Statement on potential risks from cadmium in the diet of infants aged 0 to 12 months and children aged 1 to 5 years

Introduction and Background - Statement on potential risks from cadmium in the diet of infants

In this guide

In this guide

Introduction

1. The Scientific Advisory Committee on Nutrition (SACN) is undertaking a review of scientific evidence that will inform the Government's dietary recommendations for infants and young children. The SACN is examining the nutritional basis of the advice. The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) was asked to review the risks of

toxicity from chemicals in the diet of infants, most of which has been completed, and young children. The reviews will identify new evidence that has emerged since the Government's recommendations were last formulated, and will appraise that evidence to determine whether the advice should be revised. The recommendations cover diet from birth to age five years.

2. Public Health England has produced information for the general public on the risks of exposure to cadmium but there are currently no Government dietary recommendations for infants and young children which relate to this metal.

Background

3. Cadmium (Cd) is a soft, silver-white or blue-white metal that exists in various mineral forms and is present throughout the environment. It is used in a wide variety of processes including electroplating, alloy production, paints and pigments, and is present in a wide range of industrial and consumer products. Cadmium concentrations in the environment reflect contributions both from sources that are natural, for example volcanic activity, and that are anthropogenic, for example non-ferrous metal smelting.

4. The general population is primarily exposed to cadmium via food, with drinking water and inhalation from ambient air acting as minor sources of exposure. Food is considered to be an appreciable source of exposure in non-smokers. Less than 10 % of total exposure of the non-smoking general population is due to inhalation of the low concentrations of cadmium in ambient air and through drinking water (EFSA 2009). The main food plant sources of cadmium are crops such as rice and potatoes, arising from the use of phosphate fertilisers since mineral sources of phosphate are associated with Cd ores. Kidney and liver are the main sources in food of animal origin since Cd in animal feed concentrates in these organs. Tobacco leaves accumulate cadmium from the soil and smoking may make a large contribution to intakes in smokers (EFSA 2009).

5. There are currently no data showing that cadmium is an essential micronutrient for animals, plants or microorganisms. (EFSA, 2009). Only one enzyme, an isoform of carbonic anhydrase in a marine diatom, has been shown to use cadmium as a co-factor (Lane & Morel, 2000).

6. Oral ingestion of cadmium salts in experimental animals has resulted in a wide range of adverse effects including nephrotoxicity, hepatotoxicity and metabolic effects (WHO 2011).

7. Oral bioavailability of cadmium is low, at 3 – 5% from food. Uptake is greater in individuals with low storage levels of iron (Gallagher *et al*., 2011) and is thus greater in pre-menopausal women, especially during pregnancy, than in men (EFSA, 2009). Studies in experimental animals have shown that dietary deficiency of zinc and calcium can also lead to increased Cd uptake (Asagba, 2009). Cadmium and its salts have low vapour pressures so inhalation is generally in the form of respirable particles. Absorption from smoke inhalation has been estimated to be 7 – 50%, with fractional retention of inhaled cadmium depending on particle size: 50-60 % of ultrafine particles would be retained, the remaining part being exhaled with the smoke.

8. Transport of cadmium in the blood is largely in erythrocytes but in the liver Cd binds to the sulphydryl-rich protein metallothionein (MT). This metal-protein complex is released into the blood, filtered by the glomerulus and reabsorbed by the cells of the proximal convoluted tubule. Cadmium thus concentrates primarily in the kidneys and to a lesser extent in the liver. Its biological half-life in the human body is very long, ranging from 10 to 30 years. (EFSA ,2009). Yoshida *et al*. (1993) found that expression of MT falls sharply after birth, then rises until middle age (40 – 60 years of age), in parallel with Cd accumulation, whereafter it slowly declines. Cd concentrates in the placenta but concentrations in umbilical cord blood are generally lower than in the maternal circulation (EFSA, 2009; Esteban-Vasalio *et al*., 2012).

9. Since it is poorly absorbed, ingested cadmium is largely excreted in the faeces. Cd absorbed into the blood is excreted in the urine. Blood Cd (B-Cd) levels are regarded as reflecting levels of exposure, whereas urinary Cd (U-Cd) levels, expressed as mg per g creatinine to account for changes in urine volume, are a measure of body burden (EFSA, 2009).

10. Acute toxicity from cadmium is largely an issue for workers involved in industrial applications. For the general population, chronic effects are of greater concern. The liver and kidney are the major organs of cadmium accumulation. The liver MT–Cd complex in the blood is filtered through the glomerulus and is then reabsorbed by the cells of the proximal tubule, where it is degraded by lysosomes and the Cd is sequestered by renal MT. As this process continues, the proximal tubule cells' capacity to produce MT is exceeded and free Cd causes damage at multiple sites. The protection from Cd toxicity afforded by MT and its exceedance with increasing Cd concentration has been shown *in vitro* (Leierer *et al*., 2016),

11. An early sign of renal toxicity is low-molecular-weight proteinuria, particularly of b2-microglobulin, followed by reduced filtration rate, necrosis of the nephron and high-molecular–weight proteinuria. Cadmium-induced kidney damage may be reversible in its early stages (Gao *et al* 2016) but in later stages may be irreversible and progressive, even in the absence of ongoing cadmium exposure.

12. Chronic cadmium exposure can cause osteoporosis and osteomalacia, with deformity and bone fragility either by direct displacement of calcium or by inhibiting the kidney's hydroxylation of vitamin D, causing disruption of calcium and phosphorus metabolism. In Japan, the combination of kidney dysfunction and bone degradation arising from exposure to high levels of environmental cadmium is known as Itai-Itai (ouch-ouch) disease (EFSA, 2009).

13. Cadmium affects the activity of a number of enzymes, transport systems and second messengers, for example neuronal Ca^{2+}channels (Sadiq *et al*., 2012), metal-dependant protein phosphatases (Pan *et al* 2013), ceruloplasmin (Shariat and Alinejad, 2008), lactate dehydrogenase, succinate dehydrogenase and Na^{+}-K^{+}-ATPase (Karthikeyan and Bavani, 2009) and the serine/threonine kinase ERK (Martin *et al*., 2009).

14. Cadmium indirectly induces oxidative stress, which causes damage to membranes, DNA and proteins. Oxidative stress plays a role in kidney and bone damage as well as in cadmium-induced carcinogenesis (Nair *et al*., 2013).

15. The IARC has reviewed cadmium and cadmium compounds multiple times, most recently in 2012, and has classified them as Group 1 human carcinogens that cause cancers of the lung, prostate and paranasal sinuses after inhalation (IARC, 2012).

16. Cd, although classified by IARC as a Group 1 human carcinogen, does not appear to be directly genotoxic, but can inhibit DNA repair mechanisms and can lead to DNA modifications such as production of 8-oxo-2'-deoxyguanosine (Nair *et al.*, 2013) and changes in the degree of 2'-deoxycytosine methylation (Takiguchi *et al.*, 2003). Other postulated mechanisms of Cd carcinogenicity include cellular proliferation by activation of the Wnt second messenger system (Chakraborty *et al*.,2010) and mimicry of estradiol at estrogen receptors (Aquino *et al*., 2012; Chmielowska-Bąk *et al*., 2013).

17. Exposure to cadmium by inhalation in the general population has been associated with a statistically significant increased risk of cancer such as in the

lung (Nawrot *et al* 2015), bladder and prostate (Santana *et al*., 2016). However, Golabek *et al*. (2014) found that although cadmium accumulated in bladder and other tissues with age, patients with urothelial carcinoma of the bladder had statistically significant (p 0.001) lower levels of Cd in bladder tissues than control patients.

18. Cho *et al*. (2013) reported an association between oral exposure to Cd in Western countries and incidence of cancer of the breast, endometrium and ovary. However, Adams *et al*. (2014) found no evidence of an association between oral exposure to cadmium, estimated from a dietary survey and known Cd content of various foodstuffs, and cancers of the breast, endometrium or ovary in a study involving over 155 000 postmenopausal women (age 50 – 79).

19. There is currently no consistency in the epidemiological data to suggest that cadmium compounds can cause cancer at additional sites or by additional routes, and no increases in the incidence of tumours have been observed in oral carcinogenicity studies in experimental animals. (IARC, 2012)

20. There is some evidence that the toxic effects of Cd may be ameliorated by consuming foods or treatment with substances, with antioxidant properties, for example quercetin and a-tocopherol (Prabu *et al*., 2010), grape juice concentrate (Pires *et al*.,2013; Lamas *et al*., 2015) and tetrahydrocurcurmin (Sangartit *et al*., 2014). However, Cd also appears to act synergistically with other environmental toxicants, for example chlorpyrifos (He *et al*., 2015), inorganic arsenic (Adebambo *et al* 2015) and molybdenum (Yang *et al*., 2016).