Toxicity

In this guide

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

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

29. The United States Department of Health and Human Services, Agency for Toxic Substances and Disease Registry (ATSDR) published a toxicological profile for mercury in October 2024 which characterises the toxicologic and adverse health effects information for organic and inorganic mercury. Mercury compounds exhibit a wide range of toxic effects, targeting

common cellular functions. These include disrupting intracellular calcium balance, the cytoskeleton, mitochondrial function, oxidative stress, neurotransmitter release, and DNA methylation. The array of toxic effects is due to the strong affinity of Hg^{2+} and $CH3Hg^{2+}$ for the thiolate anion, which leads to the formation of Hg^{2+} and $CH3Hg^{2+}$ S-conjugates. This allows inorganic and organic mercury to bind to and interfere with the structure and function of enzymes, transporters, and proteins that rely on functional thiol groups (ATSDR., 2024).

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

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

32. Epidemiological studies have shown that prenatal exposure to MeHg is linked to cognitive, neuromotor, and neurosensory impairments. In adults, research indicates reduced performance in fine motor coordination, speed, muscle strength, tactile sensation, colour vision, visual contrast sensitivity, as well as memory and learning. In animals, neurological effects include sensorimotor dysfunction, vision and hearing deficits, impaired learning, and memory, along with clear signs of neurotoxicity such as clumsiness, motor incoordination, lethargy, hindlimb crossing, tremors, ataxia, and partial paralysis. Both developing humans and animals are more vulnerable to MeHg-induced neurotoxic effects compared to adults (ATSDR., 2024).

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

the exposure to MeHg during the preceding year (COT., 2004).

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

35. EFSA and the COT have both highlighted that there is evidence that a number of dietary factors can reduce or prevent MeHg toxicity, including n-3 long chain polyunsaturated fatty acids (LCPUFAs), selenium, iodine, choline and vitamin E. Numerous *in vitro* and *in vivo* studies are available, but only a brief summary is provided here. The most extensively studied substance in food, regarding mechanisms of confounding of studies of mercury, is selenium. Mercury binding affinity for selenium is a million times higher than its binding affinity for sulphur in analogous forms and attempts, unsuccessful to date, have been made to identify detoxification products, which contain selenium and mercury (e.g. mercury-selenide). Whether such compounds truly detoxify the mercury species has never been demonstrated. Besides sequestration of mercury, potential protective modes of action of selenium against MeHg toxicity include antioxidant effects, increased glutathione peroxidase activity, glutathione synthesis, high selenoprotein concentration and increased demethylation of MeHg. Mechanistically, docosahexaenoic acid (DHA) seems to protect against MeHg-induced oxidative stress in neuronal cells. Additionally, in neuronal cell lines and primary cells pre-treatment with DHA was associated with decreased cellular MeHg bioavailability (EFSA, 2012; COT, 2018).

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

Recently published literature

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

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

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