Previous evaluations and Toxicity

In this guide

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

TOX/2025/03; COT., 2025).

Absorption, distribution, metabolism, and excretion (ADME) Inorganic mercury

16. Inorganic mercuric mercury has low bioavailability via the oral route. Rahola et al. (1972; 1973) measured whole-body elimination kinetics and excretion in adult humans following ingestion of a single tracer dose of mercury (6 µg as ^{203}Hg(NO3)2 in drinking water (two women) or mixed with calf liver paste (three women and five men)). As a percent of administered dose, the mean absorbed dose fraction for all subjects was 7.0% (range 1.4 – 15.6%, n = 10).

17. Studies conducted in animals indicate that the predominant site of absorption of inorganic mercury is the small intestine (ATSDR., 2024). Absorption mechanisms for Hg^{2+} in the small intestine include both active and passive processes.

18. 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 such as glutathione, cysteine metallothionine and red blood cell haemoglobin (ATSDR., 2024).

19. Mercuric mercury distribution in the body is specific to certain organs and cell types within them. The formation of thiol S-conjugates of Hg^{2+} produces molecules that can act as homologues of endogenous molecules/polypeptides. Hence, possible routes of uptake include interaction with plasma membrane amino acids, peptides, drugs, and ion transporters (Bridges and Zalups., 2010; 2017). 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; the highest concentrations being found in the periportal areas. Additionally, the mucous membranes of the intestinal tract, the epithelium of the skin and the interstitial cells of the testes have been shown to accumulate mercuric mercury (EFSA., 2012). Due to their limited lipophilicity neither mercurous nor mercuric mercury readily cross the placental or BBB.

20. There is no evidence in the literature that methylated mercury species are synthesised in human tissue (EFSA., 2012). The metabolism of mercury species, which appears to be similar between humans and experimental animals, involves oxidation and reduction processes and conjugation to glutathione.

Studies in mice have suggested that a small amount of mercuric mercury can be reduced to elemental mercury and eliminated as elemental mercury vapour.

21. Inorganic mercuric mercury is eliminated through faeces and urine. In a clinical study involving five adult men who received a single intravenous dose of ^{203}Hg(NO3)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 was 6% to 35% (Smith et al., 1995). Farris et al. (2008) reanalysed the Smith et al. (1995) data and estimated that, on average, around 30% of the dose was excreted via faeces and 25% via urine. Mercury is also excreted in human sweat and saliva (ATSDR., 2024).

22. Studies have also shown that inorganic mercury is excreted into breast milk from the plasma (Sundberg et al., 1999, Vahter et al., 2000) and correlations have been reported between levels of inorganic mercury in milk and whole blood (Oskarsson et al., 1996). However, as mentioned, inorganic mercury is poorly absorbed via the oral route (Rahola et al., 1972; 1973) and is not expected to be toxicologically significant compared to MeHg in infants nursed with breast milk (Iwai-Shimada et al., 2015).

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

Methylmercury

24. Following oral intake, MeHg is absorbed readily by the gastrointestinal tract and enters the systemic circulation, where mercuric ions can be delivered to target organs (ATSDR., 2004). MeHg has a larger oral absorption fraction than inorganic mercuric mercury, and greater accumulation in the brain and the kidneys (ATSDR., 2024).

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

26. In contrast to mercuric mercury, in human blood >90 % MeHg accumulates in the erythrocytes, where it is bound to the cysteinyl residues of

haemoglobin. The remaining blood MeHg (up to 10% of the total) is present in the plasma; about 99 % of plasma MeHg is bound to albumin. Plasma protein-bound MeHg is transferred to low molecular weight thiols (e.g., glutathione and cysteine) by ligand exchange mechanisms (EFSA., 2012).

27. Animal studies have shown that MeHg can combine with serum albumin, caseins and thiol-containing proteins on the surface of fat globules, allowing passive transfer of MeHg into breast milk from plasma (Sundberg et al., 1999); however, only up to 10% of whole blood MeHg is located in the plasma and available for lactational transfer (Kershaw et al., 1980). The concentration of MeHg in human milk and its proportion as a percentage of total mercury vary among different populations. Only a limited number of studies have reported concentrations of total mercury (THg) and MeHg in human milk (THg: Björnberg et al., 2005; Ursinyova and Masanova., 2005; Garcia-Esquinas et al., 2011; Miklavčič et al., 2011; Miklavčič et al., 2013. MeHg: Miklavčič et al., 2011; Miklavčič et al., 2013; Valent et al., 2013). Reported mean or median THg values are between 0.2 and 0.9 ng/g (or mL); mean or median percentages of MeHg in THg are 38 to 60% depending on the method of analysis and sample population. The remainder of THg is assumed to be inorganic mercury.

28. Fetal distribution of MeHg is similar to maternal distribution, although fetal brain mercury concentrations are approximately 5-7 times higher than those in maternal blood (COT, 2004). Cord blood concentrations are also reported at up to twice the maternal blood concentration at parturition (Bocca et al., 2019; FAO/WHO., 2007; Lee et al., 2010; Sakamoto et al., 2002, 2018; Vigeh et al., 2018); however, blood mercury concentrations in infants have been shown to decline significantly over the first weeks of life. Sakamoto et al. (2002) reported that at 3 months of age infants' mean red blood cell mercury concentration accounted for 54 % of the measured umbilical cord concentration and lower than the maternal blood concentration, opposite to the situation at parturition. The rapid reduction of infant blood mercury concentration was attributed to low rates of lactational mercury transfer and rapid increase in infants body weight after birth (almost 2-fold at 3 months old) (Sakamoto et al., 2002). The higher concentration of mercury in the umbilical cord is hypothesised to be due to the action of active transport mechanisms via amino acid carriers such as system L, the two isoforms of which (LAT1 and LAT2) have been shown to mediate the transport of MeHg cysteine S-conjugates in astrocytes and endothelial cells of the BBB (Aschner et al. 1990; Kerper et al. 1992; Mokrzan et al. 1995; Simmons-Willis et al. 2002). Straka et al. (2016) also found that LAT1, another amino acid transporter rBAT, and an ATP-binding cassette transporter MRP1, are all involved

in mercury toxicokinetics of trophoblast cells. The authors proposed a model involving these transporters that explains the preferential transport of mercury across the placenta towards the fetus. Other transport mechanisms have been identified in the placenta; however, their roles in the transport of MeHg are unknown (Bridges and Zalups., 2017).

29. Partial demethylation of MeHg occurs in mammals in the presence of reactive oxygen species. Demethylation occurs predominantly in the liver, intestinal tract, spleen, and to a lesser extent in phagocytic cells and the brain (Suda et al., 1992). Mercuric mercury in the brain is generally the result of either *in situ* dealkylation of organic mercury species such as MeHg or oxidation of elemental mercury. Demethylation of MeHg by intestinal bacteria also contributes to the excretion of inorganic mercuric mercury in faeces (Li et al., 2019).

30. 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). Enterohepatic recycling of MeHg by metabolism of its glutathione S-conjugate (CH3Hg-S-CysGlyGlu) and reabsorptive transport of its cysteine S-conjugate (CH3Hg-S-Cys) (Tanaka et al., 1992; Tanaka-Kagawa et al., 1993) limits the urinary excretion of MeHg.