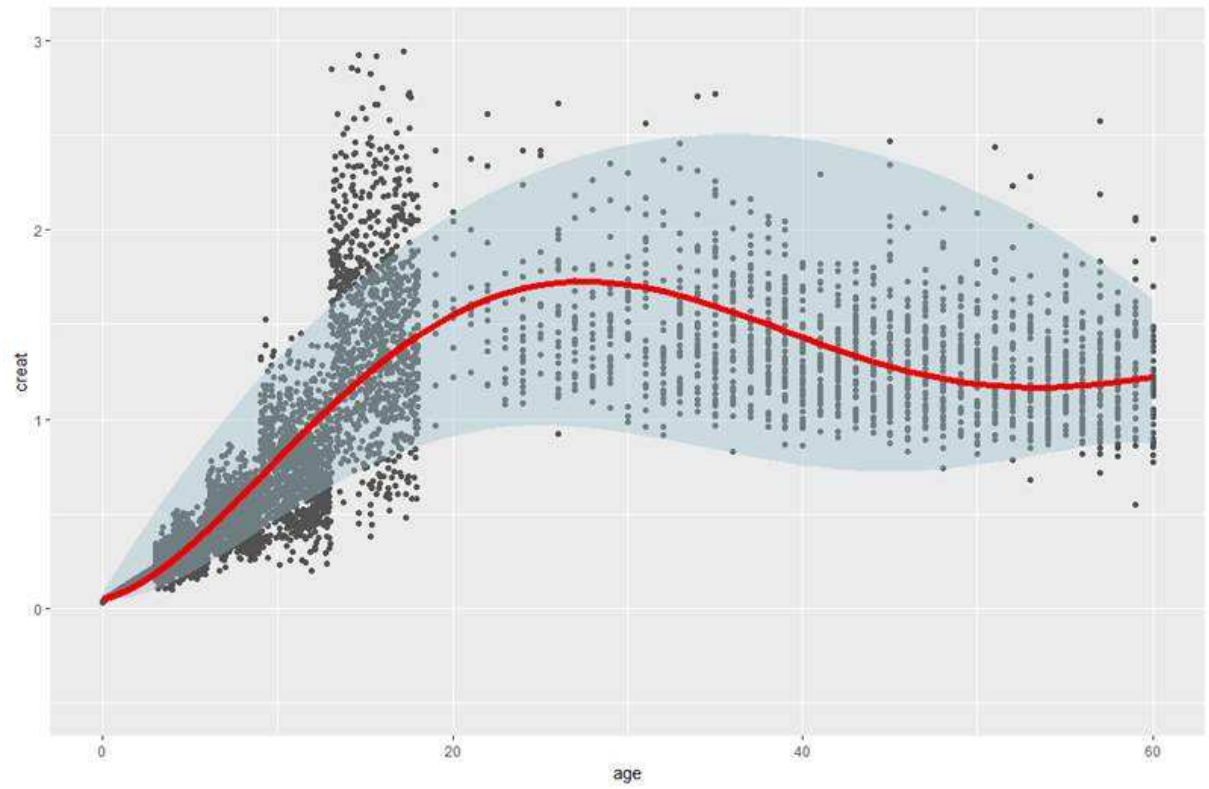


Figure 1: Change in creatinine excretion with age, based on data from the French Nutrition and Health Survey (Castetbon et al., 2009) for adults (>18 years of age) and data from Remer et al. (2012) for children.

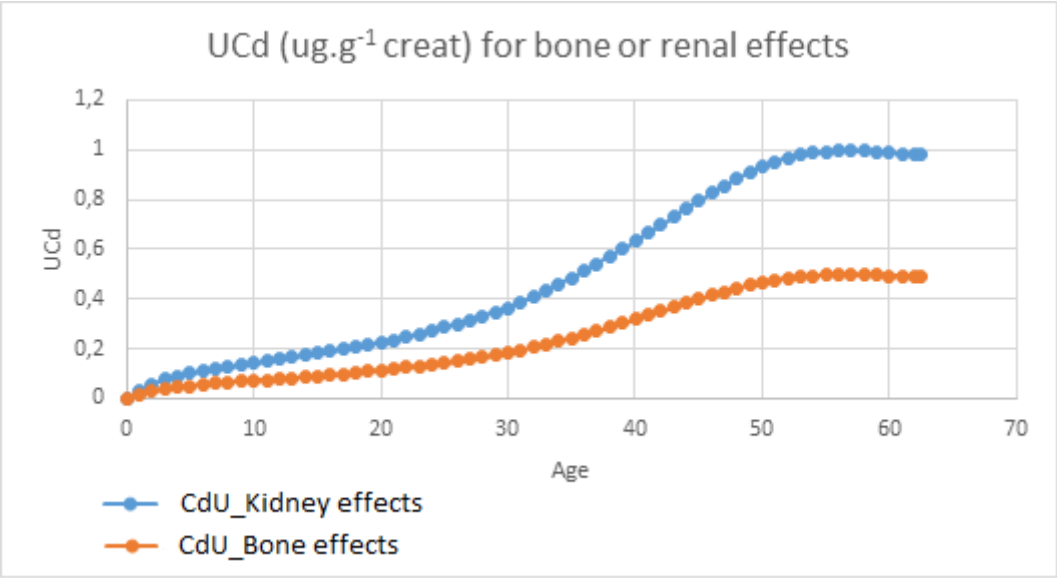


Figure 2: Predicted urinary cadmium concentrations (µg $Cd.g^{-1}$ creatinine) as a function of age (years)

To reach the critical concentrations:

(Bone effects): 0.5 µg $Cd.g^{-1}$ creat (orange)

(Kidney effects): 1.0 µg $Cd.g^{-1}$ creat (blue)

SUPPLEMENTARY MATERIAL

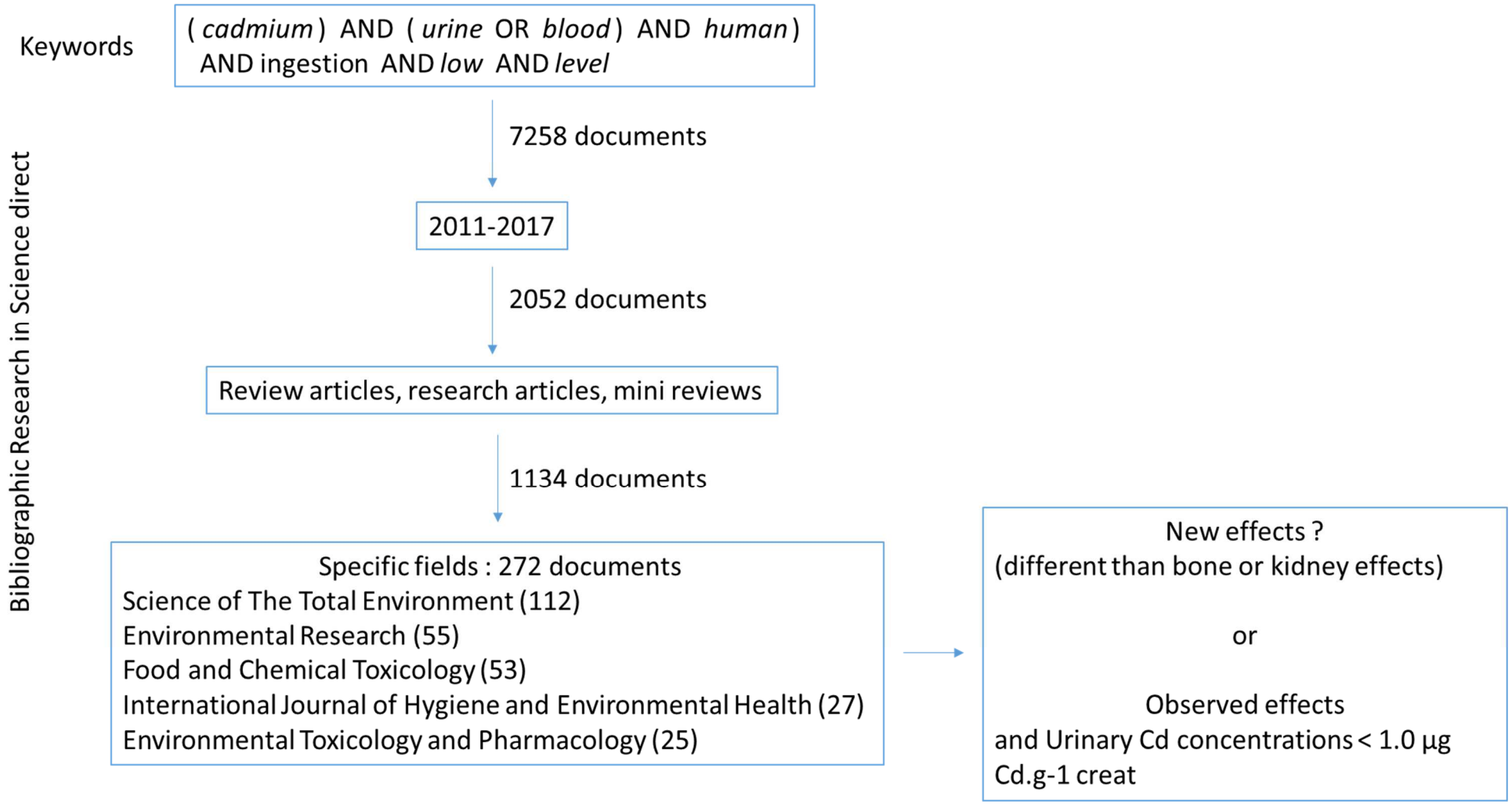
Appendix 1: Example of the literature search in Science Direct

Appendix 2: List of published epidemiological studies investigating the effects of cadmium on various diseases

Appendix 3: Summary of the epidemiological studies, published between 2011 and 2017, that investigate the effects of cadmium on various diseases

Appendix 4: Table 1-SI: Urinary cadmium concentrations (µg $Cd.g^{-1}$ creatinine) predicted by the PBPK model to reach a value of 0.5 µg $Cd.g^{-1}$ creat and 1.0 µg $Cd.g^{-1}$ creat (EFSA).

Appendix 1: Example of the literature search with Science direct



Appendix 2: List of published epidemiological studies investigating the effects of cadmium on various diseases

1. Neurodevelopmental effects and toxicity in the central nervous system

Ciesielski et al., 2012. Ciesielski T, Weuve J, Bellinger DC, Schwartz, Lanphear J B, Wright R O., (2012). Cadmium exposure and neurodevelopmental outcomes in U.S. children. Environ Health Perspect 120:758–763. https://doi.org/10.1289/ehp.1104152.

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Rodríguez-Barranco et al., 2014. Rodríguez-Barranco M, Lacasaña M, Gil F, Lorca A, Alguacil J, Rohlman DS, González-Alzaga B, Molina-Villalba I, Mendoza R, Aguilar-Garduño C. Cadmium exposure and neuropsychological development in school children in southwestern Spain. Environ Res. 134 (2014), 66-73. https://doi.org/10.1016/j.envres.2014.06.026.

Yousef et al., 2011. Yousef S, Adem A, Zoubeidi T, Kosanovic M, Mabrouk AA, Eapen V. 2011. Attention deficit hyperactivity disorder and environmental toxic metal exposure in the United Arab Emirates. J Trop Pediatr., 57 (2011), 6, 457-60. https://doi.org/10.1093/tropej/fmq121.

2. Weight-gain development

Abbas et al., 2013. Abbas S., Khan K., Khan M. P., Nagar G. K., Tewari D., Maurya S. K., Dubey J., Ansari N. G., Bandyopadhyay S., Chattopadhyay N. Developmental exposure to As, Cd, and Pb mixture diminishes skeletal growth and causes osteopenia at maturity via osteoblast and chondrocyte malfunctioning in female rats. Toxicological. Sciences. 134 (2013), 207–220. https://doi.org/10.1093/toxsci/kft093.

Bodo et al., 2010. Bodo M, Balloni S, Lumare E, Bacci M, Calvitti M, Dell'Omo M, Murgia N, Marinucci L. Effects of sub-toxic Cadmium concentrations on bone gene expression program: results of an in vitro study. Toxicol In Vitro. 24 (2010), 6, 1670-80. https://doi.org/10.1016/j.tiv.2010.05.020.

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Tian et al., 2009. Tian L-L, Zhao Y-C, Wang X-C, Gu J-L, Sun Z-J, Zhang Y-L, Wang JX. Effects of gestational cadmium exposure on pregnancy outcome and development in the offspring at age 4.5 years. Biol Trace Elem Res., 132 (2009), 1-3, 51-9. https://doi.org/10.1007/s12011-009-8391-0.

3. Bone effects

Engström et al., 2011. Engström A, Michaëlsson K, Suwazono Y, Wolk A, Vahter M, Akesson A. Long-term cadmium exposure and the association with bone mineral density and fractures in a population-based study among women. J Bone Miner Res., 26 (2011), 3, 486-95. https://doi.org/10.1002/jbmr.224.

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Moberg et al., 2017. Moberg L, Nilsson PM, Samsioe G, Sallsten G, Barregard L, Engström G, Borgfeldt C, 2017. Increased blood cadmium levels were not associated with increased fracture risk but with increased total mortality in women: the Malmö Diet and Cancer Study. Osteoporos Int. 28 (2017), 8, 2401-2408. https://doi.org/10.1007/s00198-017-4047-7.

Sughis et al., 2011. Sughis M, Penders J, Haufroid V, Nemery B, Nawrot TS. Bone resorption and environmental exposure to cadmium in children: a cross--sectional study. Environ Health. 10 (2011), 104. https://doi.org/10.1186/1476-069X-10-104.

Thomas et al., 2011. Thomas LD, Michaëlsson K, Julin B, Wolk A, Åkesson A. Dietary cadmium exposure and fracture incidence among men: a population-based prospective cohort study. 2011. J Bone Miner Res. 26 (2011), 7, 1601-8. https://doi.org/10.1002/jbmr.386.

Wallin et al., 2016. Wallin M, Barregard L, Sallsten G, Lundh T, Karlsson MK, Lorentzon M, Ohlsson C, Mellström D. Low-level cadmium exposure is associated with decreased bone mineral density and increased risk of incident fractures in elderly men: The MrOS Sweden Study. J Bone Miner Res. 31 (2016), 4, 732-741. https://doi.org/10.1002/jbmr.2743.

4. Cardiovascular effects

Barregard et al., 2016. Barregard L, Sallsten G, Fagerberg B, Borné Y, Persson M, Hedblad B, Engström G. Blood Cadmium Levels and Incident Cardiovascular Events during Follow-up in a Population-Based Cohort of Swedish Adults: The Malmö Diet and Cancer Study. Environ Health Perspect., 124 (2016), 5, pp 594-600. http://dx.doi.org/10.1289/ehp.1509735.

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Julin et al., 2013. Julin B, Wolk A, Thomas L D, Akesson A, 2013a. Exposure to cadmium from food and risk of cardiovascular disease in men: a population-based prospective cohort study, Eur J Epidemiol 28 (2013), 837–840. https://doi.org/10.1007/s10654-013-9841-8.

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Tellez-Plaza et al., 2012. Tellez-Plaza M, Navas-Acien A, Menke A, Crainiceanu C M, Pastor-Barriuso R, Guallar E. Cadmium Exposure and All-Cause and Cardiovascular Mortality in the U.S. General Population. Environmental Health Perpspectives, 120 (2012), 7, 1017-1022. https://doi.org/10.1289/ehp.1104352.

Tellez-Plaza et al., 2013a. Tellez-Plaza M, Guallar E, Howard B V, Umans J. G, Francesconi K A, Goessler W, Silbergeld E K, Devereux R B, Navas-Acien A. Cadmium Exposure and Incident Cardiovascular Disease. Epidemiology 24 (2013), 3, 421–429. https://doi.org/10.1097/EDE.0b013e31828b0631.

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Tellez-Plaza et al., 2013c. Tellez-Plaza M., Guallar E, Fabsitz R R., Howard B. V., Umans J. G., Francesconi K. A., Goessler W., Devereux R. B., Navas-Acien A. Cadmium Exposure and Incident Peripheral Arterial Disease. Circ Cardiovasc Qual Outcomes. 6 (2013), 6, 626-633. https://doi.org/10.1161/CIRCOUTCOMES.112.000134.

644
645 **Appendix 3: Summary of the epidemiological studies, published between 2011 and 2017, that investigate the effects of cadmium on**
646 **various diseases**
647

Reference	Objective	Study Design	Health Outcomes	Population	Exposure measurements	Confoundings	Model	Main results	Exposure levels	Conclusion of the authors	Quality of the study	Comments
Neurodevelopmental effects and toxicity in the central nervous system												
Ciesielski et al. (2012) Cadmium exposure and neurodevelopmental outcomes in U.S. children. Environ Health Perspect 120:758–763. https://doi.org/10.1289/ehp.1104152	to determine whether higher levels of urinary cadmium were associated with attention deficit hyperactivity disorder (ADHD), learning disability (LD), or placement in special education	Series of questionnaires (1999-2004) from the National Health and Nutrition Examination Survey (NHANES).	Attention deficit hyperactivity disorder (ADHD) Learning disability (LD) Placement in special education	2,199 children between 6 and 15 years	urine sample from children	urinary creatinine, age, sex, blood lead, smoker in the home, serum cotinine, prenatal smoke exposure (mother smoked while pregnant), and poverty income ratio	3 multivariate linear regression models	Children in the highest quartile of urinary cadmium had significantly higher odds of both LD and special education when compared with those in the lowest quartile. Adjusted ORs were 3.21 (95% CI: 1.43, 7.17) for LD, 3.00 (95% CI: 1.12, 8.01) for special education, and 0.67 (95% CI: 0.28, 1.61) for ADHD	Cd-U (median (interquartile range)) male : 0.110 (0.055-0.180) female : 0.110 (0.060-0.183)	Elevated cadmium exposure may be associated with LD and special education. However, given the cross-sectional design and the nature of parent-reported outcomes, interpretations should be cautious.	High	Outcomes were derived from parent or proxy-respondent reports rather than neuropsychological evaluations
Forns et al. (2014) Exposure to metals during pregnancy and neuropsychological development at the age of 4 years, NeuroToxicology, 40 (2014), 16–22. https://doi.org/10.1016/j.neuro.2013.10.006.	To evaluate potential neurotoxic effects of prenatal exposure to Co, Cu, As, Cd, Sb, Tl, Pb during the 1st & 3rd trim of pregnancy, on child neuropsychological development at 4 years of age.	Population-based birth cohort study	McCarthy Scales of Childrens' Abilities (MSCA) ADHD-DSM-IV criteria	385 4-year-old children	Urine samples from mothers during 1st & 3rd trimester of pregnancy	covariates with p-values of <0.20 Information on parental education, social class, country of birth, maternal smoking during pregnancy, parental educational level & social class based on occupation ;creatinine ; No HOME score; sensitivity analysis with fish intake, smoking, traffic air pollution		No statistically significant associations between metals and general cognitive scale or executive function of the MSCA. We found negative coefficients for the exposure to cadmium 1st trimester, cadmium 3rd trimester and lead 3rd trimester on the general cognitive score of MSCA, although these results were not significant.	U 1st trim : median=0.55 (0.42-0.73) µg/l U 3rd trim : 0.53 (0.41-0.75) for P25-P75 Less than 15% under LOD	Our results do not suggest that prenatal exposure to current low-levels of metals impairs children's cognitive development during preschool years.	High	Non-significant decrease of IQ score with Cd increase
Jeong et al. (2015) Performance IQ in children is associated with blood cadmium	To investigate whether performance IQ in children is associated with maternal blood	Mothers' and Children's Environmental Health (MOCEH) study, a multi-center	Wechsler Preschool and Primary Scale of Intelligence, revised	119 children at 5 y. of age	blood sample from mothers during early pregnancy	sex, educational levels of both parents, family income, and maternal BMI & age	Multivariate linear regression analysis	Maternal blood Cd during early pregnancy was inversely associated with performance IQ Maternal blood Cd was not associated	Mean blood Cd (mothers) : 1.49 +/- 0.39 µg/L	Performance IQ in children is associated with maternal blood cadmium concentration in early pregnancy	Unevaluable; Numerous informations missing	

Reference	Objective	Study Design	Health Outcomes	Population	Exposure measurements	Confoundings	Model	Main results	Exposure levels	Conclusion of the authors	Quality of the study	Comments
concentration in early pregnancy. J Trace Elem Med Biol., 30 (2015), 107-11. https://doi.org/10.1016/j.jtemb.2014.11.007.	cadmium concentration in early pregnancy.	birth cohort project in Korea	edition (WPPSI-R)					with cognitive IQ				
Kim et al. (2013) Prenatal lead and cadmium co-exposure and infant neurodevelopment at 6 months of age: the Mothers and Children's Environmental Health (MOCEH) study. Neurotoxicology. 35 (2013), 15-22. https://doi.org/10.1016/j.neuro.2012.11.006.	The aim of this study was to investigate the association between infant cognitive development and coexposure to Pb and Cd during pregnancy.	Mothers and Children's Environmental Health (MOCEH) study Multi-center prospective cohort study	Korean version of the Bayley Scales of Infant Development, Second Edition (BSID-II) with 2 specific indices (mental development index (MDI) and the psychomotor development index (PDI))	884 children aged 6months	Venous blood from mothers at their early pregnancy (<20th week of p.)	Infant sex, birth weight, maternal age at delivery, maternal education level, family income, breastfeeding status, and residential area	multivariate linear regession model	1) None of the Cd concentration were associated with MDI or PDI scores during early or late pregnancy period 2) Interaction study At low Pb level (<13,6µg/L), mean MDI score was significantly lower in low Cd group (<1,47µg/L) than in high Cd group (but NS for PDI) At high Pb level, mean MDI score was non significantly higher in low Cd group than in high Cd group (but NS for PDI) At early pregnancy period : antagonistic interaction at very low level for both Pb and Cd - No effect when Cd level is higher At late pregnancy period : synergistic effect of Cd and Pb	The geometric means for the maternal blood levels were : 13.6 µg/L for Pb and 1.4 µg/L for Cd during early pregnancy. 12.7 µg/dL for Pb and 1.5 µg/L for Cd during late pregnancy (near delivery, median = 39th week)	We observed a possible antagonistic interaction between the Pb and Cd levels in maternal blood during the early pregnancy period with respect to the MDI score at 6 months of age and a synergistic effect modification between the Pb and Cd levels during the late pregnancy period	Medium	Coherence of the results seem weak : - interaction effects at low level without significant effect of the factor alone - opposed interaction effect of Pb and Cd at early and late pregnancy period (partly discussed)
Kippler et al. (2012) Early-Life Cadmium Exposure and Child Development in 5-Year-Old Girls and Boys: A Cohort Study in Rural Bangladesh. Environ Health Perspect 120 (2012), 1462–	to evaluate the impact of prenatal and concurrent cadmium exposure on children's intelligence and behavior at 5 years of age	Population-based mother-child cohort study nested into a food and micronutrient supplementation trial during pregnancy	Wechsler Preschool and Primary Scale of Intelligence (WPPSI) Strengths and Difficulties Questionnaire (SDQ)	1305 5-year-old children	Urine sample from mothers at 8-week gestation urine sample from 5-y-old children	child's age at testing, tester, sex, birth order, birth weight, HAZ (5 years), HOME, maternal BMI (early pregnancy), maternal IQ, and SES 836 children (39%) had incomplete information. Children who were not tested	multivariate linear regession model multivariable-adjusted quantile regression analyse	Evidence of association between exposure to Cd (child-u & mother-u) and IQ scores The inverse associations of cadmium with child IQ, especially PIQ, seemed to be slightly more pronounced in girls than in boys, in families with higher than lower SES, and was about the same at low, median, and	Cd-U 0.22 µg/L (IC95% : 0.078-0.63) Pb-U 3.8 µg/L (IC95% : 1.6-11) As-U 53 µg/L (IC95% : 17-364)	Our findings suggest that early-life cadmium exposure, at levels present in most countries, may be harmful for brain development.	(Very) High	The authors recently found an inverse association between maternal Cd exposure in the present cohort and head circumference in daughters but not sons (Kippler et al. 2012b), which may influence childhood IQ (Gale et al. 2006).

Reference	Objective	Study Design	Health Outcomes	Population	Exposure measurements	Confoundings	Model	Main results	Exposure levels	Conclusion of the authors	Quality of the study	Comments
1468. https://doi.org/10.1289/ehp.1104431.						came from families with slightly higher SES, education, and maternal BMI, and lower birth order, but there was no significant difference in maternal U-Cd between tested and nontested children		high IQ levels.				
Kordas et al. (2015) Patterns of Exposure to Multiple Metals and Associations with Neurodevelopment of Preschool Children from Montevideo, Uruguay. Journal of Environmental and Public Health, vol. 2015, Article ID 493471. http://dx.doi.org/10.1155/2015/493471.	to determine if multiple metal (manganese, lead, cadmium, and arsenic) exposure is related to neurodevelopment in Uruguayan preschoolers	Cross-sectional study	Bayley Scales of Infant and Toddler Development, 3rd Edition	109 children between the ages of 13 and 55 months	Blood lead concentration Hair metal concentrations for As Mn Cd	child's age and hemoglobin level, maternal IQ and depressive symptoms score, household density, HOME score, and socioeconomic status	multivariate linear regession model	No statistically significant associations were found between clusters of metal exposure and any of the cognitive performance scales, either in the complete case or the multiple-imputation analysis	Mean hair Cd : 0.2 µg/g (range : 0.01 - 0.9) Mean blood Pb : 58 µg/L (range : 24 - 155)	We found no associations between children's exposure to multiple metals and their performance on cognitive and language scales of the Bayley Scales of Infant Development III. it is difficult to comment on the range of hair cadmium concentrations in the clusters identified in our study or on their relative contribution to cognitive deficits.	Medium	Surprisingly, no effect of lead on cognitive performance Cd hair approach

Reference	Objective	Study Design	Health Outcomes	Population	Exposure measurements	Confoundings	Model	Main results	Exposure levels	Conclusion of the authors	Quality of the study	Comments
Rodriguez-Barranco et al. (2014) Cadmium exposure and neuropsychological development in school children in southwestern Spain. Environ Res. 134 (2014), 66-73. https://doi.org/10.1016/j.envres.2014.06.026.	The aim of this study was to assess the association between postnatal cadmium exposure and neuropsychological development in children living in a coastal industrialized region in southwestern Spain.	Cross-sectional study	Wechsler Intelligence Scale for Children - Fourth Edition (WISC-IV) Time Test (RTT) Continuous Performance Test (CPT) Selective Attention Test (SAT) (3 tests from Behavioral Assessment and Research System (BAR))	261 children aged 6–9 years Separate analysis for boys and girls	Urine and hair samples. Levels of Cd, Mn, Pb, Hg and As were measured	Sex, child's age, body mass index (BMI), mother's age, IQ, education and occupation, father's education and occupation, monthly family income, residence area, family status, gestational age, weight, height and head circumference at birth, vegetables and cereals intake, and IQ assessor.	multivariate linear regession model	Significant negative association between urine cadmium levels and the scores of WISC-IV after adjustments. No association with Cd in hair. A doubling of levels of cadmium in urine was associated with 1.2 points less in the Full-Scale IQ (95%CI: 2.49 to 0.03) , affecting Verbal Comprehension most (β = 1.8 95%CI: -3.2 to -0.4) No significant associations between cadmium levels in urine and measures from the computerized tests Full-Scale IQ results were only significant in boys. Verbal comprehension was the only significant cognitive domain in boys. All others tests were not. Results on verbal comprehension were close for boys and girls	Geometric mean of urine cadmium levels was 0.75 µg/g creatinine, and 91.6% of samples were above the LOD. A total of 220 hair samples were available. Geometric mean of cadmium in hair was 0.01 µg/g, and 38.7% of samples were above the LOD. Correlation between hair and urine cadmium levels was negative and very low	The results show an inverse association between post natal cadmium exposure and neuropsychological development among boys, but not among girls	High	/
Yousef et al., 2011. Attention deficit hyperactivity disorder and environmental toxic metal exposure in the United Arab Emirates. J Trop Pediatr., 57 (2011), 6, 457-60. https://doi.org/10.1093/tropej/fmq121.	To investigate the blood levels of toxic metals and their association with ADHD in school-aged children in the UAE.	Population based case-control design from a gender-stratified random sample in 9 elementary schools	Attention Deficit Hyperactivity disorder (ADHD)	92 children 5–15 yo 18 diagnosed with ADHD and 74 control	Blood levels of heavy metals	Inattentive, hyperactive, combined Gender and age	stepwise multi-logistic regression (ADHD as dependent variable and heavy metals as independent variables)	statistically significant higher blood level of lead, zinc and manganese in the ADHD group No association with Cd.	0.25 µg / L (unit not specified)	No association with Cd.	Low	no effect of Cadmium on ADHD ; low statistical power

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Weight-gain development												
Gardner et al., 2013. Environmental exposure to metals and children's growth to age 5 years: a prospective cohort study. Am J Epidemiol., 177 (2013), 12, 1356-67. https://doi.org/10.1093/aje/kws437.	To assess the associations between early-life exposure to arsenic, cadmium, and lead, assessed via concentrations in maternal and child urine, and children's weights and heights up to age 5 years, during the period 2001–2009.	Nested prospective cohort study into a population-based randomized trial of micronutrient supplementation	children's weights and heights up to age 5 years	1,505 mother-infant pairs in rural Bangladesh	Exposure assessment was based on urinary concentrations of arsenic, cadmium, and lead in spot urine samples collected from pregnant women and their children at ages 1.5 and 5 years	child's sex, maternal anthropometric characteristics, and gestational age at birth	Mixed effects linear regression models with a random intercept and random slope, fitted using maximum likelihood estimation	In the tertile analysis, urinary cadmium was consistently inversely associated with both weight and height outcomes, though not all associations remained statistically significant after adjustment. In the analysis using log2-transformed data, urinary cadmium was consistently inversely associated with all anthropometric outcomes. The association was attenuated, though still statistically significant, after adjustment.	Urinary cadmium <0.16 : n=515 ; ≥0.16–<0.27 : n=480 ; ≥0.27 : n=510 The cadmium exposure levels observed among most children in this population were above the median reported for US and German children	persistent exposure to cadmium in early life led to a cadmium-attributable decrease in height weight by age 5 years: same magnitude as the differences observed between girls and boys at that age	high	Detailed information on confounding factors Several models tested Assessment of nonlinear association between the tertiles of each biomarker and the anthropometric outcomes. Assessment of interaction terms for each biomarker and time, for sex, Socioeconomic status and time. Lack of blood lead measurements for the children
Lin et al., 2011. Does prenatal cadmium exposure affect fetal and child growth? Occup Environ Med, 68 (2011), 641-646. http://dx.doi.org/10.1136/oem.2010.059758.	To investigate the placental transport of cadmium and the effects of prenatal cadmium exposure on fetal and child growth in Taiwan.	Part of a prospective birth cohort study : the Taiwan Birth Panel Study. From Recruitment may 2004 to October 2004	the length, weight and head circumference of newborns, and growth data up to 3 years of age.	289 pairs of maternal and cord blood measurements	Measurements of maternal and cord blood cadmium	sex, gestational age and maternal education were regarded as potential confounders.	Multivariable analysis	An increase in cord blood cadmium was found to be associated with newborn decreased head circumference and to be significantly and consistently associated with a decrease in height, weight and head circumference up to 3 years of age.	cadmium concentration : mean 1.15 mg/l for maternal blood, 0.67 mg/l for cord blood	Placental transport of cadmium is limited. However, prenatal cadmium exposure may have a detrimental effect on head circumference at birth and child growth in the first 3 years of life	Medium	Detailed information on confounding factors but potential uncontrolled confounding effects with nutritional status, other heavy metals, including lead Several models tested.
Sunn et al., 2014. The effects of prenatal exposure to low-level cadmium, lead and selenium on birth outcomes. Chemosphere. 108 (2014), 33-39. https://doi.org/10.1016/j.chemo	To evaluate the current maternal and fetal exposure to cadmium (Cd), lead (Pb) and selenium (Se), and their potential effect on newborn birth outcomes	209 pregnant women living in Eastern China The participants were recruited from three hospitals located in three different towns. All		Population in the middle of Jiangsu province, eastern China.	maternal blood, urine and cord blood samples	age, body mass index (BMI), income, education, household environment and smoking habit of the mothers	Anderson–Darling test Multivariate association evaluated with multiple linear regression model,	The blood Cd concentration in the mother could significantly affect the newborn birth weight (r = -0.22), but it was not correlated with birth height	Cd maternal blood Concentration: 0.48, µg.L-1 cord blood: 0.09, µg.L-1 urine sample: 0.13, , µg.L-1	maternal Cd, Pb, Se exposure correlated with their umbilical cord concentration, and maternal Cd exposure might affect the newborn birth weight. Increasing the Se intake might reduce the cord blood Cd concentration and promote the fetal growth.	medium	

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sphere.2014.02.080.		subjects were residents of this location for at least 2 years, The participants ranged in age from 19 to 41 years, with a mean age of 25.4 years.										
Bone effects												
Engström et al., 2011. Long-term cadmium exposure and the association with bone mineral density and fractures in a population-based study among women. J Bone Miner Res., 26 (2011), 3, 486-95. https://doi.org/10.1002/jbmr.224.	To assess the association between urinary cadmium and bone mass density in a large cohort of women not contaminated with occupational or environmental contamination. To study the association between the body load in Cd and BMD / risk of osteoporse femoral neck, hip, lumbar spine in women without pro or environmental exposure to Cd. Study the risk of fractures in retrospect and prospectively	Cross-sectional study although focusing on the population of a cohort	Long-term exposure to Cd BMD, ostéoporose fractures	The SMC cohort (Swedish mamography cohort) formed from 1987 to 1990 66,651 women from 2 counties in Sweden (Upsala and Vastmanland) born between 1914 and 1948	Urinary cadmium Cd_U measured from 2003 Fractures 1997-2008	Age, level of study, height, total fat mass, total lean mass, parity, Postmenopausal hormone therapy, corticosteroids, physical activity, smoking status, hepatic, renal and inflammatory joint disease and malabsorption (2004-2008 data) Additional adjustment on Calcium U, magnesium U, intake of food supplements Analysis of fracture risks: use of data collected in 1997 (except Cd_U measured from 2003)	BMD: by DXA Whole body, femoral neck, hips, lumbar spine, total fat mass, total lean mass Osteoporosis: T-score <2.5 Fractures: between 1997 and 2009 identified by CIM 10 in hospital registers. Linkage between population registers and patient registers Osteoporosis analysis (O./N), fractures (Y / N) by logistic regression,	Median Cd_U: 0.34 µg / g cr and 0.29 µg / g cr in non-smokers Femoral neck osteoporosis: 8.2% Fractures during follow-up 395 fractures 248 osteoporotic fractures 134 forearm end Cd_U and BMD negatively and significantly correlated in univariate. Linear regression: significant association with BMD from all sites except for BMD lumbar spine. Osteoporosis risk Risk increased by 40 to 60% for all sites (risk estimated by 0.42µg / g cr Dose-effect relationship + Sensitivity analysis done (exclusion of subjects with extreme creatinine concentration, Cd_U adjustment according to dilution instead of g cr)		The study shows that low-level cadmium exposure is modestly but significantly associated with both bone density and fracture occurrence, especially in non-smokers.	High	Large numbers, well-characterized cohort with no occupational or environmental exposure to Cd Precise information on osteoporosis and fractures

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							multiple fractures by ordinal logistic regression Cd_U in categories <0.5 µg / g cr (77%), 0.5-0.75 µg / g cr (17%), ≥0.75 µg / g cr (6%). Use of tertiles: 0.28, 0.28-0.43 and ≥0.43 µg / g cr In 2 categories: <0.50 and ≥0.50 µg / g cr Dose-effect relationship tested by cubic-spline logistic regression	Analysis in non-smokers: OR increased in osteoporosis (1.95 (1.21-3.16) for the femoral neck) Risk of fractures 1st fracture: OR 1.15 (0.92-1.43) In non-smokers: OR = 2.03 (1.33-3.09) with Cd_U in 2 categories				
Engström et al., 2012. Associations between dietary cadmium exposure and bone mineral density and risk of osteoporosis and fractures among women. Bones, 50, (2012), 1372-1378. https://doi.org/10.1016/j.bone.2012.03.018.	To study the association between dietary Cd intake and BMD / risk of osteoporse and fractures. Study if the associations are modified by other dietary factors Study the usefulness of the two indicators of Cd (U and food) on bone effects	Cohort: the Swedish Mammography Cohort (SMC) Lifetime exhibition	Long-term exposure to Cd BMD, ostéoporose fractures	The SMC cohort (Swedish mamography cohort) formed from 1987 to 1990 66,651 women from 2 counties in Sweden (Upsala and Vastmanland) born between 1914 and 1948 .	Sept 1997 and March 2009 for fractures Dietary cadmium was estimated from a 96-item questionnaire evaluating the frequency of consumption of a large number of foods and	BMD assessed by DXA: whole body, femoral neck, lumbar spine Osteoporosis: Tscore <2.5 Fractures: September 1997 to March 2009: linkage with hospital registers	Food frequenct questionnaire (FFQ) (validated) Food CD content database Food intake of Cd: frequency of consumption of each food * Cd content of each food adjusted for age From FFQ, information on calcium,	Estimation and confidence interval, relative risks, odds ratio ... Dietary intake: 13µg / d (average and median) Osteoporosis: 15%; 394 fractures Multivariate analysis BMD: Food CD negatively related to BMD whole body and lumbar spine but not to BMD femoral neck Adjustment for other food variables, clearer relationship. In non-smokers:	The median urinary cadmium concentration is 0.34 µg cadmium / g creatinine and 0.29 in women who have never smoked. The median of the cadmium concentration evaluated by questionnaire is 13 µg / day	High dietary Cd associated with low BMD, increased osteoporosis and fractures	High	Prospective cohort Population based Use of a database on the Cd content of foods Availability of food CDs and U CDs Linkage to fracture registers Not lost to follow-up The study shows that even low exposure to dietary cadmium is associated with bone fragility in postmenopausal women.

Reference	Objective	Study Design	Health Outcomes	Population	Exposure measurements	Confoundings	Model	Main results	Exposure levels	Conclusion of the authors	Quality of the study	Comments
					by linkage with a Swedish database giving the concentration of foods on sale on the market (no geographic variations) by considering portion sizes according to age. Urinary cadmium was measured by coupled plasma mass spectrometry.		magnesium, iron and fiber intake. Level of education, alcohol consumption, smoking status, postmenopausal hormone therapy Cd_U measured by inductively coupled plasma mass spectrometry, Cd_U adjusted on g cr	No change in results Osteoporosis hips or lumbar spine: OR: 1.46 (0.97-2.2) per 10µg / d of food Cd. Gold: 1.32 (1.02-1.71) after adjustment for other dietary factors Non-smokers: OR = 1.34 (0.92-1.95) Fractures No significant association if Cd_alimentaire en var continues Significant OR Food CD considered in two categories Similar result in non-smokers Combined var Cd_alimentary + Cd_U Significant associations for all variables of bone health when comparing the “high cd” category to the “low cd” category				
Moberg et al., 2017. Increased blood cadmium levels were not associated with increased fracture risk but with increased total mortality in women: the Malmö Diet and Cancer Study. Osteoporos Int. 28 (2017), 8, 2401-2408. https://doi.org/10.1007/s00198-017-4047-7.	to investigate if high levels of blood cadmium at baseline were associated with increased fracture risk during follow-up in middle-aged women.	Cohort :Malmö Diet and cancer Study (MDC)	fracture risk.	2920 Middle-age (45 to 64y women living in Malmö	Women were divided into quartiles (Q) according to their cadmium levels (Cd-Q1 <0.18 µg/L, Cd-Q2 0.18–0.28 µg/L, Cd-Q3 0.28–0.51 µg/L, and Cd-Q4 >0.51 µg/L).	risk factors not associated with blood cadmium: BMI, age, smoking status, diabetes, gastric ulcer,	survival analysis (Cox regression analysis).	998 first incident fractures occurred in women during a follow-up lasting 20.2 years (median) (12.5–21.2 years) (25th–75th percentile). Women in Cd-Q4 were more often current smokers than in Cd-Q1 78.4 vs. 3.3% ($p < 0.001$) and the number of cigarettes smoked per day correlated with B-Cd ($r = 0.49$; $p < 0.001$). The risk of fracture was not associated with baseline B-Cd in adjusted models.	B-cadmium (n = 2920) 0.28 (0.18–0.51) µg/L	Higher blood levels of cadmium did not increase fracture risk in middle-aged women but reduced overall survival.	High	Long follow-up :20.2 years (median), good reliability of Swedish registers

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								The hazard ratio (HR) Cd-Q4 vs. Cd-Q1 was 1.06 (95% confidence interval (CI) 0.89–1.27). No increased fracture risk was observed during follow-up, but women with higher levels of cadmium had an increased overall mortality.				
Sughis et al., 2011. Bone resorption and environmental exposure to cadmium in children: a cross--sectional study. Environ Health. 10 (2011), 104. https://doi.org/10.1186/1476-069X-10-104.	To investigate the association between markers of bone demineralization [urinary calcium (Ca) and deoxypyridinoline (DPD) excretion] and urinary cadmium (Cd) excretion (as an index of lifetime body burden).	155 school-children from 2 elementary schools in Lahore, Pakistan	osteoporosis	The study subjects were 8 to 12 year old children attending two private elementary schools in Lahore, Pakistan.	Urinary cadmium averaged 0.50 nmol/mmol creatinine	gender, age, height, weight and socioeconomic class	Non-normally distributed data were logarithmically transformed and presented as geometric mean (5th to 95th percentile).	Doubling of urinary Cd was associated with a 1.72 times ($p < 0.0001$) increase in urinary DPD and, a 1.21 times ($p = 0.02$) increase in urinary Ca. Additional adjustment for urinary Ca revealed still significant associations between urinary Cd and urinary DPD. The shape of the association was linear without evidence of a threshold.		Even in young children, low-level environmental exposure to cadmium is associated with evidence of bone resorption, suggesting a direct osteotoxic effect with increased calciuria. These findings might have clinical relevance at older age.	low	Low statistical power
Thomas et al., 2011. Dietary cadmium exposure and fracture incidence among men: A population-based prospective cohort study. J Bone Miner Res. 26 (2011), 7, 1601-8. https://doi.org/10.1002/jbmr.386|	To assess the association between dietary exposure to cadmium and the incidence of fractures, particularly hip fractures, in a cohort of men aged 45 to 79 years.	cohort study (COSM cohort) All men aged 45 to 79 residing in the counties of Örebro and Västmanland in central Sweden were invited in late 1997 to participate in the study and had to complete a self-administered questionnaire comprising approximatel	The first fracture, whatever the site and type (ICD code 10: S02, S12, S22, S32, S42, S52, S62, S72, S82 and S92) and the first fracture of the neck of the femur (S72.0, S72.1 and S72.2) were obtained by "linking" the file of study	48,645 (49%) of those invited returned the questionnaire. This cohort (COSM) is representative of Swedish men aged 45 to 79 in terms of age, educational level, and prevalence of obesity. The analysis covers the 23,745 people living in Västmanland County (fracture data	The cadmium ingested was evaluated using a questionnaire on the frequency of 96 items consumed. The frequency of consumption is categorized into 8 classes ranging from never / rarely to 3 or more	Height at age 20, weight, level of education, marital status, employment, alcohol consumption, smoking habits, use of cortisone and physical activity. Occupational physical activity and time of walking and cycling per day and time of exercise per week were recorded for the last year according to 5 predefined	Males were categorized into cadmium tertiles at time t0. Proportional hazard regression (Cox) models were used using attained age as a time variable. The follow-up was censored at the first event among the following:	During the 10 years of follow-up, 2,183 incident fractures were observed, including 374 fractures of the neck of the femur. The estimated average exposure is 19 + - 3.7 µg / day 96.6% of subjects ingest cadmium <weekly EU recommended dose (2.5 µg / kg body weight). • In the “all fracture” model, a relative risk of 1.19 (95% CI = 1.06-1.34) is observed in the 3rd tertile (> 20 µg / day)		Relatively low levels of cadmium exposure from food increase the risk of fractures in men. This relationship is independent of smoking and is more pronounced in low fruit and vegetable consumers	high	Good quality of the study despite the exposure estimation by questionnaire. strengths: the size of the cohort, study carried out in an industrial pollution-free area, the design of the study shows effects of diet independent of smoking

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		y 350 items on diet and other factors. constituting the way of life. The analysis covers the 23,745 people living in Västmanland County (fracture data not yet available in the other county). After exclusion of subjects (errors in merging with registers, subjects suffering from cancer or diabetes before 1998), the present study concerns 20,173 men followed for 10 years.	subjects with the national patient register and that of the regional hospital between January 1, 1998 and December 31, 2008.	not yet available in the other county). After exclusion of subjects (errors in merging with registers, subjects suffering from cancer or diabetes before 1998), the present study concerns 20,173 men followed for 10 years.	times per day. The consumption of bread and dairy products were assessed by open-ended questions. The validity of the method was assessed on a sample of 248 randomly drawn men, aged 40 to 74 years old and living in the geographical area of the study. These 248 men completed the questionnaire and were interviewed 14 times during the year for 24 hours. Cadmium exposure was calculated using the dietary questionnaire and a database of cadmium contained in all foods found on the market in Sweden. The	categories. Smoking data included smoking status, duration, and number of cigarettes smoked on average at different ages. This data has been converted into packets / years. Other confounding factors: liver disease, kidney disease, celiac disease, inflammatory joint disease, calcium and iron in food.	date of the fracture, exit from the geographical area, death or end of follow-up. Separate analyzes were done for the events "any fracture of any type" and "fracture of the neck of the femur". The conditions of use of this model seem to be respected. Tests of linear trend between categories were made by considering the median values of the categories as continuous variables.	compared to the first tertile (<17 µg / d) (trend test <0.01). Men in the highest cadmium tertile and lowest fruit and vegetable consumption tertile have a 41% increased risk compared to those in the baseline (lowest cadmium and highest fruit and vegetable consumption) . • In the “femoral neck fracture” model, a higher relative risk is also observed in the 3rd tertile compared to the first tertile, but this association is only significant in subjects who have never smoked (HR = 1, 70 (95% CI = 1.04-2.77)). • In current smokers, there is an increased risk of fracture any location and fracture of the femoral neck in the 3rd highest cadmium tertile and lowest level of fruit and vegetable consumption compared to the reference group (never smoked , low level of cadmium, high level of fruits and vegetables), HR = 1.62 (95% CI = 1.32-1.99) and HR = 1.75 (95% CI = 1, 0.7-2 , 85)				

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					cadmium intake is calculated by multiplying the frequency of consumption of each type of food by the average cadmium it contains using a serving size specific to each age. The average was used because there is no geographic variation of cadmium in Sweden. Exposure from drinking water (0.2% of total) and air (<1% of total) is low and was ignored in the analysis. The cadmium ingested was related to the total amount of energy (2600kcal / d) by the residual method.							
Wallin et al., 2016 Low level cadmium	To examine the effects of low-level exposure from	Cohort	The bone mass density of the whole	Swedish cohort of the Osteoporotic Fractures in	Urinary Cadmium Assessmen	Age, BMI, physical activity	Spearman rank correlation, t test, Anova,	Average Cd_U: 0.33 µg / g creatinine (median 0.26, range 0.01-6.98)		Relatively low levels of cadmium exposure from food and smoking increase the	high	High staff, prospective follow-up, reliable fracture data.

Reference	Objective	Study Design	Health Outcomes	Population	Exposure measurements	Confoundings	Model	Main results	Exposure levels	Conclusion of the authors	Quality of the study	Comments
exposure is associated with deceased bone mineral density and increased risk of incident fractures in elderly men: The MROS Sweden study J Bone Miner Res. 31 (2016), 4, 732-741. https://doi.org/10.1002/jbmr.2743.	diet and smoking on bone mineral density and fracture risk in a cohort of older men		body, the hip (including the femoral trochanter and the femoral neck) and the lumbar spine (vertebra L1 to L4) as well as the total fat mass and the lean mass • Hip fracture and vertebrae fracture + 3 other groups: "non-vertebral osteoporosis" (hip, pelvis, proximal humerus, distal radius), "osteoporosis, all fractures" and "other fractures" (all fractures except fractures related to osteoporosis)	Men (MrOS) study In total 936 men studied	t of urine Cd at inclusion: frozen morning urine for subsequent analysis U-Cd measured by inductively coupled plasma mass spectrometry. LOD 0.05µg / L		chi square, Fisher's exact test Cd_U and BMD Multiple linear regression with UCd in continuous variable and Cd_U in quartiles in general linear model Cox for fractures with U Cd in quartiles or continuously (risk per 1µg / g cr)	Univariate: U-Cd negatively associated with BMD: Linear regression: Cd_U in continuous var is no longer significantly associated with BMD after adjustment for age, tobacco, physical activity. But if Cd_U in quartiles: BMD lower in 3rd and 4th quartiles compared to the 1st quartile of Cd_U Incident fractures at the 2009 examination: 143 incident fractures HR: 1.5 to, 3.3 in 3rd and 4th quartiles compared to 1st, for all fractures, osteoporotic fractures, non-vertebral osteoporotic fracture Non-vertebral osteoporotic fracture: significant HR after adjustment for age, tobacco, BMI, physical activity and femoral neck sBMD. Analyzes then carried out by stratifying on tobacco: in non-smokers HR significant for osteoporotic fractures in the 4th quartile in the 2013 exam 229 fractures HR: insignificantly elevated risk for fractures in multi-layered model. HR 4th quartile vs 1st significantly high for non-vertebrae osteoporotic fracture after adjustment for		risk of low bone mass density and the risk of osteoporosis-like fractures in older men.		Taking into account tobacco and possible stratification according to smoking status. So, study of the effect of dietary Cd is possible

Reference	Objective	Study Design	Health Outcomes	Population	Exposure measurements	Confoundings	Model	Main results	Exposure levels	Conclusion of the authors	Quality of the study	Comments
								age, tobacco, BMI, physical activity but not significant if adjustment for BMD femoral neck VD_U in continuous variable: significant association for non-vertebral osteoporotic fracture. No association with non-osteoporotic fractures				
Cardiovascular effects												
Barregard et al., 2016. Blood Cadmium Levels and Incident Cardiovascular Events during Follow-up in a Population-Based Cohort of Swedish Adults: The Malmö Diet and Cancer Study. Environ Health Perspect. 2016 May;124(5):594-600. doi: 10.1289/ehp.1509735. Epub 2015 Oct 30.	Verify the hypothesis of an association between blood cadmium and cardiovascular events in a population with blood cadmium levels similar to most populations in the US and Europe	Cohort, case-controls, cross-sectional study, meta-analyzes, case report ... Cohort Cohort:Malmö Diet and cancer Study (MDC)	Acute coronary event (myocardial infarction or death due to ischemic disease), Major coronary event, Cerebrovascular accident (ischemic or hemorrhagic), Cardiovascular mortality, All-cause mortality	The study population is a subset of the Malmö Diet and Cancer Study cohort made up of men and women from the city of Malmö born between 1926 and 1945. n= 4,819 people	Blood cadmium is measured from erythrocytes obtained by centrifugation. Blood cadmium was estimated by multiplying the cadmium in erythrocytes by the hematocrit. The analysis is carried out by mass spectrography. Detection limit: 0.02 µg / L 1st quartile: 0.17 µg / L, 2nd q: 0.26 µg / L, 3rd q: 0.50 µg / L	tobacco, waist circumference, low level of education, alcohol, triglycerides, HbA1c, CRP, other cardiovascular risk factors not associated with blood cadmium in a first univariate analysis (postmenopausal status, hormonal treatment, treatment for hypertension, diabetes , taking medication to lower cholesterol, diastolic pressure, HDL and LDL cholesterols).	- Cox proportional risk regression to verify the association between blood cadmium and the incidence of pathologies. Age was taken as a time scale. The suitability of the Cox model was verified visually as well as the interaction between cadmium and cardiovascular risk factors. The fourth quartile is compared to the first quartile and a trend test is performed. 3 models were tested. Model 1: blood	The relative risks of all 4th quartile / first cardiovascular events were significant: 1.8 [1.2-2.7] for acute coronary events, 1.9 [1.3-2.9] for accidents cerebrovascular. Trends are observed according to quartiles 2 and 3 for acute events and major cardiac events, but for stroke, an association is only observed with the upper quartile. Analysis in non-smokers shows similar results as well as sensitivity analyzes.	Mean Cd sg = 0.46 µg / L (median 0.26 µg / L) Pathologies 406 coronary pathologies (527 interventions if included) 346 stroke 882deaths including 257 CV Cox: 4th quartile vs 1st quartile: HR around 2	The results of the study support the hypothesis of cadmium as a factor in cardiovascular disease in its own right.	high	Long follow-up (17 to 20 years), good reliability of Swedish registers No data on changes in cofactors since baseline, no data on urinary cadmium, blood cadmium was not measured in whole blood but was calculated from hematocrit and cadmium in erythrocytes Few lost to follow-up (30) Detailed information on confounding factors

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							cadmium in quartiles + sex. Model 2: same variables + confounding factors (tobacco, waist circumference, low level of education, alcohol, triglycerides, HbA1c, CRP. Model 3: Same variables + other cardiovascular risk factors not associated with blood cadmium in a first univariate analysis. - Blood cadmium as a continuous variable was used in generalized additive regression models - Sensitivity analyzes have been carried out. Among others: restriction to subjects with all the complete variables, time as a scale with age as a cofactor, the use of quartiles					

Reference	Objective	Study Design	Health Outcomes	Population	Exposure measurements	Confoundings	Model	Main results	Exposure levels	Conclusion of the authors	Quality of the study	Comments
							specific to each sex ...					
Borné et al., 2015. Cadmium exposure and incidence of heart failure and atrial fibrillation: a population-based prospective cohort study. BMJ Open. 2015 Jun 15;5(6):e007366. doi: 10.1136/bmjopen-2014-007366.	To study the link between blood Cd / heart failure and atrial fibrillation	Cohort :Malmö Diet and cancer Study (MDC) M and F aged 45 to 64 living in Malmö invited to participate in a study on diet and cancer In total: 4378 subjects analyzed	Heart failure (HF) Atrial fibrillation (AF) HF / AF: hospital registers	Cohort :Malmö Diet and cancer Study (MDC) 46-68 years Swedish	Cd blood Cd concentration in erythrocytes adjusted hematocrit Measurement by inductively coupled plasma mass spectrometry HDL, LDL measurement	age - systolic BP - Tt antihypertensive - Tt anti-lipid - Diabetes - ATCD coronary pathologies - waist circumference, - tobacco status - alcohol - LDL - HDL - CRP - Serum creatinine - Marital status - Level of studies	Analysis of variance for continuous variables -Logistic regression for dichotomous variables -Cox model - Monitoring curves (Kaplan meier -restricted cubic spline	Median Cd sg = 0.24 µg / L in men and 0.27 µg / L in women HF: 143 cases AF: 384 cases Cox IC HR: 2.64 (1.60-4.26) when 4th quartile compared to 1st HR: 1.95 (1.02-3.72) when adjusted on other FR CVs No dose-response relationship High risk in the 4th quartile Stratified on sex: significant result in H AF: no association observed	The 4th quartile of cadmium is 0.98 µg / L for men and 0.97 µg / L for women, the first is 0.12 µg / L for men and 0.14 µg / L for women .	Blood CD in 4th quartile associated with increased risk of HF	High	Prospective cohort Large workforce Long follow-up (16.8 years)) Few lost to follow-up (30) Validity of hospital register data
Julin et al., 2013. Exposure to cadmium from food and risk of cardiovascular disease in men: a population-based prospective cohort study. Eur J Epidemiol. 2013 Oct;28(10):837-40. doi: 10.1007/s10654-013-9841-8. Epub 2013 Aug 24.	Study the association between dietary intake of Cd and the incidence of all CV pathologies and ischemic pathologies	Cohort of Swedish men (COSM)	Myocardial infarction Ischemic or hemorrhagic stroke Death from these pathologies	Swedish Men Cohort 36,863 men aged 45-79 at baseline (1997) in		Age, level of education, family ATCD (IDM, cholesterol, http, use of aspirin, smoking status, BMI, physical activity, alcohol consumption, energy intake, Consumption of vegetables and grains	Cox model Linear trend tested	5,128 incident CV pathologies including 2,876 IDM (602 deaths) and 2,252 stroke (1,762 ischemic and 330 hemorrhagic) Average daily intake of Cd: 19 µg / d No significant association observed between CV and food CD pathologies These results are unchanged after adjustment		No association between food Cd and CV pathologies in this study	high	Prospective cohort Population-based Number of significant incident cases Almost complete monitoring with linkage of registers Exposure too low to accelerate atherosclerosis, extent of exposure too low to see an association?
Julin et al., 2013b. Cadmium in diet and risk of cardiovascular disease in women, Epidemiology, 24 (2013), 6,	To evaluate the association between quartiles of food frequency questionnaire –based	Swedish Mammography cohort, 33,333 women followed from 1997 through	cardiovascular disease	SMC 33,333 women, aged 48–83 years	Dietary intake was assessed by a 96-item food frequency questionnaire (FFQ)	BMI, smoking status, physical activity, hypertension, cholesterol	Cox proportional hazard models	3155 incident cases of total cardiovascular disease: 1322 cases of myocardial infarction and 1833 cases of total stroke [1485 ischemic and 208		no support for an overall association between cadmium exposure from food (the predominant source of cadmium among nonsmokers) and incidence of total cardiovascular	high	

Reference	Objective	Study Design	Health Outcomes	Population	Exposure measurements	Confoundings	Model	Main results	Exposure levels	Conclusion of the authors	Quality of the study	Comments
880-885. https://doi.org/10.1097/EDE.0b013e3182a777c9.	estimates of cadmium exposure from food and incident cardiovascular disease and its subtypes.	2010.			data on cadmium concentrations in foods were obtained mainly from the Swedish National Food Agency. Exposure from air and water was disregarded due to their low contribution to the total exposure (<1%20 and 0.2%,21 respectively).			hemorrhagic stroke] no association between cadmium exposure via food and risk of cardiovascular disease, myocardial infarction, stroke, ischemic stroke, or hemorrhagic stroke (neither in age-adjusted nor in multivariable-adjusted models)		disease, myocardial infarction, or stroke.		
Tellez-Plaza et al., 2012. Cadmium exposure and all-cause and cardiovascular mortality in the U.S. general population. Environ Health Perspect. 2012 Jul;120(7):1017-22. doi: 10.1289/ehp.1104352. Epub 2012 Apr 2.	To study the association between Cd blood / Cd Urine and death from cardiovascular pathologies	Prospective follow-up in NHANES Subjects surveyed 1999-2004 followed for mortality until 2006	Cardiovascular deaths and deaths from all causes	Inclusion : Subjects who participated in NHANES 1999-2004 In total, analysis on 8,989 participants over 20 years old Exclusion - 772 pregnant women - 661 subjects without blood Cd, n	Death certificate Cd blood and U log transformed Use of quintiles	Survey -Age - Gender -Level of studies - Menopausal status, - Tt anti hypertensive - Tt Diabetes - Tt hypercholesterolemia Exam - BMI - TA (with definition of HTA) - Blood sugar (with definition of diabetes) - C reactive protein (CRP) - Chlesterolemia (HDL and LDL) - Serum cotinine - Serum creatinine - eGFR	Cox model Comparison of quintiles Using restricted quadratic splines to test nonlinear relationships	The 80th and the 20th percentile of urinary cadmium are respectively: 0.57 and 0.14 µg / g of creatinine, those of blood cadmium 0.80 and 0.22 µg / L.	Estimation and confidence interval, relative risks, odds ratio ... Cd sg; geometic avg 0.44µg / L Cd_U; geometic avg 0.28µg / g cr Number of deaths All causes = 524 Deaths from cardiovascular disease = 191 Deaths from cardiac pathologies = 113 Deaths from ischemic heart disease = 88 Cox model Blood CD HR death from all causes: 1.5 (1.07-2.10) HR death from cardiovascular	Low level of exposure to Cd associated with death from all causes and death from pathologies V	high	Possible biases 1.exclusion of subjects without information on the variables of interest FR CV 2.possiblities of incorrectly coded cause of death 3. Cd biomarkers measured just at inclusion: possibility of non-differential errors and risk of underestimation of the association 4. imputed Cd values if no measurements or inf LOD values 5.Risk of overfitting 6.possibility of residual confusion for tobacco strengths : - "Representative"

Reference	Objective	Study Design	Health Outcomes	Population	Exposure measurements	Confoundings	Model	Main results	Exposure levels	Conclusion of the authors	Quality of the study	Comments
						model 1: socio-demographic variables (race / ethnicity, sex, level of education, level of income Model 2: model 1+ postmenopausal status for women, BMI, HTA, diabetes, blood lead, total cholesterol, HDL, anti cholesteol tt, CRP, eGFR Model 3: model 2 ° tobacco status, PA,			pathologies: 1.69 (1.03-2.77) HR death from cardiac pathologies: 1.98 (1.11-3.54) HR death from ischemic heart disease: 1.73 (0.88-3.40) Cd U HR death from all causes: 1.52 (1.00-2.29) HR death from cardiovascular pathologies: 1.74 (1.07-2.83) HR death from cardiac pathologies: 2.53 (1.54-4.16) HR death from ischemic heart disease: 2.09 (1.06-4.13) PAR for all causes of death Blood CD 7% Cd U 8.8%			sample of the American population - Precise information on FR - Precise Cd measurements
Tellez-Plaza et al., 2013a. Cadmium Exposure and Incident Cardiovascular Disease. Epidemiology 24 (2013), 3, 421–429. https://doi.org/10.1097/EDE.0b013e31828b0631.	Verify the hypothesis of an association between urinary cadmium considered as an established biomarker of cumulative exposure and the incidence and mortality from cardiovascular disease as well as mortality from all causes.	Cohort The cohort was formed between 1989 and 1991. Participation rate: 62%. After excluding some subjects (various missing data), it includes 3348 men and women from 13 Indian communities in Arizona, Oklahoma and North	cardiovascular incidence and mortality. They are obtained from hospitalization records and death registers and during two hospital visits made in 1993-1995 and 1998-1999. The hospital reports were reviewed by a	45-75 years old at inclusion Oklahoma, Dakota, South and North Dakota Case number:3 348 Cohort Strong Heart Study	Urinary cadmium was measured in morning urine samples and shipped by boat to Gratz where it was measured by the mass spectrometry method. Detection limit: 0.015 µg / L. These measurements were	BMI, tobacco, hypertension, socio-demographic data (age, race, postmenopausal status, level of education), smoking history, total and HDL cholesterol (hence hyperlipidemia), diabetes, estimated glomerular filtration.	The association between urinary cadmium and cardiovascular events was assessed using the Cox proportional hazard model. 3 models were used with age as a time scale and the logarithm of urinary cadmium. Model 1: fit	Urinary cadmium corrected by creatinine is associated with mortality in each of the 3 models. The adjusted relative risks of all-cause, cardiovascular and coronary mortality between the highest and the lowest cadmium level are respectively 1.58 [1.32-1.89], 1.87 [1.34-2.60] and 1.51 [1.04-2.20]. The relative risk of incident coronary artery disease is 1.48 [1.21-1.80], those for coronary artery disease, stroke and cardiac arrest are		The results of the study support the hypothesis of cadmium as a factor in cardiovascular disease in its own right. The mechanisms of action are thought to be the role of cadmium in oxidative stress, endothelial dysfunction, atherosclerosis formation, hypertension and kidney disease. Cadmium-related damage could be promoted by abnormal production of metallothionein in endothelial cells. Epigenetic and	high	Strengths: Good quality of health data High number of subjects followed for a long time. Weaknesses (excluding bias): it is based on a single measurement of urinary cadmium taken at time t0 of the study - The population studied is specific (high rate of cardiovascular pathologies and all-cause mortality). High rate of diabetes.

Reference	Objective	Study Design	Health Outcomes	Population	Exposure measurements	Confoundings	Model	Main results	Exposure levels	Conclusion of the authors	Quality of the study	Comments
		and South Dakota aged 45 to 75 (population with high rates of pathology cardiovascular). It was followed until 12/31/2008 Invitation of all eligible subjects according to age to participate (participation rate: 62%). Out of 4,218 participants selected, 517 were excluded because cadmium data was missing (not enough urine to measure it), 139 for missing data on tobacco and 214 for missing data on other variables of interest	committee of doctors to establish the diagnoses		made during the enrollment period of subjects in the cohort (1989-1991)		only on gender. Model 2: Additional adjustment for postmenopausal status, education, BMI, existence of diabetes, total cholesterol, HDL cholesterol, hypertension, and glomerular filtration rate. Model 3: previous factors + smoking status and number of pack-years. The highest quartile of urinary cadmium is compared to the lowest quartile. Other sensitivity analyzes were done on subgroups defined by age, sex, glomerular filtration rate, region ...	respectively 1.33 [1.05-1 , 68], 1.87 [1.22-2.86] and 1.61 [1.10-2.36]		endocrine disruption mechanisms could also be involved.		

Appendix 4: Table 1-SI. Urinary cadmium concentrations (µg $Cd.g^{-1}$ creatinine) predicted by the PBPK model to reach a value of 0.5 µg $Cd.g^{-1}$ creat and 1.0 µg $Cd.g^{-1}$ creat (EFSA).

The urinary concentrations obtained with our modified PBPK model correspond to the reference health values for cadmium (in µg $Cd.g^{-1}$ creat), as a function of age, not to be exceeded to remain below the threshold of the internal TRV (0.5 or 1.0 µg $Cd.g^{-1}$ of creat) in adulthood (Figure 2).

The values reported in Table 1-SI are given for information only and must be interpreted in light of the estimated values of weight and the estimates of 24-h urinary creatinine excretion.

658 ***Table 1-SI: Urinary cadmium concentration (µg Cd.g^{-1} creatinine) predicted by the PBPK model***
659 ***to reach a value of 0.5* µg Cd.g^{-1} creat *(ANSES) and 1.0* µg Cd.g^{-1} creat *(EFSA).***
660

		Cadmium Critical concentration	
		0.5 µg Cd.g^{-1} creat ANSES, 2019	1.0 µg Cd.g^{-1} creat EFSA, 2011
Time (year)	Body weight (kg)	CdU (µg Cd.g^{-1} creat)	CdU (µg Cd.g^{-1} creat)
0	**4**	**0.00**	**0.00**
1	**8**	**0.02**	**0.03**
2	**12**	**0.03**	**0.06**
3	**16**	**0.04**	**0.08**
4	**20**	**0.04**	**0.09**
5	**24**	**0.05**	**0.10**
6	**27**	**0.05**	**0.11**
7	**31**	**0.06**	**0.12**
8	**34**	**0.06**	**0.13**
9	**37**	**0.06**	**0.13**
10	**40**	**0.06**	**0.14**
11	**42**	**0.07**	**0.15**
12	**45**	**0.07**	**0.16**
13	**47**	**0.07**	**0.16**
14	**50**	**0.08**	**0.17**
15	**52**	**0.08**	**0.18**
16	**54**	**0.08**	**0.19**
17	**56**	**0.09**	**0.20**
18	**58**	**0.09**	**0.21**
19	**59**	**0.10**	**0.22**
20	**61**	**0.10**	**0.23**
21	**62**	**0.11**	**0.24**
22	**64**	**0.11**	**0.25**
23	**65**	**0.12**	**0.26**

		Cadmium Critical concentration	
		0.5 µg $Cd.g^{-1}$ creat ANSES, 2019	1.0 µg $Cd.g^{-1}$ creat EFSA, 2011
24	66	0.12	0.27
25	67	0.13	0.28
26	68	0.13	0.30
27	69	0.14	0.31
28	69	0.15	0.33
29	70	0.16	0.35
30	71	0.16	0.36
31	71	0.17	0.39
32	71	0.19	0.41
33	72	0.20	0.43
34	72	0.21	0.46
35	72	0.22	0.48
36	73	0.23	0.51
37	73	0.25	0.54
38	73	0.26	0.57
39	73	0.28	0.60
40	73	0.29	0.63
41	73	0.31	0.67
42	73	0.32	0.70
43	72	0.34	0.73
44	72	0.36	0.76
45	72	0.37	0.80
46	72	0.39	0.83
47	72	0.40	0.86
48	71	0.42	0.88
49	71	0.43	0.91
50	71	0.44	0.93
51	71	0.46	0.95

		Cadmium Critical concentration	
		0.5 µg Cd.g^{-1} creat ANSES, 2019	1.0 µg Cd.g^{-1} creat EFSA, 2011
52	**70**	**0.47**	**0.97**
53	**70**	**0.47**	**0.98**
54	**70**	**0.48**	**0.99**
55	**70**	**0.48**	**0.99**
56	**69**	**0.49**	**1.00**
57	**69**	**0.49**	**1.00**
58	**69**	**0.49**	**1.00**
59	**69**	**0.49**	**0.99**
60	**69**	**0.49**	**0.99**
61	**69**	**0.49**	**0.98**
62	**69**	**0.49**	**0.98**
62	**69**	**0.50**	**0.98**

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