Studies published on the Seychelles and Faroe Islands cohorts since the 2018 COT statement on MeHg in the infant and child diet

In this guide

128. Observation studies have been conducted in the Faroe Islands and Republic of Seychelles for over three decades now and the findings have been crucial to making informed decisions on HBGVs for inorganic and organic mercury by leading authorities such as JECFA and EFSA.

129. The 2018 COT statement on MeHg carried out a literature review of new data on the Seychelles and Faroe Islands cohorts published since the previous EFSA opinion (EFSA, 2012) to assist in risk characterisation.

130. The following section is dedicated to summarising new literature published since the last summary detailed within the 2018 COT statement on MeHg in the infant and child diet.

Faroe Islands Cohorts

131. As of now there are six cohort studies of Faroese mother-child pairs, the details of which can be found in Weihe and Grandjean (2012) and Jarlhelt et al. (2024). The primary goal of these studies has been to understand potential adverse health effects towards children after the mothers' exposure to marine contaminants during pregnancy (Weihe and Grandjean, 2012). The Faroese reside on 17 islands in the North Atlantic Ocean between Norway and Iceland, about 80% live on four connected (tunnel or bridge) northern islands (Grandjean et al, 2012). The populations rely heavily on marine resources for consumption and their economy. They also possess a long tradition of hunting pilot whales (*Globicephala melas*) for consumption and export with records back to 1584 (WHALING.FO, 2024); however, in 2008 the Chief medical officers of the Faroe Islands recommended that pilot whales no longer be considered fit for human consumption due to high levels of mercury, PCBs and DDT derivatives within the meat (Mackenzie, 2008). The high seafood diet of the Faroese makes them ideal candidates for studying adverse health effects of mercury.

132. Oulhote et al. (2019) used Faroe Islands cohort 3 to investigate joint and independent neurotoxic effects of early life exposures to a chemical mixture. Hg, PCBs, and PFAS were measured in maternal and children's blood at 5 years (n = 449 and 419). At 7 years, the children were administered the Boston Naming Test (BNT) and the strengths and difficulties questionnaire. A novel statistical approach was used for analysis to mitigate issues such as multicollinearity and model misspecification. This approach found an interquartile range (IQR) increase in maternal BHg and PFAS was associated with 0.15 SD (95% CI = –0.29, –0.03)

and 0.14 SD (95% CI = – 0.26, –0.05) lower scores in BNT, whereas a joint IQR increase in the mixture of chemicals was associated with 0.48 SD (95% CI = –0.69, –0.25) lower scores in BNT. These findings align with established negative associations between mercury and neurodevelopment in this cohort.

Seychelles Child Development Study

133. The Seychelles Child Development Study (SCDS) is a multicohort observational study. It is conducted within the Republic of Seychelles, a 115-island archipelago in the Indian Ocean where citizens consume large amounts of ocean fish. The population is exposed to MeHg primarily from fish consumption and does not consume marine mammals which can contain PCBs, other toxins, and higher MeHg concentrations than fish (Davidson et al, 1998). The islands are 1000 miles from the nearest continent with no meaningful sources of industrial pollution. Therefore, fish consumed in the Seychelles are contaminated only by natural background to MeHg (Zareba et al, 2019). The primary goal of the SCDS is to measure developmental outcomes in children whose mothers consumed a diet high in fish during pregnancy and to determine if there were associations between child developmental outcomes and prenatal MeHg exposure.

Main Cohort of the Seychelles Child Development Study

134. In 1989–90, 779 mother-infant pairs were recruited as part of the SCDS main cohort (MC). Children were enrolled at 6 months (+/−2 weeks) postpartum and cohort children have subsequently been evaluated at 19, 29, 66, and 107 months of age, and 10.5, 17, 19, 22 and 24 years of age (University of Rochester Medical Centre, 2024). More information on this cohort has been reported in detail previously (Davidson et al, 1998; Shamlaye et al, 1995; Myers et al, 2003; van Wijngaarden et al, 2013).

135. Zareba et al. (2019) evaluated prenatal MeHg exposure in relation to HRV parameters in 19-year-old adults. Prenatal MeHg exposure (mean MeHg = 6.92 ± 4.54 ppm (n=514)) was determined in maternal hair growing during pregnancy and recent exposure (mean MeHg = 10.21 ± 5.79 ppm (n = 451)) in participant's hair taken at evaluations which consisted of short (~2 h) and long (overnight) Holter recordings obtained in 514 and 203 participants, respectively. Prenatal MeHg exposure was unassociated with all 23 HRV parameters studied after adjustment for multiplicity. Recent MeHg was also not associated with any of the HRV parameters after adjustments for activity levels, polyunsaturated fatty acids (PUFAs), multiplicity and a Bonferroni adjustment. The authors concluded

that prenatal and recent MeHg exposure had no consistent pattern of association with HRV.

136. McSorley et al. (2020) examined associations between MeHg exposure and biological markers of autoimmunity and inflammation while adjusting for LCPUFAs which possess anti-inflammatory properties. Maternal total HHg was measured and at age 19, total HHg, LCPUFA status, 13 antinuclear antibodies (ANA), total serum immunoglobulins (Ig) IgG, IgA, and IgM and serum markers of inflammation (IL-1, IL-2, IL-6, IL-10, C-reactive protein, IFN- γ, TNF-α) were measured in the SCDS MC (n = 497). Mean maternal total HHg and age 19 total HHg was 6.84 ± 4.55 (n = 497) and 10.23 ± 6.02 ppm (n = 448), respectively. The study found that postnatal Hg exposure was associated with higher ANA and lower IgM but only after adjustment for the n- 3 LCPUFA or the n-6:n-3 LCPUFA ratio. The authors concluded the clinical significance of these findings was unclear but warrant a follow up study.

Nutrition Cohort 2 of the Seychelles Child Development Study

137. Participants were recruited for the SCDS nutrition cohort 2 (NC2) with the aim of investigating whether certain micronutrients in fish may benefit child development and protect against neurotoxic effects of MeHg from maternal fish consumption. In addition to hair and blood (maternal and cord) mercury, various nutritional and genetic factors were measured that may influence child developmental outcomes (University of Rochester Medical Centre, 2024). NC2 consists of 1535 healthy mothers recruited between the years 2008 to 2011 during their first antenatal visit (from 14 weeks of gestation) at eight health centres across the main Island Mahé. For further information on recruitment criteria and power calculations see Strain et al. (2015).

138. Wahlberg et al. (2018) investigated whether maternal genetic variation linked to glutathione pathways could influence MeHg concentrations in pregnant mothers and children and thereby affect early development. Three polymorphisms were genotyped in 1449 mothers. The genotypes were analysed in association with maternal HHg and BHg, cord BHg, children’s mental and motor development (assessed by Bayley Scales of Infant Development at 20 months). The authors observed that maternal genetic variation in genes involved in glutathione synthesis is statistically associated with maternal HHg, but not in maternal or foetal BHg. They also found increasing Hg in maternal and cord blood was associated with a lower PDI among GCLCrs761142 TT carriers; and increasing Hg in hair was associated with a lower MDI among GSTP1rs1695 GG carriers.

These observations suggest maternal glutathione genetics may modify associations between MeHg exposure and neurodevelopmental outcomes.

139. Xu et al. (2019) are the first to study the associations between MeHg exposure, PUFA status and mitochondrial DNA copy number. In total, 1488 mother-child pairs were included in this study. Total Hg was measured in maternal blood (mean 18.36 ng/mL) collected at 28 weeks' gestation, maternal hair at delivery, and in foetal cord blood (mean 34.76 ng/mL). PUFA (n-3 and n-6) were measured only in maternal blood. Relative mitochondrial DNA copy number (RmtDNAcn) was measured in both maternal and cord blood. Increasing maternal blood Hg and n-3 PUFA were found to be associated with higher maternal RmtDNAcn. Increasing maternal n-6 PUFA and n-6/n-3 ratio were associated with lower maternal RmtDNAcn. Increasing foetal cord blood Hg was associated with lower foetal RmtDNAcn. Neither maternal blood Hg nor PUFA status was associated with foetal RmtDNAcn. These findings suggest that MeHg and PUFA status may influence mitochondrial homeostasis however, the authors noted that the magnitude of the associations is small.

140. Yeates et al. (2020) examined the relationship between maternal LCPUFA status at week 28 and birth outcomes, controlling for MeHg exposure throughout pregnancy. From 1236 mother-child pairs non-fasting blood samples were collected at 28 weeks of gestation, they measured serum total LCPUFA concentrations and prenatal total HHg concentration was measured (female mean 3.90 ± 3.47 ppm (n = 588) and male mean 3.96 ± 3.52 ppm (n = 648)). Associations of maternal LCPUFAs and MeHg with birth outcomes were assessed by multiple linear regression models, adjusting for child sex, gestational age, maternal age, BMI, alcohol use, socioeconomic status, and parity. The authors found neither maternal LCPUFA status nor MeHg exposure were significant determinants of birth outcomes in this cohort.

141. Cediel Ulloa et al. (2021) assessed associations between prenatal MeHg exposure and DNA methylation (at the cytosine of CpGs) in three nervous system-related genes, encoding brain-derived neurotropic factor (BDNF), glutamate receptor subunit NR2B (GRIN2B), and the glucocorticoid receptor (NR3C1), in 406 seven-year-old children participating in the SCDS. They identified associations with prenatal MeHg exposure for DNA methylation of one GRIN2B CpG and two NR3C1 CpGs out of 12 total CpG sites. Higher prenatal MeHg was associated with higher methylation for each CpG site which is predicted to lower gene expression. The authors concluded these epigenetic changes could influence neurodevelopment and mental health.

142. Strain et al. (2021) examined the association of prenatal MeHg and maternal status of n-3 and n-6 PUFAs with neurodevelopment and investigated whether PUFAs might modify prenatal MeHg associations with neurodevelopment. They examined 7-year-old children from 1237 mother- child pairs. Prenatal mercury was measured as maternal HHg (mean 3.91 ± 3.47 ppm) and prenatal PUFA status was measured in maternal serum at 28 weeks gestation. A neurodevelopmental test battery was conducted on the children addressing 17 specific outcomes. Four of these outcomes encompassing executive function, cognition, and linguistic skills indicated improved performance with increasing n-6:n-3 PUFA ratio; however, after adjustments for multiple comparisons no associations were significant. Prenatal MeHg exposure, maternal DHA (22:6n-3) and arachidonic acid (20:4n-6) (AA) status were not significantly associated with any neurodevelopmental outcomes, aligning with previous findings in this cohort. Furthermore, no significant interactions were noted between MeHg and PUFA status.

143. Love et al. (2022) evaluated whether child ATP-binding cassette (ABC) transporter protein genetics may influence prenatal MeHg exposure and early child neurodevelopmental tests. Six ABC polymorphisms were genotyped in DNA from cord blood and maternal blood. Neurodevelopment in children was assessed by BSID-II at approximately 20 months of age. They used linear regression models to analyse covariate-adjusted associations of genotype with cord MeHg (n = 946) and BSID-II outcomes (n = 973) (Mental and Psychomotor). Interactions between genotypes, cord MeHg, and neurodevelopmental outcomes were also evaluated. Only one polymorphism, ABCC1rs11075290, was associated with cord blood MeHg; children homozygous for the T-allele had on average 29.99 µg/L MeHg in cord blood while those homozygous for the C-allele had on average 38.06 µg/L MeHg in cord blood. No polymorphisms in the children were associated with BSID-II outcomes. However, the association between cord MeHg and the MDI of the BSID-II differed significantly across the three genotypes of ABCB1rs10276499. With increasing cord MeHg, the MDI decreased among children homozygous for the rare C-allele. These findings support the hypothesis that child ABC genetics may influence prenatal MeHg exposure.

144. De Paula et al. (2023) investigated risks from genetic variation in genes encoding the transcription factor Nuclear factor E2-related factor 2 (NRF2) and its negative regulator Kelch-like ECH-Associated Protein 1 (KEAP1) (known to moderate MeHg metabolism and toxicity) toward prenatal mercury exposure and child neurodevelopmental outcomes at 20 months and 7 years of age in the SCDS NC2. No evidence was found that prenatal mercury exposure was associated with

the polymorphisms studied. However, at 7 years, KEAP1 polymorphisms were associated with differences in neurodevelopmental outcomes in the SCDS.

145. Wesolowska et al. (2024) evaluated dietary selenium (Se) and mercury intakes from fish consumption during pregnancy in the SCDS NC2 (n = 1419) as Se is thought to potentially alleviate MeHg toxicity. It was found that selenium intake from fish averaged 61.6 µg/d and mercury intake from fish averaged 0.38 µg/kg bw/d. The mean dietary Se:Hg molar ratio was 6. The authors concluded that consumption of fish with Se:Hg ratios above 1, may help pregnant women achieve optimum dietary selenium intakes, which may protect against MeHg toxicity.