Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment

Discussion paper on the potential risks from cadmium in the maternal diet

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 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. It was noted that the provisional list of chemicals 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. Following a discussion at the COT meeting in September 2020, 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. Public Health England (now the UK Health Security Agency (UKHSA)) has 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 include as a pigment before more recent uses in rechargeable batteries and protection coating 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 (approx. 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 cadmium containing phosphate fertilisers. 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 found in the kidney and liver due to Cd 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). Cadmium has been shown to be used as a co-factor in an isoform of carbonic anhydrase in a marine diatom (Lane & Morel, 2000) and more recently has been investigated as an alternative co-factor for zinc in carbon fixation protein complexes of marine diatoms (Srivastava *et al*. 2020).

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 over the last 15 years. The list of search terms are shown in Appendix A.

Toxicokinetics

9. 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 low intake of nutrients such as zinc and calcium in animal studies (Reeves and Chaney, 2008). Absorption of Cd via inhalation (5-50% of Cd 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. Cadmium can be transported in the blood by erythrocytes where it is taken up by the liver. Once in the liver, the cadmium stimulates the production of the cysteine-sulphur rich protein metallothionein (MT) to which it binds. This cadmium-metallothionein (Cd-MT) complex is then 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). MT expression has been shown to fall

sharply during infancy and then rise until middle age, with cadmium showing a similar rise and decline (Yoshida *et al.* 1998).

11. Most ingested cadmium is excreted in the faeces due to poor absorption. Excretion via the urine is dependent on the Cd concentration in the blood and kidney. It has been shown that women of reproductive age have higher levels of cadmium present in the blood and urine in comparison to men (Vahter *et al*. 2002) In non-occupational exposure, the adult mean urinary Cd in urine is normally < 1 µg/g creatinine (SCOEL, 2017). Urinary excretion is used to represent the body burden of cadmium, whereas blood concentrations are used as an indicator for recent and cumulative exposure (EFSA, 2009; IARC, 2012).

12. During pregnancy, cadmium directly interferes with the metabolism of calcium and decreases vitamin D synthesis in the kidneys which leads to increased absorption and body burden of cadmium (Al-Saleh *et al.* 2011; Kazantzis, 2004). Cd accumulates in the placenta with lower levels 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 (Banerjee *et al.* 2020; Cerrillos *et al.* 2019). Metallothionein is produced in the placenta as a protective barrier against cadmium entering the placenta. However, this can disrupt the zinc homeostasis in the placenta to the fetus by displacing the zinc in the metallothionein complex with cadmium (Casserta *et al.* 2013; Espart *et al.* 2018). During gestation there is a larger demand for iron required for fetal development which 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).

13. *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 cadmium exposure for

boys and negative correlation for girls (Kippler *et al.* 2013; Banerjee *et al.* 2020).

Acute toxicity

14. Acute 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 (Bernard and Lauwerys, 1986; EFSA, 2009). In non-occupational exposure, chronic exposure to cadmium is of more concern. As mentioned above, the kidney and liver are the main organs affected by cadmium exposure and is transported bound to metallothionein (Cd-MT) from the liver to the kidney. Once in the kidney the Cd-MT complex is degraded which is then bound to newly synthesized metallothionein giving some protection from cadmium toxicity (WHO, 2011; Yang and Shu, 2015).

15. One of the first signs of renal damage from cadmium exposure is low molecular weight proteinuria, with urinary excretion of β2-microglobulin used as a useful biomarker to detect tubular damage (EFSA, 2009). If detected early, cadmium damage may be reversed (Gao *et al.,* 2016), but may become irreversible and progressive even once exposure has ceased (EFSA, 2009).

Chronic toxicity

16. Chronic exposure of cadmium can result in proteinuria and loss of tubular function in the kidney. As cadmium accumulates in the kidney, vitamin D metabolism is affected along with increased levels of calcium and phosphorus 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).

17. Cadmium has a disruptive effect at the cellular level by inducing signal dysregulation, competing with Zn^{2+} and Ca^{2+} transport and permanently disrupting transducting modules and second messengers (Jacob-Estrada *et al.* 2017; Thevenod, 2009).

18. Oxidative stress can cause damage to lipids proteins and DNA and is involved in nephrotoxicity and osteotoxicity indirectly induced by cadmium (Nair *et al.* 2013).

19. Studies have shown that the oxidative stress reaction caused by Cd exposure may be ameliorated by antioxidant substances such as resveratrol, α-tocopherol, and flavonoids (Unsal *et al.* 2020). However, Cd has also been shown to work synergistically with other toxicants such as molybdenum (Zhang *et al.* 2017).

Genotoxicity

20. 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

21. Cadmium and its compounds were reviewed in 2012 by IARC who have 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).

22. 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). There have also been associations 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).

23. Studies have been conducted to determine if there is a link between oral exposure of cadmium and the development of breast cancer. Grioni *et al.* (2019) investigated the association between estrogen and progesterone receptors and HER2 status and dietary cadmium. It was determined that dietary cadmium was associated with breast cancer, albeit no variation between the receptors of HER2 status. On the other hand, Filippini *et al.* (2020) compared ten studies (6 dietary intake and four urinary excretion levels) and found that there was no association between dietary cadmium and urinary excretion of cadmium and breast cancer incidence and mortality. However, it was highlighted that the analysis was limited to post-menopausal women, smoking, and hormone receptor status was not included.

Reproductive and developmental toxicity

24. Adverse birth outcomes following cadmium exposure linked with blood and urine cadmium biomarkers and 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).

25. Placental damage caused by cadmium exposure can cause adverse effects in the developing fetus (Geng and Wang 2019). Cadmium has been shown to interfere with endocrine hormone synthesis, including progesterone and leptin 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).

26. The Guo *et al. (*2017) birth cohort study consisted of 1073 mother-newborn pairs from an agricultural population in China. Mean measurements of cadmium concentration were obtained in both cord blood and maternal urine of 0.40 and 0.19 µg/L respectively. However, there was no estimate of dietary intake of cadmium. It was shown that the cadmium concentration in cord blood was significantly negatively associated with ponderal index at birth (assesses the ratio of a person's height to weight), but there was no association shown with the urine concentrations.

27. Placental samples (n=192) were taken from participants in the RICHS cohort study assessed along-side the NICU Network Neurobehavioural Scale (NNNS) which observed the neurological integrity and behavioural functions of newborns (Tung *et al.* (2022). The study participants were recruited from the Women and Infants Hospital, Providence, Rhode Island, USA. It was assumed that most of the cadmium was obtained from the diet (although no dietary information was obtained from the cohort) as the study was not in an occupational setting and there was a low prevalence of women smoking during their pregnancy. The results showed an association between increased cadmium in the placenta (mean Cd 4.56 ng/g) and an increase in adverse neurobehavioural outcomes

28. Other studies have shown no association with adverse birth outcomes. Venous blood samples were taken during early (12-20 weeks), late (>28 weeks) pregnancy and at birth (from the umbilical cord) from participants in the MOCEH cohort study based in Korea (Shah-Kulkarni *et al.* 2020). The cadmium concentrations were 1.40, 1.52 and 0.68 µg/L cadmium for early pregnancy, late pregnancy and cord blood respectively. The diet of mothers was obtained from 24 or 48 hr recall questionnaires, although no dietary intake estimate was made. There was no significant association with prenatal cadmium exposure and the mental development index or the psychomotor development index in the 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). In Liu *et al.* (2019), cadmium levels in the red blood cells of 1274 women were determined 24 to 72 hours after birth. Results showed that the likelihood of developing preeclampsia was increased the higher the level of cadmium in the blood, with the top two quintiles showing cadmium levels ranging from 0.80-1.18 and 1.19-4.76 µg/L. There has also been an association reported between cadmium exposure and hypertension in pregnant women smokers, with animal studies showing that pregnant animals were more sensitive in comparison to non-pregnant ones to the toxic effects of cadmium (Kosanovic *et al.* 2002). However, in the Osorio-Yanez *et al.* (2016) study there were no high levels of urinary cadmium in those that developed preeclampsia.

30. Currently there is inconsistency between epidemiological data with some studies suggesting that cadmium and its compounds can lead to an increased risk of cancer and preeclampsia with others showing no effect. Some studies are also inconclusive as to cadmium exposure affecting birth weights of new-borns (Nordberg *et al.* 2018; Menai *et al*. 2021; IARC, 2012).

Health-based guidance value

31. A new tolerable weekly intake (TWI) for cadmium was established by the EFSA CONTAM panel in 2009. EFSA considered cadmium to be primarily toxic to the kidneys, and the TWI was based on renal effects. EFSA noted that the reproductive effects of cadmium, based on the available epidemiology at that time, were uncertain. To determine a $BMDL_5$ of 1 µg/g of creatinine, a meta-analysis was conducted between urinary cadmium and urinary β-2-microglobulin as the tubular damage biomarker. 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 Cd/kg bw or 2.5 µg Cd/kg bw per week (EFSA, 2009).

32. In 2011 at the 73rd meeting of the Joint FAO/WHO Committee on Food Additives (JECFA), a Provisional Tolerable Monthly Intake (PTMI) of 25 µg/kg bw was established which is equivalent to 0.8 µg/kg bw/day, reflecting the long half-life of cadmium and the bioaccumulation in the kidney. A 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.

33. A comparison was made by EFSA between the different approaches used between the EFSA CONTAM Panel and JECFA to determine a health-based guidance value (HBGV). It was concluded that the choice of toxicodynamic function played an important role on the outcome (EFSA 2011a). EFSA concluded 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 JECFA PTMI and CONTAM Panel TWI (EFSA 2011b).

34. 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 Julin *et al.* (2012), urinary concentrations of cadmium were assessed and those with a higher body burden of cadmium (>0.58 µg/g creatinine-adjusted cadmium level) showed an increased risk of breast cancer. 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).

Cadmium exposures in maternal health

Sources of cadmium exposure

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 cadmium exposing food groups were 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).

Human breast milk

37. Human breast milk has previously been discussed in the COT statement on cadmium in the infant diet (COT, 2018). 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.

Drinking water

38. 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).

39. Directive 2003/83/EC specifies a maximum level of cadmium in natural mineral waters of 3.0 µg/L. 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.

40. Levels of cadmium in drinking water in 2020 were set for England, Wales, Scotland and Northern Ireland by the Drinking Water Inspectorate and the Drinking Water Quality Regulator (DWQR) for Scotland and Northern Ireland Water respectively. The median and 97.5th percentile values calculated from this data are shown in Table 1.

Table 1. Median and 97.5th percentile concentrations (µg/L) of cadmium in water across England, Wales, Scotland, and Northern Ireland for 2020

Country	**Number of samples**	**Limit of Detection (µg/L)**	**Median concentration (µg/L)**	**97.5th Percentile concentration (µg/L)**
England and Wales	13232	0.01-0.10*	-	0.23 (99th percentile)
Scotland	1454	0.02	0.02	0.06
Northern Ireland	345	0.01-0.3	0.038	0.04

*The water companies had reported a range of Limits of Detection (LODs) that varied dependent on the analytical method used.

Environmental

Dust

41. Hinwood *et al.* (2013) assessed the levels of cadmium, lead and mercury exposure in non-smoking pregnant women. Study participants were asked to provide samples two weeks before birth of dust, residential soil, drinking water, blood, and urine (first void). The cadmium level in dust were determined by ICP-OES with a median concentration of <0.30 µg/g. Although the concentrations were low in environmental samples, the urine samples showed elevated levels. However, those participants who used iron and folic acid supplements showed an association with decreased cadmium levels.

Soil

42. Cadmium occurs naturally in the Earth's crust at a concentration of 0.1 mg/kg and is commonly found in association with zinc ores (EFSA, 2009; ATSDR, 2012). Cadmium in soil 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 and this is above the concentration found in most soils (Rawlins *et al.* 2012; Environment Agency, 2009).

43. In 2012, the British Geological Society (BGS) determined the normal background concentrations (NBC) of cadmium in soil, in England and Wales (Defra, 2012 and 2013). The upper limit of NBCs is defined as the upper 95 percent confidence limit of the 95th percentile of total Cd in soils sampled from depths between 0 and 15 cm. The soils were grouped into domains to establish meaningful NBCs, with the most significant domain for each country being the principal domain. The summary statistics reported for the principal domain for England and Wales were a NBC of 1.0 mg/kg (n = 4418) and 1.4 mg/kg (n = 681) respectively.

Air

44. 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) sets target values for four metallic elements which includes cadmium. For PM_{10} particulate fraction of ambient air, the target value for cadmium was set as 5 ng/m^3.

45. 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/m^3 and 0.057 to 1.382 ng/m^3 respectively.

46. 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).

Exposure assessment

47. The Total Diet Study was used to estimate the cadmium exposure from food consumed by women of childbearing age and presented in Table 2 (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. 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 (Table 1.) 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.

48. The food groups providing the highest cadmium exposures were miscellaneous cereals, potatoes, and bread. 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 breads, potatoes, breakfast cereals and rice (NHS, 2020). Therefore, it must also be noted that pregnant women may have a different diet in comparison to those non-pregnant females considered in the TDS.

Risk characterisation

49. The EFSA tolerable weekly intake value (TWI) of 2.5 µg/kg bw/week (equivalent to 0.36 µg/kg bw day) was used in the risk assessment following the review conducted by EFSA comparing those HBGV's laid down by JECFA and the CONTAM Panel.

Bread

50. 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 (Table 3).

Miscellaneous cereals

51. The cadmium intake based on the TDS data for miscellaneous cereals for women of child-bearing age is shown in Table 3. The mean and 97.5th percentile for consumption of miscellaneous cereals were 8.9 and 25.8% respectively of the EFSA TWI.

Table 2. Estimated cadmium exposure (µg/kg/day to 2 significant figures) from food consumed by women of child-bearing age(16 – 49 years of age) using data obtained from Total Diet Study (TDS) groups using the lower bound to upper bound (LB-UB) (Bates *et al*., 2014, 2016; Roberts *et al.,* 2018).

Food Groups	Mean	97.5th Percentile
Bread	0.022	0.054
Miscellaneous Cereals	0.032	0.093
Carcase meat	0 – 0.0021	0 – 0.0097
Offal	0.00091	0.017
Meat products	0.0039	0.017
Poultry	0 – 0.0023	0 – 0.0082
Fish and seafood	0.0052	0.025
Fats and oils	0 – 0.00051	0 – 0.0015
Eggs	0 – 0.00077	0 – 0.0038
Sugars and confectionary	0.0020	0.0081
Green vegetables	0.0031	0.012
Potatoes	0.023	0.067
Other vegetables	0.010	0.030
Canned vegetables	0.0032	0.015
Fresh fruit	0 – 0.0070	0 – 0.026
Fruit products	0 – 0.0024	0 – 0.014
Non-alcoholic beverages	0 – 0.059	0 – 0.14
Milk	0 – 0.0056	0 – 0.020
Dairy products	0 – 0.0023	0 – 0.0087
Nuts and seeds	0.0013	0.011
Alcoholic drinks	0 – 0.0053	0 – 0.037
Meat substitutes	0.00029	0.0038
Snacks	0.0065	0.029
Desserts	0.00082	0.0052
Condiments	0.0040	0.014
Tap water	0 – 0.0072	0 – 0.031
Bottled water	0 – 0.0020	0 – 0.014
Total	0.12 - 0.21	0.21 - 0.37

Potatoes

52. 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 18.6% (Table 3).

Table 3. Risk characterisation of cadmium intake for women of maternal age for bread, miscellaneous cereal, and potatoes as a percentage of the EFSA TWI (0.36 µg/kg bw/day).

Cadmium concentration (µg/L)	Mean	97.5th Percentile
Bread	6.1	15
Miscellaneous cereals	8.9	25.8
Potatoes	6.4	18.6

Total daily exposure

53. The total daily exposure from food for women of maternal age was shown in Table 2. Table 4 shows the percentage of the EFSA TWI per day based on the lower and upper bounds. The mean shows a percentage of the EFSA TWI of 22.2 to 58.3% and the 97.5th percentile between 58.3 and 102.7%.

Table 4. Risk characterisation of cadmium intake for women of maternal age for all categories in Table 2 as a percentage of the EFSA TWI (0.36 µg/kg bw/day) .

Cadmium concentration (µg/L)	Mean	97.5th Percentile
Total Cadmium LB-UB	22.2 - 58.3	58.3 – 102.7

Conclusions

54. Cadmium occurs naturally in the environment (volcanic eruptions and erosion) and from anthropogenic sources such as phosphate fertilisers and non-ferrous mining and smelting.

55. Cadmium has been classified by IARC as a Group 1 human carcinogen. Chronic exposure can lead to renal damage, osteomalacia and osteoporosis. Cadmium can interfere with vitamin D and calcium metabolism which leads to increased absorption and body burden. During pregnancy, Cd can accumulate in the placenta.

56. 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 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 preeclampsia has been observed in mice with high blood concentrations of cadmium.

57. Food is the main source of cadmium for non-smoking of maternal age. The foods making the highest contribution to cadmium are breads, miscellaneous cereals, and potatoes. 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 58-103% respectively.

58. Using the maximum 97.5th percentile, there was a slight exceedance of the EFSA Tolerable Weekly Intake of Cd (103%), however using the mean values there was no exceedance of the TWI. Caution must be taken when using the TDS data as it is based on the consumption data for those of maternal age and therefore may not be representative of the maternal diet.

Questions on which the views of the Committee are sought

Members are invited to consider the following questions:

I. Do members consider that exposure to cadmium would pose a risk to maternal health?
II. Do members have any specific comments on the cadmium in the maternal diet?
III. Does the Committee have any further comments?

Secretariat
November 2021

Abbreviations

ATSDR	Agency for Toxic Substances and Disease Registry
BGS	British Geological Survey
$BMDL_5$	Benchmark Dose Lower Confidence Limit
Ca^{2+}	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
PM_{10}	Particulate Matter ($\leq$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
Zn^{2+}	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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Appendix A - Literature Search Terms

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