Toxicity

In this guide

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 Hg2+ and $CH3Hg^{2+}$ for the thiolate anion, which leads to the formation of Hg^{2+} and $CH3Hg^{2+}$ 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 Hg2+ and $CH3Hg^{+}$ 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 $CH3Hg^{+}$ 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 Hg2+ 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.