Meeting

Annex A -First Draft Statement on the potential risks from cadmium in the maternal diet

This is a paper for discussion.

This does not represent the views of the Committee and should not be cited.

Introduction

1. The Scientific Advisory Committee on Nutrition (SACN) last considered maternal diet and nutrition in relation to offspring health in its reports on ‘The influence of maternal, fetal and child nutrition on the development of chronic disease in later life’ (SACN, 2011) and on ‘Feeding in the first year of life’ (SACN, 2018). In the latter report, the impact of breastfeeding on maternal health was also considered. In 2019, SACN agreed to conduct a risk assessment on nutrition and maternal health focusing on maternal outcomes during pregnancy, childbirth and up to 24 months after delivery; this would include the effects of chemical contaminants and excess nutrients in the diet.

2. SACN agreed that, where appropriate, other expert Committees would be consulted and asked to complete relevant risk assessments e.g., in the area of food safety advice. This subject was initially discussed by the COT during the horizon scanning item at the January 2020 meeting with a scoping paper being presented to the Committee in July 2020. This included background information on a provisional list of chemicals proposed by SACN, which was subject to change following discussion by COT who would be guiding the toxicological risk assessment process: candidate chemicals or chemical classes can be added or removed as the COT considered appropriate. The list was brought back to the COT with additional information in September 2020 where , it was agreed that papers on a number of components should be prioritised. For this paper, the advice of the COT is sought on whether exposure to cadmium would pose a risk to maternal health.

3. The UK Health Security Agency (UKHSA), previously Public Heath England, have produced information for the general public on the risk of exposure to cadmium but there are currently no Government dietary recommendations for the maternal diet that relates to this metal.

Background

4. Cadmium (Cd) is a soft malleable metallic element that is silvery-white or bluish white in appearance and exists in various mineral forms. Early uses of cadmium include the use of cadmium compounds as pigments with more recent uses being in rechargeable batteries and protection coatings for prevention of corrosion of iron and steel. Cadmium can be released into the environment by natural activities (e.g., volcanic activity, erosion and weathering), and anthropogenic activities such as mining, smelting and refining non-ferrous metals.

5. In the non-smoking population, the diet is the main source of cadmium exposure (approximately 90%), with less than 10% of exposure being due to inhalation from ambient air and drinking water (EFSA, 2009). Cereals and vegetables (e.g., potatoes) are the main food sources that contribute to cadmium exposure with levels dependent on the usage of phosphate fertilisers where cadmium is present as a contaminant. The uptake of cadmium by plants is influenced by the pH of the soil, with a low pH enhancing uptake (Jarup et al. 1998). In animal products, the main sources of cadmium are the kidney and liver due to cadmium accumulation in these organs.

6. Smoking is the main non-dietary source of exposure of cadmium due to the accumulation of cadmium in the tobacco leaves via the soil and can lead to a similar internal exposure as that acquired from the diet (EFSA, 2009).

7. At present there are no data that indicate cadmium is an essential micronutrient for animals, plants, or microorganisms (EFSA 2009, Khan et al., 2017).

Toxicity

8. As a starting point, the opinions of EFSA, JECFA, WHO and ATSDR were used. Literature searches were also conducted using PubMed and Scopus for the last 15 years. The list of search terms are provided in Appendix A.

Toxicokinetics

9. The oral bioavailability of cadmium from food and water can range from 1-10%, rising to up to 20% in individuals with iron deficiency (ATSDR, 2012; Krajnc et al. 1987). Lower iron stores are more common in women of reproductive age, especially during pregnancy, compared to men (EFSA, 2009; Romano et al. 2016). An increase in gastrointestinal absorption of cadmium has also been shown to be associated with a low intake of nutrients such as zinc and calcium in animal studies (Reeves and Chaney, 2008). Absorption of cadmium via inhalation (5-50% of cadmium inhaled) is dependent on the size of the particles with 50-60% of ultrafine particles being retained through smoking, the remainder being exhaled with the smoke (EFSA, 2009; WHO, 2000).

10. The liver and kidneys are the main organs affected by cadmium exposure. Cadmium can be transported in the blood by erythrocytes and is subsequently taken up by the liver, where it stimulates the production of the cysteine-sulphur rich protein metallothionein (MT) to which it binds.

11. Metallothionein modulates a number of biochemical processes which includes binding to a number of trace metals (including cadmium) and thereby protecting cells and tissue against heavy metal toxicity. Bound and conjugated forms of cadmium are not in themselves toxic, but the complexes release divalent cadmium which is responsible for the cellular toxicity (Jacobo-Estrada et al. 2017). Metallothionein also plays a role in homeostasis of essential metals such as zinc and copper and provides a protective function as an antioxidant against reactive oxygen species (ROS), as well as protecting against DNA damage (Thirumoorthy et al. 2011).Cadmium has a disruptive effect at the cellular level by inducing signal dysregulation, competing with Zn2+ and Ca2+ transport and permanently disrupting transducting modules and second messengers (Jacob-Estrada et al. 2017; Thevenod, 2009).

12. The cadmium-metallothionein (Cd-MT) complex is filtered through the glomerulus and reabsorbed by the proximal tubular cells (Yang and Shu, 2015; EFSA, 2009). In the human body, the biological half-life ranges from 10-35 years (EFSA, 2009; WHO, 2017).

13. Most ingested cadmium is excreted in the faeces due to poor absorption. Excretion via the urine is dependent on the cadmium concentration in the blood and kidney. In non-occupational exposure, the adult mean urinary cadmium in urine is normally < 1 µg/g creatinine (SCOEL, 2017).

14. Levels of urinary cadmium of 1 µg/g of creatinine have been associated with a decrease of bone density with increasing risk of fractures in women and height loss in men (Kazantzis, 2004). During pregnancy, absorption of cadmium is

enhanced due to physiological changes which ensure the nutritional needs of mother and fetus and it can directly interfere with the metabolism of calcium and decrease vitamin D synthesis in the kidneys, which leads to increased absorption and body burden of cadmium (Al-Saleh et al. 2011; Kazantzis, 2004; Young and Cai, 2020).

Acute toxicity

15. Acute cadmium toxicity occurs mainly from inhalation in an occupational setting, however acute toxicity from oral exposure has been reported with lethal dose ranges between 350 mg to 8900 mg of cadmium which correspond to doses of ≈ 20 to 130 mg/kg bw in a 70 kg adult (Bernard and Lauwerys, 1986; EFSA, 2009).

Chronic toxicity

16. In non-occupational exposure, chronic exposure to cadmium is of more concern. Chronic exposure can result in proteinuria and loss of tubular function in the kidney, with urinary excretion of β2-microglobulin being used as a useful biomarker to detect tubular damage (EFSA, 2009). If detected early, damage from cadmium exposure may be reversed (Gao et al., 2016), but it may become irreversible and progress even once exposure has ceased (EFSA, 2009). As cadmium accumulates in the kidney, it blocks the renal synthesis of 1,25 dihydroxyvitamin D which is essential for calcium absorption and bone mineralization. Divalent cadmium has similar physicochemical properties to calciums ion and so disrupts the calcium signalling cascade affecting the absorption of calcium increasing the levels of excess calcium and phosphorus excreted in the urine. With the reduction of calcium, osteomalacia and osteoporosis can result. The symptoms of bone fractures and kidney dysfunction were diagnosed as Itai-Itai (ouch-ouch) disease, first described in Japan in areas where the diet consisted of cadmium contaminated rice (ATSDR, 2012; Umemura and Wako, 2006; Unsal et al. 2020). In a Swedish cohort study, dietary cadmium level >13 µg/day were shown to increase the risk of osteoporosis and fractures by 32% and 31% percent respectively (Engstrom et al. 2012).

Genotoxicity

17. Although not directly genotoxic, cadmium has the potential to induce DNA damage, micronuclei, chromosomal aberrations, sister chromatid exchange (SCE) and genetic mutations (ATSDR, 2012; EFSA, 2009). The mechanisms associated with this indirect affect include increased ROS formation, DNA repair

inhibition, reduction in cell growth and resistance to apoptosis, and epigenetic changes in DNA methylation (Hartwig et al. 2020).

Carcinogenicity

18. Cadmium and its compounds were reviewed in 2012 by IARC who classified them as Group 1 (carcinogenic to humans) as there was sufficient evidence that cadmium and its compounds caused lung cancer and positive associations of cadmium with the risk of kidney and prostate cancer (IARC, 2012).

19. A statistically significant increased risk of lung cancer from inhalation exposure was originally associated with occupational exposure to cadmium, however it has now also been shown in the general population with no occupational exposure from inhalation (Nawrot et al. 2015, Satarug et al. 2017). A synergistic effect between smoking, occupational exposure and renal cancer was indicated and it was suggested that additional factors other than cadmium may have been contributing via the cigarette smoke (Kolonel, 1967). Associations have also been reported in *in vivo* studies which show an increase in cancers of the bladder and prostate, however, in human studies there are inconsistencies in the results (IARC, 2012; Nordberg et al. 2018).

20. Cohort studies have suggested that dietary exposure to cadmium below the levels suggested by EFSA and JECFA show an increased risk of breast cancer and osteoporosis in post-menopausal women. However, the EC Joint Research Council report concluded that there is currently no evidence that cadmium acts as a carcinogen following oral exposure (EFSA, 2009).

Reproductive and developmental toxicity

21. Cadmium accumulates in the placenta with lower levels being detected in the maternal and cord blood (Roles et al. 1978; Osman et al. 2000; Gundacker et al. 2012). Accumulation is associated with placental necrosis, loss of function and reduction in trophoblast cell proliferation (Thompson and Bannigan 2008; Banerjee et al. 2020; Cerrillos et al. 2019).

22. Metallothionein is produced in the placenta as a protective barrier against cadmium entering the foetus. However, this can disrupt zinc homeostasis in the placenta by displacing the zinc in the metallothionein complex with cadmium (Casserta et al. 2013; Espart et al. 2018). Cadmium has been shown to interfere with endocrine hormone synthesis which is linked to fetal growth impairment by interfering with placental steroidogenesis *in vitro* (Unsal et al. 2020; Caserta et al. 2013; Everson et al. 2017). Cadmium also inhibits 11-β-

hydroxysteroid dehydrogenase (11-β-HSD2) activity which has been linked to intrauterine growth restriction in *in vitro* and human studies (Ebrahim et al. 2015; Kippler et al. 2012).

23. During gestation there is a larger demand for iron which is required for fetal development, this is mediated by the Divalent Metal Transporter-1 (DMT-1) in the intestine and the placenta. If iron stores begin to be depleted, cadmium transport is facilitated by DMT-1 (Jacob-Estrada et al. 2017).

24. *In utero* exposure to cadmium is thought to be connected to DNA methylation which can alter the epigenetic mechanisms affecting fetal development and genomic expression (Banerjee et al. 2020; Dharmadasa et al. 2017). The DNA methylation appears to have different effects dependent on the sex of the fetus, with positive correlation with hypermethylation of SALL1 genes with cadmium exposure for boys and negative correlation of hypomethylation of SIAH3, HS3ST4 and TP53TG1 genes for girls (Kippler et al. 2013; Banerjee et al. 2020).

25. Adverse birth outcomes linked with blood and urine cadmium biomarkers of cadmium exposure and cadmium levels in placental samples at birth can include low birth weight, smaller head circumference, low Apgar score, crown-heel lengths and neurobehaviour development effects (Tung et al. 2022; Guo et al. 2017).

26. In a birth cohort study by Guo et al. *(*2017) (n = 1073 mother-newborn pairs) from an agricultural population in China, the results showed that the cadmium concentration in cord blood was significantly negatively associated with ponderal index at birth (this assesses the ratio of a person’s height to weight). No association was shown between urinary cadmium concentrations and ponderal index.

27. Placental samples (n=192) from participants in the RICHS cohort study (Tung et al. 2022) showed an association between increased cadmium concentrations in the placenta (mean cadmium 4.56 ng/g) and an increase in adverse neurobehavioural outcomes. It was assumed that most of the cadmium was obtained from the diet,although no dietary information was obtained from the cohort and there was a relatively low prevalence of women who smoked during pregnancy (10.2%).

28. In contrast, the MOCEH cohort study based in Korea (Shah-Kulkarni et al. 2020) showed no significant association with prenatal cadmium exposure and the mental development index or the psychomotor development index in infants at 6

months of age.

29. Adverse maternal effects linked to cadmium exposure include preeclampsia, proteinuria, renal dysfunction and micronutrient deficiency (Liu et al. 2019; Osario-Yanez et al. 2016). An association has also been reported between cadmium exposure and hypertension in pregnant women smokers (n= 9), although it is unclear what components in the smoke are causing the hypertension or if there were any synergistic effects with the cadmium (Kosanovic et al. 2002). Animal studies have shown that pregnant animals were more sensitive to the toxic effects of cadmium in comparison to non-pregnant ones with pregnant rats showing similar effects to those seen in human preeclampsia including blood in the urine and later development of visceral congestion, pulmonary and hemorrhagic edema, (Chisolm and Handorf, 1987). However, in one human study (Osorio-Yanez et al. 2016) high levels of urinary cadmium were not reported in those that developed preeclampsia, with no observed statistically significant differences in urinary cadmium concentrations among women who reported smoking during pregnancy (n=43), former smokers (n= 130) and never smokers (n= 441).

30. There is inconsistency in the available epidemiological data with some studies suggesting that cadmium and its compounds can lead to an increased risk of cancer, preeclampsia and affecting birth weights of new-borns, while others show no effect (Nordberg et al. 2018; Menai et al. 2021; IARC, 2012).

Health-based guidance value

31. A tolerable weekly intake (TWI) for cadmium was established by the EFSA CONTAM panel in 2009. EFSA noted that the reproductive effects of cadmium, based on the available epidemiology at that time, were uncertain and considered cadmium to be primarily toxic to the kidneys. Hence, the TWI of 2.5 μg/kg bw was based on renal effects. To determine a BMDL5 of 1 μg/g of creatinine, a meta-analysis was conducted between urinary cadmium and urinary β-2-microglobulin as the tubular damage biomarker. An elevated level of β-2-microglobulin of 4 μg/g of creatinine with an adjustment factor of 3.9, accounting for the inter-individual variation of urinary cadmium resulted in the BMDL5 of 1 μg/g creatinine. To enable 95% of the population to have a urinary concentration below 1 μg/g of creatinine by the age of 50, it was calculated that the daily intake of cadmium should not exceed 0.36 μg cadmium/kg bw or 2.5 μg cadmium/kg bw per week (EFSA, 2009).

32. The Joint FAO/WHO Committee on Food Additives (JECFA) established a Provisional Tolerable Weekly Intake (PTWI) of 7 µg/kg bw in 1988. In 2011, JECFA re-assessed cadmium and established a Provisional Tolerable Monthly Intake (PTMI) of 25 µg/kg bw (equivalent to 0.8 µg/kg bw/day), reflecting the long half-life of cadmium and the bioaccumulation in the kidney. Urinary excretion of > 5.24 µg of cadmium per gram of creatinine indicated a sharp increase in β-2-microglobulin (JECFA, 2011). Although the PTMI was not discussed at the 91st JECFA meeting, a national estimate of total dietary exposure ranged from 0.6 µg/kg bw per month (2.6% of PTMI) in adults in Mali to 24 µg/kg bw per month (96% of PTMI) in children (aged 4-11) in China. It was noted that there were high percentiles occasionally above the PTMI, but on average it was between 20 and 60% of the PTMI. UK and EU data were considered in this analysis but it is unknown where in the range these would have fallen.

33. In 2011, following JECFA's re-evaluation, EFSA compared the different approaches used by the EFSA CONTAM Panel and JECFA to determine a health-based guidance value (HBGV). EFSA concluded that the choice of toxicodynamic function played an important role on the outcome (EFSA 2011a) and that the TWI determined by the CONTAM Panel should be maintained "to ensure a high level of protection of consumers, including subgroups of the population such as children, vegetarians or people living in highly contaminated areas". Nevertheless, they also acknowledged that some subgroups could exceed both the JECFA PTMI and the CONTAM Panel TWI (EFSA 2011b).

Cadmium exposures in maternal health

Sources of cadmium exposure

Human breast milk

34. Human breast milk has previously been discussed in the COT statement on cadmium in the infant diet (COT, 2018). Cadmium intake in the average and high level exclusively breast-fed UK infants from 0 to < 6 months ranged between 11 – 68% of the EFSA TWI of 2.5 µg/kg bw/week. The highest total exposure to cadmium in the infant diet was found in solid food for 12 - <60 month old children which constituted up to 260% of the EFSA TWI of 2.5 µg/kg bw/week (0.36 µg/kg bw/day). Although there was an exceedance, it was not expected to remain at this level over the decades of bioaccumulative exposure considered by EFSA in setting the HBGV. The Committee concluded that there was no major concern, however efforts to minimise the levels of cadmium in the environment should

continue.

Food

35. Cadmium levels have been measured in the composite food samples of The Total Diet Study (TDS) (Bates et al. 2014, 2016; Roberts et al. 2018). The highest exposure to cadmium came from the food groups miscellaneous cereals, potatoes, and bread.

36. In a Swedish birth cohort study, the maternal diets with high intakes of vegetables, root vegetables, nuts, grains and rice were significantly associated with higher erythrocyte and urinary cadmium levels, whereas red meat consumption had an inverse association (Gustin et al. 2020). High accumulation of cadmium has also been reported in rice where it is a staple food in Asia and it was shown that females had a higher elevated body burden of cadmium (Simmons et al. 2005; Kippler et al. 2007; Geng and Wang, 2019).

Drinking water

37. Drinking water can be contaminated with cadmium due to leaching from corroded/galvanized pipes or solder used within taps and water heaters (WHO, 2011). In areas with high cadmium pollution, well water may also be affected, with cadmium levels in excess of 25 µg/L (WHO, 2000; Lauwerys et al. 1990) being reported.

38. Directive 2003/83/EC specifies a maximum level of cadmium in natural mineral waters of 3.0 µg/L and equivalent UK legislation. The EU adopted the revised Drinking Water Directive ((EU) 2020/2184) which came into force at the start of 2021, which upheld the set value of 5.0 µg/L of Directive 98/83/EC on the quality of water intended for human consumption.

39. Levels of cadmium in drinking water in 2020 were published for England and Wales (99th percentile 0.23 µg/L, no mean data available), Scotland (mean and 97.5th percentile 0.02 and 0.06 µg/L respectively) and Northern Ireland (mean and 97th percentile 0.038 and 0.04 µg/L respectively) by the Drinking Water Inspectorate and the Drinking Water Quality Regulator (DWQR) for Scotland and Northern Ireland Water respectively.

Environmental

Dust

40. Cadmium dust includes various cadmium compounds including cadmium chloride and cadmium oxide which is formed when moist air oxidises the cadmium (Pohanish 2017; IPCS,1992). The cadmium levels in dust were determined by ICP-OES with a median concentration of <0.30 µg/g. Although the concentrations were low in environmental samples, urine samples in a study conducted in Western Australia by Hinwood et al. (2013) showed elevated levels. It was suggested that these higher levels of cadmium were linked to the participants eating fish and not taking iron/folic acid supplements, while those participants who used iron and folic acid supplements showed an association with decreased cadmium levels. Other factors that could affect the levels of cadmium were economic status and the geographical location in Western Australia.

Soil

41. Cadmium occurs naturally in the Earth’s crust, is commonly found in association with zinc ores and is is also associated with atmospheric pollution (e.g., volcanic eruptions and emissions from smelting) and phosphate fertilisers. The Soil Guideline Value for residential soils adopted a total concentration of 10 mg/kg for cadmium which is above the concentration found in most soils (Rawlins et al. 2012; Environment Agency, 2009).The summary statistics reported for the principal domain for England and Wales were a normal background concentration (NBC) of 1.0 mg/kg (n = 4418) and 1.4 mg/kg (n = 681) respectively.

Air

42. Cadmium can be released into the atmosphere by anthropogenic sources and occurs mainly as fine respirable particles in particulate matter (<10 µm). The Fourth Daughter Directive (2004/107/EC) set the target value for cadmium as 5 ng/m3. Using the data collated by the UK Air Information Resource for 2020 the air exposure measurements of cadmium for England and Wales ranged from 0.062 to 0.725 ng/m3 and 0.057 to 1.382 ng/m3 respectively Home - Defra, UK.

43. It has been estimated that one cigarette contains between 0.2 and 1.0 µg of cadmium and although advised not to smoke tobacco products while pregnant, those mothers that continue to smoke during their pregnancy have been shown to have higher cadmium levels in comparison to non-smoking mothers (Ebrahim and Ashtarinezhad, 2015). Chao et al. (2014) sampled human milk samples during the four stages of lactation and found that the highest levels were found in colostrum, thus infants of smoking mothers were exposed to more cadmium than those with non-smoking mothers. Second-hand smoke can also

lead to a 2-fold higher exposure to cadmium in comparison to unexposed women (Stone et al*.* 2021).

44. The COT have previously considered the potential toxicological risks from electronic cigarettes (E(N)NDS) and the effects of bystander smoke (COT, 2018; 2019). The emissions from the electronic cigarettes differ from cigarette smoke (which is a well-known health hazard), with those from the electronic cigarette comprising of the residual particulates/vapour exhaled from the user. The aerosols from these devices were evaluated for metals (including cadmium) by liquid phase extraction and ICP-MS. Although the intakes of cadmium were close to the inhalation medicine permissible daily exposure level, it was concluded that the levels of emissions from the aerosols were unlikely to be of substantial concern for adverse health effects.

Exposure assessment

45. The Total Diet Study was used to estimate the cadmium exposure from food consumed by women of childbearing age (Bates et al*.* 2014, 2016; Roberts et al*.*, 2018). Childbearing age was taken to be 16-49 years of age. The National Diet and Nutrition Survey Rolling Programme (NDNS) does not provide data for pregnant or lactating women, therefore the data for women of childbearing age was used. Caution must be taken when using the data obtained as this may not be a representative reflection of the maternal diet.

46. The mean cadmium exposure from the total diet of women of childbearing age ranged between 0.12 – 0.21 µg/kg bw/day and the 97.5th percentile of 0.21-0.37 µg/kg bw/day. Using the data obtained for England and Wales for drinking water with the TDS data, the exposure assessment of the TDS on the highest 97.5th percentile for water, had a minimal effect on total exposure derived from all foods in the TDS.

47. The food groups providing the highest cadmium exposures were miscellaneous cereals, potatoes, and bread. As stated above, high intakes of rice can occur, especially in certain groups, but there are no separate concentration data for cadmium in rice in the TDS. Although the TDS data can be used to observe sub populations (e.g. vegetarian or ethnic origin), the data sets are small and therefore not robust to provide separate exposures/assessements (Appendix B). It should be noted that pregnant women are advised to eat a variety of different foods to ensure the correct amount of nutrients are being consumed. This includes bread, potatoes, breakfast cereals and rice (NHS, 2020). Therefore, pregnant women may have a different diet in comparison to non-pregnant

females considered in the TDS.

Risk characterisation

48. COT have previously concluded that the EFSA TWI of 2.5 µg/kg bw/week for cadmium was an acceptable value to use for risk assessment, following EFSA's rigorous statistical review of the derivation of its HBGV compared with that of JECFA.

49. Based on the TDS data, the cadmium intake based on bread for women of child-bearing age was 6.1% and 15% of the EFSA TWI daily amount at the mean and 97.5th percentile, respectively .

50. The mean and 97.5th percentile cadmium intake based on the TDS data for miscellaneous cereals for women of child-bearing age were 8.9% and 26% respectively of the EFSA TWI.

51. The mean total intake of cadmium from potatoes for women of maternal age was 6.4% of the EFSA TWI with the 97.5th percentile of 19%.

52. The total daily exposure from food for women of maternal age showed a percentage of the EFSA TWI of 22% to 58% and the 97.5th percentile between 58 and 100%.

53. The amount of cadmium detected in the soil in the principal domains were at the limit of detection and not further assessed.

Conclusions

54. Exposure to cadmium during pregnancy has been associated with adverse effects such as hypertension, preeclampsia, micronutrient deficiency in the mother, and adverse birth outcomes for the foetus. Hypertension has also been reported in animal studies showing pregnant animals are more sensitive to the toxicological effects of cadmium in comparison to non-pregnant animals, while preeclampsia has been observed in mice with high blood concentrations of cadmium.

55. As cadmium accumulates within the body, previous exposures will determine the body burden so, for example, it should be noted that women who give up smoking while pregnant will still carry a higher body burden of cadmium than women who have never smoked.

56. Food is the main source of cadmium for non-smoking women of maternal age who have never smoked, In this assessment, breads, miscellaneous cereals, and potatoes make the highest dietary contribution to cadmium exposure. Cadmium intake via other routes such as water, soil, and dust only contribute a small amount to total exposure. Taking the total amount of exposure from the TDS, the mean percentage and 97.5th percentile when compared to the EFSA TWI of 2.5 µg/kg bw/week was 22-58% and 58-100% respectively.

57. Overall, cadmium in the maternal diet does not appear to be a health concern.

58. However, consumption data was based on women of childbearing age and therefore may not be representative of the maternal diet. leading to an under/overestimation of the actual exposure. Furthermore, it should be noted that the 97.5th percentile is a conservative approach in relation to the HBGV, but, it is unlikely that every commodity consumed would be in the 97.5th percentile.

Abbreviations

ATSDR	Agency for Toxic Substances and Disease Registry
BGS	British Geological Survey
BMDL5	Benchmark Dose Lower Confidence Limit
Ca2+	Calcium ion
Cd	Cadmium
Cd-MT	Cadmium Metallothionein complex
CONTAM	Panel on Contaminants in the Food Chain
COT	Committee on the Toxicity
DMT-1	Divalent Metal Transporter-1
DNA	Deoxyribonucleic Acid
DWQR	Drinking Water Quality Regulator
EC	European Commission

EFSA	European Food Safety Authority
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
HBGV	Health Based Guidance Values
HER2	Human Epidermal Growth Factor Receptor 2
IARC	International Agency for Research on Cancer
ICP-OES	Inductively Coupled Plasma Optical Emission Spectroscopy
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LB-UB	Lower Bound-Upper Bound
LOD	Limit of Detection
MOCEH	Mothers & Children Environmental Health Study
MT	Metallothionein
NBC	Normal Background Concentrations
NDNS	National Diet & Nutrition Survey
ng/g	nanograms per gram
NICU	Neonatal Intensive Care Unit
NNNS	NICU Network Neurobehavioral Scales
PM10	Particulate Matter (<10 µm)
PTMI	Provisional Tolerable Monthly Intake
RICHS	Rhode Island Child Health Study
ROS	Reactive Oxygen Species
SACN	Scientific Advisory Committee on Nutrition
SCE	Sister Chromatid Exchange
SCOEL	Scientific Committee on Occupational Exposure Limits
TDS	Total Diet Study

TWI	Tolerable Weekly Intake
UKHSA	UK Health Security Agency
WHO	World Health Organisation
Zn2+	Zinc ion
11-β-HSD2	11 beta hydroxysteroid dehydrogenase 2
μg	microgram
μg/g	microgram per gram
μg/kg	microgram per kilogram
μg/L	microgram per litre
μm	micrometre or micron

References

Agency for Toxic Substances and Disease Registry (ATSDR), (2012). Toxicological Profile for Cadmium. Available at: PDF

Al-Saleh, I., Shinwari, N., Mashhour, A., Mohamed, G.E.D., Rabah, A. (2011). Heavy Metals (Lead, Cadmium and Mercury) in Maternal, Cord Blood and Placenta of Healthy Women. International Journal of Hygiene and Environmental Health. **214**: 79-101. Available at: Heavy metals (lead, cadmium and mercury) in maternal, cord blood and placenta of healthy women - PubMed (nih.gov)

Banerjee, S., Suter, M.A., & Aagaard, K.M. (2020). Interactions Between Environmental Exposures and the Microbiome: Implications for Fetal Programming. Current Opinion in Endocrine and Metabolic Research. **13**: 39-48. Available at: Interactions between environmental exposures and the microbiome: Implications for fetal programming - ScienceDirect

Bates, B.; Lennox, A.; Prentice, A.; Bates, C.; Page, P.; Nicholson, S.; Swan, G. (2014) National Diet and Nutrition Survey Results from Years 1, 2, 3 and 4 (combined) of the Rolling Programme (2008/2009 – 2011/2012) Available at: Main heading(publishing.service.gov.uk)

Bates, B.; Cox, L.; Nicholson, S.; Page, P.; Prentice, A.; Steer, T.; Swan, G. (2016) National Diet and Nutrition Survey Results from Years 5 and 6 (combined) of the Rolling Programme (2012/2013 – 2013/2014) Available at: Main heading (publishing.service.gov.uk)

Bernard, A., & Lauwerys, R. (1986). Present Status and Trends in Biological Monitoring of Exposure to Industrial-Chemicals. Journal of Occupational and Environmental Medicine, **28(8)**: 558-562. Available at: Present status and trends in biological monitoring of exposure to industrial chemicals - PubMed (nih.gov)

Caserta, D., Graziano, A., Lo Monte, G., Bordi, G., Moscarini, M. (2013). Heavy Metals and Placental Fetal-Maternal Barrier: A Mini-Review on the Major Concerns. Eur Rev Med Pharmaco Sci. **17**: 2198-2206. Available at: Heavy metals and placental fetal-maternal barrier: a mini-review on the major concerns - PubMed (nih.gov)

Cerrillos, L., Fernádez, R., Machado, M.J., Morillas, I., Dahiri, B., Paz, S., Gonzalez-Weller, D., Gutiérrez, A., Rubio, C., Hardisson, A., Moreno, I., Fernández-Palaćin, A. (2019). Placental Levels of Metals and Associated Factors in Urban and Sub-Urban Areas of Seville (Spain). Journal of Trace Elements in Medicine and Biology. **54**: 21-26. Available at: Placental levels of metals and associated factors in urban and sub-urban areas of Seville (Spain) - PubMed (nih.gov)

Chao, H., Guo, C., Huang, C., Chen, P., Li, H., Hsiung, D., Chou, Y. (2014). Arsenic, Cadmium, Lead, and Aluminium Concentrations in Human Milk at Early Stages of Lactation. Pediatrics and Neonatology, **55**: 127-134. Available at: Arsenic, Cadmium, Lead, and Aluminium Concentrations in Human Milk at Early Stages of Lactation - ScienceDirect

COT (Committee on Toxicity on Chemicals in Food, Consumer Products and the Environment) (2019). Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes). Paper 9: Bystander exposure. Available at: COT E(N)NDS statement (food.gov.uk)

COT (Committee on Toxicity on Chemicals in Food, Consumer Products and the Environment) (2018). Statement on Potential Risks from Cadmium in the Diet of Infants Aged 0 to 12 Months and Children Aged 1 to 5 Years. Available at: cot statement on cadmium. pdf (food.gov.uk)

COT (Committee on Toxicity on Chemicals in Food, Consumer Products and the Environment) (2018). Potential toxicological risks from electronic nicotine (or non-nicotine) delivery systems (e-cigarettes). Paper 2: Exposure to metals present in the aerosol of electronic nicotine (or non-nicotine) delivery systems. Available at: tox2018-15.pdf (food.gov.uk)

DEFRA (Department for Environment Food and Rural Affairs) (2012a). Technical Guidance Sheet on Normal Levels of Contaminants in English Soils: Cadmium. Technical Guidance Sheet No. TGS06. Available at: Defra, UK - Science Search

DEFRA (Department for Environment for Food and Rural Affairs) (2013). Technical Guidance on Normal Levels of Contaminants in Welsh Soil: Cadmium. British Geological Survey (Keyworth, Nottingham) and DEFRA (London). R & D Project SP1008. Available at: Defra, UK - Science Search

Dharmadasa, P., Kim, N., Thunders, M. (2017). Maternal Cadmium Exposure and Impact on Foetal Gene Expression Through Methylation Changes. Food and Chemical Toxicology, **109**: 714-720. Available at:

Ebrahim, K., & Ashtarinezhad, A. (2015). The Association of Amniotic Fluid Cadmium Levels with the Risk of Preeclampsia, Prematurity and Low Birth Weight. Iranian Journal of Neonatology. **6(2)**:1-6. Available at: [PDF] The Association of Amniotic Fluid Cadmium Levels with the Risk of Preeclampsia, Prematurity and Low Birth Weight | Semantic Scholar

EFSA (2009). Cadmium in food. Scientific Opinion of the Panel on Contaminants in the Food Chain. The EFSA Journal **980***: 1-139.* Available at: Cadmium in food - Scientific opinion of the Panel on Contaminants in the Food Chain - - 2009 - EFSA Journal - Wiley Online Library

EFSA (2011a). Comparison of the Approaches Taken by EFSA and JECFA to Establish a HBGV for Cadmium. EFSA Journal, **9(2)**: 2006. Available at: Comparison of the Approaches Taken by EFSA and JECFA to Establish a HBGV for Cadmium | EFSA (europa.eu)

EFSA (2011b). Statement on Tolerable Weekly Intake for Cadmium. EFSA Panel on Contaminants in the Food Chain (CONTAM). EFSA Journal, **9(2)**: 1975. Available at: Statement on tolerable weekly intake for cadmium | EFSA (europa.eu)

Engström, A., Michaëlsson, K., Vahter, M., Julin, B., Wolk, A., Åkesson, A. (2012). Associations Between Dietary Cadmium Exposure and Bone Mineral Density and Risk of Osteoporosis and Fractures Among Women. Bone, **50**: 1372-1378. Available at: Associations between dietary cadmium exposure and bone mineral density and risk of osteoporosis and fractures among women - ScienceDirectr

Environment Agency (EA) (2009).

Espart, A., Artime, S., Tort-Nasarre, G., Yaya-Varòn, E. (2018). Cadmium Exposure During Pregnancy and Lactation: Materno-Fetal and Newborn Repercussions of Cd(II), and Cd-Metallothionein Complexes. Metallomics. **10**: 1359-1367. Available at: Cadmium exposure during pregnancy and lactation: materno-fetal and newborn repercussions of Cd(ii), and Cd–metallothionein complexes (rsc.org)

Everson, T.M., Kappil, M., Hao, K., Jackson, B.P., Punshon, T., Karagas, M.R., Chen, J., Marsit, C.J. (2017). Maternal Exposure to Selenium and Cadmium, Fetal Growth, and Placental Expression of Steroidogenic and Apoptotic Genes. Environmental Research. **158**: 233-244. Available at: Maternal exposure to selenium and cadmium, fetal growth, and placental expression of steroidogenic and apoptotic genes - PubMed (nih.gov)

Filippini, T., Torres, D., Lopes, C., Carvalho, C., Moreira, P., Naska, A., Kasdagli, M., Malavolti, M., Orsini, N., Vinceti, M. (2020). Cadmium Exposure and Risk of Breast Cancer: A Dose-Response Meta-Analysis of Cohort Studies. Environment International. **142**: 105879. Available at: Cadmium exposure and risk of breast cancer: A dose-response meta-analysis of cohort studies - PubMed (nih.gov)

Gao Y, Zhang Y, Yi J, Zhou J, Huang X, Shi X, Xiao S, Lin D. (2016). A Longitudinal Study on Urinary Cadmium and Renal Tubular Protein Excretion of Nickel–Cadmium Battery Workers After Cessation of Cadmium Exposure. International Archives of Occupational and Environmental Health. **89(7)**: 1137– 1145. Available at: A longitudinal study on urinary cadmium and renal tubular protein excretion of nickel-cadmium battery workers after cessation of cadmium exposure - PubMed (nih.gov)

Geng, H., & Wang, L. (2019). Cadmium: Toxic Effects on Placental and Embryonic Development. Environmental Toxicology and Pharmacology. **67**: 102-107. Available at: Cadmium: Toxic effects on placental and embryonic development - ScienceDirect

Grioni, S., Agnoli, C., Krogh, V., Pala, V., Rinaldi, S., Vinceti, M., Contiero, P., Vescovi, L., Malavolti, M., Sieri, S. (2019). Dietary Cadmium and Risk of Breast Cancer Subtypes Defined by Hormone Receptor Status: A Prospective Cohort Study. International Journal of Cancer. **144**: 2153-2160. Available at: Dietary cadmium and risk of breast cancer subtypes defined by hormone receptor status: A prospective cohort study - PubMed (nih.gov)

Gundacker, C., & Hengstschläger, M. (2012). The Role of the Placenta in Fetajkll Exposure to Heavy Metals. Wien Med Wochenschr. **162/9-10**: 201-206. Available at: The role of the placenta in fetal exposure to heavy metals - PubMed (nih.gov)

Guo, J., Wu, C., Qi, X., Jiang, S., Liu, Q., Zhang, J., Cao, Y., Chang, X., Zhou, Z. (2017). Adverse Associations Between Maternal and Neonatal Cadmium Exposure and Birth Outcomes. Science of the Total Environment, **575**: 581-587. Available at: Adverse associations between maternal and neonatal cadmium exposure and birth outcomes - ScienceDirect

Gustin, K., Barman, M., Stråvik, M., Levi, M., Englund-Ögge, L., Murray, F., Jacobsson, B., Sandberg, A., Sandin, A., Wold, A.E., Vahter, M., Kippler, M. (2020). Low-Level Maternal Exposure to Cadmium, Lead and Mercury and Birth Outcomes in a Swedish Prospective Birth-Cohort. Environmental Pollution, **265**: 114986. Available at: Low-level maternal exposure to cadmium, lead, and mercury and birth outcomes in a Swedish prospective birth-cohort - PubMed (nih.gov)

Hartwig, A., Arand, M., Epe, B., Guth, S., Jahnke, G., Lampen, A., Martus, H., Monien, B., Rietjens, I.M.C.M., Schmitz-Spanke, S., Scriever-Schwemmer, G., Steinberg, P., Eisenbrand, G. (2020). Mode of action-based risk assessment of genotoxic carcinogens. Archives of Toxicology **94**:1787-1877. Available at Mode of action-based risk assessment of genotoxic carcinogens (nih.gov)

Hinwood, A.L., Callan, A.C., Ramalingam, M., Boyce, M., Heyworth, J., McCafferty, P., Odland, J.Ø. (2013). Cadmium, Lead and Mercury Exposure in Non Smoking Pregnant Women. Environmental Research, **126**: 118-124. Available at: Cadmium, lead and mercury exposure in non smoking pregnant women - ScienceDirect

International Agency for Research on Cancer(IARC)(2012). Arsenic, Metals, Fibres, and Dusts Volume 100 C A Review of Human Carcinogens*. I*ARC Monographs on the Evaluation of Carcinogenic Risks*:* 121-141. Available at: IARC Publications Website - Arsenic, Metals, Fibres, and Dusts

International Programme on Chemical Safety (IPCS). 1992. Cadmium. Poisons Information Monograph. PIM 089. Available at : Cadmium (PIM 089) (inchem.org)

Jacobo-Estrada, T., Santoyo-Sánchez, M., Thévenod, F., Barbier, O. (2017). Cadmium Handling, Toxicity and Molecular Targets Involved During Pregnancy: Lessons from Experimental Models. Int J Mol Sci. **18(7)**: 1590. Available at: Cadmium Handling, Toxicity and Molecular Targets Involved during Pregnancy: Lessons from Experimental Models - PubMed (nih.gov)

Jarup, L., Berglund, M., Elinder, C. G., Nordberg, G., Vahter, M. (1998). Health Effects of Cadmium Exposure – a review of the literature and a risk estimate.

Scandinavian Journal of Work, Environment & Health, **Vol 24**, Supplement 1, pp 1-51. Available at: [Health effects of cadmium exposure – a review of the literature and a risk estimate on JSTOR]

JECFA (Joint FAO/WHO Expert Committee on Food Additives) (2011). Evaluation of Certain Food Additives and Contaminants. WHO Technical Report Series, **960**. Available at: [Evaluation of certain food additives and contaminants: seventy-third report of the Joint FAO/WHO Expert Committee on Food Additives]

Julin, B., Wolk, A., Bergkvist, L., Bottai, M., Åkesson, A. (2012). Dietary Cadmium Exposure and Risk of Postmenopausal Breast Cancer: A Population-Based Prospective Cohort Study. Cancer Res. **72(6)**: 1459-66. Available at: [CAN-11-0735 1459..1466 (silverchair.com)]

Kazantzis, G. (2004). Cadmium, Osteoporosis and Calcium Metabolism. Biomaterials, **17(5)**: 493-8. Available at: [Cadmium, osteoporosis and calcium metabolism - PubMed (nih.gov)]

Khan, M.A., Khan, S., Khan, A., Alam, M. (2017). Soil Contamination with Cadmium, Consequences and Remediation Using Organic Amendments. Science of The Total Environment **601-602**: 1591-1605. Available at: [Soil contamination with cadmium, consequences and remediation using organic amendments - PubMed (nih.gov)]

Kippler, M., Ekström, E., Lönnerdal, B., Goessler, W., Åkesson, A., El Arifeen, S., Persson, L., Vahter, M. (2007). Influence of Iron and Zinc Status on Cadmium Accumulation in Bangladeshi Women. Toxicology and Applied Pharmacology, **22(2)**: 221-226. Available at: [Influence of iron and zinc status on cadmium accumulation in Bangladeshi women - ScienceDirect]

Kippler, M., Ekström, K., Mlakar, S.J., Bottai, M., Ahmend, S., Hossain, M.B., Raqib, R., Vahter, M., Broberg, K. (2013). Sex-Specific Effects of Early Life Cadmium Exposure on DNA Methylation and Implications for Birth Weight. Epigenetics, **8(5)**: 494-503. Available at: [Sex-specific effects of early life cadmium exposure on DNA methylation and implications for birth we (tandfonline.com)]

Kippler, M., Tofail, F., Gardner, R., Rahman, A., Hamadani, J.D., Bottai, M., Vahter, M. (2012). Maternal Cadmium Exposure During Pregnancy and Size at Birth: A Prospective Cohort Study. Environmental Health Perspectives, **120(2)**: 284-289. Available at: [Maternal cadmium exposure during pregnancy and size at birth: a prospective cohort study - PubMed (nih.gov)]

Kolonel, (1967). Association of Cadmium with Renal Cancer. Cancer, 37:1782-1787. Available at: Association of cadmium with renal cancer (wiley.com)

Kosanovic, M., Jokanovic, M., Jevremovic, M., Dobric, S., Bokonjic, D. (2002). Maternal and Fetal Cadmium and Selenium Status in Normotensive and Hypertensive Pregnancy. Biological Trace Element Research, **89**: 97-103. Available at: Maternal and fetal cadmium and selenium status in normotensive and hypertensive pregnancy - PubMed (nih.gov)

Krajnc, E.I., Van Gestel, C.A.M., Mulder, H.C.M. (1987*). Integrated criteria document.* Cadmium-Effects. Appendix. National Institute of Public Health and Environmental Protection, Bilthoven, Netherlands (Report no. 758476004).

Lane,W., & Morel, F.M. (2000). A Biological Function For Cadmium in Marine Diatoms. Proc. Nat. Acad. Sci. **97**: 4627-4631. Available at: A biological function for cadmium in marine diatoms (nih.gov)

Lauwerys, R., Amery, A., Bernard, A>, Bruaux, P., Buchet, J., Claeys, F., De Plaen, P., Ducoffre, G., Fagard, R., Lijnen, P., Nick, L., Roles, H., Rondia, D., Saint-Remy, A., Sartor, F., Staessen, J. (1990). Health Effects of Environmental Exposure to Cadmium: Objectives, Design and Organization of the Cadmibel Study: A Cross-Sectional Morbidity Study Carried Out in Belgium from 1985 to 1989. Environmental Health Perspectives, **87**: 283-289. Available at: Health effects of environmental exposure to cadmium: objectives, design and organization of the cadmibel study: a cross-sectional morbidity study carried out in Belgium from 1985 to 1989 | Environmental Health Perspectives | Vol. 87, No. (nih.gov)

Liu,T., Zhang, M., Guallar, E., Wang, G., Hong, X., Wang, X., Mueller, N.T. (2019). Trace Minerals, Heavy Metals, and Preeclampsia: Findings from the Boston Birth Cohort. Journal of the American Heart Association, **20;8(16)**. Available at: Trace Minerals, Heavy Metals, and Preeclampsia: Findings from the Boston Birth Cohort - PubMed (nih.gov)

Menai, M., Heude, B., Slama, R., Forhan, A., Sahuquillo, J., Charles, M., Yazbeck, C. (2012). Association Between Maternal Blood Cadmium During Pregnancy and Birth Weight and the Risk of Fetal Growth Restriction: The EDEN Mother-Child Cohort Study. Reproductive Toxicology, **34**: 622-627. Available at: Association between maternal blood cadmium during pregnancy and birth weight and the risk of fetal growth restriction: the EDEN mother-child cohort study - PubMed (nih.gov)

Nair, A.R., DeGheselle, O., Smeets, K., Van Kerkhove, E., Cuypers, A. (2013). Cadmium-Induced Pathologies: Where Is the Oxidative Balance Lost (or Not)? Int.

J. Mol. *Sci.* **14**: 6116-6143. Available at: Cadmium-Induced Pathologies: Where Is the Oxidative Balance Lost (or Not)? - PubMed (nih.gov)

Nawrot, T.S., Martens, D.S., Hara, A., Plusquin, M., Vangronsveld, J., Roles, H.A., Staessen, J.A. (2015). Association of Total Cancer and Lung Cancer with Environmental Exposure to Cadmium: The Meta-Analytical Evidence. Cancer Causes & Control, **26**: 1281-1288. Available at: Association of total cancer and lung cancer with environmental exposure to cadmium: the meta-analytical evidence - PubMed (nih.gov)

NHS (2020) Have a healthy diet in pregnancy. Available at: Have a healthy diet in pregnancy - NHS (www.nhs.uk)

Nordberg, G.F., Bernard, A., Diamond, G.L., Duffus, J.H., Illing, P., Nordberg, M., Bergdahl, I.A., Jin, T., Skerfving, S. (2018). Risk Assessment of Effects of Cadmium on Humand Health (IUPAC Technical Report). Pure and Applied Chemistry, **90(4)**: 755-808. Available at: De Gruyter

Osman, K., Åkesson, A., Berglund, M., Bremme, K., Schütz, A., Ask, K., Vahter, M. (2000). Toxic and Essential Elements in Placentas of Swedish Women. Clinical Biochemistry. **33(2)**: 131-138. Available at: Toxic and essential elements in placentas of swedish women - ScienceDirect

Osorio-Yañez, C., Gelaye, B., Miller, R.S., Enquobahrie, D.A., Baccarelli, A.A., Qiu, C., Williams, M.A. (2016). Associations of Maternal Urinary Cadmium with Trimester-Specific Blood Pressure in Pregnancy: Role of Dietary Intake of Micronutrients. Biol Trace Elem Res. **174(1)**: 71-81. Available at: Associations of Maternal Urinary Cadmium with Trimester-Specific Blood Pressure in Pregnancy: Role of Dietary Intake of Micronutrients (nih.gov)

Pohanish, R.P. 2017. Sittig's Handbook of Toxic and Hazardous Chemicals and Carcinogens, Seventh Edition. William Andrew, Oxford, Oxfordshire, UK.

Rawlins, B.G., McGrath, S.P., Scheib, A.J., Breward, N., Cave, M., Lister, T.R., Ingham, M., Gowing, C., Carter, S. (2012). The Advanced Soil Geochemical Atlas of England and Wales. Available at: Advanced_Soil_Geochemical_Atlas_of_England_and_Wales.pdf (nerc.ac.uk)

Reeves, P.G., & Chaney, R.L. (2008). Bioavailability as an Issue in Risk Assessment and Management of Food Cadmium: A Review. Science of the Total Environment. 398: 13-19. Available at: Bioavailability as an issue in risk assessment and management of food cadmium: A review - ScienceDirect

Roberts, C.; Steer, T.; Maplethorpe, N.; Cox, L.; Meadows, S.; Page, P.; Nicholson, S.; Swan, G. (2018) National Diet and Nutrition Survey Results from Years 7 and 8 (combined) of the Rolling Programme (2014/2015 – 2015/2016) Available at: National Diet and Nutrition Survey (publishing.service.gov.uk)

Roels, H., Hubermont, G., Buchet, J.P., Lauwerys, R. (1978). Placental Transfer of Lead, Mercury, Cadmium, and Carbon Monoxide. Environmental Research. **16**: 236-247. Available at: Placental transfer of lead, mercury, cadmium, and carbon monoxide in women. III. Factors influencing the accumulation of heavy metals in the placenta and the relationship between metal concentration in the placenta and in maternal and cord blood - PubMed (nih.gov)

Romano, M.E., Enquobahrie, D.A., Simpson, C., Checkoway, H., Williams, M.A. (2016). Maternal Body Burden of Cadmium and Offspring Size at Birth. Environmental Research. **147**: 461-468. Available at: Maternal body burden of cadmium and offspring size at birth - ScienceDirect

SACN (2011) The influence of maternal, fetal and child nutrition on the development of chronic disease later in life. Available at: SACN_Early_Life_Nutrition_Report.pdf (publishing.service.gov.uk)

SACN (2018) Feeding in the first year of life. Available at: SACN_report_on_Feeding_in_the_First_Year_of_Life.pdf (publishing.service.gov.uk)

Satarug, S., Vesey, D.A., Gobe, G.C. (2017). Current Health Risk Assessment Practice for Dietary Cadmium: Data from Different Countries. Food and Chemical Toxicology, **106**: 430-445. Available at: Current health risk assessment practice for dietary cadmium: Data from different countries - PubMed (nih.gov)

Scientific Committee on Occupational Exposure Limits (SCOEL). SCOEL/OPIN/336 Cadmium and its inorganic compounds. Available at: SCOEL/OPIN/336 cadmium and its inorganic compounds - Publications Office of the EU (europa.eu)

Shah-Kulkarni, S., Lee, S., Jeong, K.S., Hong, Y., Park, H., Ha, M., Kim, Y., Ha, E. (2020). Prenatal Exposure to Mixtures of Heavy Metals and Neurodevelopment in Infants at 6 Months. Environmental Research, **182**: 109122. Available at: Prenatal exposure to mixtures of heavy metals and neurodevelopment in infants at 6 months - ScienceDirect

Simmons, R.W., Pongsakul, P., Saiyasitpanich, D., Klinphoklap, S. (2005). Elevated Levels of Cadmium and Zinc in Paddy Soils and Elevated Levels of Cadmium in Rice Grain Downstream of a Zinc Mineralized Area in Thailand: Implications for Public Health. Environ Geochem Health, **27 (5-6)**: 501-11. Available at: Elevated levels of cadmium and zinc in paddy soils and elevated levels of cadmium in rice grain downstream of a zinc mineralized area in Thailand: implications for public health - PubMed (nih.gov)

Srivastava, N., Spielman, S. J., Morrison, S. M., Moore, E. K. (2020). Geological Factors Impacted Cadmium Availability and Use as an Alternative Cofactor for Zinc in the Carbon Fixation Pathways of Marine Diatoms. School of Earth & Environment Faculty Scholarship. 47. Available at: PDF

Stone, J., Sutrave, P., Gascoigne, E., Givens, M.B., Fry, R.C., Manuck, T.A. (2021). Exposure to Toxic Metals and Per- and Polyfluorolkyl Substances and the Risk of Preeclampsia and Preterm Birth in the United States: A Review. Amer J Obstet Gynecol MFM, **3:** 100308. Available at: Exposure to toxic metals and per- and polyfluoroalkyl substances and the risk of preeclampsia and preterm birth in the United States: a review - PubMed (nih.gov)

Thevenod, F. (2009). Cadmium and Cellular Signaling Cascades: To Be or Not To Be? Toxicology and Applied Pharmacology, **238**: 221-239. Available at: Cadmium and cellular signaling cascades: to be or not to be? - PubMed (nih.gov)

Thirumoorthy, N., Sunder, A. S., Kumar, K.T.M., Kumar, M.S., Ganesh, G.N.K., and Chatterjee, M. (2011). A Review of Metallothionein Isoforms and their Role in Pathophysiology. World Journal of Surgical Oncology, **9:** 54. Available at: A Review of Metallothionein Isoforms and their Role in Pathophysiology (nih.gov)

Thompson, J. and Bannigan, J. (2008). Cadmium: Toxic effects on the reproductive system and the embryo. Reproductive Toxicology, **25:** 304-315. Available at: Cadmium: toxic effects on the reproductive system and the embryo - PubMed (nih.gov)

Tung, P.W., Burt, A., Karagas, M., Jackson, B.P., Punshon, T., Lester, B., Marsit, C.J. (2022). Association Between Placental Toxic Metal Exposure and NICU Network Neurobehavioral Scales (NNNS) Profiles in the Rhode Island Child Health Study (RICHS). Environmental Research, **204**: 111939. Available at: Association between placental toxic metal exposure and NICU Network Neurobehavioral Scales (NNNS) profiles in the Rhode Island Child Health Study (RICHS) - ScienceDirect

Umemura, T., and Wako, Y. (2006). Pathogenesis of Osteomalacia in Itai-Itai Disease. J Toxicol Pathol: 69-74. Available at: PDF

Unsal, V., Dalkiran, T., Çiçek, M., Kölükçü, E. (2020). The Role of Natural Antioxidants Against Reactive Oxygen Species Produced by Cadmium Toxicity: A

Review. Adv Pharm Bull, **10(2)**: 184-202. Available at: The Role of Natural Antioxidants Against Reactive Oxygen Species Produced by Cadmium Toxicity: A Review (nih.gov)

Vahter, M., Åkesson, A., Lidén, C. (2002). Metals and Women's Health. Environmental Research, **88(3)**: 145-155. Available at: Metals and women's health - PubMed (nih.gov)

WHO (2000). Chapter 6.3 Cadmium. Air Quality Guidelines – Second Edition. WHO Regional Office for Europe, Copenhagen, Denmark. Available at : Microsoft Word - 6.3-Cadmium.doc (who.int)

WHO (2011). Cadmium in Drinking Water. WHO/SDE/WSH/03.04/80/Rev/1. Available at: Microsoft Word - Fourth Edition Cadmium final 14 June 2011.doc (who.int)

WHO (2017). Guidelines for Drinking-Water Quality, 4th Edition, Incorporating the 1st Addendum. Available at: Guidelines for drinking-water quality, 4th edition, incorporating the 1st addendum (who.int)

Yang, H., & Shu, Y. (2015). Cadmium Transporters in the Kidney and Cadmium-Induced Nephrotoxicity. Int. J. Mol. Sci. **16**: 1484-1494. Available at: Cadmium Transporters in the Kidney and Cadmium-Induced Nephrotoxicity (nih.gov)

Yoshida M, Ohta H, Yamauchi Y, seki Y. (1993). Age dependent changes in metallothionein levels in liver and kidney of the Japanese. Biological Trace Element Research **63**: 167 – 175.Zhang, M., Luo, J., Zhang, C., Cao, H., Xia, B., Hu, G. (2017). Alterations in Antioxidant Function and Cell Apoptosis in Duck Spleen Exposed to Molybdenum and/or Cadmium. J Vet Sci, **18(2)**: 193-200. Available at: Alterations in antioxidant function and cell apoptosis in duck spleen exposed to molybdenum and/or cadmium - PubMed (nih.gov)

Appendix A – Literature Search Terms (2006-2021)

acute toxicity

chronic toxicity

reproductive toxicity

biomarkers (exposure/ toxicity)

maternal health

preconception

conception

pregnancy

post natal

lactation

fetus/ foetus/ fetal /foetal

placenta

pre-term

preeclampsia

gestational diabetes

cancer/ carcinogen(icity)

teratogen(icity)

absorption

distribution

metabolism

excretion/ elimination

oral /food/water/soil/dust

inhalation /air/ dust

lactation

fetal/foetal growth restriction

development

Appendix B

An analysis of the ethnicity and vegetarian status of all consumers of bread, miscellaneous cereals and potatoes exposed to cadmium was carried out. The results were compared with high consumers (above the mean and 97.5th percentile exposure) (Tables 1, 2 and 3).

Table B1. Ethnicity and vegetarian status of women exposed to cadmium from bread

	Total consumers (n=1804)	Consumers with exposures above the mean (n=845)	Consumers with exposures above the 97.5th percentile (n=46)
Number (%) Asians/Asian British	82 (4.5)	41 (4.9)	5 (11)
Number (%) Black/Black British	51 (2.8)	18 (2.1)	0 (0)
Number (%) White	1598 (89)	753 (89)	39(92)
Number (%) of Vegetarians	71 (3.9)	40 (4.7)	4(8.7)
Number (%) of vegans	3 (0.17)	1 (0.12)	0 (0)

Table B2. Ethnicity and vegetarian status of women exposed to cadmium from miscellaneous cereals

	Total consumers (n=1840)	Consumers with exposures above the mean (n=752)	Consumers with exposures above the 97.5th percentile (n=35)
Number (%) Asians/Asian British	86 (4.7)	67 (8.9)	11 (31)

Number (%) Black/Black British	56 (3.0)	30 (4.0)	3 (11)
Number (%) White	1619 (88.0)	614 (82)	15 (42)
Number (%) of Vegetarians	74 (4.0)	46 (6.1)	4 (11)
Number (%) of vegans	3 (0.16)	2 (0.27)	0 (0)

Table B3. Ethnicity and vegetarian status of women exposed to cadmium from potatoes

	Total consumers (n=1653)	Consumers with exposures above the mean (n=722)	Consumers with exposures above the 97.5th percentile (n=49)
Number (%) Asians/Asian British	74 (4.5)	21 (2.9)	1 (2.0)
Number (%) Black/Black British	46 (2.8)	18 (2.4)	1 (2.0)
Number (%) White	1464 (89)	657 (91)	45 (92)
Number (%) of Vegetarians	63 (3.8)	25 (3.5)	2 (4.1)

Number (%) of vegans	3 (0.18)	0 (0)	0 (0)