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

Statement 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 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. When considering the general population, COT also concluded that the earlier guideline value of 3.3 µg/kg bw/week, which had been established by the JECFA in 1972 and confirmed in 2000, was still appropriate for breastfeeding mothers, as the resulting exposure for infants would be below 1.6 µg/kg bw/week. 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 pregnant women, women trying to get pregnant and children should avoid eating these species. The COT also concluded that consumption of two portions per week of fresh tuna, or 6 portions of canned tuna would not be expected to result in adverse effects in children of any of the age group. In pregnant or breastfeeding women, consumption of up to two 140g portions of fresh tuna, or up to four 140g portions of canned tuna, per week, before or during pregnancy would not be expected to result in adverse effects on the developing fetus.

3. The European Food Safety Authority's 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 established 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 occurring most commonly in the environment are (i) elemental or metallic mercury (Hg0), (ii) inorganic mercury [mercurous (Hg_2^{2+}) and mercuric (Hg^{2+}) cations) and (iii) organic mercury. Organic mercury in the form of 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 in humans, MeHg is much more extensively and rapidly absorbed than inorganic mercury (EFSA, 2012; FAO/WHO, 2011). Following absorption, 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, respectively. (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 placenta and the blood-brain barrier, MeHg exposure is of particular concern during embryonic neurodevelopment and in young children (COT, 2004). Thus, pregnant and breastfeeding women are sensitive sub-populations due to the fact that maternal exposure can lead to exposure of the child either via the placenta or breast milk.

10. The bioaccumulative properties of MeHg in combination with its long half-life, mean that the blood concentration of methylmercury at the time of becoming pregnant depends on the exposure to methylmercury during the preceding year.

11. 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).

Toxicokinetics

Absorption

12. In contrast to other forms of mercury, MeHg is rapidly and extensively absorbed after oral exposure. The extent of absorption is greater 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; COT, 2004). MeHg is excreted in the bile as a glutathione conjugate and can then undergoes enterohepatic recycling, with reabsorption of some of the MeHg 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, complexing with the free sulfhydryl group of 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, is 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 is excreted in breastmilk and thus can reach the infant 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). No data were available for women in the UK. Methylmercury is able to cross into 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 is estimated at 250:1 (COT,2004).

15. Fetal distribution mercury is similar to maternal distribution, although fetal methylmercury concentration in erythrocytes and total mercury concentration in brain may be higher. This is probably because binding of methylmercury to the erythrocytes retards its entry into the brain, thus the erythrocyte to plasma ratios correlate with the blood to brain ratios (EFSA, 2012). Fetal brain mercury concentration is approximately 5-7 times higher than that in maternal blood. Cord blood concentrations are reported to be 25% higher than maternal blood concentrations, estimated from maternal hair concentrations (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 NADPH cytochrome P450 oxidoreductase (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). MeHg is conjugated with glutathione catalysed by liver glutathione transferases. The conjugate is then eliminated via the biliary route and excreted in the faeces, which accounts for 90% of excreted MeHg. MeHg undergoes enterohepatic recycling. It is partly converted to mercuric mercury via the intestinal microflora. Mercuric mercury is less effectively absorbed; and thus excreted via the faeces.

Toxicity

18. The toxic effects associated with consumption of methylmercury have been extensively investigated. Repeated 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).

19. 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 it takes a year to achieve steady state, the blood concentration of methylmercury at the time of becoming pregnant depends on the exposure to methylmercury during the preceding year (COT, 2004).

20. 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 survival and weight gain of offspring than postnatal exposure in 129SvS1 mice (Spyker and Spyker, 1977).

21. There is evidence that a number of dietary factors can reduce or prevent methylmercury toxicity, including n-3 long chain polyunsaturated fatty acids (LCPUFAs), selenium, iodine, choline and vitamin E. Numerous *in vitro* and *in vivo* studies are available, but only a brief summary is provided here. The most extensively studied substance in food, regarding mechanisms of confounding of studies of mercury, is selenium. Mercury binding affinity for selenium is a million times higher than its binding affinity for sulfur in analogous forms and attempts, unsuccessful to date, have been made to identify detoxification products, which contain selenium and mercury (e.g. mercury-selenide). Whether such compounds truly detoxify the mercury species has never been demonstrated. Besides sequestration of mercury, potential protective modes of action of selenium against methylmercury toxicity include antioxidant effects, increased glutathione peroxidase activity, glutathione synthesis, high selenoprotein concentration 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 pre-treatment with DHA was associated with decreased cellular methylmercury bioavailability. (EFSA, 2012)

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

22. The basis for establishing the 2004 JECFA HBGV was the human epidemiology studies from the Faroe Islands and the Seychelles. The assessments were made on the basis of the evaluations of children at 7 years of age in the Faroe Islands and 5.5 years of age in the Seychelles.

23. Concentrations of mercury in maternal hair and/or cord blood were used as biomarkers for exposure to methylmercury *in utero.*

24. A No Observed Adverse Effect Level (NOAEL) 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. An average of the NOAEL 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.

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

26. By use of a one-compartment toxicokinetic model (WHO, 1990), refined to better reflect the situation in pregnant women, the JECFA calculated the daily ingestion of methylmercury (1.5 µg/kg bw/day) corresponding to a maternal blood mercury concentration that would have no appreciable adverse effects on the offspring in the two study populations.

27. A data derived factor of 2 for variation in hair to blood ratio of mercury 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.

28. Following application of this uncertainty factor, a PTWI of 1.6 µg/kg bw was established.

Derivation of HBGV, EFSA (2012)

29. The CONTAM Panel evaluated any available studies since their 2004 evaluation, in which the PTWI established by JECFA was also adopted. The biggest change since the evaluation of 2004 was new information on cofounding by beneficial factors in fish on associations between prenatal methylmercury exposures and neurodevelopmental endpoints.

30. Results from the first Nutrition Cohort (NC1) of the Seychelles Child Development Study (SCDS) suggested an effect at age 9 and 30 months but not at 5 years related to prenatal methylmercury exposure, whereby it appeared that the positive effects from intake of n-3 long chain polyunsaturated fatty acids (n-3 LCPUFAS) no longer outweighed detrimental effects from 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.

31. The CONTAM panel found that a methylmercury concentration of 11 mg/kg in maternal hair was an apparent NOAEL for decreased scores on neurodevelopmental indices after adjustment for prenatal blood maternal n-3 LCPUFA and this 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.

32. For the Faroe Islands cohort, the Panel could not identify a more appropriate point of departure than the $BMDL_{05}$ of 12 mg/kg selected by JECFA.

33. 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.

34. A factor of 250 was used to convert this to an equivalent concentration of mercury in maternal blood of 46 µg/L, as explained in para 25.

35. Output from the one-compartment toxicokinetic model determined that a maternal daily dietary mercury intake of 1.2 µg/kg bw corresponded to a maternal blood mercury concentration that was considered to have no appreciable adverse effects on the offspring. By applying a total uncertainty factor of 6.4 to this value, the CONTAM panel established a TWI for methylmercury of 1.3 µg/kg bw expressed as mercury.

Studies published following EFSA's 2012 review:

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

Faroe Islands cohort

37. In 2016, reports from the Faroese cohort follow up were reported at age 22 years (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 (no further details provided by the authors), 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.

38. The test battery included measures of intelligence under 8 broad domains: problem solving, comprehension, visual processing, short term memory, long term storage and retrieval, cognitive processing speed, decision and reaction speed and psychomotor speed, as reflected in a number of tests that measure neurobehavioral development. 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 (a measure of maternal intelligence), 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)].

39. Analysis of the results revealed a general negative association between cord blood mercury and performance in the tests, which translated to an inverse association between prenatal methylmercury exposure and intelligence at the age of 22 years, although most results were not statistically significant. From the test results it appeared that the most significantly affected domain was that of comprehension, which encompasses the ability to use learnt skills, knowledge and experience. The results corresponded to a drop of 2.2 IQ points for a 10-fold increase in methylmercury exposure, when the scores for comprehension and problem solving were used as general indicators of intelligence.

40. 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 were 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.

Seychelles Child Development Study (SCDS)

41. Since the EFSA report, results on the second nutrition cohort (NC2) form this study, which contained a higher number of the mother-child pairs than NC1, have been made available (Strain *et al., 2015).* Nutrition Cohort 2 of the SCDS comprised 1265 mother-child pairs. 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 for language development, cognition and psychomotor development and behaviour.

42. The main and interactive effects of MeHg and PUFAs on outcomes with or without adjustment for each other were investigated. In main effects models, DHA and arachidonic acid (AA) were evaluated because these PUFAs are considered to have a direct influence on brain development. The interaction of MeHg and PUFAs was evaluated across tertiles of total n-3, total n-6 and the n-6:n-3 ratio. The last is regarded as an indirect measure of inflammation and was used to evaluate the effect of proinflammatory status on aspects of neurobehavioural development both with and without interaction with methylmercury. 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, sex, Hollingshead socioeconomic status, and number of parents living with the child (family status). In secondary analysis, results were also adjusted for mother's cognitive ability and the child's home.

43. Prenatal methylmercury exposure with and without adjustment for PUFAs was not directly associated with neurodevelopmental outcomes. The results for interactions between n-3 PUFAs and methylmercury indicated that for psychomotor development, at the highest tertile of n-3 PUFAs, a significant improvement in the score was observed with increasing methylmercury concentration. With respect to the interaction between methylmercury and n-6:n-3 ratios, an adverse association with MeHg was observed at the highest n-6:n-3 tertile only for psychomotor development. There were no significant direct associations between methylmercury and any of the language development outcomes nor between methylmercury and PUFAs for any of the language development or behavioural outcomes.

44. In the main effects model for PUFAs associations, DHA was significantly adversely associated with the performance in tests evaluating cognitive development with or without methylmercury adjustment. This result conflicted with the findings in Nutrition Cohort 1, which showed no significant effects of PUFAs and cognition. 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 cognitive development score with or without adjustment for methylmercury exposure. No significant associations between PUFAs and the psychomotor scores were observed. Higher DHA was associated with improved total gestures scores, in the evaluation of psychomotor development. Higher n-6:n-3 ratios were associated with poorer scores on language development.

45. Overall, the authors found no overall adverse association between prenatal MeHg exposure and neurodevelopmental outcomes. However maternal PUFAs status as a putative marker of the inflammatory milieu appeared to modify the associations of prenatal MeHg exposure with psychomotor development. Increasing DHA status was positively associated with language development yet negatively associated with cognitive development. 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

46. In a paper published in 2017 (van Wijngaarden *et.al, 2017)*, the updates from the Main Cohort of the SCDS regarding prenatal methylmercury exposure impact on neurodevelopmental outcomes, at age 22 and 24 years, were discussed. Covariates selected were the same or similar in this cohort as at previous ages and included sex, socioeconomic status, maternal and child IQ, and life course stress. Prenatal and postnatal exposures were modelled separately.

47. Recent postnatal MeHg exposure as indicated from the participants' 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.

48. For age 22 years, prenatal MeHg exposure was associated with several of the developmental outcomes assessed but all regression coefficients indicated improved performance with increasing prenatal exposure. Postnatal MeHg exposure was inversely associated with only one of the 26 tests that were used to evaluate cognition. At age 24 years there were no clear patterns of association with either prenatal or recent postnatal MeHg exposure.

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

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

Sources of methylmercury exposure

Human breast milk

50. There are only 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.

51. 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 relevant studies used by the EFSA panel and reported in the literature, the mean concentration of mercury in breast milk ranged from 0.1 µg/L (Miklavčič *et al.*, 2013) in samples from Greek women to 0.68 µg/L (Miklavčič et al., 2011) in samples from Slovenian women. The mean contribution of methylmercury to total mercury ranged from 26 to 63%.

Infant formulae and food

52. 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

53. 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 chemical form in which mercury occurs 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).

54. Harmonised limit values for mercury (total) in drinking water are set by Council Directive 98/83/EC. 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/EC also sets a maximum limit for mercury in natural mineral water of 1 µg/L.

55. Concentrations of mercury (total) 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 these 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 total mercury in water across the UK for 2016. All mercury in water is assumed to be in the form of 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

56. 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, CH_3HgX. 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).

57. 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).

58. In 2012 and 2013, the Defra published data for total mercury in topsoil[1] in England and Wales (Defra, 2012 and 2013). The concentrations reported for the principal domain[2] in England were a median of 0.12 mg/kg and a 95th percentile of 0.5 mg/kg. The statistics reported for the same domain in Wales were a median of 0.09 mg/kg and a 95th percentile of 0.25 mg/kg. No relevant data were available for mercury concentrations in dust.

Air

59. 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).

60. 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 only trace amounts and hence exposure to methylmercury via the air is negligible and therefore not presented here.

Other sources

61. Although methylmercury is not present in vaccines, the possible presence of ethylmercury, a chemical that was thought to have similar toxicological properties to methylmercury had raised concerns that vaccines that contained it could cause neurodevelopmental defects.

62. Traditionally, thiomersal (ethyl(2-mercaptobenzoato-(2-)-O,S) mercurate(1-) sodium) was used as a preservative for multi-dose vaccines (Oxford Vaccine Group, 2017) with ethylmercury then being derived from the metabolism of thiomersal. Although it had been previously assumed that ethylmercury has a similar toxicological profile to methylmercury, newer data suggest that its pharmacokinetics are substantially different (EMEA, 2004). Ethylmercury is much more rapidly metabolised by the body (in less than one week) compared to methylmercury, making exposure to ethylmercury in blood comparatively brief. Further, ethylmercury is actively excreted via the gut unlike methyl-mercury, which accumulates in the body

[1] Depth of 0-15cm

[2] The area covered by the principal domains constitutes approximately 99% of England and 94% of Wales.

(WHO, 2006). In statements from both the WHO (2006) and the European Agency for the Evaluation of Medicinal Products (EMEA, 2004) it was concluded that, based on a number of population-based epidemiological studies, no evidence was found to support concerns over the safety of thiomersal-containing vaccines and neurodevelopmental disorders.

63. Thiomersal was removed from UK vaccines between 2003 and 2005 and is no longer found in any of the childhood or adult vaccines routinely used in the UK. Since 2005, thiomersal has been present only in non-routine vaccines such as hepatitis B, and occasionally in some of the annual inactivated flu vaccines. Thiomersal was present in the Swine Flu (H1N1) vaccine Pandemrix, used in the 2009-10 and 2010-11 flu seasons in the UK. However, it is not present in any of the annual flu vaccines currently in use in the UK (Oxford Vaccine Group, 2017). Based on the above, it is not expected that infants and young children will be exposed to methylmercury-like compounds from vaccines.

Exposure assessment

64. Consumption data (on a bodyweight basis) 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 for ages 4 to 18 months, and 18 to 60 months respectively. Bodyweight data used in the estimation of other mercury exposures are shown in Table 2 below.

65. Detailed 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 extensive as they are not the main focus of this statement.

Table 2. Average bodyweights used in the estimation of methylmercury exposures, where individual bodyweight data were not available

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

66. As no consumption data were available for exclusive breastfeeding in infants aged 0 to 6 months, the default consumption values used by COT in other evaluations of the infant diet of 800 and 1200 mL for average and high level consumption have been used. 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).

67. 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

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)

68. 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 0.1 µg/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.

69. 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.

MeHg breastmilk concentration	MeHg 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

70. 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]	0-0.19	0-0.28	0-0.14	0-0.22
Dry Powder [b, c]	0-0.14	0-0.21	0-0.11	0-0.16
Dry Powder [c] + TDS water of <0.2 µg/L [d]	0-0.30	0-0.45	0-0.23	0-0.34
Dry Powder [c] + median water of 0.03 µg/L [d]	0.02-0.16	0.04-0.25	0.02-0.13	0.03-0.19

Dry Powder [c] + 97.5th percentile water of 0.1 µg/L [d]	0.08-0.22	0.12-0.33	0.06-0.17	0.09-0.25

Values rounded to 2 SF

[a] Exposure based on ready-to-feed first milk infant formula mercury concentrations of 0 (lower-bound) and 0.2(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 1.0 (upper-bound) µg/kg

[d] Calculated assuming reconstituted formula comprises 85% water

71. 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. 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 concentration of mercury in water made a minimal contribution to total exposures.

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

72. 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.

73. 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

74. 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 concentration of mercury in drinking water made a minimal contribution to total exposure.

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

75. 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.

76. 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 2.0 µg/kg bw/week, respectively. 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 estimates of 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

77. In general, the food group making the highest contribution to total mercury exposure was fish, with all other 26 groups making a minimal contribution to total exposure (FSA, 2016b). The contribution of fish to total dietary mercury exposure is discussed further in paragraph 79.

Children aged 18 months to 5 years

78. 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).

79. Table 9 shows the mercury exposures that were calculated using the TDS data for children aged 18 months to 5 years. As described in paragraph 73, 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 exposure estimates to mercury from a combination of all food groups of between 0.63 and 0.84 and 1.5 to 2.0 µg/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 estimated total dietary exposure to mercury.

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

Mercury	**Mercury Exposure (LB-UB Range) (µg/kg bw/week)**

concentration in water µg/L	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

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

Exposure from fish

81. As the main source of methylmercury in the diet is fish, a summary table (Table 10) is used to indicate exposure to mercury from fish from the TDS.

Table 10: 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

82. 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 56), and it has been assumed that 3% of mercury is present as methylmercury (paragraph 55). The resulting median and 95th percentile concentrations for methylmercury in the soil are: 3.6 and 15 µg/kg respectively.

83. 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. These exposures are trivial compared to those from the diet.

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

84. The Committee agreed that the TWI of 1.3 µg/kg bw established by EFSA should be used for characterising potential risks from the exposure of infants and young children to methylmercury.

85. Based on the data presented in table 11, soil and dust make a minimal contribution to exposure to methylmercury relative to dietary sources.

86. Mercury in drinking water used for reconstitution of dry infant formula resulted in an estimated increase in overall exposure in infants exclusively fed on infant formula (by up to 1.6-fold) but made a minimal contribution to overall dietary exposure in children between 12 and 60 months.

87. 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.

88. 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).

89. The exposures to total mercury calculated for children between 0 to <6 months of age that are exclusively fed with infant formula were 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.

90. The estimated dietary exposures to total 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.

91. 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.

92. 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 in fish 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 1.3 µg/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 (1.2 µg/kg bw/week).

93. As mentioned in paragraph 86, the contribution of methylmercury to total mercury in fish varies considerably, 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.

94. 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 at this age (EFSA, 2012).

95. Fish intake is linked with both n-3 PUFA and MeHg consumption. The beneficial effects of fish intake on brain development have been extensively studied and discussed elsewhere (WHO, 2011a) and they are outwith the remit of this statement. In Nutrition Cohort 1 of the SCDS, which was the key study used by EFSA in 2012 to revise the TWI to 1.3 µg/kg bw, the positive association in neurodevelopmental scores with increasing n-3 PUFAs concentration was not observed above a specific concentration of prenatal methylmercury exposure. In contrast, the results from Nutrition Cohort 2 indicated higher performance in the neurodevelopmental tests amongst subjects with high maternal n-3 blood serum concentration, which was associated with high methylmercury levels. It is difficult to determine from these data the extent to which intake of n-3 PUFAs, as well as other dietary factors (paragraph 21), could confound the effects of methylmercury.

Conclusions

96. 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 (Hg_2^{2+}) and mercuric (Hg^{2+}) cations) and (iii) organic mercury. Organic mercury, in the form of MeHg, is by far the most common form in the food chain.

97. The general population is exposed to mercury and methylmercury through food, drinking water, soil and in trace amounts from the air. The diet, and especially fish consumption, is the main source 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.

98. Methylmercury is readily absorbed following oral exposure. Following absorption, it can accumulate in the hair and can cross the blood brain barrier, the placenta and is excreted in breastmilk. 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 than in later life.

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

100. 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 1.6 µg/kg bw. In 2012, after reviewing updates on said epidemiological studies, the EFSA established a TWI of 1.3 µg/kg bw.

101. 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 to 1.3 µg/kg bw in 2012. The results from the Main Cohort were consistent with previous observations, where no adverse association was found between prenatal methylmercury exposure and neurodevelopment in this population. Reports from the Faroese cohort at 22 years of age, showed little convincing evidence of adverse effects of prenatal exposures. The cognitive deficits observed were much smaller than those seen at younger ages and were mostly not statistically significant. There was a lack of adjustment for multiple testing, which could have led to some findings by chance. It should also be noted that these epidemiological studies were carried out on high fish-consuming populations. Thus, prenatal methylmercury exposure in the study populations is much higher than in typical Western populations

102. Exclusively breastfed infants are a vulnerable group to consider in the case of methylmercury exposure, as methylmercury can be transferred to the newborn via milk. The concentration in human milk will depend on maternal exposure to methylmercury. Data for methylmercury in the literature suggest that the concentrations in breast milk 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.

103. For infants of 0-6 months of age that are exclusively or non-exclusively breastfed, or that are fed exclusively with infant formula, dietary exposures to total mercury are below the TWI for methylmercury.

104. Fish is one of the most significant contributors to total dietary mercury exposures both in the Infant Metals 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 would be 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 advises breastfeeding mothers should avoid eating more than one portion of shark, swordfish or marlin per week and that pregnant women, women trying to get pregnant and children should avoid eating these species. Consumption of two 140g portions of fresh tuna, or four 140g portions of canned tuna, per week, before or during pregnancy would not be expected to result in adverse effects on the developing fetus.

105. Additionally, other dietary factors, such as selenium, can reduce or even prevent methylmercury effects.

106. Overall, methylmercury exposures for the categories of exclusively (0 to 6 months) and non-exclusively (4 to 18 months) breastfed children, as well as those exclusively fed with infant formula (0 to 6 months) 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. Therefore, there is no health concern from exposure to methylmercury in any of these groups. Large predatory fish are a major contributor to mercury exposure, and assuming that all of the mercury in fish is methylmercury, the TWI would be 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. The Committee agreed that when taking into consideration the conservatism in the exposure assumptions, the risk to health from the potential minor exceedance of the TWI in these groups is low but that it would be prudent to maintain existing advice regarding consumption of large predator fish.

Abbreviations

AA – Arachidonic acid

BMDL - benchmark-dose Lower Confidence Limit

bw – body weight

CNS - Central Nervous System

CONTAM – EFSA Panel on Contaminants in the Food Chain

COT – Committee on Toxicity

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 (of the USA)

EU – European Union

FAO – Food and Agriculture Organization

FSA – Food Standards Agency

g - grams

IMS – Infant metals survey

JECFA – Joint FAO/WHO Expert Committee on Food Additives

kg - kilogram

LB – Lower bound

LOD – Limit of detection

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

NDNS – National Diet and Nutrition Survey

NOAEL- No Observed Adverse Effect Level

PTWI - Provisional Tolerable Weekly Intake

PUFA – Polyunsaturated Fatty Acid

SACN - Scientific Advisory Committee on Nutrition

SCDS - Seychelles Child Development Study

SF – significant figures

TDS – Total Diet Study

TWI – Tolerable Weekly Intake

WHO - World Health Organisation

µg/kg – micrograms/kilogram

µg/L – micrograms/litre

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
- COT (2004): Annex 3. Updated COT Statement on a survey of methylmercury in fish and shellfish.
- Debes F., Weihe P., Grandjean P. (2016): Cognitive deficits at age 22 years associated with prenatal exposure to Methylmercury, *Cortex*, 74;358-369.
- Defra (2013): Technical Guidance on normal levels of contaminants in Welsh soil: Mercury. British Geological Survey (Keyworth, Nottingham) and Defra (London), Soils R&D Project SP1008, January 2013. Available at: http://www.bgs.ac.uk/gbase/NBCDefraProject.html
- Defra (2012): Technical Guidance Sheet on normal levels of contaminants in English soils: Mercury. Technical Guidance Sheet No. TGS07, July 2012. Department for Environment, Food and Rural Affairs (Defra), Soils R&D Project SP1008. Available at: http://www.bgs.ac.uk/gbase/NBCDefraProject.html
- 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/
- EFSA (2012): Scientific Opinion on the Risk for public health related to the presence of mercury and methylmercury in food, *EFSA Journal*, 10(12); 2985.
- EMEA (2004): EMEA public statement on Thiomersal in vaccines for human use-Recent evidence supports the safety of Thiomersal containing vaccines, Available online: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003904.pdf , Accessed Jan 2018
- Environment Agency (2009): Soil Guidance Values for mercury in soil. Available at: http://residus.gencat.cat/web/.content/home/ambits_dactuacio/sols_contaminats/Cercasols_recursos_sol/Soil-Guideline-Values-for-mercury-in-soil-UK-Environment-Agency-March-2009.pdf , Accessed Dec.2016
- European Commission (2011): Ambient air pollution by Mercury (Hg), Chapter 4, available at http://ec.europa.eu/environment/air/pdf/pp_mercury4.pdf , Accessed Dec 2016
- FAO/WHO (Food and Agriculture Organization of the United Nations/World Health Organization) (2004): Safety evaluation of certain food additives and contaminants. Methylmercury. WHO Food Additives Series, 52;565-623.
- FAO/WHO (Food and Agriculture Organization of the United Nations/World Health Organization) (2011a): Report of the Joint FAO/WHO Expert Consultation on the Risks and Benefits of Fish Consumption. Rome, Food and Agriculture Organization of the United Nations; Geneva, World Health Organization. WHO Food Additives Series, 50 pp.
- FAO/WHO (Food and Agriculture Organization of the United Nations/World Health Organization) (2011b): Safety evaluation of certain food additives and contaminants. Methylmercury. WHO Food Additives Series, 63, 605-684.
- FSA (2016a). Survey of metals and other elements in infant foods (to be published)
- FSA (2016b). Metals and other elements in the 2014 Total Diet Study (to be published)

- Miklavčič A., Casetta A., Tratnik J.S., Mazej D., Krsnik M., Mariuz M., Sofianou K., Špirić Z., Barbone F., Horvat M. (2013): Mercury, arsenic and selenium exposure levels in relation to fish consumption in the Mediterranean area, *Environmental Research*, 120; 7-17.
- Miklavčič A., Cuderman P., Mazej D., Snoj Tratnik J., Krsnik M., Planinsek P., Osredkar J., Horvat M. (2011): Biomarkers of low-level mercury exposure through fish consumption in pregnant and lactating Slovenian women. *Environmental Research*, 111; 1201-1207.
- Oxford Vaccine Group (2017): Vaccine Knowledge Project, University of Oxford, Available online: http://vk.ovg.ox.ac.uk/vaccine-ingredients#thiomersal , Accessed Jan 2018
- Spyker, D.A., Spyker J.M. (1977): Response model of cross-fostering studies:Prenatal versus postnatal effects of offspring exposed to methylmercury dicyandiamide, *Toxicol. Appl. Pharmacol, 40(3);511-527.*
- Strain J.J., van Wijngaarden E., Thurston S.W., Mulhem M.S., Watson G.E, Love T.M., Smith T.H., York K., Harrington T., Shamlaye C.F., Henderson J., Myres G.J., Davidson P.W. (2015): Prenatal exposure to methylmercury from fish consumption and polyunsaturated fatty acids association with child development at 20 mo of age in an observational study in the Republic of Seychelles, *The American Journal of Clinical Nutrition*, 101; 530-537.
- Suda I., Hirayama K. (1992): Degradation of methyl and ethyl mercury into inorganic mercury by hydroxyl radical produced from rat liver microsomes. *Archives of Toxicology,* 66 ;398-402.
- US-EPA (United States Environmental Protection Agency), 1997. Mercury study report to Congress EPA-452/R-97-004. Volume 5: Health Effects of Mercury and Mercury Compounds. Washington, DC, United States Environmental Protection Agency. Available from http://www.epa.gov/ttn/oarpg/t3/reports/volume5.pdf.
- van Wijngaarden E., Thurston S.W., Myers G., Harrington D., Cory-Slechta D., Strain J.J., Watson G.E & Zareba G., Love T.M., Henderson J., Shamlaye C.F., Davidson P. (2017): Methyl mercury exposure and neurodevelopmental outcomes in the Seychelles Child Development Study Main cohort at age 22 and 24years, *Neurotoxicology and Teratology,*59; DOI: 10.1016/j.ntt.2016.10.011.
- WHO (2006): Global Vaccine Safety- Statement on Thiomersal, Available online:http://www.who.int/vaccine_safety/committee/topics/thiomersal/statement_jul2006/en/ , Accessed Jan 2018
- WHO (2017): Mercury and health Fact Sheet. Available online http://www.who.int/mediacentre/factsheets/fs361/en/ , Accessed Nov 2017