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TOX/2025/03

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

Discussion paper 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, foetal 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 paper 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 compounds are salts of Hg^{+} and Hg^{2+}, 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, and 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 environment are more vulnerable to Hg 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. After oral intake in humans, MeHg is much more extensively and rapidly absorbed than inorganic mercury (EFSA, 2012; FAO/WHO, 2011). Following absorption, it is able to enter the hair follicle, and to cross the placenta as well as the blood-brain and blood-cerebrospinal fluid barriers, allowing accumulation in hair, the fetus and the brain, respectively (EFSA, 2012)

12. 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).

13. 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). Mercuric mercury in the brain is generally the result of either in situ demethylation of organic mercury species or oxidation of elemental mercury (EFSA, 2012).

Previous evaluations

Joint Food and Agriculture Organisation of the United Nations (FAO)/ World Health Organisation (WHO) Expert Committee on Food Additives (JECFA)

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14. Mercury was previously evaluated by JECFA at its tenth, fourteenth, sixteenth and twenty-second meetings (FAO/WHO, 1967; 1971; 1972; 1978). At its sixteenth meeting (FAO/WHO, 1972), the Committee allocated a provisional tolerable weekly intake (PTWI) of 0.3 mg of total mercury (5 µg/kg body weight (bw)), of which no more than 0.2 mg (3.3 µg/kg bw) should be in the form of MeHg. This value was based primarily on the relationship between the intake of mercury from fish and mercury levels in blood and hair associated with the onset of clinical disease.

15. At the sixteenth JECFA meeting the Committee noted that almost all dietary exposure to MeHg is from fish and seafood and that MeHg is probably by far the most toxic form of mercury in food; therefore, other forms of mercury could be given less weight when establishing a tolerable intake for mercury (FAO/WHO, 1972).

16. At the thirty-third JECFA meeting, the Committee noted that pregnant women and nursing mothers may be at greater risk than the general population from the adverse effects of MeHg but the available data were insufficient to recommend a specific MeHg intake for this sub-population (FAO/WHO, 1989).

17. The original 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 epidemiological studies of foetal neurotoxicity, conducted in the Faroe Islands, and the Seychelles, involving fish-eating populations (FAO/WHO, 2004). The average maternal hair-mercury concentration from the two studies was estimated at the no observed adverse effect level (NOAEL) and benchmark-dose lower confidence limit (BMDL) for neurotoxicity associated with exposure to methylmercury in utero. The average maternal hair-mercury concentration of the two studies, 14 mg/kg, was utilised to estimate the concentration of MeHg in maternal blood that reflects exposures that would have no appreciable adverse effect on the offspring in these two study populations. Based on the

average ratio of hair:blood MeHg concentration (250), 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. The blood MeHg concentration was used to calculate the average steady-state dietary intake of 1.5 µg/kg bw per day, that would result in a maternal blood-mercury concentration that would have no appreciable adverse effects on offspring in these two study populations. The committee then applied a combined uncertainty factor of 6.4 (2 x 3.2) to account for the total human interindividual variation for converting maternal blood concentration to a steady-state dietary intake. This derived the new PTWI of 1.6 mg/kg bw which is considered sufficient to protect developing foetuses, the most sensitive subgroup of the population.

18. In 2006, JECFA clarified that life stages other than the embryo and fetus may be less sensitive to the adverse effects of MeHg (FAO/WHO, 2007). For adults, up to about twice the PTWI would not pose any risk of neurotoxicity. However, available data did not allow firm conclusions to be drawn for infant and children (aged up to about 17 years), as they may be more sensitive than adults. Hence the tolerable intake established in 2003 applies also to infants and children.

19. At the seventy-second JECFA meeting the total mercury PTWI (5 µg/kg bw) was reviewed and withdrawn (FAO/WHO, 2011). The committee noted a lack of quantitative data on MeHg in non-fish products and on inorganic mercury in foods in general. The committee assumed that the predominant form of mercury in foods other than fish and shellfish is inorganic mercury.

20. A revised PTWI for inorganic mercury was established based on the lowest $BMDL_{10}$ for relative kidney weight increase in male rats of 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 day per week dosing schedule to an average daily dose and for the percent contribution of inorganic mercury to dose. After application of a 100-fold uncertainty factor, the Committee

established a PTWI for inorganic mercury of 4 µg/kg bw. The new PTWI for inorganic mercury was considered applicable to dietary exposure to total mercury from foods other than fish and shellfish (FAO/WHO, 2011). The upper limits of estimates of average dietary exposure to total mercury from foods other than fish and shellfish for adults (1 µg/kg bw per week) and for children (4 µg/kg bw per week) were at or below the PTWI (FAO/WHO, 2011).

Opinion of the EFSA Scientific Panel on Contaminants in the Food Chain (CONTAM) on a request from the Commission related to mercury and methylmercury in food, 2004.

21. The Member States gathered data on levels of mercury in foods and made limited estimates on dietary exposure as part of the Scientific Co-Operation (SCOOP) task 3.2.11 (Decision 2001/773/EC5). The results indicated that some consumers may exceed the JECFA PTWI (EFSA, 2004).

22. The maximum levels set for total mercury in Commission Regulation 466/2001 were under review. A maximum level of 0.5 mg/kg applied to fishery products, except for certain listed fish species for which 1 mg/kg was applied. Data from some Member States indicated that elevated levels of mercury could be found in other foods.

23. The data from the SCOOP report indicated that the average intake of fish and seafood products in some countries may be close to or exceed the JECFA MeHg PTWI of 1.6 µg/kg bw.

24. The EFSA CONTAM panel concluded ‘The data available in the SCOOP report do not allow reliable estimations of the intakes by high consumers in different populations. Because in some cases the estimated intakes based on the SCOOP report are close to or exceed the PTWI, specific intake studies, especially for women and children, should be performed on methylmercury’.

Scientific Opinion on the risk for public health related to the presence of mercury and methylmercury in food. EFSA Panel on CONTAM, 2012

25. EFSA was asked by the European Commission to consider new developments regarding inorganic mercury and MeHg toxicity and evaluate whether the JECFA PTWI for MeHg of 1.6 µg/kg bw and of 4 µg/kg bw for inorganic mercury were still appropriate.

26. In line with JECFA, the CONTAM Panel established a tolerable weekly intake (TWI) for inorganic mercury of 4 µg/kg bw, expressed as mercury.

27. For MeHg, new developments in epidemiological studies from the Seychelles Child Developmental Study (SCDS) Nutrition Cohort indicated that n-3 long-chain polyunsaturated fatty acids (LCPUFAs) in fish may counteract negative effects from MeHg exposure. The CONTAM panel concluded "Together with the information that beneficial nutrients in fish may have confounded previous adverse outcomes in child cohort studies from the Faroe Islands, the Panel established a TWI for MeHg of 1.3 µg/kg bw, expressed as mercury" (EFSA, 2012).

28. The 95th percentile dietary exposure was close to or above the TWI for all age groups. High fish consumers, which might include pregnant women, may exceed the TWI by up to approximately six-fold. The most vulnerable group are unborn children. Biomonitoring data from blood and hair indicate that MeHg exposure is generally below the TWI in Europe.

29. The CONTAM panel stated, "Dietary inorganic mercury exposure in Europe does not exceed the TWI, but inhalation exposure of elemental mercury from dental amalgam is likely to increase the internal inorganic mercury exposure; thus, the TWI might be exceeded."

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COT Statement on potential risks from methylmercury in the diet of infants aged 0 to 12 months and children aged 1 to 5 years, 2018

30. The COT last evaluated the risks from methylmercury in the infant diet in 2018 (COT, 2018). The conclusions of relevance to this current discussion paper on the maternal diet were as follows:

- The general population is exposed to mercury and MeHg through food, drinking water, soil and in trace amounts from the air. The diet, and especially fish consumption, is the main source of exposure to MeHg.

- MeHg is readily absorbed following oral exposure. Following absorption, it can accumulate in the hair and can cross the blood brain barrier, the placenta and is excreted in breastmilk. Thus, it can reach the developing fetus, where it tends to accumulate in the brain and can also be transferred to infants via breastfeeding. It has a long half-life and is eliminated less efficiently in newborns than in later life.

- The main adverse effect associated with exposure to MeHg is toxicity to the developing nervous system. Exposure of the fetus to MeHg depends on the maternal exposure up to a year prior to conception.

- The prenatal MeHg exposure in the high fish-consuming Faroese and Seychelles study populations focused on by EFSA and JECFA are much higher than in typical western populations.

- Exclusively breastfed infants are a vulnerable group to consider in the case of MeHg exposure, as MeHg can be transferred to the newborn via milk. The concentration in human milk will depend on maternal exposure to MeHg. Data for MeHg in the literature suggest that the concentrations in breast milk are generally low.

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- For infants of 0-6 months of age that are exclusively or non-exclusively breastfed, or that are fed exclusively with infant formula, dietary exposures to total mercury are below the TWI for MeHg.

- Fish is one of the most significant contributors to total dietary mercury exposures both in the Infant Metals Survey and the Total Diet Survey (TDS). Based on data from the TDS and a conservative assumption that 100% of the mercury in fish will be MeHg, the TWI would be marginally exceeded for the age groups of 12 to <15, 15 to <18 and 18 to <24 months of age for the high-level consumers.

- The Committee agreed that when taking into consideration the conservatism in the exposure assumptions, the risk to health from the potential minor exceedance of the TWI in infants and children is low but that it would be prudent to maintain existing advice regarding consumption of large predator fish.

- The Government currently advises breastfeeding mothers should avoid eating more than one portion of shark, swordfish or marlin per week and that pregnant women, women trying to get pregnant, and children should avoid eating these species.

- Other dietary factors, such as selenium, can reduce or even prevent MeHg effects.

Hazard Identification

ADME

Inorganic mercury

Absorption

31. Inorganic mercury exists as mercurous (Hg_2^{2+}) or mercuric (Hg^{2+}) salts of anionic species of chlorine, sulphur, or oxygen. Of the inorganic forms of Hg, the mercuric form is the most abundant in the environment.

32. Inorganic mercury has a 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).

33. Studies conducted in mice and rats indicate that the predominant site of absorption of Hg^{2+} is the small intestine (ATSDR, 2022).

34. 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 homologs of endogenous molecules/polypeptides. Hence, possible routes of uptake include interaction with plasma membrane amino acid, peptide, drug, and ion transporters. A small amount of Hg^{2+} may be transported via the divalent metal transporter 1 following ligand exchange and, possibly, via zinc carriers (Bridges and Zalups, 2010; 2018).

35. In an *in vitro* study that compared absorption of a series of inorganic mercuric compounds in rat everted intestinal sacs and intestinal brush border membrane vesicles, absorption decreased with increasing stability constant of the Hg^{2+} complex (Endo et al. 1990). These observations suggest that ligand interactions are important variables affecting absorption.

Distribution

36. The distribution of absorbed Hg^{2+} is strongly influenced by the high affinity of Hg^{2+} for the thiolate anion and formation of Hg^{2+} S-conjugates (Carty and Malone, 1979).

37. 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 and cysteine (Lash and Jones 1985).

38. Within cells, Hg^{2+} forms complexes with intracellular thiols, including glutathione, cysteine, glycinyl-cysteine, metallothionein, and red blood cell haemoglobin (ATSDR, 2022).

39. Due to its 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).

Metabolism

40. 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).

Excretion

41. 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, 2022).

42. Rahola et al. (1972, 1973) measured mercury excretion in adult subjects following ingestion of a single tracer dose of $^{203}Hg(NO_3)_2$ (6 µg) in drinking water or mixed with calf liver paste. Initially faeces were found to be the dominant route of excretion of mercury; however, five days following dosing, the rate of faecal excretion declined to be like the rate of urinary excretion (0.05–0.15% of the administered dose per day).

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

Organic mercury

Absorption

44. Following ingestion of contaminated food and/or water, 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, 2022).

45. 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, 2022).

46. MeHg likely crosses cell membranes by passive diffusion. When MeHg complexes with L-cysteine the new complex is thought to mimic L-methionine and hence utilise its respective amino acid transporter to cross membranes. MeHg L-cysteine and glutathione complexes may also be transported by organic anion transporters (EFSA, 2012).

47. In human's MeHg is recycled through the enterohepatic system and nutritional factors seem to influence MeHg reabsorption rate (Chapman and Chan, 2000). During the reabsorption of MeHg, intestinal microflora is able to convert MeHg to mercuric mercury (EFSA, 2012).

Distribution

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

49. 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).

50. MeHg is able to cross the hair follicle, the placenta and the blood-brain barrier, allowing accumulation in hair, the fetus and the brain.

51. Fetal distribution is similar to maternal distribution, although fetal brain mercury concentration is approximately 5-7 times higher than that in maternal

blood. Cord blood concentrations are also reported to be 25% higher than maternal blood concentrations, estimated from maternal hair concentrations (COT, 2004).

52. In humans, after absorption into the bloodstream, equilibrium between the blood and the body is achieved within 30-72 hours, with approximately 5% of the absorbed MeHg accumulating in the blood and 10% in the brain (Kershaw et al, 1980; Clarkson, 2002). As MeHg can pass through all membranes and barriers, its distribution across tissues is generally uniform, and tissue concentrations usually remain consistent relative to blood levels (EFSA, 2012).

Metabolism

53. Partial demethylation of MeHg occurs in mammals in the presence of reactive oxygen species (ROS). Demethylation occurs predominantly in the liver, intestinal tract, spleen, and to a lesser extent in phagocytic cells and the brain (Suda and Hirayama, 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).

Excretion

54. 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).

55. MeHg elimination in humans mainly occurs via the biliary route after conjugation with liver glutathione S-transferases (GSTs) and elimination via the faecal route (Ballatori and Clarkson, 1985).

56. Most of the mercury excreted in urine following absorption of MeHg is inorganic mercury (Farris et al, 1993; Smith et al, 1994). 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). MeHg is also partly converted to mercuric mercury via the intestinal microflora which is less effectively absorbed; and thus, excreted via the faeces (Li et al, 2019).

Toxicity

57. The literature cited in this section are of publications found in PubMed or LitFetch searches and references therein (search terms). Reviews by regulatory/government agencies and academics have been summarised first followed by toxicologic studies identified from reviews and literature searches.

Reviews of mercury toxicity

58. The United States Department of Health and Human Services, Agency for Toxic Substances and Disease Registry (ATSDR) published a draft toxicological profile for mercury in April 2022 and a complete profile in October 2024 which characterize 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 mercury to bind to and interfere with the structure and function of enzymes, transporters, and proteins that rely on functional thiol groups (ATSDR, 2022; 2024).

59. 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 (2022) identified no epidemiological studies specific for exposure to inorganic mercury salts. 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).

60. 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, 2022).

61. 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, 2022).

62. In evaluations from both JEFCA and EFSA 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 (JECFA, 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).

63. Developmental effects such as polydactyly, syndactyly, craniofacial malformations, microcornea, undescended testicles, enlarged colon, and coccyx protrusion were observed in the Minamata MeHg poisoning population. Animal studies consistently show that exposure to MeHg leads to dose- and duration-dependent decreases in offspring survival, increased foetal malformations and variations (including cleft palate, skeletal malformations, and hydronephrosis), and reduced foetal weight (ATSDR, 2022).

64. 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 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 sulfur 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).

65. Regarding carcinogenicity the International Agency for Research on Cancer 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 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).

66. Abbot and Nigussie (2021) reviewed how mercury toxicity, particularly MeHg, affects neurogenesis in the developing mammalian brain. Information on *in vitro* and *in vivo*, models used to study the mechanisms of developmental mercury toxicity and theories of pathogenesis were summarised. The developing embryonic nervous system is well known to be more susceptible to mercury toxicity compared to mature neurons. Interruption of cell signalling, and disruption of cell proliferation appear to be central to mercury toxicity rather than cell death. However, exposure to higher concentrations of mercury does result in the death of neuronal precursor cells as well as mature neurons, typically through the process of apoptosis. Currently, the predominant theories of the pathogenesis of mercury toxicity in neurogenesis fall into the following three categories: (1) disruption of cell proliferation, gene expression, cell signalling pathways, protein phosphorylation, and calcium ion homeostasis; (2) production of oxidative stress; (3) altered cell migration. The authors concluded that future research should aim to combine studies on molecular effects, such as gene expression and signal transduction, with biochemical processes like calcium ion homeostasis.

67. Balali-Mood et al. (2021) reviewed the available data on the toxic mechanisms of five heavy metals including mercury, lead, chromium, cadmium, and arsenic. The search, of 4 main databases was focused on animal and human studies involving acute and chronic exposures to the five metals and any related adverse health effects. For mercury four organ toxicities were identified including: central nervous system injuries, renal

dysfunction, gastrointestinal ulceration and hepatoxicity. The disrupted macromolecules/mechanisms of action identified for Hg include thiol binding (glutathione conjugation), enzymes inhibition, ROS production, aquaporins mRNA reduction, glutathione peroxidase inhibition and increased c-fos expression.

68. Bridges and Zalups. (2010; 2018) summarised the current literature on the mechanisms of transport of inorganic and organic forms of mercury in various tissues and organs including the intestines, kidney, liver, brain, erythrocytes, and placenta. They also propose additional mechanisms that may potentially be involved in the transport of mercuric ions into target cells. The authors concluded that the published studies identified provide strong evidence that amino acid, anion, and drug transporters play a significant role in the uptake and secretion of mercuric ions across various organs and tissues. Most research to date has focused on the transport of Hg^{2+} and CH_3Hg^+ to their target organs, the kidney and brain. However, there is a lack of knowledge on how mercuric ions are transported to other organs. There is evidence that intestinal absorption of Hg^{2+} and CH_3Hg^+ occurs although the exact mechanism is not understood. Mechanisms for handling mercuric ions across the canalicular membrane of hepatocytes have been identified; however, mechanisms by which mercuric ions enter hepatocytes at the sinusoidal membrane are uncertain. Several *in vivo* and *in vitro* studies have provided evidence for the transport and accumulation of Hg^{2+} in placentas and fetuses; however, how Hg^{2+} is transported across placental syncytiotrophoblasts has not been well defined.

69. Wu et al. (2024) provide a comprehensive review of over 210 recent works of literature summarising the types, structures, sources of mercury. It also discusses the pharmacokinetic profile of mercury, mechanisms of action, and clinical manifestation of acute and chronic toxicity in humans. The authors concluded that mercury exposure primarily affects the central nervous system and is linked to neurodegenerative disease, especially during foetal development. Prolonged exposure to MeHg can impair motor coordination,

cause visual and tactile dysfunction, and lead to paralysis. Pregnant women exposed to mercury risk infertility, birth defects, and adverse effects on foetal brain development. There is also evidence that mercury may induce genotoxic, immunotoxic and cardiotoxic effects and pulmonary and renal diseases.

Reproductive toxicology

Blood pressure

Inorganic mercury

70. Studies in laboratory animals have evaluated effects of inorganic mercuric mercury on cardiovascular function following intermediate duration oral exposure. Results indicate that exposure to mercuric chloride alters some cardiovascular functions, including systolic and diastolic blood pressure, ventricular pressure, baroreflex sensitivity, and cardiac inotropism (ATSDR, 2022). The ATSDR (2022) identified no epidemiological studies on cardiovascular effects of exposure to inorganic mercury salts.

71. In rats exposed to mercuric chloride systolic and diastolic blood pressures were elevated at doses of 24 mg Hg/kg/day for 180 days or 6 mg Hg/kg/day for 350 days, and systolic blood pressure was also increased in rats exposed to 0.66 or 1.3 mg Hg/kg/day for 365 days; though no change was observed at 3.3 mg Hg/kg/day for 365 days, potentially due to poor general health at this dose (Carmignani and Boscolo, 1984; Carmignani et al, 1992; Perry and Erlanger, 1974). Aortic blood pressure similarly rose in rats exposed to ≥6 mg Hg/kg/day for 350 days (Boscolo et al, 1989; Carmignani et al, 1989).

72. In dietary studies, normotensive Wistar rats showed no changes in systolic blood pressure when exposed to up to 2.2 mg Hg/kg/day of mercuric chloride for 21 weeks (Takahashi et al., 2000a). Conversely, spontaneously

hypertensive Wistar rats experienced a 6–10% increase in systolic blood pressure after exposure to doses of ≥0.1 mg Hg/kg/day for 4 or 5 weeks. However, no significant effects were observed at doses up to 3 mg Hg/kg/day for 6–12 weeks (Takahashi et al., 2000b).

73. Exposure to mercuric chloride in rats has been linked to changes in cardiac function, including increased left ventricular end diastolic pressure, positive inotropic effects, and altered baroreceptor reflex sensitivity. These effects were observed at daily doses ranging from 0.012 to 24 mg Hg/kg/day over periods of 1 month to 350 days (Boscolo et al., 1989; Carmignani et al., 1989, 1992; Jindal et al., 2011).

74. Decreased baroreceptor reflex sensitivity was noted in Wistar and Sprague-Dawley rats after exposure to mercuric chloride in drinking water, with a ≥27% reduction in the change in aortic blood pressure at doses ≥6 mg Hg/kg/day following administration of vasoactive drugs (e.g., norepinephrine, phenylephrine) (Boscolo et al., 1989; Carmignani and Boscolo, 1984; Carmignani et al., 1989). However, no exposure-related changes were observed in electrocardiogram parameters, stroke volume, cardiac output, left ventricular wall thickness, or carotid artery diameter or thickness in rats exposed to mercuric chloride in drinking water at doses up to 5.91 mg Hg/kg/day for 4 weeks (Wildemann et al., 2015a, 2015b, 2016).

75. No exposure-related changes in heart histology were observed in random-bred domestic adult cats following oral exposure to methylmercuric chloride at doses of up to 0.176 mg Hg/kg/day for 16 weeks, 0.074 mg Hg/kg/day for 55 weeks, or 0.046 mg Hg/kg/day for 2 years (Charbonneau et al., 1976). The control group used 10 cats, and the treatment groups used 8 cats with equal numbers of male and female.

Organic mercury

76. There is evidence in experimental animals that the cardiovascular system might be adversely affected by organic mercury. Grotto et al, (2009) reported statistically significant increases in systolic blood pressure in adult male rats given methylmercuric chloride by oral gavage for 100 days at 0.1 mg/kg bw per day, equivalent to 0.08 mg/kg bw per day expressed as mercury.

77. Studies of the Faroe Island population evaluated blood pressure in children at ages 7 and 14 (Grandjean et al., 2004; Sørensen et al., 1999). In 7-year-olds, a positive association was found between cord blood mercury (BHg) and maternal hair mercury (HHg) with systolic blood pressure, and between cord BHg and diastolic blood pressure. Specifically, an increase in cord BHg from 1 to 10 µg/L was associated with increases of 13.9 mmHg in systolic blood pressure and 14.6 mmHg in diastolic blood pressure (Sørensen et al., 1999).

78. In the follow-up study assessing blood pressure at age 14, no association was found between BHg, maternal HHg (at parturition), or child HHg (Grandjean et al., 2004). Similarly, in a study of children in the Seychelles Islands, no link was observed between prenatal exposure and systolic or diastolic blood pressure in girls at ages 12 and 15, or in boys at age 12 (Thurston et al., 2007). However, a positive association was noted between maternal HHg and diastolic blood pressure in boys at age 15. Additionally, a study of Nunavik Inuit children at age 11 found no association between cord BHg and blood pressure, even after adjusting for exposure to lead and polychlorinated biphenyls (PCBs) (Valera et al., 2012).

79. Chan et al, (2021) found that prenatal MeHg exposure was associated with decreased heart rate variability (HRV), reflecting reduced parasympathetic activity, and a sympathovagal balance shift toward sympathetic predominance in children aged 7-8 years. Adjustments for recent fish consumption increased the significance of the adverse associations.

80. Zareba et al. (2019) evaluated prenatal MeHg exposure in relation to HRV parameters in a large cohort of 19-year-old adults from the main cohort of the Seychelles Child Development Study. After adjustments for activity levels, polyunsaturated fatty acids, and multiplicity no statistically significant trends were found. The authors concluded, prenatal and recent MeHg exposure had no consistent pattern of association in this high fish consumer study population.

Pregnancy outcomes

Inorganic mercury

81. Reproductive animal studies consistently reported dose-related impairments in fertility in male and female rodents following oral exposure. No epidemiological studies evaluating associations between exposure to inorganic mercury salts and reproductive effects have been identified (ATSDR, 2022).

82. Generational studies in rats and mice have shown that reproductive capacity decreases in a dose- and duration-dependent manner following oral exposure to mercuric chloride. In a 2-generation study with rats, both males and females exhibited dose-related reductions in fertility index, live birth index, implantation efficiency, and the number of live pups per litter in the F0 generation at all tested doses (≥0.37 mg Hg/kg/day in males; ≥0.55 mg Hg/kg/day in females). Pre-cohabitation, males were dosed for 60 days and females for 16 days (one complete cycle of spermatogenesis and oogenesis). Both sexes were dosed for 21 days during cohabitation. Males were euthanised and necropsied after cohabitation and females were dosed for a further 42 days throughout gestation and lactation periods then euthanised and necropsied. However, no significant impairments were observed in the F1 generation at doses up to 1.31 mg Hg/kg/day in males and 1.98 mg Hg/kg/day in females (Atkinson et al., 2001).

83. In a 1-generation study with mice, premating exposure to mercuric chloride for 40 days in males and 16 days in females led to a reduced fertility index at doses ≥0.18 mg Hg/kg/day. Additionally, a decreased live birth index was observed at a dose of 0.74 mg Hg/kg/day (Khan et al., 2004).

84. In female rats, exposure to 1.5 mg Hg/kg/day before mating resulted in a reduced number of implantations and increased resorptions (Heath et al., 2012). In mice, exposure to 0.4 mg Hg/kg/day from before mating through lactation led to fewer live pups per litter (Huang et al., 2011). No signs of impaired fertility were observed in male or female rats exposed to doses of ≤0.7 mg Hg/kg/day when mated with untreated animals (Heath et al., 2012; Szász et al., 2002).

85. Studies have not observed histopathological lesions in the female reproductive organs of rats and mice exposed to mercuric chloride via gavage. No lesions were reported at acute-duration doses up to 9.24 mg Hg/kg/day in rats (Lecavalier et al, 1994), intermediate-duration doses up to 4 mg Hg/kg/day in rats or 15 mg Hg/kg/day in mice (Khan et al. 2004; NTP 1993), or chronic-duration doses up to 4 mg Hg/kg/day in rats or 7.4 mg Hg/kg/day in mice (NTP 1993).

86. In a 2-generation study, no changes in ovary or uterus weight were noted in F0 or F1 rats given gavage doses up to 1.98 mg Hg/kg/day for 79 days during premating, cohabitation, gestation, and lactation (Atkinson et al., 2001). Similarly, no changes in ovary weight were observed in mice exposed to gavage doses up to 0.74 mg Hg/kg/day for 79 days during premating, gestation, and lactation (Khan et al., 2004).

87. Data on female reproductive hormones are limited to a 60-day gavage study, which found an 18% reduction in serum progesterone and a 19% increase in pituitary luteinizing hormone levels at a dose of 1.5 mg Hg/kg/day, compared to the control group. These hormone levels were not affected at a

dose of 0.7 mg Hg/kg/day, and pituitary follicle stimulating hormone levels remained unchanged at doses up to 1.5 mg Hg/kg/day (Heath et al., 2009).

88. In a low-dose two-generation study on lead, cadmium and mercury (Lukačínová et al, 2011, 2012), Wistar rats were given 1 µM mercuric chloride in their drinking water, starting with the parental generation from 52 days of age and continuing through the F1 and F2 generations, terminating at the 156th week in each generation. The control group was given pure drinking water. Ten males and females per group were used to breed each generation and all animals were allowed to breed repeatedly between 13 and 78 weeks of age. The concentration of mercuric chloride in the drinking water corresponds to 270 µg/L. At 78 weeks of age, there were statistically significant reductions in body weight of 26 %, 27 % and 40 % in parental, F1 and F2 mercuric chloride-treated generations compared with controls. Exposure to mercuric chloride was reported to cause a statistically significant reduction in percentage survival to three years of age (controls 90 - 100 % versus treated 30 - 35 %), and consequently in lifespan, in all three generations. In those exposed to mercuric chloride, the number of litters from the parental generation was higher than in controls, comparable to controls in the F1 and statistically significantly lower than controls in the F2. The number of pups per litter at birth was reduced in the F2 generation in those exposed to mercuric chloride compared with controls. The proportion of weanlings surviving from birth was also lower in the breeding's from all three generations of those exposed to mercuric chloride (56 - 64 % compared with 90 - 91 % in controls). Serum total protein, albumin, transferrin, and ferritin levels, considered to be biomarkers for exposure to heavy metals, were statistically significantly increased following mercuric chloride treatment.

Organic mercury

89. Reproductive animal studies consistently reported dose-related impairments in fertility in male rats and female monkeys following oral exposure. Evidence for exposure-related impairments in female rodent fertility

following oral exposure is inconsistent. Available oral data suggest that organic mercury can impair male and female fertility in monkeys and male fertility in rats. Data in male mice are too limited to draw conclusions. Available data in rodents do not provide consistent evidence of impaired female rodent fertility following oral exposure to organic mercury (ATSDR, 2022).

90. Chemelo et al. (2022) investigated the effects of MeHg exposure during gestation and lactation on the developing alveolar bone of offspring rats after maternal exposure. Eight pregnant Wistar rats were divided equally and randomly into a control group which received vehicle only and a MeHg group which received 40 µg/kg/day. MeHg was administered during the gestational (21 days) and lactation (21 days) periods only for the parent generation. After the MeHg administration period the offspring were separated from the dams and divided by gender. Each dam had an average proportion of 2 males to one female per litter resulting in around 5 males per group. At 41 days old between adolescence and early adulthood the rats were euthanised and their mandibles were collected. Exposure to MeHg was found to change the mineral composition and cause histological damage, leading to a decrease in the quantity and thickness of bone trabeculae, as well as a reduction in osteocyte density and collagen fibre content. Observations included a decrease in trabecular thickness and bone volume, along with an increase in trabecular spaces, which were linked to anatomical compromise of the vertical bone dimensions. These findings suggest that developing alveolar bone is vulnerable to MeHg toxicity during intrauterine and lactation periods.

91. Vigeh et al. (2018) assessed the relationship between prenatal mercury exposure and newborn anthropometric characteristics in 334 mother-child pairs from the early stages of pregnancy to delivery in Tokyo, Japan, between December 2010 and October 2012. A negative correlation was found between BHg levels during the first and second trimesters of gestation and birth weight ($r = -0.134$ and -0.119, respectively; $p < 0.05$). Multiple linear regression analysis confirmed the relationship between first-trimester maternal BHg

levels and birth weight when adjusted for independent variables (β = −0.170, t = −2.762; p = 0.006). Mean mercury levels in umbilical cord blood were twice as high as maternal blood levels (10.15 ± 7.74 and 4.97 ± 3.25 μg/L, respectively; r = 0.974, p < 0.001). The authors findings suggest that pregnant women and women of reproductive age should avoid mercury exposure, even at low levels, because of its potentially adverse effects on foetal development.

92. Thomas et al. (2015) measured lead, mercury, cadmium, and arsenic levels in blood samples from the first and third trimesters in 1835 pregnant women from across Canada. Relative risks and 95% confidence intervals were estimated using log binomial multivariate regression. Important covariates including maternal age, parity, pre-pregnancy body mass index (BMI), and smoking, were considered in the analysis. Analysis was performed to examine potential effect modification of these relationships by single nucleotide polymorphisms in GST Pi 1 (GSTP1) and GST Omega 1 (GSTO1) genes. No association was found between blood lead, cadmium or arsenic and risk for small-for-gestational age (SGA). An increased risk for SGA was observed for the highest compared to the lowest tertile of exposure for mercury (41.6 mg/L, RR¼1.56.; 95% CI¼1.04–2.58) and arsenobetaine (42.25 mg/L, RR¼1.65; 95% CI¼1.10–2.47) after adjustment for the effects of parity and smoking. The authors concluded these results suggest there is a small increase in risk for SGA in infants born to women exposed to mercury and arsenic.

93. Lee et al. (2010) assessed the total Hg concentration in maternal and cord blood from 417 Korean women and newborns in the Mothers and Children's Environmental Health study from 2006 to 2008. Information on birth weight was collected from the patients' medical records. The genotyping of glutathione S-transferase M1 (GSTM1) and glutathione S-transferase T1 (GSTT1) polymorphisms was carried out to determine the association between the BHg concentration and birth weight in mothers with GSTM1 and GSTT1 polymorphisms. The geometric mean levels of Hg in the maternal

blood during late pregnancy and in cord blood were 3.30 µg/L and 5.53 µg/L, respectively. For mothers with the GSTT1 null genotype, elevated Hg levels in maternal blood during late pregnancy were associated with an increased risk of lower birth weight. The authors concluded in mothers with both GSTM1 and GSTT1 null genotype, both maternal and cord BHg levels were associated with lower birth weight.

94. Al-Saleh. (2014) conducted a cross-sectional study to assess the association between exposure to heavy metals (lead, cadmium, and mercury) during pregnancy and birth outcomes in 1578 women aged 16–50 years who delivered in Al-Kharj hospital, Saudi Arabia, in 2005 and 2006. The levels of lead, cadmium and mercury were measured in umbilical cord blood, maternal blood, and the placenta. Outcome variables were anthropometric measures taken at birth, along with risk of SGA. The 10th percentile was selected as the cutoff for dichotomizing measures of birth outcome. Mercury in both umbilical cord and maternal blood was marginally associated with placental thickness and placental weight, respectively. Conversely, placental mercury levels significantly influenced head circumference ($p = 0.017$), the Apgar 5-minute score ($p = 0.01$) and cord length ($p = 0.026$). The predictions of these models were further assessed with the area under the curve of the receiver operating curves, which were modest (larger than 0.5 and smaller than 0.7). The independence of gestational age or preterm births on the observed effect of metals on some measures of birth outcome, suggested detrimental effects of exposure on foetal development.

95. Guo et al. (2013) determined the levels of prenatal Hg exposure in Wujiang City, located in the southeast of Taihu Lake in China’s Jiangsu Province, and analysed the relationship between prenatal exposure to Hg and neonatal anthropometry, including birth weight, body length, and head circumference. From June 2009 to July 2010, a total of 213 mother-infant pairs were enrolled. The geometric means of Hg levels in maternal hair, foetal hair, placentas, and cord blood were 496.76 mg/kg, 233.94 mg/kg, 3.58 mg/kg, and 1.54 mg/L, respectively. The authors concluded the Hg levels

detected in their study were significantly lower than those reported by previous studies. In addition, no significant correlations were found between Hg levels in maternal hair, foetal hair, placenta, or cord blood and neonatal anthropometrics.

96. Kim et al. (2018) evaluated prenatal mercury exposure, fish intake and neurocognitive development during first three years of life in participants enrolled in the Mothers and Children's Environmental Health (MOCEH) study. The pregnant women enrolled were all older than 18 years, living in Seoul, Cheonan, or Ulsan (South Korea) and were in early pregnancy (before the 20th week). In the study 1751 mothers of singletons were enrolled. The maternal BHg levels were assessed during pregnancy and in cord blood. Maternal fish intake was assessed by weekly interview during pregnancy and fatty acid intake was estimated based on 24-hour recall food intake interview. The mental (MDI) and psychomotor (PDI) development index scores were assessed using the Bayley Scales of Infant Development II (BSID-II) at 6, 12, 24, 36 months of age. The authors found that after adjustments for weekly fish intake and fatty acid intake the BHg concentrations during early pregnancy showed adverse associations with the MDI and PDI at 6 months. The authors concluded these results suggest consuming fish high in fatty acids and low in Hg during early pregnancy may be important to neurodevelopment in infants.

97. Barbone et al. (2019) evaluated prenatal mercury exposure and child neurodevelopmental outcomes at 18 months in a Mediterranean (Italy, Slovenia, Croatia, and Greece) cohort. The study includes 1308 mother-child pairs enrolled in the Public Health Impact of long-term, low-level, Mixed Element exposure in a susceptible population EU Sixth Framework Programme (PHIME). Total Hg (THg) levels were measured in maternal hair and venous blood, cord blood and breast milk samples. Demographic, socioeconomic, lifestyle and diet information were collected through questionnaires. At 18 months of age children underwent neurodevelopment testing using the BSID, third edition. The authors concluded the study found an inverse relation between THg levels and developmental motor scores at 18

months, although the evidence was weak and inconsistent. There was no evidence for adverse effects of THg on cognitive and language outcomes in this cohort study.

98. A prospective UK birth cohort called the Avon Longitudinal Study of Parents and Children (ALSPAC) based in Bristol was established to explore genetic and environmental factors impacting health and development. Only women with expected delivery dates between April 1991 and December 1992 who were resident in the former county of Avon were recruited. As of 2023 there are 14,833 unique mothers enrolled in ALSPAC, with 15,447 associated pregnancies enrolled (Major-Smith et al, 2023).

99. Golding et al. (2022) analysed the ALSPAC cohort to investigate any association between prenatal mercury exposure and child outcomes. The authors aimed to contrast the ALSPAC cohort with longitudinal studies in the Seychelles where fish consumption is higher, and studies have not demonstrated harmful cognitive effects in children with increasing maternal mercury levels. Prenatal mercury exposure had been measured in maternal whole blood and umbilical cord tissue, and the offspring were followed up at frequent intervals. An assessment was made of foetal growth during pregnancy regarding maternal Hg levels by analysing birthweight, birth head circumference and crown-heel length (Taylor et al, 2016). Analyses, adjusted for maternal age, education, parity, height, BMI, smoking and alcohol consumption during pregnancy, as well as the gestational age and sex of the offspring. The unadjusted results show positive associations between Hg and all three birth measurements. However, on adjustment for whether or not the mother ate fish, it was found that if the mother ate fish there was no association between Hg and birthweight, whereas if she did not eat fish, there was a negative association. The difference between the adjusted birthweights of the offspring of the fish and non-fish eaters was statistically significant. Estimates of foetal mercury exposures were also compared with a variety of cognitive outcomes measured during the child's development. No associations were found between the MacArthur Communication

Development Inventory and either the cord tissue Hg level or fish consumption, but for the Griffiths test there were positive associations with maternal fish consumption. Preschool children were also assessed by their mothers using the Denver Developmental Screening Test (DDST) on four occasions between 6 and 42 months; for each age four subtests were carried out. The results suggested improved development with increasing Hg at two of the four ages however, of the 20 tests of interaction between maternal BHg level, fish intake and DDST, only one was significant (i.e., no more than expected by chance). There were no indications of adverse associations of cognition with maternal Hg level, as measured by the Weschler Intelligence Scale for Children, which had been administered to the 8-year-old children. There were significant interactions with maternal blood levels such that the prenatal Hg level of the mother was positively associated with the IQ level of her offspring if the mother had eaten fish in pregnancy, but not if she had not. This interaction was true of five cognitive outcomes: full IQ, performance IQ, mathematical comprehension, science comprehension and social cognition. If the mother had eaten fish during the pregnancy, (although adjustments had been made for a variety of different socioeconomic and biological factors), there were beneficial associations between prenatal levels of Hg and a number of outcomes, in contrast with the associations when the mother did not eat fish.

100. Golding et al. (2022) contains a table that lists ten other ALSPAC studies prior to this publication that concern prenatal mercury exposure and outcome to the child after birth including measurements of cognition and behaviour. All these studies reported either no significant associations or a positive association between prenatal mercury exposure and child outcomes.

101. Dack et al. (2023) studied 544 mother-child pairs from the ALSPAC cohort to assess the relationship between prenatal mercury exposure and infant weight trajectories. BHg was measured in early pregnancy and infant weight at 10 intervals between 4 and 61 months. Mixed-effect models were used to estimate the change in infant weight associated with prenatal mercury

exposure. The estimated difference in monthly weight gain was −0.02 kg per 1 standard deviation increase in Hg (95% confidence intervals: −0.10 to 0.06 kg). When restricted to the 10th decile of Hg, the association with weight at each age level was consistently negative but with wide confidence intervals. The lack of evidence for an association may indicate that at Hg levels in this cohort (median 1.9 µg/L) there is minimal biological impact, and the effect is too small to be either clinically relevant or detectable.

Effects on maternal health

102. Wang et al. (2022) conducted a case-control study with 84 participants in China. Logistic models were used to estimate odds ratios for preeclampsia (PE) risk and birth outcomes according to maternal blood Hg levels. Elevated BHg levels were found and associated with increased risks of mild PE (aOR, 7.03; 95% CI, 1.61, 30.62; P < 0.01) and severe PE (aOR, 47.55; 95% CI, 5.27, 429.05; P < 0.05). Increased blood Hg levels were also associated with low birth weight (aOR, 1.12; 95% CI, 1.00, 1.25; P < 0.05) and preterm birth (aOR, 1.22; 95% CI, 1.08, 1.38; P < 0.05).

103. McClam et al. (2023) investigated associations between blood concentrations of Pb, Cd, Hg, and their mixture and infertility and long-term amenorrhea in women aged 20-49 years using the US National Health and Nutrition Examination Survey (NHANES) 2013-2018 cross-sectional survey. A total of 1,990 women were included for the analysis of infertility and 1,919 women for long-term amenorrhea. The blood concentrations of Pb and heavy metal mixtures were significantly higher in ever-infertile women than pregnant women, but the concentrations of Cd and Hg were comparable. After full adjustment, multiple logistic regression analyses revealed a significant and dose-dependent positive association between blood Pb concentrations and women's historical infertility, a negative association between Cd and women's long-term amenorrhea, and no associations between Hg and heavy metal mixture and women's infertility or long-term amenorrhea.

104. Zhang et al. (2023) measured whole blood metal(loid)s in women at preconception, 16, 24 and 32 weeks of gestation and in cord blood in 100 mother-newborn pairs. the Mean concentrations of Hg, Pb, Rb, Mn, and Fe were lower during early-, mid-, and late-pregnancy than at preconception. Concentrations at preconception were correlated with those during pregnancy for all examined metal(loid)s. Maternal Hg, Pb, and Se concentrations at late pregnancy were correlated with those in newborn cord blood in various degrees (correlation coefficients: Hg 0.66, Pb 0.29, Se 0.39). The estimated placental transfer ratio for toxic metal(loid)s ranging from 1.68 (Hg) to 0.18 (Cd). The authors concluded a high degree of transplacental passage was observed in toxic metals Pb and Hg which may pose hazards to the developing fetus.

105. Wang et al. (2019) studied 1442 mother-child pairs recruited at birth and followed up to age 15 years from the Boston Birth Cohort in the United States. Maternal blood Hg levels were found to positively associate with child overweight or obesity (OWO) from age 2-15 years, independent of maternal pre-pregnancy OWO, diabetes, and other covariates. The relative risk (RR = 1.24, 95% CI 1.05-1.47) of child OWO associated with the highest quartile of Hg exposure was 24% higher than those with the lowest quartile. Maternal pre-pregnancy OWO and/or diabetes additively enhanced Hg toxicity. The highest risk of child OWO was found among children of OWO and diabetic mothers in the top Hg quartile (RR = 2.06; 95% CI 1.56-2.71) compared to their counterparts.

106. Yu et al. (2019) chose from a prospective birth cohort of 3201 women in Shanxi Province, China to study associations between spontaneous preterm birth (SPB) and As, Cd, Cr, Hg, and Pb maternal serum concentrations. The study found no significant associations of the serum concentrations of the five concerned toxic metals with the SPB likelihood.

107. Sakamoto et al. (2018) compared maternal and cord blood concentrations of biochemical substances, total Hg and Se, vitamin E, DHA,

and other elements, fatty acids, and amino acids in 54 Japanese mother–newborn pairs to elucidate the foetal risk of MeHg toxicity. Cord blood had higher haematocrit and amino acid values and lower concentrations of lipid components, including fatty acids compared with maternal blood. THg levels in cord blood (7.26 ng/g) were 1.9 times higher than levels in maternal blood (3.79 ng/g). Se concentrations in cord blood (176 ng/g) were slightly higher than concentrations in maternal blood (156 ng/g). Levels of vitamin E (0.31 mg/dL) and DHA (58.8 μg/mL) in cord blood were much lower than levels in maternal blood (1.38 mg/dL and 147 μg/mL, respectively). Therefore, the ratios of Se/THg, vitamin E/THg, and DHA/THg in cord blood were lower than ratios in maternal blood. As Se, vitamin E and DHA are thought to be protective factors against MeHg the lower ratios of these against THg in cord blood suggests that foetuses are at higher risk of MeHg toxicity.

108. Molina-Mesa et al. (2022) investigated deposits of four heavy metals (Pb, As, Cd, and Hg) in the placentas of women who gave birth at term in their setting. 103 placentas were studied, obtained by consecutive sampling, of women that delivered in the Regional Maternity Hospital of Malaga between March and June 2021. Detectable concentrations of mercury were found in 100% of placental samples (mean 38.1 ng/g, SD: 30.4) compared to 14.56%, 44.6% and 81.5% of samples for As, Cd, and Pb, respectively. The mean placental Hg concentration, 38.1 ng/g, is high compared to mean and median values from populations that consume less fish reported at 1.4 ng/g (Iowa United States, n = 38), 4.99 ng/g (Six rural counties of Northern China, n = 140), 10 ng/g (Upper Silesia Region in Poland, n = 40) (Pitkin et al., 1976; Tong et al., 2020; Kozikowska et al., 2013).

109. Bocca et al. (2019) assessed the concentrations of selected toxic (As, Cd, Cr, Hg, Ni, Pb) and essential trace elements (Co, Cu, Mn, Se and Zn) in blood and urine samples of delivering women at different periods of gestation and in cord blood, as well as to evaluate the placental permeability for these elements. A total of 53 women participating in the HEALS-EXHES (Health and Environment-wide Associations based on Large population Surveys -

European Exposure and Health Examination Survey) study were enrolled (conducted in Spain). Specifically, 48 blood samples from 1st trimester of pregnancy, 40 blood samples at delivery, and 31 cord blood at delivery were collected. Mothers' urines were sampled at the 1st (53 samples), 2nd (53 samples) and 3rd trimester (49 samples) of pregnancy. Results showed that Hg and Mn levels in cord blood were about 2.0 times higher than in maternal blood, suggesting that these elements may be transferred from mother to fetus. Correlation between paired maternal and cord blood samples for As, Hg and Pb was statistically significant indicating that the foetal body burden may reflect the maternal exposure. Maternal urinary concentrations of trace elements, including As, Cr, Cu, Hg, Se, and Zn decreased along pregnancy, which may cause variations in foetal exposure. The authors concluded "the levels of toxic and essential elements in maternal blood and urine, as well as in cord blood, were for most elements at the lower end of the ranges found in the scientific literature not being of special concern for pregnant women and the unborn".

Biomarkers of mercury exposure

110. Basu et al. (2018) undertook a review of mercury biomarkers in human populations worldwide between 2000 and 2018. The most used biomarkers are the concentrations of mercury in hair, urine, blood, cord blood, toenails and fingernails and their selection can depend on factors such as the potential source of exposure, chemical form, and exposure life stage.

111. Analysis of hair is commonly used to assess exposure to MeHg, which accounts for 80–90% of the total mercury content within this matrix (Clarkson and Magos 2006; UNEP/WHO 2008; NRC 2000). Once incorporated, the mercury remains in the hair, and this biomarker can therefore provide an integrated measurement of internal exposure to MeHg. Because hair grows at approximately 1 cm per month, measuring total mercury in 1-cm segments of mothers' hair can be used to assess the monthly maternal MeHg exposure throughout pregnancy (e.g., Sakamoto et al, 2012).

112. MeHg in hair is quite stable over time, indicating that demethylation within the hair is minimal (al-Shahristani and Shihab, 1974; Berglund et al, 2005). However, it has to be taken into account that hair treatment as well as inter-individual variability in the toxicokinetics of mercury uptake from blood to hair shaft and hair growth rate may affect mercury hair content. A frequently cited total mercury blood to hair ratio of 1:250 was also used by JECFA (FAO/WHO, 2004). It is well known, that large inter-study and inter-individual variations exist, especially in populations with infrequent fish consumption (WHO, 1990; FAO/WHO, 2004; Berglund et al, 2005) and there are some indications that the total mercury blood to hair ratio is lower (Sakamoto et al, 2007; Yaginuma-Sakurai et al, 2012); however, the EFSA CONTAM Panel considered the evidence insufficient to identify a more appropriate ratio (EFSA, 2012).

113. Similarly to HHg, total toenail and fingernail mercury are used as indicators of average MeHg exposure over time, serving as a biomarker for long term MeHg (Mozaffarian et al, 2011). Reported hair to toenail ratios for total mercury are in the range 2.38 – 3 (EFSA, 2012).

114. Urine analysis primarily provides information about exposure to inorganic and elemental mercury, although in people with high seafood consumption MeHg may also contribute to the mercury content (Sherman et al. 2013). Because the concentration of the analyte may depend on the dilution of the urine, which can vary, the measurement of mercury is often expressed in terms of its concentration per unit of creatinine or in relation to the specific gravity of the urine sample.

115. Mercury measured in whole blood and provides information about recent (~1 to 2 months) exposures to both MeHg and inorganic mercury (Clarkson and Magos, 2006). In most communities, the measurement of blood total mercury is an accepted biomarker for MeHg exposure because it correlates relatively well to seafood consumption (Sheehan et al, 2014). The

use of speciation can provide an indication of potential mercury sources but requires careful sample preparation and sophisticated instrumentation. The measurement of mercury in cord blood provides information about developmental exposure (UNEP/WHO, 2008).

116. In general, careful measurement of mercury content in hair and urine offers the most convenient and cost-effective scheme to monitor mercury in a given population, particularly those situated in resource-limited settings (UNEP/WHO, 2008).

117. Cord tissue and cord blood are extensively discussed and summarised in a previous evaluation (FAO/WHO, 2007). In summary, total mercury and MeHg are in general higher (by a factor of 1.7 – 2.2) in cord blood than in maternal blood at parturition (e.g., Kim et al, 2011; Sakamoto et al, 2012). Total mercury in cord tissue correlates with MeHg in cord tissue, and total mercury and MeHg in cord tissue correlate with total mercury in cord blood. A significant relationship was reported between fish consumption during pregnancy and total mercury in cord blood (FAO/WHO, 2007). Recently, total mercury in cord blood has been shown to correlate with maternal hair total mercury; the strongest correlation was observed with maternal hair in the first 1 cm-segment from the scalp at parturition (Sakomoto et al, 2012).

118. Basu et al. (2018) stated that individuals in select general background populations worldwide with insignificant exposures to mercury sources have BHg levels that generally fall below 5 µg/L, HHg levels that generally fall below 2 µg/g, and urine mercury levels that fall below 3 µg/L, although these general background values can vary across certain geographic regions.

Epigenetic alterations via mercury exposure

119. Recent studies have indicated that epigenetic changes may be a key regulator of the mechanisms associated with Hg exposure and the development of a variety of human disorders (Bollati and Baccarelli, 2010).

The human epigenome carries the inherited alterations to the genome that directly influences the regulation and expressions of genes. Epigenetic alterations are genetically heritable modifications that do not affect the already existing DNA sequence, but rather result in changing the expression of the genes. The examples of epigenetic alterations are perturbations of the promoter methylation pattern, histone modifications and non-coding RNA dysregulations (Loscalzo and Handy, 2014).

120. Hanna et al. (2012) identified candidate methylation changes associated with exposure to mercury in women undergoing *in vitro* fertilisation (IVF). Methylation of the GSTM1/5 promoter was increased for women with higher mercury exposure ($p = 0.04$); however, no correlation was observed ($r = 0.17$, $p = 0.27$). These results were obtained from the blood samples of the women, where an elevated level of Hg was observed (exceeding 2.9 µg/L). Though, no statistical association was detected between different levels of Hg and the GSTM1 in the exposed individuals and the study did not establish the expression level of GSTM1.

121. Carazza-Kessler et al, (2024) evaluated the transgenerational effects of exposure to MeHg and/or vitamin A (VitA) on epigenetic and toxicological parameters in Wistar rats. They found persistent toxicological effects in generations F1 and F2 following low/mild doses of MeHg and/or VitA exposure during dams' (F0) gestation and breastfeeding. Toxicological effects observed in the F2 generation included chronic DNA damage, bone marrow toxicity, altered microglial content, reduced neuronal signal, and diminished male longevity. Additionally, the study demonstrated that MeHg and VitA affected histone methylation and caused consistent effects in the F2 generation. While MeHg exposure has been associated with transgenerational inheritance effects in other organisms, this study provides the first evidence of transgenerational inheritance of MeHg and VitA-induced toxicological effects in rodents.

122. Aung et al. (2020) tested whether metals are associated with concurrent differential maternal whole blood DNA methylation. In the Early Autism Risk Longitudinal Investigation (EARLI) cohort, first or second trimester maternal blood metals concentrations (cadmium, lead, mercury, manganese, and selenium) and DNA methylation were measured. A subset sample of 97 women had both measures available for analysis, all of whom did not report smoking during pregnancy. The authors observed exposure to mercury was associated with gene ontologies for organ morphogenesis, tube development (a precursor for neural tube development), and tissue development but no significant correlations in single-site results for Hg in EARLI were observed.

123. Kupsco et al. (2022) isolated extracellular vesicle (EV) RNA from 333 milk samples collected between 2 and 74 days postpartum from a Faroese birth cohort born 1997–2000 and sequenced 2083 microRNA (miRNA) using a targeted library preparation method. The authors used negative binomial regressions to estimate associations between individual pollutants and 418 reliably expressed EV-miRNAs adjusted for potential confounders. They performed sparse principal components (PCs) analysis to derive the first four components of the EV-miRNA data and examined associations between pollutants and PCs using Bayesian kernel machine regression (BKMR). The authors observed no associations between pollutants and individual EV-miRNA expression; however, BKMR suggested that miRNA's: miR-200b-3p, miR-664a-3p, miR-6738-5p, miR-429, miR-1236-5p, miR-4464, and miR-30b-5p may be related to mercury neurotoxicity.

124. Longo et al. (2022) measured the serum concentration of a suite of inorganic and organic pollutants and their association to serum miRNA-30b, miRNA-223 and Let-7a miRNA expression in 68 healthy pregnant women from the NEHO birth cohort sited in a highly industrialized area. The authors found Hg levels were associated with miRNA-30b and the higher tertile of Hg showed a positive association with miRNA-223 also. Statistical analysis also shows a driving effect of Hg on significant increased expression of Let-7a (p =

0.045) and significantly amplified expression of miRNA-30b (p = 0.038). The authors concluded modified expression of circulating miRNAs in the serum of pregnant women, exposed to low-medium dose contaminants offers innovative early-warning approaches to human health risk assessment.

125. Onishchenko et al. (2008) observed an elevated trimethylation of the histone H3K27, together with a declined H3 histone acetylation of the brain-derived neurotrophic factor gene in perinatal MeHg exposed mice. This study indicated that exposure to MeHg at the developmental levels, predisposed mice to depression and enhanced epigenetic suppression.

126. Maccani et al. (2015) investigated the methylation status of > 485,000 CG dinucleotides (CpGs) loci in 192 placental samples. Hg concentrations were analysed in toenail clippings from a subset of 41 infants. Neurobehavior was assessed using the NICU Network Neurobehavioral Scales (NNNS) in an independent subset of 151 infants. 339 loci were identified with an average methylation difference > 0.125 between any two toenail Hg tertiles. Variation among these loci was found to be associated with a high-risk NNNS profile. Ten loci had $p < 0.01$ for the association between methylation and the high-risk NNNS profile. Six of 10 loci reside in the EMID2 gene and were hypomethylated in the 16 high-risk profile infants' placentas. Methylation at these loci was moderately correlated (correlation coefficients range, –0.33 to –0.45) with EMID2 expression. EMID2 hypomethylation may represent a novel mechanism linking *in utero* Hg exposure and adverse infant neurobehavioral outcomes.

127. Sanders et al. (2015) assessed the association between miRNA expression in the cervix during pregnancy with lead and mercury levels. They obtained cervical swabs from 60 pregnant women and quantified cervical miRNA expression. Women's blood lead, bone lead and toenail mercury levels were analysed. Seventeen miRNAs were found to be negatively associated with toenail mercury levels, and tibial bone lead levels were associated with decreased expression of miR-575 and miR-4286. The authors

concluded these findings highlight miRNAs in the human cervix as novel responders to maternal chemical exposure during pregnancy.

Studies published on the Seychelles and Faroe Islands cohorts since the 2018 COT statement on MeHg in the infant and child diet

128. Observation studies have been conducted in the Faroe Islands and Republic of Seychelles for over three decades now and the findings have been crucial to making informed decisions on HBGVs for inorganic and organic mercury by leading authorities such as JECFA and EFSA.

129. The 2018 COT statement on MeHg carried out a literature review of new data on the Seychelles and Faroe Islands cohorts published since the previous EFSA opinion (EFSA, 2012) to assist in risk characterisation.

130. The following section is dedicated to summarising new literature published since the last summary detailed within the 2018 COT statement on MeHg in the infant and child diet.

Faroe Islands Cohorts

131. As of now there are six cohort studies of Faroese mother-child pairs, the details of which can be found in Weihe and Grandjean (2012) and Jarlhelt et al. (2024). The primary goal of these studies has been to understand potential adverse health effects towards children after the mothers' exposure to marine contaminants during pregnancy (Weihe and Grandjean, 2012). The Faroese reside on 17 islands in the North Atlantic Ocean between Norway and Iceland, about 80% live on four connected (tunnel or bridge) northern islands (Grandjean et al, 2012). The populations rely heavily on marine resources for consumption and their economy. They also possess a long tradition of hunting pilot whales (*Globicephala melas*) for consumption and export with records back to 1584 (WHALING.FO, 2024); however, in 2008 the Chief medical officers of the Faroe Islands recommended that pilot whales no

longer be considered fit for human consumption due to high levels of mercury, PCBs and DDT derivatives within the meat (Mackenzie, 2008). The high seafood diet of the Faroese makes them ideal candidates for studying adverse health effects of mercury.

132. Oulhote et al. (2019) used Faroe Islands cohort 3 to investigate joint and independent neurotoxic effects of early life exposures to a chemical mixture. Hg, PCBs, and PFAS were measured in maternal and children's blood at 5 years (n = 449 and 419). At 7 years, the children were administered the Boston Naming Test (BNT) and the strengths and difficulties questionnaire. A novel statistical approach was used for analysis to mitigate issues such as multicollinearity and model misspecification. This approach found an interquartile range (IQR) increase in maternal BHg and PFAS was associated with 0.15 SD (95% CI = –0.29, –0.03) and 0.14 SD (95% CI = –0.26, –0.05) lower scores in BNT, whereas a joint IQR increase in the mixture of chemicals was associated with 0.48 SD (95% CI = –0.69, –0.25) lower scores in BNT. These findings align with established negative associations between mercury and neurodevelopment in this cohort.

Seychelles Child Development Study

133. The Seychelles Child Development Study (SCDS) is a multicohort observational study. It is conducted within the Republic of Seychelles, a 115-island archipelago in the Indian Ocean where citizens consume large amounts of ocean fish. The population is exposed to MeHg primarily from fish consumption and does not consume marine mammals which can contain PCBs, other toxins, and higher MeHg concentrations than fish (Davidson et al, 1998). The islands are 1000 miles from the nearest continent with no meaningful sources of industrial pollution. Therefore, fish consumed in the Seychelles are contaminated only by natural background to MeHg (Zareba et al, 2019). The primary goal of the SCDS is to measure developmental outcomes in children whose mothers consumed a diet high in fish during

pregnancy and to determine if there were associations between child developmental outcomes and prenatal MeHg exposure.

Main Cohort of the Seychelles Child Development Study

134. In 1989–90, 779 mother-infant pairs were recruited as part of the SCDS main cohort (MC). Children were enrolled at 6 months (+/−2 weeks) postpartum and cohort children have subsequently been evaluated at 19, 29, 66, and 107 months of age, and 10.5, 17, 19, 22 and 24 years of age (University of Rochester Medical Centre, 2024). More information on this cohort has been reported in detail previously (Davidson et al, 1998; Shamlaye et al, 1995; Myers et al, 2003; van Wijngaarden et al, 2013).

135. Zareba et al. (2019) evaluated prenatal MeHg exposure in relation to HRV parameters in 19-year-old adults. Prenatal MeHg exposure (mean MeHg = 6.92 ± 4.54 ppm (n=514)) was determined in maternal hair growing during pregnancy and recent exposure (mean MeHg = 10.21 ± 5.79 ppm (n = 451)) in participant's hair taken at evaluations which consisted of short (~2 h) and long (overnight) Holter recordings obtained in 514 and 203 participants, respectively. Prenatal MeHg exposure was unassociated with all 23 HRV parameters studied after adjustment for multiplicity. Recent MeHg was also not associated with any of the HRV parameters after adjustments for activity levels, polyunsaturated fatty acids (PUFAs), multiplicity and a Bonferroni adjustment. The authors concluded that prenatal and recent MeHg exposure had no consistent pattern of association with HRV.

136. McSorley et al. (2020) examined associations between MeHg exposure and biological markers of autoimmunity and inflammation while adjusting for LCPUFAs which possess anti-inflammatory properties. Maternal total HHg was measured and at age 19, total HHg, LCPUFA status, 13 antinuclear antibodies (ANA), total serum immunoglobulins (Ig) IgG, IgA, and IgM and serum markers of inflammation (IL-1, IL-2, IL-6, IL-10, C-reactive protein, IFN-γ, TNF-α) were measured in the SCDS MC (n = 497). Mean maternal total

HHg and age 19 total HHg was 6.84 ± 4.55 (n = 497) and 10.23 ± 6.02 ppm (n = 448), respectively. The study found that postnatal Hg exposure was associated with higher ANA and lower IgM but only after adjustment for the n-3 LCPUFA or the n-6:n-3 LCPUFA ratio. The authors concluded the clinical significance of these findings was unclear but warrant a follow up study.

Nutrition Cohort 2 of the Seychelles Child Development Study

137. Participants were recruited for the SCDS nutrition cohort 2 (NC2) with the aim of investigating whether certain micronutrients in fish may benefit child development and protect against neurotoxic effects of MeHg from maternal fish consumption. In addition to hair and blood (maternal and cord) mercury, various nutritional and genetic factors were measured that may influence child developmental outcomes (University of Rochester Medical Centre, 2024). NC2 consists of 1535 healthy mothers recruited between the years 2008 to 2011 during their first antenatal visit (from 14 weeks of gestation) at eight health centres across the main Island Mahé. For further information on recruitment criteria and power calculations see Strain et al. (2015).

138. Wahlberg et al. (2018) investigated whether maternal genetic variation linked to glutathione pathways could influence MeHg concentrations in pregnant mothers and children and thereby affect early development. Three polymorphisms were genotyped in 1449 mothers. The genotypes were analysed in association with maternal HHg and BHg, cord BHg, children's mental and motor development (assessed by Bayley Scales of Infant Development at 20 months). The authors observed that maternal genetic variation in genes involved in glutathione synthesis is statistically associated with maternal HHg, but not in maternal or foetal BHg. They also found increasing Hg in maternal and cord blood was associated with a lower PDI among GCLCrs761142 TT carriers; and increasing Hg in hair was associated with a lower MDI among GSTP1rs1695 GG carriers. These observations suggest maternal glutathione genetics may modify associations between MeHg exposure and neurodevelopmental outcomes.

139. Xu et al. (2019) are the first to study the associations between MeHg exposure, PUFA status and mitochondrial DNA copy number. In total, 1488 mother-child pairs were included in this study. Total Hg was measured in maternal blood (mean 18.36 ng/mL) collected at 28 weeks' gestation, maternal hair at delivery, and in foetal cord blood (mean 34.76 ng/mL). PUFA (n-3 and n-6) were measured only in maternal blood. Relative mitochondrial DNA copy number (RmtDNAcn) was measured in both maternal and cord blood. Increasing maternal blood Hg and n-3 PUFA were found to be associated with higher maternal RmtDNAcn. Increasing maternal n-6 PUFA and n-6/n-3 ratio were associated with lower maternal RmtDNAcn. Increasing foetal cord blood Hg was associated with lower foetal RmtDNAcn. Neither maternal blood Hg nor PUFA status was associated with foetal RmtDNAcn. These findings suggest that MeHg and PUFA status may influence mitochondrial homeostasis however, the authors noted that the magnitude of the associations is small.

140. Yeates et al. (2020) examined the relationship between maternal LCPUFA status at week 28 and birth outcomes, controlling for MeHg exposure throughout pregnancy. From 1236 mother-child pairs non-fasting blood samples were collected at 28 weeks of gestation, they measured serum total LCPUFA concentrations and prenatal total HHg concentration was measured (female mean 3.90 ± 3.47 ppm (n = 588) and male mean 3.96 ± 3.52 ppm (n = 648)). Associations of maternal LCPUFAs and MeHg with birth outcomes were assessed by multiple linear regression models, adjusting for child sex, gestational age, maternal age, BMI, alcohol use, socioeconomic status, and parity. The authors found neither maternal LCPUFA status nor MeHg exposure were significant determinants of birth outcomes in this cohort.

141. Cediel Ulloa et al. (2021) assessed associations between prenatal MeHg exposure and DNA methylation (at the cytosine of CpGs) in three nervous system-related genes, encoding brain-derived neurotropic factor (BDNF), glutamate receptor subunit NR2B (GRIN2B), and the glucocorticoid

receptor (NR3C1), in 406 seven-year-old children participating in the SCDS. They identified associations with prenatal MeHg exposure for DNA methylation of one GRIN2B CpG and two NR3C1 CpGs out of 12 total CpG sites. Higher prenatal MeHg was associated with higher methylation for each CpG site which is predicted to lower gene expression. The authors concluded these epigenetic changes could influence neurodevelopment and mental health.

142. Strain et al. (2021) examined the association of prenatal MeHg and maternal status of n-3 and n-6 PUFAs with neurodevelopment and investigated whether PUFAs might modify prenatal MeHg associations with neurodevelopment. They examined 7-year-old children from 1237 mother-child pairs. Prenatal mercury was measured as maternal HHg (mean 3.91 ± 3.47 ppm) and prenatal PUFA status was measured in maternal serum at 28 weeks gestation. A neurodevelopmental test battery was conducted on the children addressing 17 specific outcomes. Four of these outcomes encompassing executive function, cognition, and linguistic skills indicated improved performance with increasing n-6:n-3 PUFA ratio; however, after adjustments for multiple comparisons no associations were significant. Prenatal MeHg exposure, maternal DHA (22:6n-3) and arachidonic acid (20:4n-6) (AA) status were not significantly associated with any neurodevelopmental outcomes, aligning with previous findings in this cohort. Furthermore, no significant interactions were noted between MeHg and PUFA status.

143. Love et al. (2022) evaluated whether child ATP-binding cassette (ABC) transporter protein genetics may influence prenatal MeHg exposure and early child neurodevelopmental tests. Six ABC polymorphisms were genotyped in DNA from cord blood and maternal blood. Neurodevelopment in children was assessed by BSID-II at approximately 20 months of age. They used linear regression models to analyse covariate-adjusted associations of genotype with cord MeHg (n = 946) and BSID-II outcomes (n = 973) (Mental and Psychomotor). Interactions between genotypes, cord MeHg, and

neurodevelopmental outcomes were also evaluated. Only one polymorphism, ABCC1rs11075290, was associated with cord blood MeHg; children homozygous for the T-allele had on average 29.99 µg/L MeHg in cord blood while those homozygous for the C-allele had on average 38.06 µg/L MeHg in cord blood. No polymorphisms in the children were associated with BSID-II outcomes. However, the association between cord MeHg and the MDI of the BSID-II differed significantly across the three genotypes of ABCB1rs10276499. With increasing cord MeHg, the MDI decreased among children homozygous for the rare C-allele. These findings support the hypothesis that child ABC genetics may influence prenatal MeHg exposure.

144. De Paula et al. (2023) investigated risks from genetic variation in genes encoding the transcription factor Nuclear factor E2-related factor 2 (NRF2) and its negative regulator Kelch-like ECH-Associated Protein 1 (KEAP1) (known to moderate MeHg metabolism and toxicity) toward prenatal mercury exposure and child neurodevelopmental outcomes at 20 months and 7 years of age in the SCDS NC2. No evidence was found that prenatal mercury exposure was associated with the polymorphisms studied. However, at 7 years, KEAP1 polymorphisms were associated with differences in neurodevelopmental outcomes in the SCDS.

145. Wesolowska et al. (2024) evaluated dietary selenium (Se) and mercury intakes from fish consumption during pregnancy in the SCDS NC2 (n = 1419) as Se is thought to potentially alleviate MeHg toxicity. It was found that selenium intake from fish averaged 61.6 µg/d and mercury intake from fish averaged 0.38 µg/kg bw/d. The mean dietary Se:Hg molar ratio was 6. The authors concluded that consumption of fish with Se:Hg ratios above 1, may help pregnant women achieve optimum dietary selenium intakes, which may protect against MeHg toxicity.

Hazard Characterisation

This is a paper for discussion. This does not represent the views of the Committee and should not be cited.

146. The derivation of a health-based guidance value (HBGV) for MeHg has been reviewed and summarised in the 2018 COT statement. These are summarised in brief in the following paragraphs.

Derivation of HBGV for MeHg JECFA, 2004

147. The basis for establishing the 2004 JECFA HBGV was the human epidemiology studies from the Faroe Islands and the Seychelles. 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.

148. Concentrations of mercury in maternal hair and/or cord blood were used as biomarkers for exposure to methylmercury *in utero*.

149. A NOAEL for neurobehavioural effects of 15.3 mg/kg mercury in maternal hair was established in the Seychelles study. A mathematical analysis of the concentration to response relationship was used to determine a $BMDL_{05}$ 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 methylmercury in maternal hair that reflects exposures that would have no appreciable effect on the offspring in these two study populations.

150. The concentration of methylmercury in maternal hair was converted to mercury in maternal blood using an average overall ratio of 250 (paragraph 17). Based on this factor, the methylmercury 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.

151. 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 methylmercury (1.5 µg/kg bw/day) corresponding to a maternal BHg concentration that would have no appreciable adverse effects on the offspring in the two study populations.

152. 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.

153. Following application of this uncertainty factor, a PTWI of 1.6 µg/kg bw was established.

EFSA, 2012

154. The CONTAM Panel evaluated any available studies since their 2004 evaluation, in which the PTWI established by JECFA was also adopted. The biggest change since the evaluation of 2004 was new information on cofounding by beneficial factors in fish on associations between prenatal methylmercury exposures and neurodevelopmental endpoints.

155. Results from the first Nutrition Cohort (NC1) of the SCDS suggested an effect at age 9 and 30 months but not at 5 years related to prenatal methylmercury exposure, whereby it appeared that the positive effects from intake of n-3 LCPUFAs no longer outweighed detrimental effects from methylmercury exposure. The Nutrition study examined associations between methylmercury, maternal nutrition, and children's scores on the Bayley's scale of infant development-II test.

156. The CONTAM panel found that a methylmercury 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 methylmercury in maternal hair derived from the Seychelles main cohort.

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

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

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

160. 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 methylmercury of 1.3 µg/kg bw expressed as mercury.

Derivation of HBGV for inorganic mercury JECFA, 2011

161. The Committee noted that there was a lack of quantitative data on MeHg in non-fish products and on inorganic mercury in general.

162. The Committee assumed that the predominant form of mercury in foods other than fish and shellfish is inorganic mercury.

163. 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. The adverse effects observed in human cases however still provides evidence that supports findings from experimental species studies.

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

165. For JECFA's risk assessment the 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 higher than those generated for all other endpoints investigated, such as terminal body weight, serum alkaline phosphatase, serum cholinesterase and incidence of nephropathy. Short term exposure of mercury(II) chloride to weanling rats administered orally also yielded similar results.

166. 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).

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

168. The new PTWI for inorganic mercury was considered applicable to dietary exposure to total mercury from foods other than fish and shellfish.

EFSA CONTAM Panel, 2012

169. EFSA 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.

170. The more recent studies EFSA evaluated reported other effects at low levels of exposure to mercuric chloride; however, no NOAELs or BMDLs could be identified due to limitations of these studies.

171. The Panel derived the same TWI for inorganic mercury as JECFA, 4 µg/kg bw.

COT, 2018

172. The COT Committee agreed that the TWI of 1.3 µg/kg bw established by EFSA could be used for characterising potential risks from the exposure of infants and young children to MeHg. Therefore, to characterise the potential risks from the exposure of women of maternal age to total mercury in the diet the EFSA TWIs for MeHg and inorganic mercury have been applied in the below exposure assessment.

173. The Committee has not previously evaluated the EFSA TWI for inorganic mercury.

Exposure assessment

Exposure from food

174. 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 TDS (FSA, 2015).

175. 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 0.018 and 0.010 µg/kg bw/day, and 97.5th percentile values of 0.089 and 0.024 µg/kg bw/day, respectively.

176. 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 (97.5th percentile) ranges from 0.62-0.84 µg/kg bw/week.

Table 1. Estimated exposure (in µg/kg bw/day) 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

177. 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).

178. 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).

179. 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 (FSA, 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 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

180. 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).

181. The WHO estimates that the average inhalation rate for a 70 kg adult is 20 m^3/day (WHO, 2000). Defra's UK-Air Data Selector tool was used to retrieve total mercury air concentrations and the most recent data available was 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).

182. 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.

183. 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

184. 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).

185. 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).

186. 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).

187. 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 3. Median and 75th percentile exposure values for women of childbearing age to mercury from soil.

Measure	**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
Median	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).

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

Pica behaviour

189. 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.

190. 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.

191. 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).

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

193. 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.

194. 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.

Aggregate exposure

195. 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.

196. 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 industrial site in England and Wales. 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).

197. Table 4. Aggregate exposure to Mercury 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*.

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*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

198. 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

199. 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.

200. 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

201. 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.

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Soil

Table 4. Median and 75th percentile exposure to soil mercury as a proportion of the inorganic and organic mercury EFSA TWI's.

Measure	Region	Mercury exposure (µg/kg bw/week)*	% inorganic mercury TWI (4 µg/kg bw)	% organic mercury 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

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

203. The soil mercury concentrations used for the exposure estimate are from England only. No values were available for Wales, Scotland and NI.

204. 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

205. 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 (4 µg/kg bw) and organic (1.3 µg/kg bw) mercury. As aggregate exposure estimates under all scenarios are below the EFSA TWI's the risk of toxicity

from mercury is low.

Conclusions

206. Mercury is a metal that is released into the environment from both natural and anthropogenic sources. Mercury bioaccumulates in fish as methylmercury (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.

207. 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.

208. 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.

209. 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).

210. The high individual and aggregate exposure assessments to mercury from food, water, soil and air all estimated exposures below the EFSA TWI for MeHg and inorganic mercury. Therefore, for the UK population there is low

risk to women of maternal age and their foetuses.

Questions for the Committee

a) Does the Committee think that the current level of exposure to mercury from the diet, drinking water, soil and air is a cause for concern for pregnant women or their foetuses?

b) Does the Committee think that the EFSA TWIs for MeHg and inorganic Hg are acceptable for this risk assessment?

c) Does the Committee have any other comments on this discussion paper?

Secretariat

January 2025

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List of Abbreviations and Technical terms

Acronym	Definition
ALSPAC	Avon longitudinal study of parents and children
ANA	Antinuclear antibody
ABC	ATP-binding cassette
ATSDR	Agency for Toxic Substances and Disease Registry
BDNF	Brain-derived neurotropic factor
BHg	Blood mercury
BKMR	Bayesian kernel machine regression
BMDL	Benchmark-dose lower confidence limit
BMI	Body mass index
BSID-II	Bayley's scale of infant development-II
Bw	Bodyweight
CONTAM	Panel on Contaminants in the Food Chain
COT	Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment
CpG	CG dinucleotides
DDE	p,p'-dichlorodiphenyldichloroethylene
DDST	Denver Developmental Screening Test
DDT	Dichlorodiphenyltrichloroethane
Defra	Department for Environment, Food and Rural Affairs
DHA	Docosahexaenoic acid
EARLI	Early Autism Risk Longitudinal Investigation
EFSA	European Food Safety Authority
EV	Extracellular vesicle
FAO	Food and Agriculture Organisation of the United Nations
NR3C1	Glucocorticoid receptor
GRIN2B	Glutamate receptor subunit NR2B
GST	Glutathione S-transferase

GSTM1	Glutathione S-transferase M1
GSTT1	Glutathione S-transferase T1
Hg	Mercury
HHg	Hair mercury
HRV	Heart rate variability
Ig	Immunoglobulin
IVF	*In vitro* fertilisation
JECFA	Joint Food and Agriculture Organisation of the United Nations / World Health Organisation Expert Committee on Food Additives
LCPUFA	Long chain polyunsaturated fatty acid
MC	SCDS main cohort
MDI	Mental development index
MeHg	Methylmercury
miRNA	Micro RNA
MOCEH	Mothers and Children's Environmental Health
NC1	SCDS nutrition cohort 1
NC2	SCDS nutrition cohort 2
NNNS	NICU network neurobehavioral scales
NOAEL	No observed adverse effect level
OWO	Overweight or obesity
PC	Principal component
PCB	Polychlorinated biphenyls
PDI	Psychomotor development index
PE	Preeclampsia
PFAS	Perfluoroalkyl substances
PHIME	Mixed Element exposure in a susceptible population EU Sixth Framework Programme
PTWI	Provisional tolerable weekly intake
PUFA	Polyunsaturated fatty acid
RmtDNAcn	Relative mitochondrial DNA copy number
ROS	Reactive oxygen species

S	Sulfur
SACN	Scientific Advisory Committee on Nutrition
SCDS	Seychelles child development study
SCOOP	Scientific cooperation
Se	Selenium
SGA	Small-for-gestational age
TDS	Total diet survey
THg	Total mercury
TWI	Tolerable weekly intake
VitA	Vitamin A
WHO	World health organisation

Search terms

The references cited in this discussion paper 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,

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Preeclampsia,
Abortion,
United Kingdom,
Republic of Seychelles,
Faroe Islands.

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