Previous evaluations and Toxicity - Statement on the effects of lead on maternal health

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Previous evaluations

7. The safety of lead in food has previously been evaluated by the European Food Safety Authority (EFSA) Panel on Contaminants in the Food Chain (CONTAM Panel) (EFSA, 2010) and JECFA (2011). The US Agency for Toxic Substances and Disease Registry has also reviewed the toxicity of lead (ATSDR, 1999). These evaluations are discussed in more detail in the discussion paper for Lead in the Maternal Diet (COT, 2022).

ADME

8. Lead absorption has been determined in a number of studies, and in adult humans is approximately 10 % of the ingested dose (Rabinowitz *et al.*, 1976). Lead absorption from the gastrointestinal tract appears to be higher in infants and children than in adults, with an average lead absorption in infants of

about 42 % of intake (Ziegler *et al.*, 1978). This is supported by animal studies which indicate that gastrointestinal absorption rates for lead are greater in the very young than in older animals (Forbes *et al.*, 1972; McMichael *et al.*, 1986).

9. Approximately 95 % of lead in adult tissues and 70 % in children resides in mineralised tissues such as bones and teeth. This reflects changing turnover rates throughout an individual's lifetime, with a slower turn-over of lead in the bones of adults than those of children. The lead which has accumulated in adult bone, can replenish lead eliminated from the blood by excretion, long after the external exposure has ended. It can also be a source of lead transfer to the fetus when the maternal skeleton is resorbed for the production of the fetal skeleton. Gulson *et al*. (1997) found that increases in blood lead (bPb) of 20 % were detected in the mother during pregnancy. Additionally, it is worth noting that previous studies have suggested that bPb levels increased only in the second half of pregnancy, however, Gulson (1997) found two subjects with increased bPb levels in the first trimester of pregnancy. Skeletal contribution to bPb level was 31 ± 19 % (mean ± SD), with the remaining increase suggested to be due to increased absorption of dietary lead and decreased elimination of lead. These results showed that mobilisation from long-term stores (i.e., bone) was a significant contributor to bPb levels during pregnancy. However, it is pertinent to clarify that lead levels in bone accumulate over a period of many years before pregnancy and are largely determined by the pre-maternal rather than maternal diet and as such fall beyond the remit of this paper.

10. Bolan *et al* (2021) examined the intestinal permeability/bioaccessibility of lead, as influenced by gut microbes and chelating agents using an *in vitro* gastrointestinal/Caco-2 cell intestinal epithelium model. In the presence of gut microbes and chelating agents, there was a significant decrease of 7.9 % in the permeability coefficient of lead, indicative of a decrease in lead absorption from the gut.

11. Rădulescu and Lundgren (2019) reviewed the recent pharmacokinetic models for lead. Absorption takes place via ingestion, inhalation and to a lesser extent through the skin. The effectiveness of gastrointestinal absorption depends on the quantity and type of food consumed prior to lead ingestion. The efficiency of gastrointestinal absorption of water-soluble lead is also age-dependent and is higher in children than in adults. The authors cited several older studies regarding the different distributions of lead in human soft tissues, highlighting that the major organ is the liver (Barry, 1975; Gross *et al.* 1975; Schroeder, H. A. & Tipton, I. H. 1968; Barregård *et al.* 1999; and Gerhardsson *et al.* 1995).

Toxicity

12. The acute effects of lead, from exposure of short duration, can manifest as muscle pain, fatigue, abdominal pain, headache, vomiting, seizures, and coma. While there are insufficient data to establish a dose-response relationship for acute toxicity relative to bPb, anecdotally, symptoms that cause individuals to seek medical intervention can occur at bPb levels of ~ 30 µg/dL with signs and symptoms increasing in severity with increasing bPb. Chronic lead poisoning from low level, repeated exposure can result in clinical signs of persistent vomiting, encephalopathy, lethargy, delirium, convulsions and coma. Depending on the location or organ in question, chronic adverse effects can occur at bPb levels ≤5 µg/dL (ATSDR, 2020).

13. The International Agency for Research on Cancer (IARC) has classified lead compounds as probably carcinogenic to humans (Group 2A) on the basis of limited evidence of carcinogenicity in humans and sufficient evidence in animals. Organic lead compounds were considered not to be classifiable as to their carcinogenicity to humans (Group 3) because there was inadequate evidence for carcinogenicity in humans and animals. The mechanisms of lead-induced cancer in experimental systems are complex, appearing to involve oxidative stress, interaction with zinc finger proteins, altered cell signalling pathways and interactions with cellular genetic machinery by high affinity lead-binding proteins (IARC, 2006).

14. Flora *et al*. (2012) and Wani *et al*. (2015) reviewed the toxicity of lead. They determined that the central nervous system, erythropoietic system and the kidneys are the most affected systems but overall, all bodily systems are adversely affected by the presence of this metal.

15. It has been estimated that systolic pressure is approximately 1 mm Hg higher for each doubling of bPb level, without any clearly identifiable threshold (EFSA, 2010). In the dose response (DR) modelling for cardiovascular effects, EFSA selected a 1 % change in systolic blood pressure as a benchmark response (BMR), which was within the range that could have significant consequences for human health at a population level. An average BMDL01 of 36 µg/L bPb was calculated from two longitudinal and two cross-sectional studies (Glenn *et al.*, 2003; Vupputuri *et al.*, 2003; Nash *et al.*, 2003; Glenn *et al.*, 2006).

16. Both reduced glomerular filtration rate (GFR) associated with exposures to average bPb levels of <200 µg/L and increased serum creatinine in subjects

with blood lead levels below 100 µg/L have been observed. EFSA (2010) selected a 10 % increase in the prevalence of chronic kidney disease as a BMR for renal effects and a BMDL10 of 15 µg/L bPb was calculated using data from a cross-sectional study conducted in the USA (Navas-Acien *et al*., 2009).

17. The COT (2013), like EFSA (2010), determined that neurodevelopmental effects represent the most sensitive endpoint for effects in the developing fetus whilst also being protective of the other toxicological end points in the mother. The study used for the benchmark dose modelling undertaken by EFSA (2010) is described in the following paragraph.

18. Data from a study by Lanphear *et al*. (2005), were used by both EFSA and JECFA for DR modelling of neurodevelopmental effects (EFSA, 2010; and FAO/WHO, 2011). EFSA commissioned their own analysis of the raw data from the respective author's study in contrast to JECFA who used the dose-response data presented in the publication. The Lanphear *et al*. (2005) study was a pooled analysis of data from seven prospective cohort studies concerning the quantitative relationship between performance on IQ tests and measures of bPb concentration, among children who have had regular follow-ups from infancy. The primary outcome measure was full-scale IQ, assessed at an age between four years 10 months and 10 years. This was related to four measures of bPb: concurrent bPb (the most recent measurement before IQ was assessed), maximum bPb (the highest concentration of bPb that had been measured at any time before IQ was assessed), average lifetime bPb (the mean of bPb measurements from age 6 months up to the time that IQ was assessed), and early childhood bPb (the mean of measurements between 6 and 24 months of age). After adjustment for covariates, IQ was inversely related to each of these measures of bPb (Lanphear *et al*., 2005). A reduction in IQ of 1 point was selected as the BMR and this corresponds to a BMDL01 of 0.5 µg lead/kg bw/day.

19. The toxicology of lead specifically in the context of pregnancy outcomes and its effects on maternal health have also been previously reviewed and the results are briefly described below.

20. Maternal lead exposure is associated with multiple poor birth outcomes including pre-term delivery and small for gestational age (SGA) births (Chen, (2006); Jelliffe-Pawlowski *et al*. (2006); Taylor *et al*. (2015); Vigeh *et al*. (2011); and Zentner *et al*., (2006)).

21. Low to moderate lead exposure may also increase the risk of spontaneous abortion during early pregnancy (Hertz-Picciotto, 2000; Ou *et al*.

2020). Additionally, Lamadrid-Figueroa *et al*. (2007) determined that women in the upper tertile of the plasma/blood Pb ratio had twice the incidence rate for spontaneous abortion than those in the lower tertile ($p = 0.02$). Borja-Aburto *et al*. (1999) evaluated the risk of spontaneous abortion from low or moderate Pb exposures during the first trimester. The odds ratio for spontaneous abortion was 1.8 for every 5 µg/dL increase in bPb. Conversely, however, Vigeh *et al*. (2011) did not find a significant difference between spontaneous abortion cases and ongoing pregnancies, suggesting that in apparently healthy women, low bPb levels (mean <5 µg/dL) in early pregnancy may not be a risk factor for spontaneous abortion. Based on available data, there is a concern that long-term lead exposure may adversely affect fetal viability as well as fetal and early childhood development, as lead is reported to cross the placenta readily.

22. Hu *et al*. (2006) found that both maternal plasma and whole blood lead, during the first trimester (but not in the second or third trimester), were significant predictors ($p < 0.05$) of poorer Mental Development Index (MDI) scores. Postnatal blood lead levels in the offspring were less strongly correlated with MDI scores indicating that the adverse effect of lead exposure on neurodevelopment may be most pronounced during the first trimester.

23. Poropat *et al*. (2017, from abstract) and Ikechukwu *et al*. (2012, from abstract) found a correlation between an increase in blood lead and the development and progression of preeclampsia. Ikechukwu *et al*. (2012) further state that the increases observed in lead levels were paralleled by decreases in serum calcium and phosphorus levels. Conversely, Liu *et al.* (2019) did not find an association between the development of preeclampsia and bPb levels.