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COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Discussion paper on potential risks from methylmercury in the diet of infants aged 0 to 12 months and children aged 1 to 5 years

Introduction

1. The Scientific Advisory Committee on Nutrition (SACN) is undertaking a review of scientific evidence that will inform the Government's dietary recommendations for infants and young children. The SACN is examining the nutritional basis of the advice. The Committee on Toxicity in Food, Consumer Products and the Environment (COT) was asked to review the risks of toxicity from chemicals in the diet of infants, most of which has been completed, and young children. The reviews will identify new evidence that has emerged since the Government's recommendations were formulated, and will appraise that evidence to determine whether the advice should be revised. The recommendations cover diet from birth to age five years.

2. In 2004, the COT concluded that the Provisional Tolerable Weekly Intake (PTWI) of 1.6 µg/kg bw for methylmercury (MeHg) established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2003 was sufficient to protect against neurodevelopmental effects on the fetus and should be used in assessing risks from dietary exposure to MeHg in women who are pregnant or may become pregnant the following year. The COT also concluded that a guideline of 3.3 µg/kg bw/week was also appropriate for breastfeeding mothers. The COT further advised that regular consumption of certain types of fish could result in the above values being exceeded. The Government, therefore, currently advises that breastfeeding mothers should avoid eating more than one portion of shark, swordfish or marlin per week and that children should avoid eating these species.

3. The European Food Safety Authority's (EFSA) Panel on Contaminants in the Food Chain (CONTAM) evaluated the safety of mercury and methylmercury in 2012. A TWI of 1.3 µg/kg bw (expressed as mercury) was established for MeHg.

4. More recently, the COT commented on a survey of metals and other elements in infant foods (FSA, 2016a). The Infant Metals Survey measured the concentrations of metals and other elements in food 'as sold', in the following categories: infant formula, commercial infant foods, and groups of food comprising the top 50 most commonly consumed varieties of foods not specifically marketed for infants, including fish. The results from this survey were used together with food consumption data from the Diet and Nutrition Survey for Infants and Young Children (DNSIYC) (DH, 2013) to estimate dietary exposures for children aged 4 to 18

months. The results for methylmercury indicated that exposures were below the TWI of 1.3 µg/kg bw set by EFSA.

5. This statement gives an overview of the potential risks from MeHg in the diets of infants and young children in the UK aged 0 to 12 months and 1 to 5 years, respectively

Background

6. Mercury (Hg) is a metal that is released into the environment from both natural and anthropogenic sources. After release into the environment, it undergoes complex transformations and cycles between atmosphere, land and aquatic systems. The three chemical forms of mercury are (i) elemental or metallic mercury (Hg0), (ii) inorganic mercury [mercurous ($Hg_2^{(2+)}$] and mercuric (Hg^{2+}) cations) and (iii) organic mercury. MeHg is by far the most common form in the food chain.

7. All forms of mercury entering the aquatic environment from either anthropogenic activities or geological sources are converted into MeHg by microorganisms. MeHg bioaccumulates and biomagnifies in fish either directly through the water or via the food chain, through the consumption of other species. MeHg has a half –life of two years in fish. Thus, larger, older predatory fish are more likely to have high levels of mercury making populations with a high intake of fish and seafood particularly vulnerable (EFSA, 2012; COT, 2004; WHO,2017).

8. After oral intake, MeHg is much more extensively and rapidly absorbed by human volunteers (EFSA, 2012; FAO/WHO, 2011). It is able to enter the hair follicle, and to cross the placenta as well as the blood-brain and blood-cerebrospinal fluid barriers, allowing accumulation in hair, the fetus and the brain. (EFSA, 2012)

9. The main adverse effect associated with methylmercury exposure is toxicity to the central and peripheral nervous systems. (WHO, 2017). Due to its ability to cross the blood-brain barrier and the placenta, methylmercury exposure is of particular concern during embryonic development (COT, 2004).

10. Methylmercury can also affect the kidneys. Acute neuro- and nephrotoxicity have been reported in cases of human MeHg poisoning; whereas neurotoxicity is usually associated with lower level chronic exposures, especially in the developing fetus (COT, 2004).

11. The developing embryo and young children are considered particularly susceptible to MeHg neurotoxicity. Thus, pregnant and breastfeeding women are also within the sensitive population due to the fact that maternal exposure can lead to exposure of the child either via the placenta or breast milk. The bioaccumulative properties of MeHg in combination with its long half-life mean that women who could potentially become pregnant the following year would also be part of the at risk population.

Toxicokinetics

Absorption

12. In contrast to other forms of mercury, MeHg is rapidly and extensively absorbed. The absorption rates are higher than 80%, with up to 95% of an oral dose being absorbed in human volunteers in the form of either methylmercury(II) chloride or methylmercury in fish tissue (EFSA, 2012; JECFA, 2011). MeHg undergoes enterohepatic cycling, which allows for the reabsorption of some of the MeHg excreted in the bile from the intestine (EFSA, 2012).

Distribution

13. Of the MeHg that enters the systemic circulation >90% is accumulated in the erythrocytes. In plasma, most methylmercury (about 99 %) is bound to albumin, which has a free sulphydryl group in a terminal cysteinyl residue. By complex ligand exchange mechanisms, methylmercury is transferred from plasma proteins to the low molecular weight thiols glutathione and cysteine (EFSA, 2012).

14. It is believed that methylmercury can cross membranes by passive diffusion, by forming a complex with L cysteine and, by mimicking the transport of L-methionine due to their structural similarity, be transported via amino acid transporters. Additionally, Methylmercury L-cysteine and glutathione complexes might also be transported by organic anion transporters. (EFSA, 2012; EPA,1997). Methylmercury can cross the mammary gland, is excreted in milk and thus can reach the child during breastfeeding. In human milk, a mean of 26 - 63 % of total mercury was found to be methylmercury, however the proportion can rise with increased methylmercury intake (EFSA, 2012). Moreover, methylmercury is able to cross the hair follicle, the placenta and the blood-brain barrier, allowing accumulation in hair, the fetus and the brain. The ratio of hair to maternal blood level (mg/L) is estimated at 250:1(COT,2004).

15. Fetal distribution is similar to maternal distribution, although fetal methylmercury levels in erythrocytes and total mercury levels in brain may be higher. This is probably because binding of methylmercury to the erythrocytes retards its entry into the brain, thus the erythrocytes to plasma ratios correlate with the blood to brain ratios (EFSA, 2012). Fetal brain mercury levels are approximately 5-7 times higher than in maternal blood. Cord blood concentrations are reported to be 25% higher than maternal blood concentrations, based on comparisons to hair levels (COT, 2004).

Metabolism

16. Partial demethylation of MeHg occurs in mammals in the presence of reactive oxygen species. In the liver, these may be formed through the involvement of nicotinamide adenine dinucleotide phosphate (NADPH) cytochrome P450 reductase (Suda and Hirayama, 1992). Apart from the liver, demethylation occurs predominantly in the intestinal tract, the spleen, and to a lesser extent in phagocytic cells and slowly in the brain. Thus, mercuric mercury in the brain is generally the

result of either in situ dealkylation of organic mercury species, including methylmercury, or oxidation of elemental mercury. Demethylation also cannot be excluded in other tissues, including the kidney and the gallbladder.

Excretion

17. The half-life of MeHg in humans is approximately 70-80 days. Steady state is achieved within a year (COT, 2004). Excretion predominantly occurs via the faecal route, which accounts for 90% of excreted MeHg. Elimination of MeHg in humans is via the biliary route. MeHg is conjugated with glutathione by liver glutathione transferases. The conjugate is then excreted via the faeces. MeHg undergoes enterohepatic cycling. It is partly converted to mercuric mercury via the intestinal microflora. Mercuric mercury is less effectively absorbed; and thus excreted via the faeces.

18. Elimination of mercury in suckling animals is lower than that of adults. Based on a study by Doherty and Gates the excretion rate of mercury in suckling rodents was less than 1% than adults. This remained low until lactation day (Sundberg *et al.,2000).*

Toxicity

19. The toxic effects associated with consumption of methylmercury have been extensively investigated. Oral exposure of laboratory animals to methylmercuric chloride at doses of > 0.5 mg /kg bw per day, expressed as mercury, has resulted in damage to the kidneys, stomach and large intestine, changes in blood pressure and heart rate, as well as adverse effects on sperm and male reproductive organs. In addition, several studies have reported an increase in embryonic lethality, decrease in fetal body weight and teratogenicity in rats (cleft palate, vertebral defects, histological abnormalities in the cerebellum, effects on lachrymal glands and ribs).

20. 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 as a result of exposure to methylmercury (JECFA, 2004; EFSA, 2012). This makes pregnant women a susceptible population. Because of the long half-life of MeHg and the fact that steady state is achieved within a year, the blood concentration of methylmercury at the time of becoming pregnant depends on the exposure to methylmercury during the preceding year (COT, 2004).

21. Methylmercury exposure via breast milk appears to have less serious consequences than prenatal exposure (COT, 2004). Prenatal exposure to methylmercury dicyandiamide resulted in more serious effects on the offspring compared to postnatal exposure on the survival and weight gain in 129SvS1 mice (Spyker and Spyker, 1977).

22. Dietary factors that have been proposed to reduce or prevent methylmercury toxicity include n-3 long chain polyunsaturated fatty acids (LCPUFAs), selenium, iodine, choline and vitamin E. Numerous *in vitro* and *in vivo* studies exist, but are not discussed in detail here. The most extensively studied substance in food, regarding

mechanisms of confounding, is selenium. Mercury binding affinity for selenium is a million times higher than its binding affinity for sulphur in analogous forms and attempts have been made to identify detoxification products, which contain selenium and mercury (e.g. mercury-selenide). Whether those compounds really detoxify the mercury species has never been demonstrated. Besides a sequestration of mercury, potential protective modes of action of selenium against methylmercury toxicity include antioxidant effects, increased glutathione peroxidase activity, glutathione synthesis, high selenoprotein levels and increased demethylation of methylmercury. Mechanistically, Docosahexaenoic acid (DHA) seems to protect against methylmercury-induced oxidative stress in neuronal cells. Additionally, in neuronal cell lines and primary cells a pre-treatment with DHA was associated with decreased cellular methylmercury bioavailability. (EFSA, 2012)

Derivation of Health-based Guidance Value (HBGV), JECFA (2004):

23. The basis for establishing the 2004 JECFA evaluation were the human epidemiology studies from Faroe Islands, the Seychelles and New Zealand. The assessments were made on the basis of the evaluations of children at 7 years of age in the Faroe Islands, 5.5 years of age in the Seychelles and 6 years of age in New Zealand.

24. Concentration of mercury in maternal hair and/or the cord blood were used as biomarkers for exposure to methylmercury *in utero*. The Committee confirmed the suitability of cord blood concentration as biomarker for short-term exposure and of maternal hair concentration as a biomarker for longer-term exposure to mercury.

25. A No Observed Effect Level (NOEL) for neurobehavioural effects of 15.3 mg/kg mercury in maternal hair was established in the Seychelles study. A mathematical analysis of the concentration to response relationship was used to determine a benchmark-dose lower confidence limit ($BMDL_{05}$) of 12.0 mg/kg mercury in maternal hair in the Faroe Islands. For New Zealand, the mercury in maternal hair concentration for one child (from a total of 237) was 86 mg/kg, which was more than 4 times the next highest concentration in the study sample. This resulted in a great disparity between the BMDL value when that result was included (17-24 mg/kg), versus omitting the result for that particular child (7.4-10 mg/kg). Due to the high uncertainty regarding which was the most valid BMDL value to use, it was decided not to include the New Zealand cohort results in establishing the HBGV. The committee noted that inclusion of the New Zealand results did not materially alter its evaluation.

26. An average of the NOEL and $BMDL_{05}$ from the Seychelles and Faroe Island studies was used (14 mg/kg mercury in maternal hair) as an estimate of the concentration of methylmercury in maternal hair that reflects exposures that would have no appreciable effect on the offspring in these two study populations.

27. The methylmercury in maternal hair concentration was converted to mercury in maternal blood using an average overall ratio of 250. Based on this factor, the methylmercury in maternal blood that would be expected to have no appreciable adverse effects on the offspring was calculated to be 0.056mg/L.

28. By use of a one-compartment toxicokinetic model as described in formula (WHO, 1990), the JECFA calculated the steady state concentration in blood related to an average daily intake of mercury. JECFA incorporated some refinements in the parameters used by the WHO in order to better reflect the situation in pregnant women. The following parameters were used by the JECFA:

$$d = \frac{C \times b \times V}{A \times f \times bw}$$

Where:
d=daily dietary mercury intake (µg/kg bw/day)
C=mercury concentration in maternal blood
b=elimination rate constant (0.014per day^{-1})
V=blood volume (9% of body weight for a pregnant female)
A=fraction of the dose absorbed (0.95)
f=the absorbed fraction distributed to blood (0.05)
bw=body weight (65kg for a pregnant female)

29. From the above equation, the resulting value of 1.5 µg/kg bw/day steady state daily ingestion of methylmercury would result in a maternal blood mercury concentration that would have no appreciable adverse effects on the offspring in the two study populations.

30. A data derived factor of 2 for variation in hair to blood ratio was applied by JECFA. Interindividual variation in toxicokinetics when converting the concentration of mercury in blood to an estimated daily intake was taken into account by a standard factor of 3.2($10^{0.5}$). This resulted in an overall uncertainty factor of 6.4.

31. Following application of the uncertainty factor, the PTWI of 1.6 µg/kg bw was established.

Derivation of HBGV, EFSA (2012)

32. The CONTAM Panel evaluated any other available studies since their 2004 evaluation, in which the PTWI established by JECFA was also adopted. The Panel referred to one study in rats on developmental immunotoxicity (Tonk *et al.,* 2010) which indicated effects at low doses and the $BMDL_{05}$ for reduction in antibody response was 0.01 mg/kg bw/day expressed as methylmercuric chloride (0.008 mg/kg bw/day expressed as mercury). The BMD was below the lowest dose tested. The Panel decided that this data had to be confirmed and therefore did not identify any new experimental animal studies that could provide a better basis than the human data for the establishment of a HBGV.

33. The biggest change since the evaluation of 2004 was new information of cofounding beneficial factors in fish on associations between prenatal methylmercury exposures and neurodevelopmental endpoints.

34. Results from Nutrition Cohort 1 of the Seychelles Child Development and Nutrition Study (SCDNS) suggested an effect at age 9 and 30 months but not at 5 years related to prenatal methylmercury exposure. The Nutrition study examined associations between methylmercury, maternal nutrition and children's scores on the

Bayley's scale of infant development-II test. The results at 9 and 30 months examinations indicated that the positive effects from n-3 long chain polyunsaturated fatty acids (n-3 LCPUFAS) intake no longer outweighed detrimental effects from methylmercury exposure, at a mercury concentration in maternal hair of above 11 mg/kg hair. The results from the Main Cohort were not adjusted for n-3 LCPUFA and the Panel noted that based on the newest data, the previous interpretation of the main Seychelles cohort that there were no effects on children's cognitive development should be reconsidered.

35. The CONTAM panel found that a methylmercury concentration of 11 mg/kg in maternal hair was an apparent NOEL which had been adjusted for maternal blood concentration of n-3 LCPUFA and which formed a better point of departure than the unadjusted figure of 15.3 mg/kg methylmercury in maternal hair derived from the Seychelles main cohort.

36. For the Faroe Islands cohort, the Panel took into consideration cofounding exposure by PCB which was found to be weak when analysing results from Cohorts 1 and 2 together. There was some evidence for cofounding by the beneficial effects of maternal fish consumption, however the evidence was stronger in the Seychelles cohort. Thus, the Panel could not identify a more appropriate point of departure from the $BMDL_{05}$ selected by JECFA.

37. Based on the above, a maternal hair methylmercury concentration of 11.5 mg/kg (the mean of the two values) was used as an estimate of the concentration of methylmercury in maternal hair that reflects exposures that would have no appreciable effect on the offspring in these two study populations.

38. A factor of 250 was used to convert this to an equivalent concentration of mercury in maternal blood of 46µg/L. The Panel did not identify studies providing a sufficient basis to change the parameter of the one-compartment toxicokinetic model as described in paragraph 28 or the uncertainty factors used in the JECFA evaluation (paragraph 30).

39. Output from the one-compartment toxicokinetic model determined a maternal blood mercury level to a daily dietary mercury intake of 1.2 µg/kg bw. By applying a total uncertainty factor of 6.4 to this result, the CONTAM panel established a TWI for methylmercury of 1.3 µg/kg bw expressed as mercury.

40. The Panel noted that this TWI provided a margin of about 40 compared to the $BMDL_{05}$ reported by Tonk *et al.* (2010) in rats.

Studies following EFSA's 2012 review:

41. A literature search was carried out in order to locate any new data published since the 2012 EFSA review.

Faroe Islands cohort

42. In 2016, reports from the Faroese cohort follow up were reported at age 22 (Debes *et al., 2016*), where 847 cohort members (83%) participated in the clinical examinations. All cohort members underwent physical examination and completed a

questionnaire on past medical history and current health status to determine any diagnoses that might affect the subject's psychological performance. Of the cohort members examined, 31 were excluded from the analyses due to neurological diagnoses and two due to psychiatric diagnoses, thus rendering a total of 814 study subjects for analysis. Concomitant methylmercury exposure was determined from mercury analysis of the subject's whole blood and hair. Postnatal exposures were very low and considered negligible compared to the prenatal exposure.

43. The test battery was classified and categorized by the taxonomy used in the Cattell-Horn-Carroll Three Stratum Theory (CHC-theory) of intelligence under eight broad ability domains. The latent first-order factors reflecting these domains were Gf (Fluid Reasoning, often referred to as fluid intelligence), Gc (Comprehension-knowledge, often referred to as crystallized intelligence), Gv (Visual processing), Gsm (Short-term memory), Glr (Long-term storage and retrieval), Gs (Cognitive processing speed), Gt (Decision and reaction speed), Gps (Psychomotor speed). Tests included the Boston Naming Test (BNT), Continuous performance test (CVLT) and the different variations of Woodcock-Johnson III Tests of Cognitive abilities (WJ III) amongst others. For analysis, the following covariates were chosen as based on previous examinations at ages 7 and 14 years: age, sex, maternal fish intake during pregnancy (number of fish dinners per week), maternal Raven score, employment of mother and father at age 14, school grade at age 14, tested in Faroese (or Danish), examination in the morning or the afternoon, PCB exposure [log (PCB concentration in cord blood)] and lead exposure [log (lead in cord blood)]. Multiple regression analysis was used to evaluate the effect of prenatal methylmercury exposure (as measured in cord blood and maternal hair) on cognitive development. Additionally, structural equation models were used for evaluation as follows: a brief higher order structural model (Fig.1, Annex C) whereby the general intelligence factor (*g*) was reflected in two broad first-order factors: Gc and Gf. *g* was affected by a latent variable for prenatal exposure to methylmercury (cord blood and maternal hair used as indicators of exposure) and with the manifest test variables corrected for a set of covariates. A second, higher-order broad structural model (Fig.2, Annex C) was also constructed, where the latent variable for prenatal methylmercury exposure affected the second-order factor *g* which was reflecting in the results of all domains. The model was corrected for local dependence of highly similar tests and covariates were entered into the model to correct manifest test variables. This model produced a small negative standardized residual (-0.047) for Gf, and a standardized coefficient slightly above one (1.023) for the path from g to Gf. After fixing the negative residual to zero, the coefficient from g to Gf then necessarily became 1.000, meaning that there was identity between g and Gf, thereby rendering either of the two redundant. Due to the identity occurring between *g* and Gf, the measurement model was redefined, and the indicators for Gf were taken for indicators of Gv instead. Finally, a first order structural model was used. This was a modified version of the model described above, without the *g* factor, and with prenatal methylmercury affecting every orthological first order factor.

44. The multiple regression results confirmed the associations with cord blood mercury for tests of verbal comprehension, BNT, Synonyms and Antonyms (Annex C, Table 1). Further, a significant negative association was found for cord blood

mercury and supraspan[1] reproduction in the first trial of CVLT. Moreover, all coefficients were in the direction of poorer performance, except for Spatial Span, which showed a slightly positive value in the forward and backward condition for mercury in cord blood. As indicated by results of the BNT and the other tests, crystallised intelligence[2] appeared to be the most affected by prenatal mercury exposure even at age 22. Parallel calculations for maternal hair-mercury showed similar patterns, although with higher *p* values (Annex C Table 2). A significant negative association was seen for Synonyms and, at a weaker level of statistical significance, Antonyms, Spatial Span forward condition, as well as the first trial of CVLT and the Long Delay Recognition. However, maternal hair was positively associated with Block Design, Face Recognition Delayed, and Decision Speed. Because the positive associations were weak and non-significant, the true direction of these associations is uncertain. When comparing to regressions without covariate adjustments, the full model generally resulted in smaller estimated mercury effects.

45. For the brief structural model, the standardised coefficient (β) of the latent mercury variable on the *g* factor was β= - 0.145 and was highly significant (p = 0.002). At a ten-fold increase of mercury exposure the performance was therefore 14.5% lower, thus indicating a strong negative association between prenatal methylmercury exposure and the general intellectual ability at 22 years of age. Inclusion of covariates only slightly modified the size of regression coefficient, strengthening it from β= -0.145 to -0.15. The β of -0.145 corresponds to a drop of 2.2 IQ points for a 10-fold increase to methylmercury exposure.

46. In the broad structural equation model, the unstandardized estimate for this the path from mercury to *g* was -0.226 (p =0 .045), thus meaning that a 10-fold increase in the latent variable for mercury reduced g by 0.2 on the scale of the Analogies subtest from WJ III. The standardized coefficient for mercury on g was -0.093, p =0.041. A statistically significant negative association was found between prenatal methylmercury exposure and general intellectual ability. Again, the covariates only slightly modified the size of the regression coefficient, weakening it from -0.11 to -0.09.

47. In the first order broad structural model, prenatal exposure to methylmercury had a negative effect on all ability domains, manifesting significantly in Gc (β=-.164, p=0.000), near significantly in Gv (β=-.093, p=0.059) and Glr (β=-.075, p=0.079) and non-significantly in all other domains.

48. Overall, cognitive deficits associated with prenatal methylmercury exposure from maternal seafood diets remained detectable in a Faroese birth cohort re-examined at age 22 years. The changes associated with a 10-fold increase in prenatal methylmercury exposure seemed fairly low in comparison with the results from previous examinations and it was thus concluded that the deficits appeared to be less serious than at previous examinations at ages 7 and 14 years.

[1] Supraspan: When material to be learn exceeds immediate memory capacity and performance relies on a stable memory store (“long-term memory”) that permits the organization and retrieval of large amounts of information (Jeneson and Squire, 2012).
[2] Crystallised Intelligence: The ability to use learned skills, knowledge and experience.

Seychelles Child Development and Nutrition Study

49. Since the EFSA report, results on the newer cohort for the nutrition study which contained a higher number of the mother-child pairs have been made available (Strain *et al., 2015).* The Nutrition Cohort 2 of the SCDNS was comprised of 1265 mother-child pairs. Mothers were recruited during their first antenatal visit (from week 14 of gestation), between January 2008 and January 2011. Mothers reported consuming an average of 8.5 fish meals per week during pregnancy, as evaluated by a Fish Use questionnaire. At delivery, maternal hair was collected to determine prenatal MeHg exposure. For polyunsaturated fatty acid (PUFA) measurements non-fasting maternal blood samples were collected at week 28 of gestation and analysed later. At the age of 20 months, the children were evaluated by the Bayley Scale of Infant Development- II (BSI-II) to evaluate the Mental Development Index (MDI) and Psychomotor Developmental Index (PDI), the Mac Arthur Bates Communicative Development Inventories (CDI) test and the Infant Behaviour Questionnaire-revised.

50. Pearson correlations between prenatal MeHg exposure and polyunsaturated fatty acid (PUFA) status were calculated and linear regression to evaluate the main and interactive effects of MeHg and PUFAs on outcomes with or without adjustment for each other. In main effects models, DHA and AA were evaluated because these PUFAs are considered to have a direct influence on brain development. In the MeHg by PUFA interaction models, tertiles of total n–3, total n–6, and the n–6: n–3 ratio[3] were used. The n-6: n-3 ratio was evaluated in models both with and without interaction with MeHg. All models were adjusted for covariates known to be associated with child development: maternal age, child age at testing, child sex, Hollingshead socioeconomic status, and number of parents living with the child (family status). In secondary regression models, results were also adjusted for mother's cognitive ability [Kaufman Brief Intelligence Test (KBIT)] and the child's home environment [Pediatric Review of Children's Environmental Support and Stimulation (PROCESS)]. These data were available on only a subset of mothers (n = 1155 for KBIT and n = 1070 for PROCESS). To evaluate whether differences in MeHg and PUFA effects between the primary and secondary models resulted from adjustment for KBIT and PROCESS or from the different sample sizes, models were also fit by using the smaller set of observations without adjusting for KBIT and PROCESS. A 2-sided α of 0.05 was used to determine statistical significance

51. Prenatal methylmercury exposure with and without adjustment for PUFAs was not associated with any score. In models including both total n-3 and total n-6 there were no statistically significant interactions between methylmercury and n-6 for any outcome. For MDI, interactions between methylmercury and n-3 PUFAs were not significant (p= 0.47, 2df test). For the PDI there was a significant methylmercury by n-3 interaction (p<0.01) indicating that the effect of methylmercury differed across tertiles of n-3 PUFAs. For the low (< 0.228mg/L) and medium (0.228-0.308 mg/L) tertiles, increasing methylmercury exposure was not significantly associated with decrease in PDI scores. However, for PDI scores at the highest tertile (>0.308mg/L)

[3] The n–6:n–3 ratio can be regarded as an indirect measure of inflammation, reflecting the potential for greater production of n–6 PUFA–derived eicosanoids, which are more proinflammatory than those derived from n–3 PUFAs. The physiologic effects of a higher n–6:n–3 ratio have been associated with increased systemic inflammation and increased risk of disease.

of PUFAs, the estimated methylmercury slope showed a significant (p<0.01) improvement in PDI scores with increasing methylmercury concentration. The methylmercury by n-3 PUFA tertile interactions were also significant (p=0.05) in secondary models adjusted for KBIT and PROCESS with similar slopes. In primary interaction models of n–6: n–3 ratio tertiles, the interactions between methylmercury and n–6/n–3 were not significant for the MDI (P = 0.93; 2 df test). For the PDI, however, there were significant MeHg by n–6: n–3 interactions (P = 0.02), indicating that the MeHg direct association differed across n–6: n– 3 ratio tertiles. However, increased MeHg exposure was significantly associated with lower scores among subjects in the highest n–6: n–3 ratio tertile (>4.496mg/L) only (P = 0.03), indicating an adverse MeHg association. The estimated MeHg slopes for MDI and PDI within n–6: n–3 ratio tertiles were similar in secondary models adjusted for KBIT and PROCESS. There were no significant direct associations between methylmercury and any of the CDI outcomes nor between methylmercury and PUFAs for any of the CDI and IBQ-R outcomes.

52. In the main effects model for PUFA associations, DHA was significantly adversely associated with the MDI score with (β = -9.73, p=0.02) or without (β=-10.11, p=0.02) methylmercury adjustment. This result conflicted with the findings of the Nutrition Cohort 1, which showed no significant effects of PUFAs on the MDI. The authors hypothesised that this might be due to an antagonistic relationship between DHA and arachidonic acid at a high DHA status (in contrast, at a low DHA status the relationship would be synergistic). The n-6: n-3 ratio was significantly associated with an improved MDI score with (β=0.38, p=0.04) or without (β=0.39, p= 0.03) adjustment for methylmercury exposure. No significant associations between PUFA and the PDI scores were observed. Higher DHA was associated with improved total gestures (p<0.01) scores when evaluating the PDI. Higher n-6: n-3 ratios were associated with poorer scores on the CDI tests: vocabulary produced (p=0.02), vocabulary understood (p<0.01) and total gestures (p<0.01). IBQ-R scores were not significantly associated with PUFA status.

53. Overall, the authors found no overall adverse association between prenatal MeHg exposure and neurodevelopmental outcomes. However maternal PUFA status as a putative marker of the inflammatory milieu appeared to modify the associations of prenatal MeHg exposure with the PDI. Increasing DHA status was positively associated with language development yet negatively associated with the MDI. They noted that these findings may indicate the existence of an optimal DHA balance with respect to arachidonic acid for different aspects of neurodevelopment.

Updates from the Main Cohort of the Seychelles Child Development Study

54. In a paper published in 2017 (van Wijngaarden *et.al, 2017)*, the updates from the Main Cohort of the Seychelles Child Development Study (SCDS)regarding methylmercury exposure impact on neurodevelopmental outcomes were discussed, at age 22 and 24 years. Neurodevelopmental tests at 22 years included the Boston Naming Test, Cambridge Neuropsychological Test Automated Battery (CANTAB), and the Profile of Mood States. At 24 years: Stroop Word-Color Test, the Barkley Adult ADHD Rating Scale, the Test of Variables of Attention, and the Finger Tapping test. The healthy behaviours survey was carried out at both ages. Primary analyses examined covariate-adjusted associations in multiple linear regression models with prenatal MeHg exposure. In secondary analyses associations with recent postnatal

MeHg exposure were examined. Covariates selected were the same or similar outcomes in this cohort at previous ages and included child sex, socioeconomic status, maternal and child IQ, and life course stress. Prenatal and postnatal exposures were modelled separately. Primary prenatal exposure models did not include recent postnatal exposure as a covariate. Secondary postnatal models did include prenatal exposure as a covariate. A two-tailed alpha level of 0.05 was used to determine the significance of independent variable effects.

55. Recent postnatal MeHg exposure in the participant's hair was lower with an average of about 5 ppm; exposure was significantly greater for men (6.57 ppm) than for women (4.05 ppm). Pre- and postnatal exposure was not associated with any of the other covariates of interest. The correlation between prenatal exposure and recent postnatal exposure was low (r = 0.11 for age 22 and r=0.07 for age 24).

56. For age 22, prenatal MeHg exposure was associated with several of the developmental outcomes assessed (5-choice reaction time, DMS % correct 12 ms delay, and SOC 5-move problem), but all regression coefficients indicated improved performance with increasing prenatal exposure. Postnatal MeHg exposure was associated with one of 26 outcomes; higher hair MeHg levels were associated with worse performance on the IED total errors adjusted measure. At age 24 there were no clear patterns of association with either prenatal or recent postnatal MeHg. Only the TOVA auditory mean response time showed improved performance with increasing prenatal MeHg exposure.

57. Overall the authors concluded that prenatal MeHg exposure at ages 22 and 24 years in the SCDS Main Cohort was not adversely associated with neuropsychological endpoints.

Other Studies

58. A smaller Italian cohort study (n=606 mother-child pairs) (Valent *et al.,* 2013) also studied the association between maternal total mercury exposure and neurodevelopment at age 18-months. The mothers had very low fish consumption (less than 2 servings of fish/week) during pregnancy and there were a number of limitations in the study(questionnaire completeness, insufficient statistical power to detect subtle Hg effects, total mercury used as proxy for methylmercury) , therefore the results are not discussed in detail.

Summary of new data

59. In summary, the data from the Faroese cohort for the follow up at age 22 are in alignment with observations from previous years. The new data indicated that the adverse effect of prenatal methylmercury exposure on cognitive development remains through young adulthood, however the deficits were less serious than those seen in younger ages. The data from the Main Cohort follow ups both at age 22 and 24 are consistent with the observations from this cohort at younger ages, as no association was found between prenatal methylmercury exposure and developmental outcomes. The data from the new, bigger cohort of the Seychelles Child Development and Nutrition Study (Nutrition cohort 2), indicate no adverse association of methylmercury with developmental outcomes for infants at the age of 20 months with or without adjustment for PUFAs in contrast to the observation from

Nutrition cohort 1. A positive association was found between prenatal methylmercury exposure and PDI performance in subjects with high n-3 PUFA blood concentrations only. For subjects whose mothers had high n-6: n-3 blood levels, increased MeHg exposure was significantly associated with lower scores on the PDI.

Methylmercury exposures in infants aged 0 to 12 months and young children aged 1 to 5 years.

Sources of methylmercury exposure

Human breast milk

60. There are limited data available on the concentration of methylmercury in breast milk. A literature search has not identified any appropriate data for methylmercury concentrations in breast milk in the UK.

61. EFSA, in their most recent review, have identified three European studies in which both methylmercury and total mercury were analysed in human milk. No new studies on methylmercury in human milk from European populations have been identified following the EFSA review. Based on the studies used by the EFSA panel, listed below, the mean contribution of methylmercury to total mercury ranged from 26 to 63 %. The mean concentration of methylmercury from the studies is 0.27µg/L

62. Valent *et al*. (2011) studied mother-infant pairs living in the region Friuli Venezia Giulia (Italy). Total mercury was measured in 77 samples of human milk with a mean concentration of 0.70 µg/kg and methylmercury in 79 samples with a mean concentration of 0.20 µg/kg. For the 77 human milk samples in which both methylmercury and total mercury were measured, the mean contribution of methylmercury to total mercury was 0.31 (median: 0.25; P75: 0.42; P100: 1.00). A statistically significant, but weak correlation was observed between methylmercury in human milk and the total fish consumption (Spearman correlation coefficient (rs) = 0.29, p = 0.085, n = 79) and fresh fish consumption (rs = 0.31, p = 0.0054, n = 79).

63. A mean concentration of 0.3 µg/kg for total mercury was established in an analysis by Miklavčič et al. (2011). Eleven human milk samples from mothers with a concentration of total mercury in hair of at least 1.0 mg/kg were also analysed for methylmercury and a mean concentration of 0.68 µg/kg was reported. Both total mercury and methylmercury were measured in nine human milk samples. Mean contribution of methylmercury to total mercury was 0.39 (Miklavčič *et al.*, 2013). No correlation was observed between total mercury concentrations in human milk and the frequency of fish consumption (rs = 0.08, 95 % confidence interval (CI): -0.04 - 0.20), but a weak correlation was observed between total mercury in human milk and calculated methylmercury concentrations in the most frequently eaten fish species (rs = 0.14; 95 % CI: 0.02 - 0.25).

64. Miklavčič *et al.* (2013) analysed total mercury in human milk from Italian, Croatian and Greek women and compared the data on human milk with a subset of the results reported by Miklavčič et al. in 2011. Methylmercury was also analysed in

the cases where total mercury concentration in the mother's hair was at least 1.0 mg/kg. The highest concentrations of total mercury in human milk were reported in Greek women (n = 44) with a median concentration of 0.6 µg/kg (range: < LOD - 12 µg/kg). Statistically significant lower concentrations were reported for Italian (n = 605), Slovenian (n = 284) and Croatian (n = 125) women, all with a median concentration of 0.2 µg/kg (Miklavčič et al., in press). The mean contributions of methylmercury to total mercury were 0.59 (0.17µg/L) in Italian women (n = 224), 0.63 (0.18 µg/L) in Croatian women (n = 26) and 0.26 (0.1µg/L) in Greek women (n = 21). The highest median methylmercury concentration (0.17 µg/kg) among women with hair mercury of at least 1 mg/kg was found in Croatian women. The authors reported a statistically significant but weak correlation for total and methylmercury in human milk from Mediterranean women (Italy, Slovenia, Croatia and Greece) and frequency of total fish consumption (total mercury: rs = 0.0977, p = 0.002, n = 1 005; methylmercury: rs = 0.1377, p = 0.027, n = 259)

65. Garcia-Esquinas et al. (2011) reported a geometric mean total mercury concentration of 0.53 µg/L (n = 100) in human milk in Spain. Total mercury in human milk was not statistically significant correlated with the presence of dental amalgam fillings and fish and shellfish consumption. A mean concentration of 0.94 µg/L was reported by Ursinyova and Masanova (2005) in Slovakia republic (n = 158) and Björnberg et al. (2005) reported a median concentration of 0.29 µg/L, 4 days postpartum and 0.14 µg/L, 6 weeks postpartum in human milk from Sweden.

66. In contrast to the above-mentioned studies, Aballe et al. (2008) reported higher mean concentrations of total mercury between 2.63 (n = 13) and 3.53 µg/L (n = 10) in samples from Rome and Venice However, the concentrations did not appear to be related to the amount of fish and fishery products consumed.

Infant formulae and food

67. Concentrations of total mercury have recently been measured in an FSA survey of metals and other elements in infant formulae and foods (e.g. commercial infant foods) (referred to as the Infant Metals Survey (FSA, 2016a), and in the composite food samples of the 2014 Total Diet Study (TDS) (FSA, 2016b).

Drinking water

68. The main chemical forms in which mercury occurs in water are elemental mercury, complexes of mercuric mercury with various inorganic and organic ligands, and organic mercury forms, mainly methylmercury and dimethylmercury. The occurrence of these chemical forms depends on the pH, redox potential and the concentration of inorganic and organic complexing agents. The contribution of methylmercury to total mercury is typically less than 5 % in estuarine and marine waters, but can be up to 30 % in fresh water (EFSA, 2012).

69. Harmonised levels for mercury in drinking water are set by Council Directive 98/83/EC.17 The Directive stipulates that Member States set limit values of 1 µg/L for mercury in water intended for human consumption. Commission Directive 2003/40/EC18 also sets a maximum limit for mercury in natural mineral water of 1 µg/L.

70. Levels of mercury in drinking water in 2016 from England and Wales, Northern Ireland and Scotland were provided by the Drinking Water Inspectorate (DWI), Northern Ireland Water and the Drinking Water Quality Regulator for Scotland, respectively. Median and 97.5th percentile values calculated from this data are shown in Table 1. These values represent the concentration of mercury in public water supplies.

Table 1. Median and 97.5th percentile concentrations (µg/L) of mercury in water across the UK for 2016, all mercury in water is assumed to be methylmercury.

Country	Number of samples	Limit of Detection (µg/L)	Median concentration (µg/L)	97.5th Percentile concentration (µg /L)
England and Wales	8851	<0.00002 - <0.1*	0.03	0.1
Northern Ireland	395	0.01	0.01	0.05
Scotland	16424	0.02	0.03	0.03

* The DWI noted that the water companies had reported a range of LODs that varied with the analytical method used, and clarified that the relevant drinking water regulations specify that the LOD must not be more than 10% of the prescribed value 1 µg /L for mercury).

Environmental

Soil

71. Mercury is most commonly encountered in the environment in elemental form, as inorganic mercuric (Hg^{2+}) compounds, or as monomethylmercury compounds with the general formula, CH3HgX.2 The most important source of mercury is the naturally occurring mineral, cinnabar (HgS). Monomethylated mercury compounds are most likely to be found in soil as a result of natural microbial transformation of inorganic mercury (Environmental Agency, 2009).

72. In surface soils, about 1–3 per cent of total mercury is in the methylated form with the rest predominantly as Hg^{2+} compounds (Environmental Agency, 2009).

73. In 2012 and 2013, the Defra published normal background concentrations (NBCs) for mercury in soil in England and Wales (Defra, 2012 and 2013). An NBC is the 95th percentile upper confidence interval of the available data; it is defined as a contaminant concentration that is seen as typical and widespread in top-soils (depth 0 - 15 cm). In order to establish meaningful NBCs, the available soil data were grouped in domains (e.g. principal, urban, and ultrabasic) that were defined by the most significant controls on a contaminant's high concentrations and distribution. The NBCs for each domain in England and Wales were published following a Defra-commissioned BGS project to define the typical background concentrations for soil contaminants.

74. As part of the BGS project, summary statistics were derived from topsoil data from 2 or 3 core datasets held for England and Wales (Ander *et al*., 2012 and 2013). Although the NBCs and summary statistics were derived for several domains for England and Wales, the most significant domain for each country was the principal domain. The principal domains are areas which do not contain significantly elevated levels of mercury. Overall, for England and Wales, the area covered by the principal domains constitutes approximately 99% and 94% of each country respectively. The summary statistics reported for the principal domain in England were a median of 0.12 mg/kg and a 95th percentile (upper-confidence interval) of 0.5 mg/kg (n = 1126 samples). The statistics reported for the same domain in Wales were a median of 0.09 mg/kg and a 95th percentile (upper confidence interval) of 0.25 mg/kg (n = 104 samples). No relevant data were available for methylmercury concentrations in dust.

Air

75. Mercury is naturally emitted from land and ocean surfaces as elemental mercury. Anthropogenic sources result in the emission of elemental mercury, mercuric mercury and particle-bound mercury. In general, elemental mercury is the predominant form of mercury in the atmosphere (EFSA,2012).

76. Based on a study by the European Commission (2011), the concentration of methylmercury in the air is very low (1-20 pg/m^3). Methylmercury is present in the air in trace amounts and therefore exposure to methylmercury via the air is negligible and therefore not presented

Exposure assessment

77. Consumption data from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) (DH, 2013), and from years 1-4 of the National Diet and Nutrition Survey Rolling Programme (NDNS) (Bates *et al.*, 2014) have been used for the estimation of dietary exposures. Bodyweight data used in the estimation of mercury exposures are shown in Table 2 below.

78. Thorough exposure assessments have been performed for the dietary sources of exposure to mercury, which is the main route of exposure for this metal. The assessments for the non-dietary sources of exposure (i.e. soil) have been included to give a more holistic view of exposures, but are not as thorough as they are not the main focus of this statement.

Table 2. Average bodyweights used in the estimation of methylmercury exposures

Age group (months)	Bodyweight (kg)
0 to <4	5.9[a]
>4 to <6	7.8[b]
>6 to <9	8.7[b]
>9 to <12	9.6[b]
>12 to <15	10.6[b]
>15 to <18	11.2[b]

>18 to <24	12.0[c]
>24 to <60	16.1[c]

[a] DH, 1994
[b] DH, 2013
[c] Bates *et al*., 2014

Infants (0 to 12 months)

Breast milk

79. As no consumption data were available for exclusive breastfeeding in infants aged 0 to 6 months, the default consumption values used by COT in its evaluations of the infant diet of 800 and 1200 mL for average and high level consumption. In accordance to the approach followed by EFSA in their 2012 evaluation, the data for methylmercury occurrence in human milk, as reported in the literature were used to calculate exposure from breastfeeding (Table 3).

80. The values are calculated as µg/ kg bw/week to allow for direct comparisons with the TWI. The lowest and highest mean values of methylmercury in human milk are used for the evaluation. These are 0.1µg/L (Miklavčič *et al.* ,2013) in samples from Greek women and 0.68 µg/L (Miklavčič et al., 2011) in samples from Slovenian women, as a worst case exposure scenario for exclusively breastfed infants.

Table 3. Estimated methylmercury exposure from exclusive breastfeeding in 0 to 6 month old infants, with breast milk containing total methylmercury at 0.1µg/L and 0.68 µg/L.

Methylmercury concentration (µg/L)	**Exposure (µg/kg week)**			
	Average consumer (800 mL/day)		**High consumer (1200 mL/day)**	
	0 to <4 months	**>4 to <6 months**	**0 to <4 months**	**>4 to <6 months**
0.1	0.095	0.072	0.14	0.11
0.68	0.65	0.49	0.97	0.73

Values rounded to 2 significant figures (SF)

81. Data on breast milk consumption for infants aged 4 to 18 months were available from the DNSIYC, and have been used to estimate exposures at these ages (Table 4), based on a lower and higher mean methylmercury concentrations of 0.1µg/L and 0.68 µg/L respectively. There were too few records of breast milk consumption for children older than 18 months in the NDNS to allow a reliable exposure assessment, and breast milk is expected to contribute minimally in this age group.

82. The exposures are calculated as µg/kg bw/week to allow direct comparison with the TWI.

Table 4. Estimated methylmercury exposure in 4 to 18 month old infants from breast milk.

Exposure (µg/kg bw/week)	Age group (months)				
	4 to <6	6 to <9	9 to <12	12 to <15	15 to <18
Mean (0.1µg/L)	0.064	0.047	0.027	0.021	0.018
97.5th percentile (0.1µg/L)	0.11	0.11	0.081	0.053	0.036
Mean (0.68µg/L) mercury	0.43	0.32	0.18	0.14	0.12
97.5th percentile(0.68µg/L)	0.73	0.76	0.55	0.36	0.25

Values rounded to 2 SF

Infant formulae and complementary foods

83. Exposure estimates for this category were derived using occurrence data for total mercury from the Infant Metals Survey (FSA, 2016a). Exposure estimates for 0 to 6 month olds were calculated for exclusive feeding on infant formulae using the default consumption values of 800 and 1200 mL (Table 5). Consumption data from the DNSIYC were used to estimate exposures for 4 to 12 month olds (DH, 2013) In 0 to 6 month olds, exposures to total mercury from ready-to-feed formula were 0 to 0.21 µg/kg bw/week in average consumers, and 0 to 0.28 µg/kg bw/week in high level consumers. Exposures to total mercury calculated for reconstituted formula incorporating the water concentration from the TDS, and the highest median and 97.5th percentile concentrations for total mercury in water reported in Table 1 were 0 to 0.28 µg/kg bw/week in average consumers, and 0 to 0.42 µg/kg bw/week in high level consumers (Table 5).

Table 5. Estimated average and high level exposures to total mercury from exclusive feeding on infant formulae for 0 to 6 month olds.

Infant Formula	Mercury Exposure (µg/kg bw/week)			
	0 to <4 months		4 to <6 months	
	Average consumer (800 mL/day)	High level consumer (1200 mL/day)	Average consumer (800 mL/day)	High level consumer (1200 mL/day)
Ready-to-Feed [a]	0-0.21	0-0.28	0-0.14	0-0.21
Dry Powder [b, c]	0-0.14	0-0.21	0-0.14	0-0.14
Dry Powder [c] + TDS water of <0.2 µg/L [d]	0-0.28	0-0.42	0-0.21	0-0.35
Dry Powder [c] + median	0-0.14	0-0.25	0-0.14	0-0.14

water of 0.03 µg/L [d]				
Dry Powder [c] + 97.5th percentile water of 0.1 µg/L [d]	0-0.21	0-0.28	0-0.14	0-0.21

Values rounded to 2 SF

[a] Exposure based on first milk infant formula mercury concentrations of 0 (lower-bound) and 1.0(upper-bound) µg/L
[b] Exposure does not include the contribution from water
[c] Exposure based on first milk dry infant formula using mercury concentrations of 0 (lower-bound) and 0.2 (upper-bound) µg/kg
[d] Calculated assuming reconstituted formula comprises 85% water

84. Total upper-bound (UB) mean exposures (excluding water) to total mercury from infant formulae, commercial infant foods, and other foods, for 4 to 12 month olds were 0.064 to 0.25 µg/kg bw/week, and 97.5th percentile exposures were 0.36 to 1.1 µg/kg bw/week. Detailed exposure assessments for 4 to 18 month old infants and young children are provided in Annex A. Total mean and 97.5th percentile exposures were also calculated using the highest median and 97.5th percentile concentrations for mercury in water reported in Table 1. The resulting total mean and 97.5th percentile exposures indicated that levels of mercury in water made a minimal contribution to total exposures (Table 6).

Table 6. Estimated exposures to total mercury from infant formulae, commercial infant foods and other foods for 4 to 12 month olds.

	Mercury Exposure (µg/kg bw/week)					
Food	**4 to <6 Months (n=116)**		**6 to <9 Months (n=606)**		**9 to <12 Months (n=686)**	
	Mean	**97.5th**	**Mean**	**97.5th**	**Mean**	**97.5th**
Infant formula	0-0.091	0-0.20	0-0.077	0-0.015	0-055	0-0.13
Commercial infant foods	0.0084-0.040	0.056-0.17	0.012-0.057	0.070-0.24	0.013-0.051	0.091-0.22
Other foods	0.0091-0.029	0.054-0.15	0.070-0.12	0.67-0.7	0.15-0.22	0.98-1.1
Total (excl. water)	0.023-0.064	0.22-0.36*	0.084-0.16	0.67-0.77*	0.17-0.25	0.98-1.1*

Values rounded to 2 SF

* Determined from a distribution of consumption of any combination of categories rather than by summation of the respective individual 97.5th percentile consumption value for each of the three food categories

Children aged 12 to 18 months

85. Estimated exposures to total mercury from food for children aged 12 to 18 months were calculated using occurrence data from both the Infant Metals Survey (FSA, 2016a), and the 2014 TDS (FSA, 2016b). The exposure data derived from the Infant Metals Survey allow estimation of mercury exposure in infant formula, commercial infant foods and the most commonly consumed adult foods ('other

foods') as sold, whereas the results from the TDS are based on analysis of food that is prepared as for consumption. In addition, the Infant Metals Survey included analysis of infant formulae and commercial infant foods which are not included in the TDS.

86. The consumption data from the DNSIYC were used for the estimation of exposure for children aged 12 to 18 months (DH, 2013).

Exposure estimates based on the Infant Metals Survey

87. The ranges of total UB mean and 97.5th percentile exposures (excluding water) to total mercury from infant formula, commercial infant foods and other foods were 0.25 to 0.29 and 0.98 to 1.1 µg/kg bw/week, respectively. Total mean and 97.5th percentile exposures were also calculated using the highest median and 97.5th percentile concentrations for mercury in water reported in Table 1. The resulting total mean and 97.5th percentile exposures indicated that levels of mercury in drinking water made a minimal contribution to total exposure (Table 7).

88. Table 7. Estimated exposures to total mercury from infant formulae, commercial infant foods and other foods in children aged 12 to 18 months.

Food	**Mercury Exposure (µg/kg bw/week)**			
	12 to <15 Months (n=670)		**15 to <18 Months (n=605)**	
	Mean	**97.5th**	**Mean**	**97.5th**
Infant formula	0-0.021	0-0.098	0-0.012	0-0.07
Commercial infant foods	0.0052-0.031	0.051-0.18	0.0026-0.016	0.039-0.11
Other Foods	0.2-0.32	0.98-1.1	0.18-0.29	0.91-1.1
Total (excl. water)	0.2-0.29	0.98-1.1 *	0.18-0.25	0.91-0.98*

Values rounded to 2 SF
* Determined from a distribution of consumption of any combination of categories rather than by summation of the respective individual 97.5th percentile consumption value for each of the three food categories

Exposure estimates based on the TDS

89. Table 8 shows the estimated exposures calculated using the TDS data for children aged 12 to 18 months. The mercury concentration for the tap water group in the TDS was reported to be <0.2 µg/L (the LOD). Exposure calculations were also performed using the highest median (0.03 µg/L) and 97.5th percentile (0.1 µg/L) total mercury concentration in tap water reported in Table 1.

90. Total UB mean and 97.5th percentile exposures to mercury from a combination of all food groups are in the region of 0.7 and 2.0µg/kg bw/week,

respectively (Table 8). These are higher than those estimated from the Infant Metals Survey due to the inclusion of a greater number of foods in the exposure estimate for the TDS. Overall the figures in Table 8 demonstrate that the mercury content of drinking water, even when present at the highest 97.5th percentile value does not increase the total dietary exposure to mercury in young children in the UK.

Table 8: Estimated dietary exposure to mercury based on the TDS data in children aged 12 to 18 months

Mercury concentration in the water µg/L	**Mercury Exposure (LB-UB Range) (µg/kg bw/week)**			
	12 to <15 Months (n=670)		**15 to <18 Months (n=605)**	
	Mean	**97.5th**	**Mean**	**97.5th**
<0.2 (TDS)	0.35-0.70	1.5-1.9	0.28-0.70	1.5-2.0
0.03 (highest median)	0.35-0.70	1.5-1.9	0.28-0.70	1.5-2.0
0.1 (highest 97.5th percentile)	0.35-0.70	1.5-1.9	0.28-0.70	1.5-2.0

Values rounded to 2 SF

91. In general, the food group making the highest contribution to total mercury exposure were fish, with all other categories making a minimal contribution to total exposure (FSA, 2016b). The contribution of fish to total dietary mercury exposure is discussed further in paragraph 96.

Children aged 18 months to 5 years

92. Exposure estimates for these age groups were derived using occurrence data for total mercury from the 2014 TDS, and consumption data from the NDNS (Bates *et al.,*2014).

93. Table 11 shows the mercury exposures that were calculated using the TDS data for children aged 18 months to 5 years. Detailed exposure assessments are presented in Annex B. As described in paragraph 93, the exposures have been estimated using the TDS water concentration 0.2 µg/L), and the highest median (0.03 µg/L) and 97.5th percentile (0.1 µg/L) mercury concentrations in water reported in Table 1. This results in total UB mean and 97.5th percentile exposures to mercury from a combination of all food groups of between 0.63 and 0.84 and 1.5 to 2.0µg/kg bw/week, respectively (Table 9). Overall the figures in Table 9 demonstrate that the mercury content of tap water does not result in an increase in total dietary exposure to mercury.

Table 9: Estimated dietary exposure to total mercury in children aged 18 months to 5 years.

Mercury concentration in water µg/L	**Mercury Exposure (LB-UB Range) (µg/kg bw/week)**			
	18 to <24 Months (n=70)		**24 to <60 Months (n=429)**	
	Mean	**97.5th**	**Mean**	**97.5th**
<0.2 (TDS)	0.42-0.84	1.6-2.0	0.28-0.63	1.2-1.5
0.03 (highest median)	0.42-0.84	1.60-2.0	0.28-0.63	1.20-1.50
0.1 (highest 97.5th percentile)	0.42-0.84	1.60-2.0	0.28-0.63	1.20-1.50

Values rounded to 2 SF

94. As with the younger children, the food groups making the main contribution to mercury exposure in the TDS were fish (FSA, 2016b).

Exposure from fish

95. As the main source of methylmercury in the diet is fish, a summary table (Table10) is used to indicate exposure to mercury from fish from the TDS. Contribution of other food groups to exposure to total mercury in the TDS are shown in Annexes A and B.

Table10: Summary of mercury exposure from fish group in the TDS

Mercury Exposure from fish (µg/kg bw/week)								
Age(months)	**12 to <15**		**15 to <18**		**18 to <24**		**24 to <60**	
	Mean	**97.5th percentile**	**Mean**	**97.5th percentile**	**Mean**	**97.5th percentile**	**Mean**	**97.5th percentile**
TDS	0.32	1.5	0.30	1.5	0.40	1.6	0.31	1.2

Soil/dust

96. Potential exposures of UK infants aged 6 to 12 months and young children aged 1 to 5 years to methylmercury in soil and dust were calculated assuming ingestion of 60 or 100 mg/day, respectively (US EPA, 2011a). Children of these age groups are likely to consume more soil and dust than younger infants who are less able to move around and come into contact with soil and dust. Median and 95th percentile soil mercury concentrations of 0.12 and 0.5 mg/kg respectively were used in these exposure estimations (paragraph 74), and it has been assumed that 3% of mercury is present as methylmercury (paragraph 72). The resulting median and 95th

percentile concentrations for methylmercury in the soil are: 3.6 and 15 µg/kg respectively.

97. Data specific to dust were not available therefore for the purposes of this evaluation, it is assumed that they could be similar to soil in a relatively conservative exposure estimate. Exposures are estimated as µg/kg bw/ week to allow for direct comparison to the TWI.

Table 11: Possible methylmercury exposures from soil and dust in infants and young children aged 6 months to 5 years.

Methylmercury concentration (µg/kg)	Exposure (µg/kg bw/week)					
	Age (months)					
	6 to 9	9 to 12	12 to 15	15 to 18	18 to 24	24 to 60
3.6 (Median)	0.00017	0.00016	0.00024	0.00023	0.00021	0.00016
15 (95th percentile)	0.00072	0.00066	0.00099	0.00094	0.00088	0.00065

Values rounded to 2 SF

Risk Characterisation

98. Potential risks from the exposure of infants and young children to methylmercury were characterised by comparing dietary exposures to the TWI of 1.3µg/kg bw set by EFSA

99. Based on the data presented in table 1, soil makes a minimal contribution to exposure to methylmercury relative to dietary sources.

100. Similarly, water does not significantly contribute to overall mercury exposure, as estimated dietary exposures to mercury when using the highest median and 97.5th percentile values reported from the water companies are the same as those calculated using the value for mercury in water from the TDS.

101. When considering the toxicity of methylmercury, exclusively breast-fed infants are a potential vulnerable group, as methylmercury can be transferred via maternal milk. For infants aged 0-6 months that are exclusively breast-fed exposures to methylmercury were below the TWI, even for the high consumer group, assuming the highest value of methylmercury in human milk reported in the literature (0.97 µg/kg bw/week for the highest 97.5th percentile of the high consumer group). The same is true for infants between 4-<18 months of age that are non exclusively breast fed.

102. For the Infant Metal Survey and the TDS, total mercury was measured. Apart from fish and shellfish, methylmercury does not contribute significantly to other food categories (EFSA, 2012). The contribution of methylmercury to total mercury in fish is extremely variable. The JECFA reported contribution of methylmercury to total mercury generally ranged between 30 % and 100 %, depending on species of fish, size, age and diet (FAO/WHO, 2011a), with some cases the contribution being as low as 10% (EFSA, 2012).

103. The exposures calculated for children between 0 to <6 months of age that are exclusively fed with infant formula are significantly lower than those that are breast fed either exclusively or non-exclusively and are about 3 times lower than the TWI for methylmercury. Methylmercury is not expected to contribute to dietary mercury exposures for any other food categories apart from fish and shellfish. Exposure to methylmercury for this particular group is likely to be very low.

104. The estimated dietary exposures to mercury for the age groups of 4 to 12 and 12-18 months are below the TWI for methylmercury as well as the TWI for inorganic mercury (4.0 µg/kg bw/d) established by EFSA, based on the Infant Metals Survey data.

105. This is not the case for exposures based on the TDS data, where exceedance of the TWI for methylmercury occurred at the 97.5th percentile for the age groups of 12 to <15 months, 15 to <18, 18 to <24 and 24 to <60 months. The values were within the TWI for inorganic mercury. Since the main source of methylmercury in the diet is fish, it would be extremely conservative to compare total mercury dietary exposures to the TWI for methylmercury.

106. For this reason, the summary table (Table10) was compiled to allow for evaluation of the contribution of fish to the total mercury exposures. From the table, and taking a conservative approach by assuming 100% of the mercury will be methylmercury, the data from the TDS for the 97.5th percentile for the age groups of 12 to<15, 15 to <18 and 18 to <24 months would marginally exceed the TWI of 1.3µg/kg bw/week (by 0.2 µg/kg bw/week for the ages between 12 to <18 months of age and by 0.3 µg/kg bw/week for the age group of 18 to <24 months). The total dietary mercury exposures for high consumers (from the TDS) for children between 2 to 5 years of age are 1.2-1.5 µg/kg bw/week, however for the fish category, and assuming that 100% of the mercury is methylmercury, the exposure is below the TWI (1.2µg/kg bw/week).

107. As mentioned in paragraph 103, the contribution of methylmercury to total mercury in fish varies extremely, depending on the age, size and diet of the fish (*i.e.* large, predatory fish will have higher methylmercury concentration than smaller fish). Thus, the actual exposure to methylmercury from fish for these age groups is likely to be lower in practice.

108. At these age groups the children will also be able to eliminate methylmercury more efficiently compared to newborns, as the parts of the digestive system that are associated with elimination of methylmercury (including the gut microflora) are fully developed (EFSA, 2012).

109. Additionally, there are a number of other dietary factors that can reduce or prevent the toxicity of methylmercury (paragraph 22). A factor that should also be taken into account is the beneficial effects of fish consumption. The FAO and WHO convened a Joint Expert Consultation on the Risks and Benefits of Fish Consumption in 2010.The consultation concluded that among women of childbearing age, pregnant women and nursing mothers, considering the benefits of docosahexaenoic acid (DHA) versus the risks of methylmercury, fish consumption

lowers the risk of suboptimal neurodevelopment in their offspring compared with not eating fish in most circumstances evaluated. Among infants, young children and adolescents, the evidence was insufficient to derive a quantitative framework of health risks and benefits. They noted, however, that healthy dietary patterns that include fish consumption and are established early in life influence dietary habits and health during adult life (FAO/WHO, 2011a).

110. Data from the Nutrition Cohorts suggest that n-3 PUFAs have a positive effect on neurodevelopmental outcomes. Results from Nutrition Cohort 2 of the Seychelles study suggest that increased maternal DHA concentrations were associated with an improved CDI vocabulary understood score.

111. Although in Nutrition Cohort 1 the positive effects of n-3 PUFAs could not outweigh the negative effects of prenatal methylmercury exposure above a specific concentration, the results of Nutrition Cohort 2 showed higher PDI performance with increasing methylmercury concentration, amongst subjects with high maternal n-3 blood serum levels.

Conclusions

112. Mercury is a metal that is released into the environment from both natural and anthropogenic sources. After release into the environment, it undergoes complex transformations and cycles between atmosphere, land and aquatic systems. The three chemical forms of mercury are (i) elemental or metallic mercury (Hg0), (ii) inorganic mercury (mercurous (Hg22+) and mercuric (Hg2+) cations) and (iii) organic mercury. MeHg is by far the most common form in the food chain.

113. The general population is exposed to mercury and methylmercury through food, drinking water, soil and in trace amounts in the air. The diet, and especially fish consumption, is the main route of exposure to methylmercury. Since methylmercury tends to bioaccumulate in aquatic organisms, older, predatory fish are more likely to have higher methylmercury concentrations than smaller and/or younger fish. Infants and young children can also be exposed to methylmercury via breast milk.

114. Methylmercury is readily absorbed following oral exposure. It can accumulate in the hair and can cross the blood brain barrier, the placenta and the mammary gland. Thus it can reach the developing fetus, where it tends to accumulate in the brain and can also be transferred to infants via breastfeeding. It has a long half life and is eliminated less efficiently in newborns.

115. The main adverse effects associated with exposure to methylmercury is toxicity to the developing nervous system. Exposure of the fetus to methylmercury depends on maternal exposure up to a year prior to conception.

116. The EFSA and the JECFA have published risk assessments on exposure to methylmercury in food. In 2003, based on the results of epidemiological studies in high-fish consuming populations, the JECFA established a PTWI of 1.6µg/kg bw. In 2012, after reviewing updates on said epidemiological studies, the EFSA calculated a TWI of 1.3µg/kg bw.

117. Recent updates from these epidemiological studies have found no evidence of an adverse effect of prenatal exposure to methylmercury on cognitive development at 20 months of age for the Seychelles Nutrition cohort 2, in contrast to the results from Nutrition Cohort 1 that led to the re-evaluation of the HBGV for methylmercury by EFSA. The results from the Main Cohort were consistent with previous observations where no adverse association was found between prenatal methylmercury exposure and neurodevelopment. Reports from the Faroese cohort at 22 years of age, on the other hand, have suggested that the negative effects seen at younger ages are still seen, albeit at a lower degree as the subjects age. It should be noted, however that these epidemiological studies are carried out on high fish-consuming populations. Thus, prenatal methylmercury exposure is much higher than western populations.

118. Exclusively breastfed infants are a vulnerable group to consider in the case of methylmercury exposure, as methylmercury can be transferred to the new born via milk. The concentration in human milk will depend on maternal exposure to methylmercury. Data for methylmercury in the literature suggest that the concentrations are generally low. For two of the studies, (Miklavčič et al. 2011 &2013), methylmercury was analysed in cases where maternal total mercury exposure was high (>1mg/kg in the hair) and, considering that methylmercury accumulates in the hair, could therefore represent the cases where maternal exposure to methylmercury is high.

119. For infants of 0-6 months of age that are exclusively breastfed, exposure based on the literature data for occurrence of methylmercury in milk is below the TWI of 1.3µg/kg bw. This is also the case for the non exclusively breastfed infants from 4 to <18 months of age. In comparison, for the groups that are fed exclusively with infant formula, dietary exposure to total mercury is much lower than breastfed infants. This is not surprising, as methylmercury can be transferred in breast milk, its concentration depending on maternal exposure. In contrast, since methylmercury does not contribute to dietary mercury exposures for any other food categories apart from fish and shellfish, it is likely that the actual exposure to methylmercury in children that are exclusively fed with infant formula, is far lower.

120. Fish is one of the most significant contributors to total dietary mercury exposures both in the Infant Metal Survey and the TDS. Based on data from the TDS and a conservative assumption that 100% of the mercury in fish will be methylmercury, the TWI is marginally exceeded for the age groups of 12 to <15, 15 to <18 and 18 to <24 months of age for the high level consumers. The contribution of methylmercury to total mercury in fish varies greatly and can be as low as 10%. Larger, predator species are likely to have higher methylmercury concentrations due to bioaccumulation. However, the Government currently advices that children should avoid eating species such as shark, swordfish or marlin. Additionally, other dietary factors, such as selenium, can reduce or even prevent methylmercury exposures. In evaluating methylmercury toxicity, the risk of methylmercury exposure versus the overall health benefits associated with fish consumption should be taken into account. As noted in the earlier evaluation of Methylmercury in fish by the COT (2004), it was likely that the PTWI set by JECFA (1.6µg/kg bw) would be exceeded in younger children consuming one weekly portion of either shark, swordfish or marlin.

However, when taking into account the evidence for the beneficial effects of eating fish exceedance was not expected to result in adverse health effects.

121. Overall, methylmercury exposures for the categories of exclusively (0 to 6 months) and non-exclusively (4 to 18 months) breastfed children (0 to 6 months), as well as those exclusively fed with infant formula are below the TWI. Estimated exposures to mercury from infant formulae, commercial infant foods and other foods for 4 to 12 month olds based on the Infant Metals Survey are also below the TWI for methylmercury. Fish is a major contributor in mercury exposures, and assuming that all of the mercury in fish is methylmercury the TWI is slightly exceeded for the high consumers in the age groups of 12 to <15, 15 to <18 and 18 to<24 months old, but not for the 24 to <60 month age group. When taking into consideration the conservatism in the exposure assumption as well as the overall beneficial effects of fish consumption and other elements of the diet that can counteract methylmercury toxicity, the risk to health from the minor exceedance of the TWI is low for these groups.

Questions to be asked to the Committee

I. Do members have any comments on the updated epidemiology data?
II. Do the Committee wish to continue using the TWI established by EFSA in 2012?
III. Are members content that exposure to methyl mercury by infants and young children is not of concern?
IV. Do the Committee have any other comments on this paper?

Secretariat
January 2018

Abbreviations

BMDL - benchmark-dose Lower Confidence Limit

Boston Naming Test- BNT

BSID-II - Bayley's scale of infant development- II

bw – body weight

CANTAB - Cambridge Neuropsychological Test Automated Battery

CDI - Mac Arthur Bates Communicative Development Inventories

CNS - Central Nervous System

CONTAM - Panel on Contaminants in the Food Chain

COT – Committee on Toxicity

CVLT- Continuous performance test -CVLT

Defra – Department for Environment, Food and Rural Affairs

DHA- Docosahexaenoic acid

DNSIYC – Diet and Nutrition Survey of Infants and Young Children

DWI – Drinking Water Inspectorate

EA – Environment Agency

EC – European Commission

EFSA - European Food Safety Authority

EPA - Environmental Protection Agency

EU – European Union

FAO – Food and Agriculture Organization

FSA – Food Standards Agency

g - General Intellectual factor

g - grams

Gc - crystallized intelligence

Gf - Fluid Reasoning/fluid intelligence

Glr - Long-term storage and retrieval

Gps - Psychomotor speed.

Gs - Cognitive processing speed

Gsm- Short-term memory

Gt- Decision and reaction speed

Gv - Visual processing

IMS – Infant metals survey

JECFA – Joint FAO/WHO Expert Committee on Food Additives

KBIT- Kaufman Brief Intelligence Test

kg - kilogram

LB – Lower bound

LOD – Limit of detection

MDI - Mental Development Index

MeHg - Methylmercury

mg – milligram

mg/kg – milligrams/kilogram

mL – millilitre

MOE – Margin of Exposure

n – number

n-3 LCPUFAS - n-3 Long Chain Polyunsaturated Fatty Acids

NADPH- Nicotinamide Adenine Dinucleotide Phosphate

NBC – Normal Background Concentration

NDNS – National Diet and Nutrition Survey

NOEL- No Observed Effect Level

PDI - Psychomotor Developmental Index

PROCESS- Pediatric Review of Children's Environmental Support and Stimulation

PTWI - Provisional Tolerable Weekly Intake

PUFA – Polyunsaturated Fatty Acid

rs - Spearman correlation coefficient

SACN - Scientific Advisory Committee on Nutrition

SCDNS - Seychelles Child Development and Nutrition Study

SCDS - Seychelles Child Development Study

SF – significant figures

TDS – Total Diet Study

TWI – Tolerable Weekly Intake

UK – United Kingdom

WHO - World Health Organisation

WJ III - Woodcock-Johnson III Tests of Cognitive abilities -WJ III

µg/kg – micrograms/kilogram

µg/L – micrograms/litre

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COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Review of potential risks from Mercury in the diet of infants aged 0 to 12 months and children aged 1 to 5 years

Possible Mercury exposure from dietary sources in children aged 4 to 18 months

Two surveys were conducted during 2014 which measured the concentrations of elements in food consumed by infants (4 to 18 months) and young children (18 months to 5 years). The first survey was a survey on types of foods eaten by infants (referred to as the Infant Metals Survey), the other was a total diet study (TDS) which focused on sampling foods eaten by young children. Both studies measured the concentrations of Mercury.

The Infant Metals Survey measured the concentrations of metals and other elements in food 'as sold', in the following categories: infant formula (Table B1) commercial infant foods (Table B2), and groups of food comprising the top 50 most commonly consumed varieties of foods not specifically marketed for infants (Table B3). The results from this survey were used together with food consumption data from the Diet and Nutrition Survey for Infants and Young Children (DNSIYC) (DH, 2013) to estimate dietary exposures for children aged 4 to 18 months.

The TDS consisted of: (i) selecting foods based on food consumption data, to represent as best as possible a typical diet; (ii) their preparation to food as consumed and (iii) the subsequent pooling of related foods before analysing the composite samples for elements. The concentrations of 26 elements, including Mercury, were measured in the 2014 TDS. The composite samples for 27 food groups (Table B4) were collected from 24 UK towns and analysed for their levels of Mercury and other elements. Where appropriate, tap water was used in the preparation and cooking of food samples. The results from this survey were also used together with food consumption data from the DNSIYC (DH, 2013) to estimate dietary exposures for children aged 12 to 18 months.

Table B1. Infant formula

Infant Formula	
Dry Powder	**Made Up Formula**
First and Hungrier Milk	First Milk and Hungrier Milk
Follow On Milk	Follow On milk
Growing Up Milk	Growing up Milk
Soy Milk	
Goat Milk	
Organic Milk	

Comfort Milk	

Table B2. Commercial infant foods

Commercial Infant Foods
Cereal Based Foods and Dishes
Dairy Based Foods and Dishes
Fruit Based Foods and Dishes
Meat and Fish Based Foods and Dishes
Snacks (Sweet and Savoury)
Other Savoury Based Foods and Dishes (excluding Meat)
Drinks

Table B3. Other foods commonly eaten by infants.

Other Foods	
Beverages	Fruit Products
Bread	Green Vegetables
Canned Vegetables	Meat Products
Cereals	Milk
Dairy Products	Other Vegetables
Eggs	Potatoes
Fish	Poultry/Chicken
Fresh Fruit	

Table B4. The 27 food groups used for analysis of Mercury and other elements in the 2014 TDS

TDS Food Groups*	
Bread	Fresh Fruit
Miscellaneous Cereals	Fruit Products
Carcase Meat	Non-alcoholic Beverages
Offal	Milk
Meat Products	Dairy Products
Poultry	Nuts
Fish	Alcoholic Drinks
Fats and Oils	Meat Substitutes
Eggs	Snacks
Sugars	Desserts
Green Vegetables	Condiments
Potatoes	Tap Water
Other Vegetables	Bottled Water
Canned Vegetables	

*Food samples representative of the UK diet are purchased throughout the year in 24 towns covering the UK and 137 categories of foods are combined into 27 groups of similar foods for analysis

Exposure Assessments

Infant Metals Survey

Tables B5, B6 and B7 summarise lower- (LB) and upper-bound (UB) total dietary exposures to Mercury calculated using results from the infants Metal Survey for ages 4 to 18 months.

Table B5: Estimated Mercury exposure from infant formula in children aged 4 to 18 months using data from the Infant Metals Survey

Food Groups	Exposure- LB-UB (ug/kg bw/day)									
	4 to <6		6 to <9		9 to <12		12 to <15		15 to <18	
	Mean	97.5th Percentile	Mean	97.5th Percentile	Mean	97.5th Percentile	Mean	97.5th Percentile	Mean	97.5th Percentile
Comfort	0	0	0-0.00002	0	0-0.00007	0	0	0	0	0
First Milk: From Birth (Powder)	0-0.00006	0-0.00115	0-0.00008	0	0-0.00002	0	0	0	0	0
Follow On Milk: 6 Months (Powder)	0	0	0-0.00005	0	0-0.00008	0-0.00057	0	0	0-0.00001	0
Growing Up Milk: 12 Months (Powder)	0	0	0	0	0	0	0-0.00003	0	0-0.00001	0
Goat Milk Formula	0	0	0-0.00003	0	0	0	0	0	0	0
Hipp Organic	0	0	0-0.00001	0	0	0	0	0	0	0
Soy	0-0.00011	0	0-0.00006	0	0-0.00006	0	0-0.00002	0	0-0.00001	0
First Milk: From Birth (Ready to Feed)	0-0.0114	0-0.02809	0-0.0047	0-0.021	0-0.00203	0-0.01314	0-0.0003	0-0.0056	0-0.00007	0
Follow on: 6 Months (Ready to Feed)	0-0.00154	0-0.01592	0-0.00561	0-0.0193	0-0.00546	0-0.01753	0-0.00133	0-0.01129	0-0.00069	0-0.00736
Growing up Milk: 12 Months (Ready to Feed)	0	0	0-0.00001	0	0-0.00016	0	0-0.00138	0-0.01105	0-0.00089	0-0.00853
Total	0-0.01311	0-0.02809	0-0.01057	0-0.02209	0-0.00788	0-0.01814	0-0.00307	0-0.01376	0-0.00168	0-0.00992

Table B6. Estimated Mercury exposure from commercial infant foods in children aged 4 to 18 months using data from the Infant Metals Survey

Food Groups	Commercial Infant Foods Mercury LB to UB									
	4 to <6		6 to <9		9 to <12		12 to <15		15 to <18	
	Mean	97.5th Percentile	Mean	97.5th Percentile	Mean	97.5th Percentile	Mean	97.5th Percentile	Mean	97.5th Percentile
Cereal Based Dishes	0	0	0	0	0	0	0	0	0	0
Dairy Based Dishes	0-0.0012	0-0.01169	0-0.0012	0-0.01086	0-0.00075	0-0.00776	0-0.00039	0-0.00535	0-0.00014	0-0.00213
Fruit Based Dishes	0-0.00176	0-0.01353	0-0.00259	0-0.01463	0-0.00245	0-0.01328	0-0.00154	0-0.01128	0-0.00095	0-0.0082
Meat Based Dishes	0-0.00269	0-0.01733	0-0.00436	0-0.0221	0-0.00413	0-0.02072	0-0.00242	0-0.01675	0-0.00124	0-0.00991
Drinks	0	0	0	0	0	0	0	0	0	0
Other savoury based dishes	0-0.00123	0-0.00806	0-0.00178	0-0.01017	0-0.0019	0-0.01317	0-0.00075	0-0.00731	0-0.00037	0-0.00556
Snacks - sweet and savoury	0	0	0	0	0	0	0	0	0	0
Total	0.00123-0.00565	0.00806-0.02381	0.00178-0.00816	0.01017-0.03451	0.0019-0.00733	0.01317-0.03195	0.00075-0.00435	0.00731-0.02512	0.00037-0.00232	0.00556-0.01505

Table B7. Estimated Mercury exposure from other foods commonly eaten by children aged 4 to 18 months using data from the Infant Metals Survey

Food Groups	Other Food Mercury LB to UB									
	4 to <6		6 to <9		9 to <12		12 to <15		15 to <18	
	Mean	97.5th Percentile	Mean	97.5th Percentile	Mean	97.5th Percentile	Mean	97.5th Percentile	Mean	97.5th Percentile
Beverages	0-0.00008	0-0.00121	0-0.00022	0-0.00176	0-0.00017	0-0.0022	0-0.00014	0-0.00169	0-0.00021	0-0.00349
Bread	0-0.00005	0-0.00068	0-0.00044	0-0.00286	0-0.00123	0-0.00491	0-0.00186	0-0.00619	0-0.00207	0-0.00682
Canned Vegetables	0-0.00005	0-0.00061	0-0.00022	0-0.0023	0-0.00051	0-0.00369	0-0.00077	0-0.00434	0-0.00068	0-0.00315
Cereal	0-0.00007	0-0.00082	0-0.00114	0-0.0063	0-0.00172	0-0.00768	0-0.00213	0-0.00868	0-0.00263	0-0.00917
Dairy Products	0-0.00078	0-0.0046	0-0.00164	0-0.00692	0-0.00202	0-0.00759	0-0.00204	0-0.00732	0-0.00187	0-0.00644
Egg	0-0.00002	0-0.00002	0-0.00016	0-0.00166	0-0.00033	0-0.00255	0-0.00053	0-0.00323	0-0.00055	0-0.00334
Fish	0.00133	0.0078	0.01014	0.09586-0.09587	0.02164	0.1431-0.14311	0.0282	0.13505-0.13506	0.02495	0.13205
Fresh fruit	0-0.00037	0-0.0025	0-0.00071	0-0.00332	0-0.00107	0-0.00439	0-0.00147	0-0.00519	0-0.00179	0-0.00522
Fruit products	0-0.0001	0-0.00164	0-0.00016	0-0.00165	0-0.00016	0-0.00161	0-0.00026	0-0.00241	0-0.00037	0-0.00279
Green vegetables	0-0.00009	0-0.00075	0-0.00019	0-0.00089	0-0.00021	0-0.00141	0-0.0002	0-0.00099	0-0.00021	0-0.00103
Meat products	0	0	0-0.00004	0-0.00073	0-0.0001	0-0.00098	0-0.00021	0-0.0014	0-0.00028	0-0.00227
Milk	0-0.00009	0-0.00101	0-0.0005	0-0.00275	0-0.00127	0-0.0104	0-0.00523	0-0.01496	0-0.00523	0-0.01274
Other vegetables	0-0.00084	0-0.00613	0-0.00111	0-0.00518	0-0.00101	0-0.00432	0-0.00069	0-0.003	0-0.00067	0-0.00262
Potato	0-0.00024	0-0.00165	0-0.00053	0-0.00246	0-0.00073	0-0.0029	0-0.00078	0-0.00348	0-0.00071	0-0.00282
Poultry	0-0.00004	0-0.00029	0-0.00013	0-0.00108	0-0.00018	0-0.00126	0-0.00018	0-0.00106	0-0.00017	0-0.00114
Total	0.00133-0.00414	0.0078-0.02076	0.01014-0.01733	0.09586-0.10335	0.02164-0.03234	0.1431-0.15417	0.0282-0.04469	0.13505-0.15821	0.02495-0.04239	0.13205-0.15265

Total Diet Study

Table B8 summarise lower- and upper-bound total dietary exposures to Mercury calculated using the 2014 TDS for ages 12 to 18 months. The data for each food category is reported separately so that the contribution to exposure from each class could be assessed more transparently for the most relevant infant age group. In addition the total exposure from the diet has also been provided.

Table B8. Estimated Mercury exposure from food eaten by young children aged 12 months to 18 months using data from the TDS Groups.

Food Groups	**Exposure-LB-UB (ug/kg bw/day)**			
	12 to <15		**15<18**	
	Mean	**97.5th Percentile**	**Mean**	**97.5th Percentile**
Bread	0-0.00253	0-0.00691	0-0.00284	0-0.00764
Miscellaneous Cereals	0-0.00281	0-0.00882	0-0.0034	0-0.01001
Carcase meat	0-0.00096	0-0.00494	0-0.0012	0-0.00595
Offal	0.00001	0	0.00009	0
Meat products	0-0.00048	0-0.00252	0-0.00059	0-0.00271
Poultry	0-0.00052	0-0.00227	0-0.00058	0-0.0025
Fish	0.04609	0.21389	0.04322	0.21907
Fats and oils	0-0.00013	0-0.00053	0-0.00016	0-0.00058
Eggs	0-0.00034	0-0.00178	0-0.00035	0-0.00183
Sugars	0.00038	0.00231	0.00057	0.00285
Green vegetables	0-0.00051	0-0.00226	0-0.00056	0-0.0021
Potatoes	0-0.00351	0-0.01289	0-0.00325	0-0.01064
Other vegetables	0-0.00329	0-0.01197	0-0.00334	0-0.01093
Canned vegetables	0-0.00086	0-0.00439	0-0.00084	0-0.00387
Fresh fruit	0-0.00566	0-0.01944	0-0.00697	0-0.02
Fruit products	0-0.00093	0-0.00664	0-0.00106	0-0.00701
Non-alcoholic beverages	0-0.00608	0-0.02867	0-0.00735	0-0.03453
Milk	0-0.01311	0-0.03741	0-0.01315	0-0.03185
Dairy products	0-0.00498	0-0.02656	0-0.00421	0-0.01849
Nuts	0-0.00004	0-0.00016	0-0.00002	0-0.00016
Alcoholic drinks	0	0-0.00003	0	0
Meat substitutes	0-0.00001	0	0-0.00003	0-0.00032
Snacks	0.00007	0.00051	0.00012	0.00081
Desserts	0-0.00008	0-0.00066	0-0.0001	0-0.00076
Condiments	0-0.00009	0-0.00055	0-0.0001	0-0.00053
Tap water	0-0.00197	0-0.00752	0-0.00224	0-0.00899
Bottled water	0-0.0001	0-0.0009	0-0.00014	0-0.00207
Total	0.04655-0.09553	0.21435-0.27489	0.04399-0.09646	0.21944-0.27635

Secretariat

References

DH (2013). Diet and Nutrition Survey of Infants and Young Children (DNSIYC), 2011. Available at: http://transparency.dh.gov.uk/2013/03/13/dnsiyc-2011/

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Review of potential risks from Mercury in the diet of infants aged 0 to 12 months and children aged 1 to 5 years

Possible Mercury exposure from dietary sources in young children aged 18 to 60 months

A Total Diet Study (TDS) was conducted during 2014 which measured the concentrations of Mercury by young children (18 months and older).

The TDS consisted of: (i) selecting foods based on food consumption data, to represent as best as possible a typical diet; (ii) their preparation to food as consumed and (iii) the subsequent pooling of related foods before analysing the composite samples for elements. The concentrations of 26 elements, including Mercury, were measured in the 2014 TDS. The composite samples for 27 food groups (Table C1) were collected from 24 UK towns and analysed for their levels of Mercury and other elements. Where appropriate, tap water was used in the preparation and cooking of food samples. The results from this survey were also used together with food consumption data from years 1 to 4 of the National Diet and Nutrition Survey Rolling Programme (NDNS) (Bates *et al.,* 2014) to estimate dietary exposures for young children aged 18 months to 5 years.

Table C1. Food groups used for analysis of Mercury and other elements in the 2014 TDS.

TDS Food Groups*	
Bread	Fresh Fruit
Miscellaneous Cereals	Fruit Products
Carcase Meat	Non Alcoholic Beverages
Offal	Milk
Meat Products	Dairy Products
Poultry	Nuts
Fish	Alcoholic Drinks
Fats and Oils	Meat Substitutes
Eggs	Snacks
Sugars	Desserts
Green Vegetables	Condiments
Potatoes	Tap Water
Other Vegetables	Bottled Water
Canned Vegetables	

*Food samples representative of the UK diet are purchased throughout the year in 24 towns covering the UK and 137 categories of foods are combined into 27 groups of similar foods for analysis

Exposure Assessment

Table C2 summarises lower- and upper-bound total dietary exposures to Mercury calculated using the 2014 TDS for young children aged 18 months to 5 years. The data for each food category is reported separately so that the contribution to exposure from each class could be assessed more transparently for the most relevant infant age group. In addition the total exposure from the diet has also been provided.

Table C2. Estimated Mercury exposure from food eaten by young children aged 18 months to 5 years using data from the TDS Groups.

Food Groups	**Exposure-LB to UB**			
	18 to <24		**24 to <60**	
	Mean	**97.5th Percentile**	**Mean**	**97.5th Percentile**
Bread	0-0.003	0-0.00675	0-0.00342	0-0.00795
Miscellaneous Cereals	0-0.00363	0-0.00761	0-0.00297	0-0.00751
Carcase meat	0-0.00132	0-0.00679	0-0.0008	0-0.00427
Offal	0.00002	0	0.00003	0
Meat products	0-0.0007	0-0.00324	0-0.00085	0-0.00284
Poultry	0-0.00067	0-0.00191	0-0.00057	0-0.00245
Fish	0.05715	0.22825	0.04378	0.16803
Fats and oils	0-0.00021	0-0.00068	0-0.00019	0-0.00063
Eggs	0-0.00026	0-0.00147	0-0.00027	0-0.00152
Sugars	0.00067	0.00319	0.00097	0.00408
Green vegetables	0-0.00048	0-0.00286	0-0.00049	0-0.002
Potatoes	0-0.00333	0-0.00703	0-0.00303	0-0.00886
Other vegetables	0-0.00202	0-0.00674	0-0.00211	0-0.00751
Canned vegetables	0-0.00143	0-0.00547	0-0.00088	0-0.0034
Fresh fruit	0-0.0085	0-0.02228	0-0.00614	0-0.01618
Fruit products	0-0.00237	0-0.00915	0-0.00216	0-0.0104
Non-alcoholic beverages	0-0.00992	0-0.041	0-0.00956	0-0.02774
Milk	0-0.01229	0-0.03868	0-0.00869	0-0.02506
Dairy products	0-0.00455	0-0.02165	0-0.00254	0-0.01016
Nuts	0-0.00001	0-0.00001	0-0.00003	0-0.0004
Alcoholic drinks	0-0.00001	0	0	0
Meat substitutes	0-0.00001	0-0.00012	0-0.00003	0-0.00045
Snacks	0.00014	0.00082	0.00016	0.00083
Desserts	0-0.00016	0-0.00087	0-0.00018	0-0.00085
Condiments	0-0.00007	0-0.00036	0-0.00011	0-0.00059
Tap water	0-0.00223	0-0.01171	0-0.00201	0-0.00759
Bottled water	0-0.00007	0-0.0007	0-0.00018	0-0.00191
Total	0.05798-0.11522	0.22825-0.2918	0.04494-0.09213	0.16925-0.21561

References

Bates, B.; Lennox, A.; Prentice, A.; Bates, C.; Page, P.; Nicholson, S.; Swan, G. (2014) National Diet and Nutrition Survey Results from Years 1, 2, 3 and 4 (combined) of the Rolling Programme (2008/2009 – 2011/2012) Available at:

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/310995/NDNS_Y1_to_4_UK_report.pdf

Annex C: Data from updates of the epidemiological studies on methylmercury

1. Faroese cohort:

Table 1. Test score change associated with mercury in cord blood (logarithmically transformed), as indicated by multiple regression analysis with adjustment for covariates.

Cognitive domain	Test variable	N	Change associated with 10-fold increase	Standardized coefficient (Beta)	*p*
Gf	WJ III Concept Formation	662	−.284	−.022	.585
	Raven Standard Progressive Matrices Plus	661	−.990	−.048	.235
Gc	Boston Naming Test, without cues	662	−1.295	−.079	.046
	Boston Naming Test, with cues	662	−1.382	−.097	.014
	Synonyms, WJ III	662	−.769	−.112	.005
	Antonyms, WJ III	662	−.453	−.080	.046
	Verbal Analogies, WJ III	662	−.137	−.024	.547
Gv	Block Design WISC-R	659	.015	.001	.986
	Block Design WISC-R + 3 WAIS-R	333	−1.579	−.065	.247
	Spatial Relations, WJ III	657	−.551	−.043	.290
Gsm	Numbers Reversed, WJ III	659	−.289	−.028	.491
	Memory for words, WJ III	659	−.196	−.034	.403
	Spatial Span Forward, WMS-III	659	.266	.052	.197
	Spatial Span Backwards, WMS-III	659	.073	.016	.696
Glr	CVLT, Trial 1, Correct	662	−.489	−.097	.015
	CVLT, Learning trials 1–5	662	−.170	−.006	.869
	CVLT, List B, Correct	662	−.081	−.015	.706
	CVLT, Short Delay, Free Recall	662	−.135	−.018	.657
	CVLT, Long Delay, Free Recall	662	−.093	−.013	.751
	CVLT, Long Delay, Recognition	659	−.157	−.043	.293
	Incidental Memory for Boston Naming and Picture Vocabulary, WJ-III	662	−.517	−.047	.248

Cognitive domain	Test variable	N	Change associated with 10-fold increase	Standardized coefficient (Beta)	*p*
	Warrington's Face Recognition Test, Set2, Immediate Recall	656	−.476	−.041	.319
	Warrington's Face Recognition Test, Set 2, Delayed Recall	656	−.056	−.004	.918
Gs	Visual Matching, WJ III	659	−.748	−.043	.285
	Decision Speed, WJ III	659	.926	.049	.225
Gt	CPT, NES II, Mean RT of 4 last Blocks	656	4.082	.033	.432
	CPT, NES II, SD of 4 last Blocks	656	.861	.017	.685
	CPT, NES II, false negative errors last 4 blocks	656	.047	.016	.693
	CPT, NES II, false positive errors last 4 blocks	656	−.066	−.019	.645
	CPT-90, Proportion correct non-target (minus first 20 stimuli)	641	−.022	−.033	.419
	CPT-90, Noise corrected proportion correct non-target (minus first 20 stimuli)	641	−.019	−.028	.491
Gps	Finger Tapping, NES2, preferred hand	656	−1.218	−.041	.275
	Finger Tapping, NES2, non-preferred hand	656	−1.381	−.035	.338
	Finger Tapping, NES2, alternate hands	656	−1.199	−.023	.551

Covariates: Sex, Maternal fish dinners during pregnancy, Maternal Raven, Mother employed (age 14), Father employed (age 14), Age at examination, Tested in language, School grade (age 14), Lead logarithmic, PCB's logarithmic.

Table 2 – Test score change associated with mercury in mother's hair (logarithmically transformed), as indicated by multiple regression analysis with adjustment for covariates.

Cognitive domain	Test variable	N	Change	Standardized	*p*
Gf	WJ III Concept Formation	830	-.694	-.041	.303
	Raven Standard Progressive Matrices Plus	828	-.434	-.016	.677
Gc	Boston Naming Test , without cues	830	-.417	-.020	.615
	Boston Naming Test, w. stim. and phon. cues	830	-.495	-.027	.493
	Synonyms, WJ III	830	-.775	-.087	.028
	Antonyms, WJ III	830	-.504	-.071	.078

	Verbal Analogies, WJ III	830	-.069	-.010	.813
Gv	Block Design WISC-R	826	.603	.021	.598
	Block Design WISC-R + 3 WAIS-R	426	.588	.018	.726
	Spatial Relations, WJ III	824	-.031	-.002	.964
Gsm	Numbers Reversed, WJ III	826	-.456	-.035	.395
	Memory for words, , WJ III	826	-.401	-.053	.192
	Spatial Span Forward, WMS-III	826	.327	.051	.206
	Spatial Span Backwards, WMS-III	826	-.097	-.017	.680
Glr	CVLT, Trial 1, Correct	830	-.423	-.066	.099
	CVLT, Learning trials 1-5	830	-1.350	-.039	.310
	CVLT, List B, Correct	830	-.183	-.027	.499
	CVLT, Short Delay, Free Recall	830	-.301	-.031	.435
	CVLT, Long Delay, Free Recall	830	-.105	-.011	.786
	CVLT, Long Delay, Recognition	827	-.349	-.074	.070
	Incidental Memory for Boston Naming and Picture Vocabulary, WJ-III	830	-.757	-.053	.186
	Warrington's Face Recognition Test, Set2, Immediate Recall	822	-.099	-.006	.872
	Warrington's Face Recognition Test, Set 2, Delayed Recall	822	.074	.004	.915
Gs	Visual Matching, WJ III *)	826	-.191	-.009	.831
	Decision Speed, WJ III *)	826	1.304	.054	.177
Gt	CPT, NES2, Mean RT of 4 last Blocks	823	9.074	.057	.164
	CPT, NES2, SD of 4 last Blocks	823	.584	.009	.826
	CPT, NES2, false negative errors last 4 blocks	823	.150	.043	.288
	CPT, NES2, false positive errors last 4 blocks	823	.037	.008	.842
	CPT-90, Proportion correct non-target (minus first 20 stimuli)	803	-.026	-.030	.460
	CPT-90, Noise corrected proportion correct non-target (minus first 20 stimuli)	803	-.027	-.031	.442
Gps	Finger Tapping, NES2, preferred hand	823	-2.337	-.061	.102
	Finger Tapping, NES2, non-preferred hand	823	-1.480	-.030	.411
	Finger Tapping, NES2, alternate hands	823	-2.585	-.038	.324

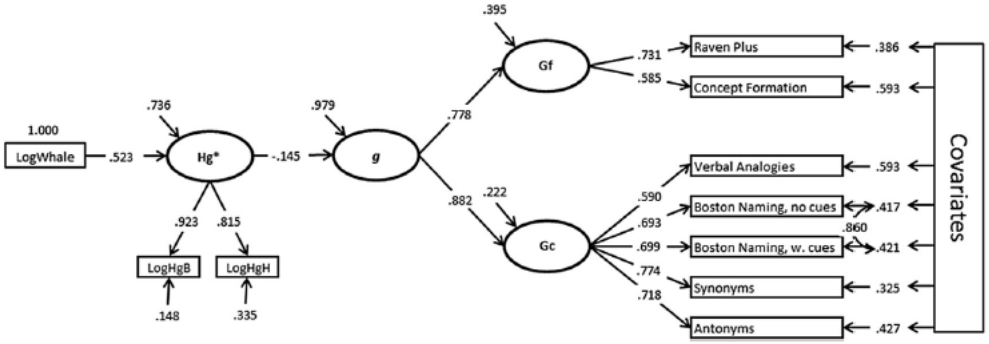

Fig. 1 – A structural equation model showing the standardized negative effect of a latent variable for prenatal exposure to methylmercury on a second-order latent variable for general mental ability in a measurement model with two first-order factors, and with the manifest test variables corrected for a set of covariates. LogWhale = Log10(Maternal Whale Dinners +1); LogHgB = Log10(Hg in Cord Blood + 1); LogHgH = Log10(Hg in Mother Hair + 1); Hg* = Latent Hg-variable; *g* = Latent variable for general mental ability; Gf = Latent variable for fluid reasoning; Gc = Latent variable for verbal comprehension. Coefficients are standardized values. Double headed arrow indicates correlation of residuals. Numbers at arrows are residual variances. For simplicity, covariates are only shown schematically with no values or intercorrelations. Covariates are: Sex, Maternal fish dinners during pregnancy, Maternal Raven, Mother employed (age 14), Father employed (age 14), Age at examination, Tested in language, School grade (age 14), Lead exposure, and PCB exposure.

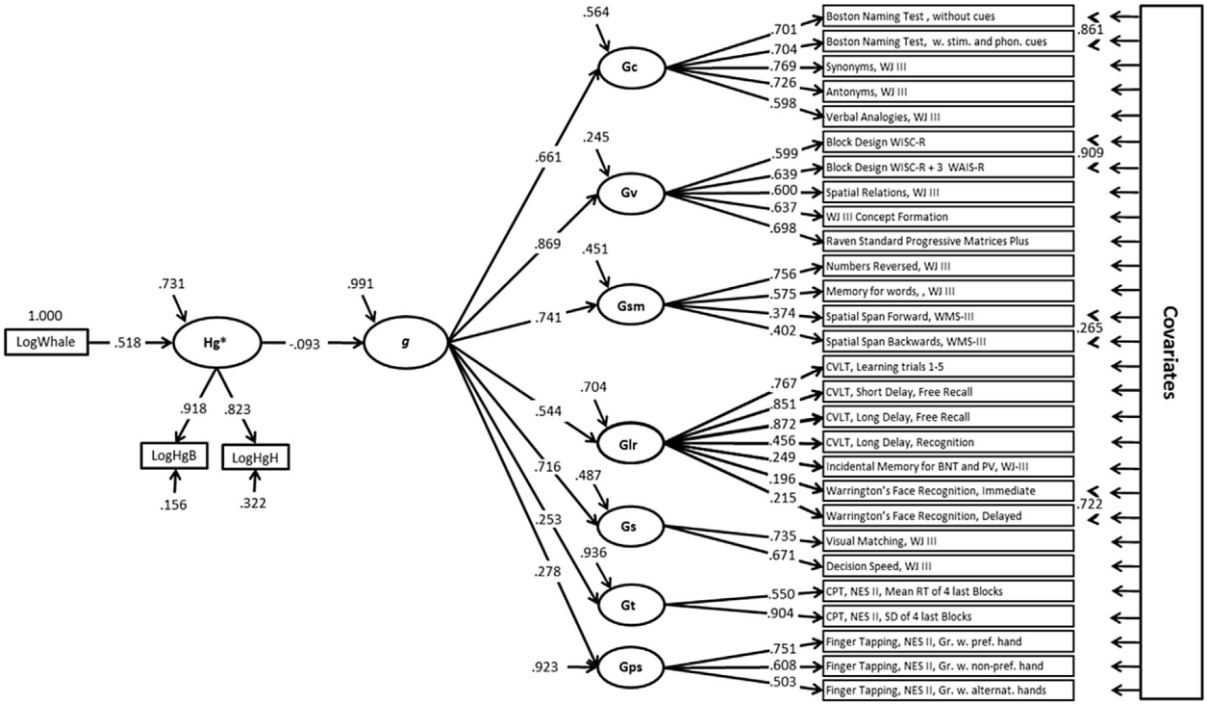

Fig. 2 e A Structural Equation Model (SEM) showing the standardized negative effect of a latent variable for prenatal exposure to methylmercury on a second-order latent variable for general mental ability in a measurement model with seven first-order factors, and with the manifest test variables corrected for a set of covariates. Coefficients are standardized values. Double headed arrows
indicate correlation of residuals. Numbers at arrows are residual variances. As in Fig. 1, residual variances for manifest variables, and covariates, are not shown. Covariates are: Sex, Maternal fish dinners during pregnancy, Maternal Raven, Mother employed (age 14), Father employed (age 14), Age at examination, Tested in language, School grade (age 14), Lead exposure, and PCB exposure

ANNEX D: Terms used for literature search:

Methylmercury AND:

- Breast milk
- Human milk
- Seychelles
- Faroe
- Fish
- Humans
- Nutrition cohort
- Toxicity
- Neurodevelopment