TOX/2025/22

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

First Draft Statement on the Effects of Mercury on Maternal Health

Introduction

1. As part of the current programme of work on the maternal diet initiated by the Scientific Advisory Committee on Nutrition (SACN), the COT agreed to prioritise papers on iodine, vitamin D, dietary supplements, and heavy metals including lead, mercury, cadmium, and arsenic, each to be considered in separate papers.

2. In March 2025, the discussion paper on the on the effects of mercury on maternal health was presented to the Committee (TOX/2025/03). This paper was a review of the available data on toxicity of inorganic mercury and methylmercury (MeHg) to maternal health focusing on maternal outcomes and development effects on the fetus or embryo. In the current statement a summary of the toxicity of mercury has been provided but most of the studies identified by literature searches in the discussion paper have not been included in this statement as the Committee concluded the recently published data only confirmed the current knowledge on the toxicity of inorganic and MeHg and did not constitute a basis for revising the current health-based guidance values (HBGVs).

3. Since the review of the discussion paper, at the request of the Committee, a section on exposure to mercury from dietary supplements has been included in this draft statement and the absorption, distribution,

metabolism, and excretion (ADME) section has been simplified and checked for consistency. The UK Governments advice on foods to avoid during pregnancy has been reiterated in the conclusions and the fact that inorganic mercury and MeHg could not be separated in the exposure data has also been addressed in the conclusions.

4. The draft statement (Annex A) includes a summary of ADME and toxicity of mercury, the derivation of HBGVs for MeHg and inorganic mercury, an exposure assessment from all major sources including food, drinking water, soil and air, the risk characterisation and conclusions.

Questions for the Committee

5. The Committee are asked to consider the following questions:

a) Are Members content with the layout and structure of the statement?
b) Do Members agree with the risk characterisation and conclusions?
c) Does the Committee have any further comments on the content of the statement?

TOX/2025/22 Annex A

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

First Draft Statement on the Effects of Mercury on Maternal Health

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.

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 by COT 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 statement discusses the risks posed to maternal health by mercury in the diet and the environment.

Background

5. Mercury (Hg) is a d-block element in the periodic table and is the only metallic element known to be liquid at standard temperature and pressure. It is also known as quicksilver and was formerly named hydrargyrum. It is a group 12 metal, with atomic number 80, a relative atomic mass of 200.592 and its most abundant isotope is ^{202}Hg with atomic mass 201.970 (Laeter et al., 2003). Mercury occurs naturally in the earth's crust at an abundance of 0.0000085%, chiefly as mercury (II) sulfide, also known as cinnabar, cinnabarite or mercurblende (Haynes, Lide and Bruno., 2016). Mercury has been used in thermometers, barometers, manometers, sphygmomanometers, float valves, mercury switches, mercury relays, fluorescent lamps, and other devices. However, the element's toxicity has led to phasing out of such mercury containing instruments. It remains in use for scientific research purposes, fluorescent lighting and in amalgam for dental restoration.

6. The three chemical forms of mercury are (i) elemental or metallic mercury (Hg^0), (ii) inorganic mercury (mercurous (Hg_2^{2+}) and mercuric (Hg^{2+}) cations) and (iii) organic mercury.

7. Inorganic mercury exists as mercurous (Hg_2^{2+}) and mercuric (Hg^{2+}) salts, which are used in several industrial processes and can be found in batteries, fungicides, antiseptics, or disinfectants (EFSA., 2008).

8. Organic mercury compounds have at least one carbon atom covalently bound to the mercury atom (FAO/WHO., 2011). Methylmercury (MeHg) is by far the most common form in the food chain (FAO/WHO., 2011). Other organic mercury compounds like phenylmercury, thiomersal and merbromin (also known as Mercurochrome) have been used as fungicides and in pharmaceutical products (EFSA., 2008).

9. Mercury is a metal that is released into the environment from both natural and anthropogenic sources. After release into the environment, it undergoes complex transformations and cycles between atmosphere, land, and aquatic systems. It ultimately settles in the sediment of lakes, rivers or bays, where it is transformed into MeHg, absorbed by phytoplankton, ingested by zooplankton and fish, and accumulates especially in long-lived predatory species, such as sharks, swordfish, and tuna in the ocean, and trout, pike, walleye, and bass in freshwater systems (WHO/IPCS., 1990). Populations that predominately depend on foods derived from fish or other aquatic environments are more vulnerable to MeHg exposure.

10. Food sources other than fish and seafood products may contain mercury, but mostly in the form of inorganic mercury. Based on the available data the contribution to MeHg exposure from non-seafood sources is insignificant (EFSA., 2012).

11. The main adverse effect associated with MeHg exposure is toxicity to the central and peripheral nervous systems (WHO., 2017). Due to its ability to cross the placenta and the blood-brain barrier, MeHg exposure is of particular concern during embryonic neurodevelopment and in young children (COT., 2004). Thus, pregnant and breastfeeding women are sensitive sub-populations since maternal exposure can lead to exposure of the unborn child either via the placenta or breast milk. The bio accumulative properties of MeHg in combination with its long half-life, mean that the blood concentration of MeHg at the time of becoming pregnant depends on the exposure to MeHg during the preceding year. MeHg can also affect the kidneys. Acute neuro- and nephrotoxicity have been reported in cases of human MeHg poisoning, whereas neurotoxicity is usually associated with lower-level chronic exposures, especially in the developing fetus (COT., 2004).

12. The critical target for inorganic mercury toxicity is the kidney but other targets include the liver, nervous system, immune system, reproductive and developmental systems (EFSA., 2012). Inorganic mercury in food is considerably less toxic than MeHg (EFSA., 2004). This is attributed to the lower absorption of inorganic mercury and due to its low lipophilicity, mercuric mercury does not readily cross the placental, the blood-brain or the blood-cerebrospinal fluid barriers (EFSA., 2012).

Previous evaluations and Toxicity

13. The safety of mercury in food has previously been evaluated by the EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) (EFSA., 2004; 2012), the Joint Food and Agriculture Organisation of the United Nations (FAO)/ World Health Organisation (WHO) Expert Committee on Food Additives (JECFA) (FAO/WHO., 2004; 2011) and the COT (COT., 2018). The US Agency for Toxic Substances and Disease Registry (ATSDR) has also recently reviewed the toxicological profile for mercury (ATSDR., 2024). These

evaluations are discussed in more detail in the discussion paper for mercury in the maternal diet (TOX/2025/03; COT., 2025).

Absorption, distribution, metabolism, and excretion (ADME)

Inorganic mercury

14. Inorganic mercury has low bioavailability via the oral route, with an average absorption rate of 7% in human studies and a range of 1.4 – 15.6% based on the amount of inorganic mercury consumed (Tokar et al., 2012).

15. Studies conducted in mice and rats indicate that the predominant site of absorption of inorganic mercury is the small intestine (ATSDR., 2024). There are several absorption mechanisms for Hg^{2+} in the small intestine, including active and passive processes. The formation of thiol S-conjugates of Hg^{2+} produces molecules that can act as homologues of endogenous molecules/polypeptides. Hence, possible routes of uptake include interaction with plasma membrane amino acids, peptides, drugs, and ion transporters (Bridges and Zalups., 2010; 2018).

16. In human blood, mercuric mercury is divided between plasma and erythrocytes, with more being present in plasma (EFSA., 2012). In plasma, the main sulfhydryls that form S-conjugates with Hg^{2+} are albumin (Ikegaya et al, 2010) and low molecular weight thiols like glutathione, cysteine metallothionine and red blood cell haemoglobin (ATSDR., 2024).

17. Due to their low lipophilicity neither mercurous nor mercuric mercury easily cross the placental or blood-brain barriers. Mercuric mercury distribution in the body is specific to certain organs and cell types within them. The kidney bears the greatest mercuric mercury burden, predominantly in the proximal convoluted renal tubule (EFSA., 2012). The next largest deposition

occurs in the liver, with highest concentrations found in the periportal areas. Additionally, the mucous membranes of the intestinal tract, the epithelium of the skin, the interstitial cells of the testes as well as the choroid plexus in the brain are likely to accumulate mercuric mercury (EFSA., 2012).

18. The metabolism of mercury species involves oxidation and reduction processes along with conjugation to glutathione and appears to be similar between humans and experimental animals. Mice studies have provided some evidence that suggests a small amount of mercuric mercury can be reduced to elemental mercury and eliminated as elemental mercury vapour. In contrast, elemental mercury can be readily oxidised by hydrogen peroxide and catalase to mercuric mercury. There is no evidence in the literature that methylated mercury species are synthesised in human tissue (EFSA., 2012).

19. Inorganic mercuric mercury is eliminated through faeces and urine. In a clinical study involving five adults who received a single intravenous dose of $^{203}Hg(NO_3)_2$ (0.6–2.8 µg Hg), faecal excretion measured over 70 days ranged from 18% to 38% of the administered dose, while urinary excretion ranged from 6% to 35% (Hall et al., 1995). Farris et al. (2008) reanalysed the Hall et al. (1995) data and estimated that, on average, around 30% of the dose was excreted via faeces and 25% via urine. Mercury is also excreted in human sweat and saliva (ATSDR., 2024).

20. The half-life of absorbed mercuric mercury in the human body is approximately 40 days (EFSA., 2012).

Organic mercury

21. Following oral intake, MeHg is absorbed readily by the gastrointestinal tract and enters the systemic circulation, where mercuric ions can be delivered to target organs (ATSDR., 2004). MeHg has a larger oral absorption

fraction than inorganic mercuric mercury, and greater accumulation in the brain and the kidneys (ATSDR., 2024).

22. Studies conducted in humans and experimental animals have demonstrated that gastrointestinal absorption of mercury is almost 100% following ingestion of MeHg as the chloride salt or when incorporated into fish or other protein (ATSDR., 2024). Following absorption, it is able to cross the placenta, the blood-brain and blood-cerebrospinal fluid barriers, allowing accumulation in the fetus and brain, respectively (EFSA., 2012). MeHg can also enter the hair follicle which is relevant for biomonitoring purposes (EFSA., 2012).

23. In contrast to mercuric mercury, in human blood >90 % MeHg accumulates in the erythrocytes, where it is bound to the cysteinyl residues of haemoglobin and in plasma, about 99 % MeHg is bound to albumin. By ligand exchange mechanisms, MeHg is transferred from plasma proteins to low molecular weight thiols glutathione and cysteine (EFSA., 2012).

24. MeHg can cross the mammary gland to be excreted in milk and thus children can be exposed during breastfeeding. In human milk, a mean of 26 - 63 % of total mercury has been found as MeHg, however the proportion can rise with increased MeHg intake (Miklavčič et al., 2011).

25. Fetal distribution is similar to maternal distribution, although fetal brain mercury concentration is approximately 5-7 times higher than that in maternal blood (COT, 2004). Cord blood concentrations are also reported at up to twice the maternal blood concentration (Bocca et al., 2019; FAO/WHO., 2007; Lee et al., 2010; Sakamoto et al., 2018; Vigeh et al., 2018).

26. Partial demethylation of MeHg occurs in mammals in the presence of reactive oxygen species. Demethylation occurs predominantly in the liver, intestinal tract, spleen, and to a lesser extent in phagocytic cells and the brain (Suda et al., 1992). Mercuric mercury in the brain is generally the result of

either in situ dealkylation of organic mercury species, such as MeHg, or oxidation of elemental mercury. Demethylation of MeHg by intestinal bacteria also contributes to the excretion of inorganic mercuric mercury in faeces (Li et al., 2019).

27. MeHg has a half-life of approximately 70 - 80 days in the human body and steady state is achieved within a year (COT., 2004). Approximately 90 % is excreted by the faecal route as mercuric mercury (EFSA., 2012). Urinary excretion of MeHg is limited by enterohepatic recycling by metabolism of the S-conjugate of glutathione (CH_3Hg-S-CysGlyGlu) and reabsorptive transport of the S-conjugate of cysteine (CH_3Hg-S-Cys) (Tanaka et al., 1992; Tanaka-Kagawa et al., 1993).

Toxicity

28. For greater detail, the previous discussion paper (TOX/2025/03) on mercury in the maternal diet conducted a comprehensive literature review on the toxicological effects of inorganic and organic mercury exposure including summaries of recent reviews and toxicologic/epidemiologic studies identified therein. The literature review predominantly covered reproductive toxicology i.e., pregnancy outcomes and effects on maternal health, in addition to blood pressure, biomarkers and epigenetic effects of mercury exposure. Paragraphs 29-36 provide a brief summary of the information on the toxicity of mercury.

29. The United States Department of Health and Human Services, Agency for Toxic Substances and Disease Registry (ATSDR) published a toxicological profile for mercury in October 2024 which characterises the toxicologic and adverse health effects information for organic and inorganic mercury. Mercury compounds exhibit a wide range of toxic effects, targeting common cellular functions. These include disrupting intracellular calcium balance, the cytoskeleton, mitochondrial function, oxidative stress, neurotransmitter

release, and DNA methylation. The array of toxic effects is due to the strong affinity of Hg^{2+} and CH_3Hg^{2+} for the thiolate anion, which leads to the formation of Hg^{2+} and CH_3Hg^{2+} S-conjugates. This allows inorganic and organic mercury to bind to and interfere with the structure and function of enzymes, transporters, and proteins that rely on functional thiol groups (ATSDR., 2024).

30. For inorganic mercury, information on health effects is primarily from oral studies in laboratory animals, with supporting data from acute poisoning case reports in humans. The ATSDR (2024) identified no epidemiological studies specific for exposure to inorganic mercury salts; however, animal studies consistently report dose-related impairments in fertility in male and female rodents following oral exposure. The critical target organ for inorganic mercury toxicity is the kidney. Other targets include the liver, nervous system, immune system, reproductive system, and the developing organism (EFSA., 2012).

31. Organic mercury oral studies in humans and animals provide some evidence of renal, cardiovascular, immune, reproductive, and developmental effects but neurological and neurodevelopmental effects are established as the most sensitive effects of oral organic mercury exposure (ATSDR., 2024).

32. Epidemiological studies have shown that prenatal exposure to MeHg is linked to cognitive, neuromotor, and neurosensory impairments. In adults, research indicates reduced performance in fine motor coordination, speed, muscle strength, tactile sensation, colour vision, visual contrast sensitivity, as well as memory and learning. In animals, neurological effects include sensorimotor dysfunction, vision and hearing deficits, impaired learning, and memory, along with clear signs of neurotoxicity such as clumsiness, motor incoordination, lethargy, hindlimb crossing, tremors, ataxia, and partial

paralysis. Both developing humans and animals are more vulnerable to MeHg-induced neurotoxic effects compared to adults (ATSDR., 2024).

33. JECFA and EFSA have evaluated the safety of mercury multiple times (EFSA, 2004; and 2012; FAO/WHO, 1966; 1970; 1972; 1978; 1988; 2004; 2007; and 2011). In their evaluations it was agreed that the most sensitive endpoint is neurotoxicity and that life *in utero* is the critical period for the occurrence of neurodevelopmental toxicity because of exposure to MeHg (FAO/WHO., 2004; EFSA., 2012). This makes pregnant women a susceptible population. Because of the long half-life of MeHg and the fact that it takes a year to achieve steady state, the blood concentration of MeHg at the time of becoming pregnant depends on the exposure to MeHg during the preceding year (COT., 2004).

34. In the Minamata MeHg poisoning population, developmental effects such as polydactyly, syndactyly, craniofacial malformations, microcornea, undescended testicles, enlarged colon, and coccyx protrusion were observed. Animal studies also consistently show that exposure to MeHg leads to dose- and duration-dependent decreases in offspring survival, increased fetal malformations and variations (including cleft palate, skeletal malformations, and hydronephrosis), and reduced fetal weight (ATSDR., 2024).

35. EFSA and the COT have both highlighted that there is evidence that a number of dietary factors can reduce or prevent MeHg toxicity, including n-3 long chain polyunsaturated fatty acids (LCPUFAs), selenium, iodine, choline and vitamin E. Numerous *in vitro* and *in vivo* studies are available, but only a brief summary is provided here. The most extensively studied substance in food, regarding mechanisms of confounding of studies of mercury, is selenium. Mercury binding affinity for selenium is a million times higher than its binding affinity for sulphur in analogous forms and attempts, unsuccessful to date, have been made to identify detoxification products, which contain selenium and mercury (e.g. mercury-selenide). Whether such compounds

truly detoxify the mercury species has never been demonstrated. Besides sequestration of mercury, potential protective modes of action of selenium against MeHg toxicity include antioxidant effects, increased glutathione peroxidase activity, glutathione synthesis, high selenoprotein concentration and increased demethylation of MeHg. Mechanistically, docosahexaenoic acid (DHA) seems to protect against MeHg-induced oxidative stress in neuronal cells. Additionally, in neuronal cell lines and primary cells pre-treatment with DHA was associated with decreased cellular MeHg bioavailability (EFSA, 2012; COT, 2018).

36. The International Agency for Research on Cancer (IARC) concluded that elemental mercury and inorganic mercury compounds are not classifiable as to their carcinogenicity to humans (Group 3) and MeHg compounds are possibly carcinogenic to humans (Group 2B) based on inadequate evidence in humans for mercury and mercury compounds, inadequate evidence in experimental animals for elemental mercury, limited evidence for carcinogenicity of mercuric chloride in experimental animals (forestomach tumours in rats), and sufficient evidence for carcinogenicity of methylmercuric chloride in experimental animals (kidney tumours in male mice) (IARC, 1993). The U.S. Department of Health and Human Services has not classified the potential for elemental mercury, inorganic mercury compounds, or MeHg compounds to cause cancer in humans (NTP, 2016).

Recently published literature

37. As part of the previous discussion paper (TOX/2025/03) in addition to the literature search covering general toxicologic/epidemiologic studies of mercury exposure, a literature search was also performed to specifically identify recent publications on the Faroese and Seychelles birth cohorts that have been crucial to deriving health-based guidance values (HBGVs) for

MeHg and inorganic mercury by leading authorities JECFA and EFSA (search terms in Annex B).

38. The COT statement on MeHg in the infant and child diet had included a similar literature search for the 2012-2018 period (year of last EFSA evaluation to year of COT discussion) hence the most recent literature search specified years 2018-2025.

39. Upon review of the recent literature, the COT concluded that the data confirmed the current knowledge on the toxicity of inorganic and organic mercury and did not constitute a basis for revising the current HBGVs. Therefore, the below section describes the JECFA and EFSA evaluations and derivation of HBGVs for MeHg and inorganic mercury.

Derivation of health-based guidance value (HBGV)

Derivation of HBGV for MeHg

40. The original provisional tolerable weekly intake (PTWI) for MeHg (3.3 µg/kg bw) was revised at the sixty-first JECFA meeting to protect the developing fetus from neurotoxic effects. This change was based on findings from two major epidemiology studies from the Faroe Islands and the Seychelles (FAO/WHO, 2004). The assessments were made on the basis of the evaluations of children at 7 years of age in the Faroe Islands and 5.5 years of age in the Seychelles.

41. A no observed adverse effect level (NOAEL) for neurobehavioural effects of 15.3 mg/kg mercury in maternal hair was established from the Seychelles main cohort study. A mathematical analysis of the concentration to response relationship was used to determine a benchmark dose lower confidence limit ($BMDL_{05}$) of 12.0 mg/kg mercury in maternal hair in the Faroe

Islands. An average of the NOAEL and $BMDL_{05}$ from the Seychelles and Faroe Island studies was used (14 mg/kg mercury in maternal hair) as an estimate of the concentration of MeHg in maternal hair that reflects exposures that would have no appreciable effect on the offspring in these two study populations.

42. The concentration of MeHg in maternal hair was converted to mercury in maternal blood using an average overall ratio of 250. Based on this factor, the MeHg concentration in maternal blood that would be expected to have no appreciable adverse effects on the offspring was calculated to be 0.056 mg/L.

43. By use of a one-compartment toxicokinetic model (WHO, 1990), refined to better reflect the situation in pregnant women, the JECFA calculated the daily ingestion of MeHg (1.5 µg/kg bw/day) corresponding to a maternal blood mercury (BHg) concentration that would have no appreciable adverse effects on the offspring in the two study populations.

44. A data derived factor of 2 for variation in hair to blood ratio of mercury was applied by JECFA. Interindividual variation in toxicokinetics when converting the concentration of mercury in blood to an estimated daily intake was taken into account by a standard factor of 3.2 ($10^{0.5}$). This resulted in an overall uncertainty factor of 6.4.

45. Following application of this uncertainty factor, a PTWI of 1.6 µg/kg bw was established by JECFA (FAO/WHO, 2004).

46. In 2012 the EFSA CONTAM Panel assessed new literature published since the 2004 JECFA evaluation (EFSA, 2012). The CONTAM Panel identified new information on confounding by beneficial factors in fish on associations between prenatal MeHg exposures and neurodevelopmental endpoints.

47. Results from the first nutrition cohort of the Seychelles Child Development Study (SCDS) suggested an effect at age 9 years and at 30 months, but not at 5 years, related to prenatal MeHg exposure, whereby it appeared that the positive effects from intake of n-3 LCPUFAs no longer outweighed detrimental effects from MeHg exposure. The Nutrition study examined associations between MeHg, maternal nutrition, and children's scores on the Bayley's scale of infant development-II test.

48. The CONTAM panel found that a MeHg concentration of 11 mg/kg in maternal hair was an apparent NOAEL for decreased scores on neurodevelopmental indices after adjustment for prenatal blood maternal n-3 LCPUFAs and this formed a better point of departure than the unadjusted figure of 15.3 mg/kg MeHg in maternal hair derived from the Seychelles main cohort.

49. For the Faroe Islands cohort, the CONTAM Panel could not identify a more appropriate point of departure than the $BMDL_{05}$ of 12 mg/kg selected by JECFA.

50. Based on the above, a maternal hair MeHg concentration of 11.5 mg/kg (the mean of the two values) was used as an estimate of the concentration of MeHg in maternal hair that reflects exposures that would have no appreciable effect on the offspring in these two study populations.

51. A factor of 250 was used to convert this to an equivalent concentration of mercury in maternal blood of 46 µg/L.

52. Output from the one-compartment toxicokinetic model determined that a maternal daily dietary mercury intake of 1.2 µg/kg bw corresponded to a maternal BHg concentration that was considered to have no appreciable adverse effects on the offspring. By applying a total uncertainty factor of 6.4 to this value, the CONTAM Panel established a TWI for MeHg of 1.3 µg/kg bw expressed as mercury (EFSA, 2012).

Derivation of HBGV for inorganic mercury

53. The first HBGV for inorganic mercury was derived by JECFA in 2011 based on animal studies as human data on the adverse effects to inorganic mercury exposure is limited to case reports or series that do not allow identification of dose-response relationships and hence an HBGV cannot be derived (FAO/WHO, 2011).

54. JECFA agreed that the toxicological database for mercury(II) chloride was relevant for assessing the health risk of foodborne inorganic mercury.

55. For JECFA's risk assessment the National Toxicology Program (NTP) 1993 rat bioassay study was considered the most important as it used low-dose exposures to mercury(II) chloride administered via the oral route. Mercury(II) chloride was administered by gavage, 5 days/week, for 6 months to rats in the NTP (1993) bioassay. The most sensitive endpoint was found to be relative kidney weight. The BMDLs generated for relative kidney weight were lower than those generated for all other endpoints investigated.

56. The lowest $BMDL_{10}$ for relative kidney weight increase in male rats was calculated to be 0.11 mg/kg bw per day as mercury(II) chloride. This corresponds to 0.06 mg/kg bw per day as mercury, adjusted from a 5 days/week dosing schedule to an average daily dose and for the percent contribution of inorganic mercury to mercury(II) chloride dose. After application of a 100-fold uncertainty factor, the Committee established a PTWI for inorganic mercury of 4 µg/kg bw (rounded to one significant number).

57. The previous PTWI of 5 µg/kg bw for total mercury, established at the sixteenth JECFA meeting, was withdrawn. The new PTWI for inorganic

mercury was considered applicable to dietary exposure to total mercury from foods other than fish and shellfish.

58. In 2012 the EFSA CONTAM Panel evaluated the same evidence as JECFA as well as more recent studies and the Panel agreed with the rationale of JECFA in setting a HBGV based on relative kidney weight in rats as the pivotal effect. The Panel derived the same TWI for inorganic mercury as JECFA, 4 µg/kg bw (EFSA, 2012).

Exposure Assessment

Exposure from food

59. The FSA Exposure Assessment Team provided dietary exposure data on mercury for women of childbearing age (16-49 yrs of age) as a proxy for the maternal diet (Table 1). Exposure to mercury was determined using data from the National Diet and Nutrition Survey (NDNS) (Bates et al., 2014, 2016, 2020; Roberts et al., 2018), and 2014 total diet survey (TDS) (FERA, 2015).

60. Exposure estimates are presented as lower- and upper-bound mean and 97.5th percentile. Lower bound: concentration values below the limit of quantification (LOQ) are treated as zero. Upper bound: concentration values below the LOQ are treated as at the LOQ. The food commodities that result in the highest exposures to mercury are fish and seafoods, and non-alcoholic beverages with mean exposure values of 0.13 and 0.07 µg/kg bw/week, and 97.5^{th} percentile values of 0.62 and 0.17 µg/kg bw/week, respectively.

61. Mean total exposure (combined exposure from all food groups) to mercury for women of child-bearing age ranges from 0.13-0.29 µg/kg bw/week, whilst exposure in high consumers (97.5^{th} percentile) ranges from 0.62-0.84 µg/kg bw/week.

Table 1. Estimated exposure (in µg/kg bw/day and µg/kg bw/week) to mercury from foods consumed by women of childbearing age (16-49 years).

Food Groups	**Daily exposure to mercury LB to UB (µg/kg bw/day) * Mean**	**Daily exposure to mercury LB to UB (µg/kg bw/day) * 97.5th Percentile**	**Weekly exposure to mercury LB to UB (µg/kg bw/week) * Mean**	**Weekly exposure to mercury LB to UB (µg/kg bw/week) * 97.5th Percentile**
Bread	0-0.00099	0-0.0026	0-0.0069	0-0.018
Misc Cereals	0-0.0010	0-0.0029	0-0.007	0-0.020
Carcass meat	0-0.00034	0-0.0016	0-0.0024	0-0.011
Offal	0.000045	0.00075	0.00032	0.0053
Meat products	0-0.00027	0-0.0011	0-0.0019	0-0.0077
Poultry	0-0.00039	0-0.0014	0-0.0027	0-0.0098
Fish and seafood	0.018	0.089	0.13	0.62
Fats and oils	0-0.000086	0-0.00027	0-0.00060	0-0.0019
Eggs	0-0.00014	0-0.00067	0-0.00098	0-0.0047
Sugars and confectionary	0.00033	0.0013	0.0023	0.0091
Green vegetables	0-0.00028	0-0.0011	0-0.0020	0-0.0077
Potatoes	0-0.0011	0-0.0032	0-0.0077	0-0.022
Other vegetables	0-0.0013	0-0.0043	0-0.0091	0-0.030
Canned vegetables	0-0.00026	0-0.0012	0-0.0018	0-0.0084
Fresh fruit	0-0.0012	0-0.0045	0-0.0084	0-0.032

Fruit products	0-0.00038	0-0.0021	0-0.0027	0-0.015
Non-alcoholic beverages	0-0.010	0-0.024	0-0.07	0-0.17
Milk	0-0.00090	0-0.0033	0-0.0063	0-0.023
Dairy products	0-0.0004	0-0.0015	0-0.0028	0-0.011
Nuts and seeds	0-0.000043	0-0.00037	0-0.00030	0-0.0026
Alcoholic beverages	0-0.00083	0-0.0055	0-0.0058	0-0.039
Meat alternatives	0-0.000024	0-0.00029	0-0.00017	0-0.0020
Snacks	0.000055	0.00025	0.00039	0.0018
Desserts	0-0.000039	0-0.00025	0-0.00027	0-0.0018
Condiments	0-0.00010	0-0.00038	0-0.0007	0-0.0027
Tap water only	0-0.0014	0-0.0061	0-0.0098	0-0.043
Bottled water still or carbonated	0-0.00034	0-0.0028	0-0.0024	0-0.020
Total	0.019-0.041	0.089-0.12	0.13-0.29	0.62-0.84

LB= Lower-bound; UB = Upper-bound.

Exposure from drinking water

62. The main chemical forms in which mercury occurs in water are elemental mercury, complexes of mercuric mercury with various inorganic and organic ligands, and organic mercury forms, mainly MeHg and dimethylmercury. The chemical form in which mercury occurs depends on the pH, redox potential, and the concentration of inorganic and organic complexing agents. The contribution of MeHg to total mercury is typically less than 5 % in estuarine and marine waters but can be up to 30 % in fresh water (EFSA, 2012).

63. Concentrations of mercury in water were provided by the Drinking Water Inspectorate for England and Wales, the Drinking Water Quality Regulator for Scotland and Northern Ireland (NI) Water. 2023 median and 97.5th percentile concentrations were provided for England and Wales. 2023 data for NI and Scotland was requested however NI had no results greater than the LOQ (0.041 µg/L) and Scotland had no results greater than the limit of detection (LOD) (0.02 µg/L). The LOD and LOQ were therefore used as proxies for 97.5th percentiles for Scotland and NI. For median concentrations, 2016 data were used for Scotland and NI from a previous COT paper (COT, 2018).

64. The FSA Exposure Assessment Team has provided values for water consumption for women of child-bearing age of 8 (mean) and 32 (97.5th percentile) g (ml) of water per kg bodyweight per day using data from the 2014 TDS (FERA, 2015). Using the median mercury concentration values in drinking water of 0.04, 0.03 and 0.01 µg/L for England/Wales, Scotland and NI respectively, then 97.5th percentile concentration of 0.12 for England/Wales, and LOD and LOQ concentrations of 0.041 and 0.02 µg/L for Scotland and NI respectively, the calculated exposures to mercury from drinking water are shown in Table 2.

Table 2. Calculated mean and 97.5th percentile exposures (in µg/kg bw/day and µg/kg bw/week) for women of childbearing age to Mercury from drinking water.

Region	**N (number of samples)**	**Median (µg/kg bw/day)***	**Median (µg/kg bw/week)***	**97.5th percentile (µg/kg bw/day)***	**97.5th percentile (µg/kg bw/week)***
England and Wales	7944	0.00032	0.00224	0.0038	0.027
Scotland	Median 16424; LOD 585	0.00016	0.00112	0.0013^{L}	0.0091^{L}
Northern Ireland	Median 395; LOQ 1782	0.000080	0.00056	0.00064^{L}	0.0045^{L}

* Average body weight for women of childbearing age = 70.3 kg, value provided by the FSA Exposure Assessment Team from years 1 – 11 of the rolling National Diet and Nutrition Survey, NDNS (Bates et al., 2014, Bates et al., 2016, Roberts et al., 2018). L = calculated using 2023 LOD/LOQ.

Exposure from the air

65. Mercury is naturally emitted from land and ocean surfaces as elemental mercury. Anthropogenic sources result in the emission of elemental mercury, mercuric mercury, and particle-bound mercury. In general, elemental mercury is the predominant form of mercury in the atmosphere (EFSA, 2012).

66. The WHO estimates that the average inhalation rate for a 70 kg adult is 20 m^3/day (WHO, 2000). The Department for Environment, Food and Rural Affairs (DEFRA) UK-Air Data Selector tool was used to retrieve total mercury air concentrations and the most recent data available were from 2018 at two sites. The average air mercury concentration in London Westminster (urban background) was 2.68 ng/m^3 and 15.34 ng/m^3 from Runcorn Weston Point (urban industrial site).

67. As a worst-case scenario, if an adult female were to be constantly exposed to an air mercury concentration of 15.34 ng/m^3 then this would result in a daily exposure to 306.8 ng of mercury from the air. For women with an average body weight of 70.3 kg, (value provided by the FSA Exposure Assessment Team from years 1 – 11 of the rolling National Diet and Nutrition Survey, NDNS (Bates et al., 2014, Bates et al., 2016, Roberts et al., 2018) this gives an exposure of 4.36 ng/kg bw/day equivalent to 0.031 µg/kg bw/week.

68. This assumes that there is full absorption of all mercury in the particles inhaled, but this depends upon particle sizes and some of the inhaled dose may become trapped in other parts of the nasopharynx.

Exposure from the soil

69. Mercury is most commonly found in the environment in elemental form, as inorganic mercuric (Hg^{2+}) compounds, or as monomethylmercury compounds with the general formula, CH_3HgX. Monomethylated mercury compounds are most likely to be found in soil as a result of natural microbial transformation of inorganic mercury (Environmental Agency, 2009). In surface soils, about 1–3 % of total mercury is in the methylated form with the rest predominantly as Hg^{2+} compounds (Environment Agency, 2009).

70. Mercury was measured in topsoil from England from a depth of 0-15 cm as part of a DEFRA-commissioned project (Ander et al, 2013).

71. Table 3 shows the mercury exposures from soil for women of child-bearing age. Mean and 75th percentile mercury concentrations from soil in regions classified as principal (non-urban) and urban were used to assess potential exposures of adults through soil ingestion (Ander et al, 2013).

72. 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 the U.S. EPA (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 the U.S. EPA (1997) cautioned that the value is highly uncertain and based on a low level of confidence.

Table 3. Median and 75th percentile exposure values (in µg/kg bw/day and µg/kg bw/week) for women of childbearing age to mercury from soil.

Median / 75th percentile	Region	Soil concentration of mercury (mg/kg)	Mercury exposure (µg/kg bw/day)*	Mercury exposure (µg/kg bw/week)*
Median	Non-urban	0.12	0.000085	0.00060
Nedian	Urban	0.33	0.00024	0.0017
75th percentile	Non-urban	0.23	0.00016	0.0011
75th percentile	Urban	0.65	0.00046	0.0032

* Average body weight for women of childbearing age = 70.3 kg, value provided by the FSA Exposure Assessment Team from years 1 – 11 of the rolling National Diet and Nutrition Survey, NDNS (Bates *et al*., 2014, Bates *et al*., 2016, Roberts *et al*., 2018).

73. The data presented are representative of mercury concentrations in the soil in England only.

Pica behaviour

74. A discussion paper on the effects of pica during pregnancy was presented to the COT in 2023 but was unpublished. The key points are summarised below.

75. Pica behaviour is described as the craving for and intentional ingestion of substances that are not described as food. The most frequently reported pica behaviours globally are: geophagia- the consumption of earth, soil or clay, amylophagia- the consumption of starch, and pagophagia- the consumption of ice (Miao et al., 2015). Globally, it is thought to affect up to 28 % of pregnant women, albeit with a high degree of geographic variability (Fawcett et al, 2016). The majority of pica in pregnant women in the UK is geophagia and therefore the risks posed to women of maternal age is likely to be from contaminants present within these substances.

76. Geophagia primarily occurs in migrant populations from Africa and South Asia where the practice is commonplace. As such, the soils, chalks and clays that are consumed are not of UK origin. The soils are frequently imported from regions where the practice is prevalent following rudimentary processing such as being oven baked into blocks (Dean et al., 2004).

77. The most likely health risks from geophagia were reported to be heavy metal contamination by lead, arsenic and cadmium, not mercury.

78. The discussion paper highlighted several uncertainties regarding the toxicological risk of pica to pregnant women. These include: the mineralogical and contaminant profile of the soil and clays consumed is highly variable; the soils and clays are often imported from a variety of countries resulting in variation; and studies rely on self-reporting of pica behaviour through questionnaires which could lead to bias in the data and underreporting of pica potentially due to stigma associated with consuming non-food substances.

79. In summary, pica presents a potential route of exposure to mercury from soils/clays. However, pica has not been considered as part of this statement due to the lack of data available on pica behaviour.

Exposure from food supplements

80. The FSA has no analytical data on the presence of mercury in supplements, but the levels are regulated in the UK under Assimilated Regulation (EC) 629/2008 at a maximum level of 0.1 mg/kg.

81. The EFSA evaluation of mercury and MeHg in food (EFSA, 2012) conducted a consumer only exposure assessment and found that the 95th percentile dietary exposure estimations in dietary supplements consumers varied from a minimum LB of 0.00 µg/kg bw per week to a maximum UB of

0.24 µg/kg bw per week in adults. EFSA did not consider dietary supplements a major source of mercury exposure.

Aggregate exposure

82. Aggregate exposure to mercury from food, drinking water, soil and dust, and air were derived by considering a number of scenarios based on the available data. Table 4 shows scenarios of aggregate exposure from the sources listed above and includes estimate of average and high exposure from these sources as indicated below.

83. Average and high exposure for food and drinking water represents the mean and 97.5th percentile exposure. Data for exposure from drinking water in England and Wales were used as this represented the highest exposure compared to Scotland and Northern Ireland. The contribution from air in all scenarios is based on average inhalation rates and the average concentration from an urban industrial site in England. For exposure from soil, the average and high exposure represents the mean and 75th percentile exposure respectively for the region with the highest exposure (i.e., urban region as shown in Table 3).

Table 4. Aggregate exposure to Mercury (in µg/kg bw/day and µg/kg bw/week) from food, drinking water, soil and air*.

Scenarios	**Aggregate exposure (µg/kg bw/day)**	**Aggregate exposure (µg/kg bw/week)**
Average exposure from all sources[a]	0.045	0.315
High exposure from all sources[b]	0.13	0.91

High exposure from food and mean exposure from all other sources[c]	0.12	0.84
High exposure from drinking water and mean from other sources[d]	0.049	0.34
High exposure from soil and mean from other sources[e]	0.046	0.32

a This scenario represents a summation of average exposure from food, water and soil and a value for air*.
b Exposure is based on summation of 97.5th percentile estimates for food and water, 75th percentile for urban soil and a value for air*.
c Exposure is based on summation of 97.5th percentile estimates for food and the averages for water, urban soil and a value for air*
d Exposure is based on summation of 97.5th percentile estimates for drinking water and the averages for food, urban soil and a value for air*
e Exposure is based on summation of 75th percentile estimate for urban soil and averages for food, water and a value for air*.
*The contribution from air in all scenarios is based on average inhalation rates and the maximum concentration identified for England and Wales.

Risk characterisation

Food

84. Mean total exposure to mercury from food for women of child-bearing age ranges from 0.13-0.29 µg/kg bw/week, whilst exposure in high consumers (97.5th percentile) ranges from 0.62-0.84 µg/kg bw/week. Without considering exposure from non-dietary sources and assuming all mercury is in the form of MeHg, these estimates are below the EFSA TWI of 1.3 µg/kg bw for MeHg (EFSA, 2012).

Drinking water

85. The 97.5th percentile mercury exposure from drinking water for a woman of childbearing age in England & Wales, Scotland and NI is 0.027,

0.0091 and 0.0045 µg/kg bw/week respectively. Assuming all the drinking water mercury is in the form of MeHg, compared to the EFSA TWI (1.3 µg/kg bw), these exposures represent 2.1 %, 0.70 % and 0.35 % of the TWI.

86. The exposures from drinking water alone are far below the TWI. The 97.5% percentile water consumption in women of childbearing age was used and hence the exposures calculated are considered conservative.

Air

87. An average adult female is at worst expected to be exposed to 0.031 µg/kg bw/week of mercury if they live near an urban industrial site. This exposure is equivalent to 0.78% of the inorganic mercury TWI (4 µg/kg bw) and 2.38% of the MeHg TWI (1.3 µg/kg bw). The industrial site air mercury concentration is 5.7 times higher than the urban background concentration so for the general population this value is conservative.

Soil

88. Only soil mercury values from England were used to estimate the UK's exposure to mercury from soil as there were no values available for Scotland, Wales and NI. The exposure to mercury from soil in both urban and non-urban regions is presented in Table 5 and shown as a percentage proportion of the EFSA TWI's for MeHg and inorganic mercury.

Table 5. Median and 75th percentile exposure to soil mercury in urban and non-urban regions as a proportion of the inorganic mercury and MeHg EFSA TWI's.

Median / 75th percentile	Region	Mercury exposure (µg/kg bw/week)*	% inorganic mercury TWI (4 µg/kg bw)	% MeHg TWI (1.3 µg/kg bw)
Median	Non-urban	0.00060	0.015	0.046
Median	Urban	0.0017	0.042	0.13
75th percentile	Non-urban	0.0011	0.028	0.086
75th percentile	Urban	0.0032	0.081	0.25

89. The 75th percentile exposure to mercury through soil ingestion is far below the TWIs and therefore of low concern for the general population.

90. There is uncertainty regarding sub-populations that exhibit pica behaviour that may regularly consume soils/clays containing mercury; however, due to a lack of data this is not incorporated into the risk assessment.

Aggregate characterisation

91. A combined exposure assessment considered exposure to mercury from all sources at average and high levels. In a scenario where there are high exposures to mercury from all sources (food, drinking water, soil and air) the estimated aggregate exposure is 0.13 µg/kg bw/day (Table 3) equivalent to 0.91 µg/kg bw/week which is below both the EFSA TWI's for inorganic mercury (4 µg/kg bw) and MeHg (1.3 µg/kg bw). As aggregate exposure estimates under all scenarios are below the EFSA TWI's for inorganic mercury and MeHg, the risk of toxicity from mercury is low.

Conclusions

92. Mercury is a metal that is released into the environment from both natural and anthropogenic sources. Mercury bioaccumulates in fish as MeHg, especially in long-lived predatory species such as swordfish and tuna. Populations that consume large quantities of foods derived from fish are more vulnerable to mercury exposure. Food sources other than fish and seafood products may contain mercury, but mostly in the form of inorganic mercury.

93. After oral intake in humans, MeHg is more extensively and rapidly absorbed than inorganic mercury. MeHg can enter the hair follicle, cross the placental, blood-brain and blood-cerebrospinal fluid barriers, allowing accumulation in hair, the fetus and the brain, respectively. Inorganic mercury in food is considerably less toxic than MeHg due to its low lipophilicity hence it does not readily cross the same fluid barriers.

94. The main adverse effect associated with MeHg exposure is toxicity to the central and peripheral nervous systems. Due to MeHg's ability to cross barriers, exposure during embryonic neurodevelopment and in young children is of high concern. Thus, pregnant and breastfeeding women are sensitive sub-populations.

95. The most recent HBGVs derived for mercury were calculated by EFSA in 2012 to determine whether the earlier JECFA derived values were still appropriate. EFSA derived a lower TWI for MeHg of 1.3 µg/kg bw (JECFA TWI was 1.6 µg/kg bw) and a TWI for inorganic mercury of 4 µg/kg bw (identical to the JECFA TWI).

96. Inorganic mercury could not be separated from MeHg in the exposure data. This was considered irrelevant for the risk assessment; however, as previous evaluations have highlighted the fact that most mercury exposure from the diet is MeHg and furthermore, MeHg is considered more toxic than inorganic mercury. Regardless the high individual and aggregate exposure

assessments to mercury from food, water, soil and air all estimated exposures were below the EFSA TWIs for both MeHg and inorganic mercury. Therefore, for the UK population there is low risk to women of maternal age and their fetuses.

97. The current Government advice on foods to avoid in pregnancy should be maintained. Mothers should avoid eating more than more than 2 portions of oily fish a week and no more than 2 tuna steaks (about 140g cooked or 170g raw). Shark, swordfish, marlin, raw shellfish and uncooked cold-smoked or cured fish should also be avoided by pregnant women and women trying to get pregnant. If pregnant women and women trying to get pregnant are following Government advice the exposure assessment is highly conservative as fish and seafood is the major source of MeHg exposure in the diet.

Secretariat
May 2025

List of Abbreviations and Technical terms

Acronym	Definition
ADME	Absorption, distribution, metabolism, and excretion
ATSDR	Agency for Toxic Substances and Disease Registry
BHg	Blood mercury
BMDL	Benchmark-dose lower confidence limit
Bw	Bodyweight
CONTAM	Panel on Contaminants in the Food Chain
CLEA	Contaminated Land Exposure Assessment
COT	Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment
DEFRA	Department for Environment, Food and Rural Affairs
DHA	Docosahexaenoic acid
EFSA	European Food Safety Authority
FAO	Food and Agriculture Organisation of the United Nations
HBGV	Health-based guidance value
Hg	Mercury
JECFA	Joint Food and Agriculture Organisation of the United Nations / World Health Organisation Expert Committee on Food Additives
LCPUFA	Long chain polyunsaturated fatty acid
MeHg	Methylmercury
MOCEH	Mothers and Children's Environmental Health
NOAEL	No observed adverse effect level
OWO	Overweight or obesity
PTWI	Provisional tolerable weekly intake
SACN	Scientific Advisory Committee on Nutrition
SCDS	Seychelles child development study
SCOOP	Scientific cooperation

TDS	Total diet survey
TWI	Tolerable weekly intake
WHO	World health organisation

Definitions

Benchmark-dose lower confidence limit (BMDL). The BMDL is the lower boundary of the confidence interval on the benchmark dose. The BMDL accounts for the uncertainty in the estimate of the dose response that is due to characteristics of the experimental design, such as sample size. The BMDL can be used as the point of departure for derivation of a health-based guidance value or a margin of exposure. Numbers in subscript after the BMDL such as $BMDL_{05}$ or $BMDL_{10}$ specify the lower confidence limit of the dose that causes a 5% or 10% change in the response rate.

No observed adverse effect level (NOAEL). The NOAEL is the greatest concentration or amount of a substance, found by experiment or observation, that causes no adverse alteration of morphology, functional capacity, growth, development or lifespan of the target organism distinguishable from those observed in normal (control) organisms of the same species and strain under the same defined conditions of exposure.

Health-based guidance value (HBGV). A numerical value derived by dividing a point of departure (a no observed adverse-effect level, benchmark dose or benchmark dose lower confidence limit) by a composite uncertainty factor to determine a level that can be ingested over a defined time period (e.g. lifetime or 24 h) without appreciable health risk.

Tolerable weekly intake (TWI). Estimated maximum amount of an agent, expressed on a body mass basis, to which each individual in a

(sub)population may be exposed over a specified period without appreciable risk.

Provisional tolerable weekly intake (PTWI). The endpoint used by the Joint FAO/WHO Expert Committee on Food Additives for food contaminants such as heavy metals with cumulative properties. Its value represents permissible human weekly exposure to those contaminants unavoidably associated with the consumption of otherwise wholesome and nutritious foods.

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Official -For Public Release

This is a draft statement for discussion.

It does not reflect the final views of the Committee and should not be cited.

Secretariat

May 2025

TOX/2025/22 Annex B

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

First Draft Statement on the Effects of Mercury on Maternal Health

Search terms

The references cited in this draft statement are of publications found in PubMed or LitFetch searches and references therein, using the following search terms:

Hg AND Maternal,
Maternal health,
Pre-conception,
Conception,
Post-partum,
Toxicity,
Reproductive,
Mechanism,
ADME,

Toxicokinetics,
Absorption,
Distribution,
Metabolism,
Excretion,
Biomarker,
Exposure,
Preeclampsia,
Abortion,
United Kingdom,
Republic of Seychelles,
Faroe Islands.