Cadmium in the Maternal Diet - Toxicity

In this guide

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8. The assessment started with a review of the opinions of the European Food Safety Authority (EFSA), Joint FAO/WHO Expert Committee on Food Additives (JECFA), World Health Organisation (WHO) and the Agency for Toxic Substances and Disease Registry (ATSDR) were used. This was supplemented with a literature review conducted using PubMed and Scopus over 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 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 $Zn2+$ and $Ca2+$ 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).

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).

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 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 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).

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, 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).

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).