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Committee on Toxicity

Independent report

Cadmium in the maternal diet

Published 24 November 2022

Contents

OGL

This publication is available at https://draft-origin.publishing.service.gov.uk/government/publications/cadmium/cadmium-in-the-maternal-diet

1. 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, including cadmium, should be prioritised for review.

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.

2. 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 include the use of cadmium compounds as pigments with more recent uses being in rechargeable batteries and 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 in smokers 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. There are no data that indicate cadmium is an essential micronutrient for animals, plants, or microorganisms (EFSA 2009, Khan et al., 2017).

3. Toxicity

3.1 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 is inhaled) is dependent on the size of the particles with 50-60% of ultrafine particles through smoking being retained, the remainder being exhaled with the smoke (EFSA, 2009; WHO, 2000).

10. 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-sulfur 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 the 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 Zn^{2+} and Ca^{2+} transport and 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 in non-smokers is normally < 1 µg/g creatinine (SCOEL, 2017).

3.2 Acute toxicity

14. 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 elemental cadmium which correspond to doses of ≈ 5 to 130 mg/kg bw in a 70 kg adult, and acute fatal doses of 5 g (cadmium iodide) and 150 g (cadmium chloride) (IPCS, 1992; EFSA, 2009).

3.3 Chronic toxicity

15. In non-occupational exposure, chronic exposure to cadmium is of more concern. The kidney is the main target organ, although effects on the liver can also occur. Chronic exposure can result in proteinuria and loss of

tubular function in the kidney, with urinary excretion of β_2-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 calcium ion and so disrupts the calcium signalling cascade affecting the absorption of calcium increasing the levels of 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% respectively (Engstrom et al. 2012).

16. Levels of urinary cadmium of the order 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).

3.4 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).

3.5 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, an EC Joint Research Council report (EC, 2007) concluded that there is currently no evidence that cadmium acts as a carcinogen following oral exposure (cited by EFSA, 2009).

3.6 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 fetus. 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 associated with changes in 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 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 neurobehavioural developmental 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 length 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 (levels of 1.40, 1.52 and 0.68 µg/L in early pregnancy, late pregnancy and cord blood respectively) 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 pre-eclampsia, 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 pre-eclampsia including blood in the urine and later development of visceral congestion, pulmonary and haemorrhagic oedema, (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

pre-eclampsia, 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, pre-eclampsia and affecting birth weights of new-borns, while others show no effect (Nordberg et al. 2018; Menai et al. 2021; IARC, 2012).

4. 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. At the 33rd meeting, 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 (73rd meeting) 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). At its 91st meeting in 2021, JECFA calculated national estimates of total dietary exposure to cadmium and compared these to the PTMI established in 2011. Estimates 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 (JECFA 2021). (https://www.fao.org/fileadmin/user_upload/codexalimentarius/doc/Webinar/Cadmium_JECFA_91.pdf)

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).

5. Sources of cadmium exposure

5.1 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.

5.2 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).

5.3 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 2003/40/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.

5.4 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.

5.5 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 (https://uk-air.defra.gov.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 on bystanders of secondary emissions (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 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.

6. Exposure assessment

45. The National Diet and Nutrition Survey Rolling Programme (NDNS) and Total Diet Study does not include pregnant or lactating women, therefore the data for women of childbearing age (Bates et al. 2014, 2016; Roberts et al., 2018) were used as a surrogate to estimate cadmium exposure from food. Childbearing age was taken to be 16-49 years of age. Caution must be taken when using these data as they may not be entirely representative 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. Combining 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 for exposure in specific sub populations (e.g. vegetarian or ethnic origin), the data sets are small and therefore not sufficiently robust to provide separate, statistically reliable exposure estimates in these sub-populations. (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.

7. 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.

8. Conclusions

54. Exposure to high levels of cadmium during pregnancy has been associated with adverse effects such as hypertension, pre-eclampsia, micronutrient deficiency in the mother, and adverse birth outcomes for the fetus. 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 pre-eclampsia 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 were 22-58% and 58-100% respectively.

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

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

9. 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

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11. 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

12. 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.

Ethnicity & Diet	**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

Ethnicity & Diet	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.

Ethnicity & Diet	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)

Ethnicity & Diet	Total consumers (n=1653)	Consumers with exposures above the mean (n=722)	Consumers with exposures above the 97.5th percentile (n=49)
Number (%) of vegans	3 (0.18)	0 (0)	0 (0)