The effects of mercury on maternal health - Reproductive toxicology

In this guide

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 ($\beta = -0.170$, $t = -2.762$; $p = 0.006$). 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.