TOX/2022/32

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

First draft statement on the effects of lead on maternal health

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.

2. 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.

3. 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 and to this end, papers on iodine, vitamin D and dietary supplements have been or will be presented to the Committee. The remaining list of compounds were to be triaged on the basis of toxicity and exposure.

4. Following discussion of the first prioritisation paper on substances to be considered for risk assessment by the COT, the Committee decided that each of the heavy metals (lead, mercury, cadmium and arsenic) should be considered in separate papers. The following paper discusses the risks posed to maternal health by lead (Pb) in the diet and the environment.

5. From their conversations on the discussion paper on lead in the maternal diet, the committee concluded that the $BMDL_{01}$ for developmental neurotoxicity was the most relevant benchmark dose and critical effect. It would be this effect that was used as the critical endpoint within this assessment.

6. Members requested an emphasis on the body burden effect which impacts the demineralisation process of the bone marrow during pregnancy potentially releasing significant concentrations of Pb into the plasma.

7. It was noted when discussing the long-term exposure to Pb from the diet that emphasis is to be placed on the chronic / sub chronic effects rather than an acute risk.

8. Members concluded that an exposure assessment of Pb contamination of soil and dust should be undertaken as part of this evaluation, taking geographical considerations into account.

Questions for the Committee

9. The Committee are asked to consider the following question:

a) Does the Committee have any comments on the structure or content of the draft Statement?
b) Does the Committee have any comments on the additional information presented in this draft statement regarding the air and soil/ dust assessments?
c) Does the Committee have any comments on the additional information presented in this draft statement regarding lead resorption from bone?

Secretariat

May 2022

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

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Introduction

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supplements have been or will be presented to the Committee. The remaining list of compounds were to be triaged on the basis of toxicity and exposure.

4. Following discussion of the first prioritisation paper on substances to be considered for risk assessment by the COT, the Committee decided that each of the heavy metals (lead, mercury, cadmium and arsenic) should be considered in separate papers. The following paper discusses the risks posed to maternal health by lead in the diet and the environment.

Background

5. The Merck Index (12th Edition, 1996) describes lead (Pb) as a bluish-white-to-silvery grey Group 14 metal, with atomic number 82 and a relative atomic mass of its most abundant isotope of 208. It occurs naturally in the Earth's crust at an abundance of about 0.002%, chiefly as lead sulphide (PbS), It is very soft and malleable and has a long history of use in domestic articles such as drinking vessels and plates and in water and drainage pipes (plumbing, from "plumbum", the Latin word for lead). More recently it has been used in paints, ceramic pigments and as the "anti-knock" agent tetraethyl lead in petrol. Due to its long-known toxicity, many of these uses have been substituted with less toxic alternatives but lead is still used in various applications such as car batteries and as radiation shielding in the nuclear industry.

6. The Joint FAO/WHO Committee on Food Additives (JECFA) (FAO/WHO, 2011) state that lead contamination of food arises mainly from the environment or from food processing, handling and packaging. Atmospheric lead can contaminate food through deposition on agricultural crops. Water is another source of lead contamination of food. Although lead exists in both organic and inorganic forms, only inorganic lead has been detected in food. Specifically, the major contributors to lead exposure are; cereal products, potatoes, cereal grains (except rice), cereal-based mixed dishes and leafy vegetables.

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, updated 2013) 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 on the Maternal Diet (COT, 2022).

ADME

8. Lead absorption has been measured 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 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. Naylor et al. (2009) found that by week 36 of pregnancy there was an increase in levels of bone resorption markers between 58 % and 202 % and a change in bone formation markers of between -58 % and +88 % suggesting a significant change in the rate of bone turnover during the gestation and post-partum period. Gulson et al. (1997, from abstract) found 20 % increases in blood lead (bPb) were detected in the mother during pregnancy of which the skeletal contribution to bPb level was 31 % ± 19 % (mean ± SD). 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 contributed by the pre-maternal rather than maternal diet and as such falls beyond the remit of this paper.

10. Bolan et al (2021) examined the intestinal permeability of lead, as influenced by gut microbes and chelating agents using an in vitro gastrointestinal/Caco-2 cell intestinal epithelium model. The results showed that, for lead, in the presence of gut microbes or chelating agents, there was a significant decrease in the permeability (-7.9%).

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 the 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 intense exposure of short duration, manifest at blood levels of 1000 – 1200 µg/L with muscle pain, fatigue, abdominal pain, headache, vomiting, seizures, and coma. Chronic lead poisoning from low level, repeated exposure leading to blood levels of 40 – 60 µg/L gives clinical signs of persistent vomiting, encephalopathy, lethargy, delirium, convulsions and coma (ATSDR, 1999).

13. The International Agency for Research on Cancer (IARC) 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 cancers in experimental systems are complex, appearing to involve oxidative stress, interaction with zinc

finger proteins, induction of apoptosis, 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, 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), this 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 $BMDL_{10}$ 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) 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. An analysis by Lanphear et al. (2005), was used by both EFSA and JECFA for dose-response (DR) modelling of neurodevelopmental effects (EFSA, 2010; and FAO/WHO, 2011). This 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 followed 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).

19. The toxicology of lead specifically in the context of pregnancy outcomes and its effects on maternal health have also been previously reviewed by ; Borja-Aburto et al. (1999), Chen et al. (2006), Hertz-Picciotto, (2000), Hu et al. (2006), Ikechukwu et al. (2012), Jelliffe-Pawlowski et al. (2006), Karri et al (2004), Lamadrid-Figueroa et al. (2007), Liu et al (2019), Ou et al. (2020), Poropat et al. (2017), Taylor et al. (2015), Vigeh et al. (2011), Wells et al. (2011) and Zentner et al., (2006).

Derivation of a health-based guidance value

20. The dose response modelling and derivation of an HBGV have been reviewed and summarised in the COT statement (2013). The COT discussed the three endpoints assessed by EFSA (cardiovascular, renal and neurodevelopmental effects) and concluded that the most relevant was neurodevelopmental effects. This is summarised in brief in the following paragraphs.

Benchmark Dose Modelling

21. An analysis by Lanphear et al. (2005) (paragraph 24), was used by both EFSA and JECFA for dose-response (DR) modelling of neurodevelopmental effects (EFSA, 2010; and FAO/WHO, 2011). The DR modelling was previously described in a COT statement in 2013 relating to Pb in the infant diet and has been summarised in the following paragraphs (COT, 2013).

22. Budtz-Jørgensen (2010) was commissioned by EFSA to calculate a BMDL for the association of lead with the development of intellectual function, by modelling of data from the pooled analysis by Lanphear et al. (2005). The benchmark calculations

used regression models with full IQ score as the dependent variable, and adjustment for birth weight, Home Observation for Measurement of the Environment (HOME) score (The HOME Inventory is an index that reflects the quality and quantity of emotional and cognitive stimulation in the home environment (Lanphear *et al.*, 2005)), maternal education and maternal IQ, all of which were significantly associated with IQ in the dataset. BMD and BMDL values were calculated for a 1% change in full scale IQ score (a decrease in IQ by 1 point), taking concurrent blood lead, maximum blood lead, average lifetime blood lead and early childhood blood lead as alternative exposure metrics. The dose-response models applied were logarithmic, linear, and a piecewise linear function with breakpoint at 100 µg/L.

23. For the assessment of risk, EFSA took as a point of departure, the $BMDL_{01}$ value of 12 µg/L from the piecewise linear dose-response model for concurrent blood lead. Concurrent blood lead concentration exhibited the strongest relationship with IQ, and the piecewise linear model showed a better fit to the data than the linear model. The logarithmic model generally gave an even better fit than the piecewise linear model, but the differences were small, and EFSA preferred the latter because, taking into account the mathematical properties of the logarithmic model, they considered that it provided "less uncertain estimates of the $BMDL_{01}$". Using the US EPAs Integrated Exposure and Uptake Biokinetic (IEUBK) toxicokinetic model, the blood lead $BMDL_{01}$ of 12 µg/L was estimated to correspond to a dietary lead exposure in infants and children of 0.5 µg lead/kg bw per day (EFSA, 2010).

24. JECFA (FAO/WHO, 2011) also used data from the Lanphear *et al.* (2005) analysis for dose-response modelling. Models were based on concurrent blood lead levels since they showed the highest correlation with IQ. Initially, six different models were considered – four with linear form and two sigmoidal. From these, a bilinear model (unlike the piecewise linear model used by EFSA, this did not constrain the inflexion in the dose-response relationship to be at a pre-specified blood lead concentration) was chosen to characterise the relationship of blood lead to IQ, since it provided a better fit than four of the other models, and it was considered that it would give better estimates of effect than the one other model with similar fit, when non-dietary exposures to lead were unknown or highly variable. Using this model, the chronic dietary exposure of a 20 kg child corresponding to a decrease of 1 IQ

point was estimated to be 0.6 µg/kg bw per day with a 90 % confidence interval of 0.2 - 7.2 µg/kg bw per day.

25. The differences between the EFSA and JECFA analyses are small and reflect inevitable uncertainties in the specification of the mathematical models. The COT noted that both were influenced by an apparently steep dose-response at low levels of lead exposure (blood lead levels less than 75 µg/L), which was based on few data from a single study in Rochester, USA, and may have rendered the BMDL values conservative. In this statement, the COT has based its risk characterisation on the EFSA $BMDL_{01}$, which is between the EFSA BMD_{01} and the lower 90 % confidence limit for the BMD_{01} calculated by JECFA. The EFSA $BMDL_{01}$ corresponds to a dietary exposure of 0.5 µg/kg bw/day.

Exposure Assessment

Exposure from food

26. The FSA Exposure Assessment Team has provided dietary exposure data on the lead for women of childbearing age (16 – 49 years of age) (Table 1, Appendix 1). The food commodities which result in the highest exposure to lead are green vegetables, miscellaneous cereals and other vegetables with mean exposure values of 0.0088, 0.0080 and 0.0063 µg/ kg bw/day and 97.5th percentile values 0.034, 0.028 of 0.019 µg/kg bw/day, respectively. The total exposures via food were calculated as 0.12 µg/kg bw/day (mean) and 0.23 µg/kg bw/day (97.5th percentile).

Exposure from drinking water

27. Data on concentrations of lead in water had previously been provided by the Drinking Water Inspectorate (DWI) (for England and Wales), the Drinking Water Quality Regulator (DWQR) for Scotland and Northern Ireland Water. The concentration data from 2019 for lead in drinking water are given in Table 2, Appendix 1.

28. The FSA Exposure Assessment Team has provided values for water consumption for women of child-bearing age of 8 (median) and 32 (97.5th percentile) g (ml) of water per kg bodyweight per day. Using the upper bound mean lead

concentration values in drinking water, the calculated exposures to lead from drinking water are shown in Table 1.

Table 1. Calculated median and 97.5th percentile exposures for women of childbearing age to lead from drinking water, using the mean upper bound concentration values (μg/kg bw/day).

Region	N	Median **	97.5th percentile **
England and Wales*	10967	0.00024	0.00098
Scotland	436	0.000054	0.00021
Northern Ireland	122	0.00013	0.00050

*using 99th percentile lead concentration

** Average body weight of 70.3Kg for women of childbearing age used for exposure calculation. Value provided by the FSA Exposure Assessment Team from years 1 – 11 of the rolling National Diet and Nutrition Survey, NDNS.

Exposure from the air

29. Defra provide data on air pollution throughout the UK. An interactive map (Defra, 2020) shows that the majority of the country in 2020 had an average air concentration of <10 ng lead/m^3, with major urban centres in England and Wales having concentrations of 10 – 50 ng lead/m^3.

30. The WHO estimates that the average inhalation rate for a 70 kg adult is 20 m^3/day (WHO, 2000).

31. As a worst-case scenario, if an adult female were to be constantly exposed to an air concentration of 50 ng lead/m^3 then this would result in a daily exposure to 1000 ng of lead from the air. For women with an average body weight of 70 kg, (value provided by the FSA Exposure Assessment Team from years 1 – 11 of the rolling National Diet and Nutrition Survey, NDNS) this gives an exposure of 14 ng/kg bw (0.014 μg/kg bw/day).

32. This assumes full absorption of all lead in particles inhaled, but this depends upon particle sizes and since some of the inhaled dose may become trapped in other

parts of the nasopharynx, these inhalation values are probably an overestimate, but may contribute in a small way to ingested lead.

Exposure from soil and dust

33. People may be exposed to lead through swallowing dirt that contains lead. Ingestion of contaminated soil is often as a result of “hand-to-mouth” activity and while being a more important route of exposure for toddlers and children, still presents a potential source of intake in adults, for example, from the surface of unwashed vegetables.

34. Lead concentrations in soil are influenced both by underlying lithological lead concentrations and by anthropogenic release of lead. Lead was measured in topsoil from England from a depth of 0-15 cm as part of a DEFRA-commissioned project (Ander et al. 2011).

35. Table 2 shows the lead exposures from soil for women of child-bearing age. Mean and 75th percentile lead concentrations from soil in regions classified as rural, semi-urban or urban were used to assess potential exposures of adults through soil ingestion. An ingestion rate of 50 mg soil/day was assumed based on the rate used by the Environment Agency in their Contaminated Land Exposure Assessment (CLEA) model (Environment Agency, 2009) and was based on a consensus value from studies by USEPA (1997) and Otte et al. (2001). It is a combined value for soil and dust as most of the evidence used to determine the ingestion rate does not differentiate between soil and household dust. Furthermore, the evidence base for selecting a representative soil ingestion rate for adults is much smaller than that for children and as such USEPA (1997) cautioned that the value is highly uncertain and based on a low level of confidence.

Table 2. Median and 75th percentile exposure values for women of childbearing age to lead from soil. Soil lead concentrations taken from the Defra-commissioned contaminants in the soils of England report (Ander et al. 2011) and an ingestion of 50 mg soil/day provided by the Environment Agency (2009).

	Region	Soil concentration of lead (mg/ kg)	Lead ingestion (µg/ kg bw/ day)*
Mean	Rural	35	0.025
	Semi-Urban	57	0.041
	Urban	166	0.118
75th percentile	Rural	46	0.033
	Semi-Urban	100	0.071
	Urban	322	0.229

* Average body weight for women of childbearing age used for ingestion rate = 70.3 kg, value provided by the FSA Exposure Assessment Team from years 1 – 11 of the rolling National Diet and Nutrition Survey, NDNS.

36. The data presented are representative of lead concentrations in the soil in England only. There have been no individual studies investigating the lead levels in soils of Wales, Scotland or Northern Ireland.

37. Pica behaviour is described as the craving for and intentional ingestion of substances that are not described as food. Whilst it presents a potential route of exposure to lead in the maternal diet, it has not been considered as part of this paper due to the uncommon nature of the behaviour and lack of data available for assessment. No recent data were available for levels of lead measured in household dust in the UK.

Risk characterisation

38. Potential risks from maternal exposures to lead were characterised by margins of exposure (MOEs), calculated as the ratio of the BMDL of 0.5 µg/kg bw/day to estimated exposures from diet, soil and air. As the BMDL was for a small effect (a one-point difference in IQ), derived from pooled analysis of multiple cohort studies of exposures in infants and children, and is likely to be conservative (see paragraph 40), EFSA therefore concluded that a margin of exposure of 10 or greater should be sufficient to ensure that there was no appreciable risk of a clinically

significant effect on IQ. At lower MOEs, but greater than 1.0, the risk is likely to be low, but not such that it could be dismissed as of no potential concern. (EFSA, 2010)

39. In 2013, the COT further concluded that an MOE of >1 can be taken to imply that at most, any risk is likely to be small. MOEs <1 do not necessarily indicate a problem, but scientific uncertainties (e.g. because of potential inaccuracies in the assessment of exposures, failure to control completely for confounding factors, and the possibility that the samples of children studied have been unrepresentative simply by chance) mean that a material risk cannot be ruled out. This applies particularly when MOEs are substantially <1 (COT, 2013).

Food

40. Using the dietary value of 0.5 µg/kg bw/day, corresponding to the calculated $BMDL_{01}$ for neurodevelopmental toxicity from EFSA (2010, updated 2013), the MOEs for women of childbearing age from the highest-lead-containing food groups in the total diet study are given in Table 3

Table 3. Calculated MOEs for lead in the food groups with the highest measured mean lead concentrations (upper bound) for the total diet in women aged 16 to 49 years of age.

Commodity	Mean lead exposure (µg/kg bw/day)*	MOE for 0.5 µg/kg bw/day
Green vegetables	0.0088	57
Misc. cereals	0.0080	63
Other vegetables	0.0063	79
Total in all food	0.12	4.2

The calculated exposures were compared to the dietary intake value of 0.5 µg/kg b.w. per day which corresponds to the blood $BMDL_{01}$ of 0.5 µg/kg bw/day for developmental neurotoxicity.

* Average body weight for women of childbearing age used for exposure = 70.3 kg, value provided by the FSA Exposure Assessment Team from years 1 – 11 of the rolling National Diet and Nutrition Survey, NDNS

Table 4. MOEs for lead in the dietary commodities with the highest measured 97.5th percentile lead concentrations (upper bound) and for the total diet in women aged 16 to 49 years of age.

Commodity	97.5th percentile lead exposure (μg/kg bw/day)*	MOE for 0.5 μg/kg bw/day
Green vegetables	0.034	15
Misc. cereals	0.023	22
Other vegetables	0.019	26
Total in all food	0.23	2.2

The calculated exposures were compared to the dietary intake value of 0.5 μg/kg b.w. per day which corresponds to the blood $BMDL_{01}$ of 0.5 μg/kg bw/day for developmental neurotoxicity.

*Average body weight for women of childbearing age used for exposure = 70.3 kg, value provided by the FSA Exposure Assessment Team from years 1 – 11 of the rolling National Diet and Nutrition Survey, NDNS.

41. Neither the mean nor the 97.5th percentile consumption MOEs for the foods with the highest measure of lead, nor for the total amount of lead in food as a whole as reported by the NDNS, has a value of 1 or lower, indicating that any risk of toxicity from lead in food is likely to be small.

Drinking water

42. The MOEs for lead in drinking water are shown in Table 5.

Table 5. MOEs for lead in drinking water using the concentration data provided by the water regulators for England and Wales, Scotland and Northern Ireland and consumption data provided by the FSA Exposure Assessment Team.

Region	97.5th percentile lead exposure (µg/kg bw/day) **	MOE for 0.5 µg/kg bw/day
England and Wales *	0.00098	510
Scotland	0.00021	2400
Northern Ireland	0.00050	1000

The calculated exposures were compared to the dietary intake value of 0.5 µg/kg b.w. per day which corresponds to the blood $BMDL_{01}$ of 0.5 µg/kg bw/day for developmental neurotoxicity MOEs rounded to 2 s.f.

*Using 99th percentile lead concentration

**Average body weight for women of childbearing age used for exposure = 70.3 kg, value provided by the FSA Exposure Assessment Team from years 1 – 11 of the rolling National Diet and Nutrition Survey, NDNS

43. The MOEs for intake of lead from drinking water from the four countries of the United Kingdom are all greater than 10; indicating that there is no appreciable risk of a clinically significant effect on IQ.

Air

The inhaled exposure level would have minimal impact upon total lead exposure. Relative to the $BMDL_{01}$ corresponding dietary intake value derived by EFSA, a conservative intake from air gives an MOE of 36 for developmental neurotoxicity.

Soil and Dust

44. The MOEs for exposures from lead in soil are shown in Table 6 and Table 7.

Table 6. MOEs for lead in soil from regions in England using the mean concentrations of lead. Soil lead concentration data are taken from Defra (Ander et al. 2011) and a soil ingestion rate from the Environment Agency (2009).

Region	Mean lead exposure (µg/ kg bw/ day) *	MOE for 0.5 µg/kg bw/day
Rural	0.025	20
Semi-Urban	0.041	12
Urban	0.118	4

The calculated exposures were compared to the dietary intake value of 0.5 µg/kg b.w. per day which corresponds to the blood $BMDL_{01}$ of 0.5 µg/kg bw/day for developmental neurotoxicity

* Average body weight for women of childbearing age used for ingestion rate = 70.3 kg, value provided by the FSA Exposure Assessment Team from years 1 – 11 of the rolling National Diet and Nutrition Survey, NDNS

Table 7. MOEs for lead in soil from regions in England using the highest measured (75^{th} percentile) lead concentrations. Soil lead concentration data taken from Defra (Ander et al. 2011) and a soil ingestion rate from the Environment Agency (2009).

Region	75^{th} Percentile lead exposure (µg/ kg bw/ day) *	MOE for 0.5 µg/kg bw/day
Rural	0.033	15
Semi-Urban	0.071	7
Urban	0.229	2

The calculated exposures were compared to the dietary intake value of 0.5 µg/kg b.w. per day which corresponds to the blood $BMDL_{01}$ of 0.5 µg/kg bw/day for developmental neurotoxicity.

* Average body weight for women of childbearing age used for ingestion rate = 70.3 kg, value provided by the FSA Exposure Assessment Team from years 1 – 11 of the rolling National Diet and Nutrition Survey, NDNS)

45. The MOEs for soil ingestion from regions across England are all greater than 1, therefore, any risk of toxicity from lead in soil is likely to be small. Furthermore, the soil ingestion rate could be an overestimate, particularly as it is a combined value for soil and dust. The ingestion rate is also highly uncertain as it is based upon a

small and variable evidence base. Consequently, the actual soil ingestion rate and lead exposure through this route could be much lower.

Conclusions

46. Lead is a heavy metal pollutant that is ubiquitous in the environment and is thus present in the diet of the general population, including women of childbearing age. Levels have, nonetheless, fallen since the phasing out of lead in petrol, plumbing and paints.

47. Lead in pregnant women can cause increased blood pressure and may be associated with preeclampsia and premature birth.

48. Lead accumulates in the body, so adverse effects can occur from long term dietary exposures at levels below those which cause acute toxicity. Neurotoxicity has been identified at lower levels of exposure, and the developing brain appears to be more vulnerable than the mature brain. It has not been possible to demonstrate a threshold level of exposure below which the neurodevelopmental effects of lead do not occur.

49. EFSA (2010, updated 2013) derived BMDLs for neurodevelopment, renal function and systolic blood pressure and provided values as both µg/ml in blood and the corresponding dietary intake values in µg/kg bw per day. The COT determined that the most relevant endpoint was the $BMDL_{01}$ for neurodevelopmental toxicity as this value is the most sensitive whilst also being protective of the other endpoints in the mother.

50. Exposure of women of childbearing age to lead, in food at the mean and 97.5^{th} percentile of consumption of commodities with the highest concentrations and from soil and dust give MOEs exceeding 1, for effects of developmental neurotoxicity relative to the dietary intake value of 0.5 µg/kg bw/day corresponding to the $BMDL_{01}$. These MOEs indicate, that any risk of toxicity from lead in food is likely to be small.

51. There is no appreciable risk of a clinically significant effect on IQ following exposure of women of childbearing age to lead in air in the UK.

52. The calculated MOEs for soil exposure indicate that in semi-urban and urban areas in the 75th percentile of measured lead levels, there is a low risk to human health, however, this is based upon ingestion rates of high uncertainty.

53. Toxicity will depend on total exposure to lead from all sources, so it is important to consider exposures from all sources.

Secretariat

May 2022

Abbreviations

AGA	Adequate for gestational age
ALA	D-aminolaevulinic acid
ALAD	D-aminolaevulinic acid dehydratase
ATSRD	Agency for Toxic Substances and Disease Registry
BMD	Benchmark Dose
$BMDL_{01}$	Benchmark Dose Lower Limit for 1% change in effect
BPb	Blood lead
CI	Confidence interval
CLEA	Contaminated Land Exposure Assessment
COT	Committee on Toxicity
DNA	Deoxyribonucleic acid
DWI	Drinking Water Inspectorate
DWQR	Drinking Water Quality
Regulator EFSA	European Food Safety Authority
FSA	Food Standards Agency
IQ	Intelligence Quotient
JECFA	Joint FAO/WHO Committee on Food Additives
kPa	KiloPascals
L	Litre
MDI	Mental development index
mmHg	Millimetres of mercury
MOE	Margin of exposure
NDNS	National diet and nutrition survey
OR	Odds ratio
Pb	Lead
SBP	Systolic blood pressure
SD	Standard deviation
SGA	Small for gestational age
µg	Microgram

Search terms

The references cited in this discussion paper are of publications found in PubMed searches and references therein, using the following search terms:

Pb AND	Maternal health
	Pre-conception
	Conception
	Post-partum
	Toxicity
	Mechanism
	ADME
	Toxicokinetics
	Absorption
	Distribution
	Metabolism
	Excretion
	Biomarker
	Exposure
	Pre-eclampsia
	Abortion

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Appendix 1

Lead exposure from food in women of childbearing age

Table 1. Estimated exposure (in µg/kg bw/day) to lead from foods consumed by women of childbearing age (16-49 years) using data from the total diet study food groups (Bates *et al*., 2014, 2016; Roberts *et al.,* 2018).

Food Groups	Mean Exposure to lead LB to UB (µg/kg bw/day)*	97.5th Percentile Exposure to lead LB to UB (µg/kg bw/day) *
Bread	0.0061	0.015
Miscellaneous Cereals	0.0080	0.023
Carcase meat	0-0.0014	0-0.0065
Offal	0.00057	0.011
Meat products	0.0022	0.010
Poultry	0.0015	0.0055
Fish and seafood	0.0015	0.0071
Fats and oils	0-0.00034	0-0.0010
Eggs	0-0.00052	0-0.0025
Sugars and	0.0020	0.0081
Green vegetables	0.0088	0.034
Potatoes	0-0.0045	0-0.013
Other vegetables	0.0063	0.019
Canned vegetables	0.0027	0.013
Fresh fruit	0-0.0047	0- 0.018
Fruit products	0.0041	0.024
Non-alcoholic beverages	0-0.039	0-0.091
Milk	0-0.0037	0-0.014
Dairy products	0.0023	0.0087
Nuts and seeds	0-0.00013	0-0.0011

Alcoholic drinks	0.0053	0.037
Meat substitutes	0.00020	0.0027
Snacks	0.00055	0.0025
Desserts	0.00062	0.0039
Condiments	0.0045	0.016
Tap water	0-0.0048	0-0.021
Bottled water	0-0.0013	0-0.0093
Total	0.057-0.12	0.12-0.23

*Values have been rounded to two significant figures. LB=lower bound; UB=upper bound, average body weight for women of childbearing age used for exposure = 70.3 kg, value provided by the FSA Exposure Assessment Team from years 1 – 11 of the rolling National Diet and Nutrition Survey, NDNS.

Lead exposures from water in women of childbearing age

Table 2. Concentration of lead in tap water sampled in the nations of the United Kingdom in 2019 (μg/l).

Region	N	LB mean	LB SD	UB mean	UB SD
England and Wales*	10967	0.38	0.38	2.15	1.9
Scotland	436	0.34	1.2	0.48	1.2
Northern Ireland	122	0.24	0.79	1.1	0.75

*99th percentile concentration

LB = lower bound: values below the limit of detection assumed to be zero.

UB = upper bound: values below the limit of detection assumed to be the same as the limit of detection

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