Hazard Identification

In this guide

ADME

Inorganic mercury

Absorption

31. Inorganic mercury exists as mercurous (Hg22+) 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 Hg2+ is the small intestine (ATSDR, 2022).

34. There are several absorption mechanisms for Hg2+ in the small intestine, including active and passive processes. The formation of Thiol S-conjugates of Hg2+ 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 Hg2+ 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 Hg2+ complex (Endo et al. 1990). These observations suggest that ligand interactions are important variables affecting absorption.

Distribution

36. The distribution of absorbed Hg2+ is strongly influenced by the high affinity of Hg2+ for the thiolate anion and formation of Hg2+ 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 Hg2+ are albumin (Ikegaya et al, 2010) and low molecular weight thiols like glutathione and cysteine (Lash and Jones 1985).

38. Within cells, Hg2+ 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(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 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(NO3)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 (CH3Hg-S-CysGlyGlu) and reabsorptive transport of the S- conjugate of cysteine (CH3Hg-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).