

27. The 3 species with the highest mercury content were shark, swordfish and marlin. These fish had mean mercury levels of 1.52, 1.36, and 1.09 mg/kg respectively and were therefore above the levels defined in European Commission Regulation 221/2002. Fresh tuna contained mercury levels ranging from 0.141 to 1.50 mg/kg with a mean of 0.40 mg/kg (only one sample out of 20 exceeded 1 mg/kg, the maximum mercury concentration in the other 19 samples was 0.62 mg/kg), whereas canned tuna had a lower mean mercury level of 0.19 mg/kg.

Blood mercury levels in British adults

28. A report produced by the Medical Research Council Human Nutrition Research in March 2002 detailed the provisional blood total mercury data obtained from 1320 adults (aged 19-64 years) participating in the National Diet and Nutritional Survey (NDNS)².

29. The mean and 97.5th percentile blood mercury levels in the survey were 1.6 and 5.88 µg mercury/L respectively. The highest blood mercury level found in the study was approximately 26 µg/L in an individual with a high fish intake. If the blood mercury level was at steady state, and assuming a body weight of 70 kg and a blood volume of 9% of the body weight, then using the same pharmacokinetic model employed by JECFA in its 2003 evaluation, this would correspond to a mercury intake of approximately 5.39 µg/kg bw/week (0.77 µg/kg bw/day).

30. Of the population covered by the survey, 97.5% had blood mercury levels indicating that their mercury intakes were within the 2003 JECFA PTWI of 1.6 µg/kg bw/week.

COT evaluation

31. The Committee discussed the possible risks associated with dietary exposure to methylmercury, in the light of the new JECFA PTWI and the information on intakes from fish and on blood mercury levels in the UK population.

Toxicokinetic considerations

32. Following ingestion, approximately 95% of methylmercury is absorbed through the gastrointestinal tract, and it is subsequently distributed to all tissues in about 30 hours with approximately 5% found in blood and 10% in the brain. The methylmercury concentration in red blood cells is approximately 20 times higher than that in the plasma. Methylmercury readily crosses the placental barrier. Fetal brain mercury levels are approximately 5-7 times higher than in maternal blood. Methylmercury readily accumulates in hair and the ratio of hair mercury level (µg/g) to maternal blood mercury level (µg/L) is approximately 250:1. Based on comparisons to hair concentrations, cord blood concentrations are reported to be 25% higher than the concentrations in maternal blood¹⁰.

33. The excretion process for methylmercury involves transfer of the glutathione-mercury complex into the bile, demethylation by gut microflora to the inorganic form, then elimination from the body in the faeces. The half-life of mercury in the body is approximately 70 days in adults, with steady state being reached in about one year. Significant amounts of methylmercury also pass into the breast milk of lactating women, resulting in a decreased mercury half-life of approximately 45 days²⁸.

34. Doherty and Gates²⁹ reported that the excretion rate of mercury in the suckling rodent is less than 1% of the adult excretion rate. Sundberg *et al.*³⁰ reported a low elimination of mercury in suckling mice until lactational day 17. This is probably because biliary secretion and demethylation by microflora (which lead to faecal excretion) do not occur in suckling animals. The role of these processes in suckling human infants is unknown⁴.

35. The concentration of mercury in breast-milk is approximately 5% of the blood mercury concentration of the mother²⁸. Amin-Zaki *et al.*³¹ reported that in women exposed to high levels of methylmercury during the Iraqi poisoning incident, 60% of the mercury in breast-milk was in the form of methylmercury. Therefore it may be estimated that the concentration of methylmercury in the breast-milk is approximately 3% of the total mercury concentration in the blood. For an infant to be exposed to methylmercury at the new JECFA PTWI of 1.6 µg/kg bw/week, the mother would have to be exposed to the following methylmercury level:

Methylmercury intake of infant: = 0.23 µg/kg bw/day

Assuming a daily milk intake of 150 mL/kg bw
Concentration of methylmercury in milk = 1.53 µg/L

Assuming 3% methylmercury transfer from maternal blood to milk
Maternal blood mercury level = 51.1 µg/L

Using the pharmacokinetic model employed by JECFA in its 2003 evaluation, and assuming a maternal body weight of 65kg
Maternal methylmercury intake = 1.36 µg/kg bw/day (9.5 µg/kg bw/week)

Susceptible populations

36. In its 2003 evaluation of methylmercury, JECFA established a PTWI of 1.6 µg/kg bw/week in order to protect against neurodevelopmental effects but found no information to indicate that the previous PTWI of 3.3 µg/kg bw/week was not sufficiently protective for groups not susceptible to neurodevelopmental effects. The COT has been asked to advise on safety guidelines for methylmercury that could be used in assessing risks associated with fish consumption. The Committee concluded that the previous JECFA PTWI of 3.3 µg/kg bw/week could be used for the general population.

37. In its 2002 statement, the Committee had used the EPA reference dose of 0.1 µg/kg bw/day (0.7 µg/kg bw/week) in considering dietary exposure of

the subpopulations at risk of neurodevelopmental effects. Members therefore discussed the differences between the 2003 JECFA PTWI and the EPA reference dose. The major differences related to the use of default uncertainty factors in derivation of the EPA reference dose, whereas chemical-specific data had been incorporated into the JECFA PTWI. The 2003 JECFA evaluation also took into account data published since the EPA review. The Committee had previously noted that the EPA reference dose was precautionary and agreed that the 2003 JECFA PTWI of 1.6 µg/kg bw/week should be used to protect against neurodevelopmental effects in susceptible populations. This PTWI is only necessary for the neurodevelopmental endpoint and therefore does not apply to the general population.

38. Due to this approach of applying different guidelines for different population groups, the Committee has given particular consideration to determining which groups are at higher risk and can be considered to be susceptible populations.

39. The critical effect of methylmercury is on the developing central nervous system and therefore pregnant women are considered to be the most susceptible population because of the risk to the fetus. There have been no studies of the effects of exposure prior to becoming pregnant. However, because the half-life of methylmercury in the human body is approximately 70 days, steady state concentration is attained in approximately one year and a woman's blood mercury level at the time of becoming pregnant is dependent on the exposure to methylmercury during the preceding year. The Committee therefore agreed that women who may become pregnant within the next year should also be considered as a susceptible population.

40. The evidence regarding consideration of other susceptible populations is not conclusive. Animal experiments indicate that exposure via breast-milk has less serious consequences to the central nervous system than prenatal exposure. Spyker and Spyker³² reported that the effects of prenatal exposure to methylmercury dicyandiamide on the survival and weight gain of the offspring were more severe than those seen with postnatal exposure, and were greatest when the methylmercury was administered late in the period of organogenesis. However, these results are not necessarily relevant to the health effects of concern in human exposure.

41. Data from a 5-year longitudinal study following the Iraq poisoning incident have suggested that some children exposed to methylmercury via breast-milk demonstrated delayed motor development³¹. The maternal blood mercury levels immediately following the incident were estimated by extrapolation to be in the range of approximately 100µg/L to 5000 µg/L. Mothers who showed signs and symptoms of poisoning (ataxia, dysarthria, visual disturbance etc.) tended to have the higher blood levels (3000 to 5000 µg/L) although some women with levels in this range were asymptomatic.

42. The affected infants all had blood mercury levels above those associated with the 2000 JECFA PTWI of 3.3 µg/kg bw/week, and most of them had blood mercury levels higher than the minimum toxic level for adults of 200

µg/L, defined by JECFA. There was no paralysis, ataxia, blindness or apparent sensory change and there were no cases of the severe mental destruction and cerebral palsy that had been seen in the prenatally exposed infants of Minamata. However, language and motor development of the children were delayed. The authors of the study concluded that breast-fed infants are at less risk than the fetus, since most of the brain development has already occurred and the effects seen in the breast-feeding infant are different from those seen in infants exposed prenatally and not as severe.

43. There is no evidence that chronic exposure to methylmercury via breast milk at levels below those observed in the Iraqi incident has any adverse effect on the neurophysiological/psychological development of the child. Data from the Faroe Islands study suggests that the beneficial effects of nursing on early motor development are sufficient to compensate for any adverse impact that prenatal exposure to low concentrations of methylmercury might have on these endpoints^{33,34}. Grandjean *et al.*³³ looked at the relationship between seafood consumption and concentrations of contaminants in breast-milk in the Faroes Island population. Of 88 samples of breast-milk, three had a mercury level that would cause the infant to exceed the old PTWI for mercury.

44. There have been few studies of the effects of methylmercury on young children. Most information has come from the poisoning incidents in Minamata, Niigata and Iraq. In all of these cases the exposures were very high, and in Iraq, the exposure was acute. Methylmercury is excreted by children as efficiently as by adults⁴. In the incidents where children were exposed to methylmercury directly rather than prenatally, the damage seen in the brain was similar to that seen in adults: focal lesions of necrosis. The damage seen when the fetus is exposed is much more widespread⁴.

45. The longitudinal study in the Seychelles has attempted to examine the effects of postnatal exposure to methylmercury¹². This is complicated by the facts that in the Seychelles, the children exposed to methylmercury postnatally are also exposed prenatally, and the study has been unable to demonstrate any mercury-related deficits in the neurological development of children. However higher postnatal methylmercury exposure had a positive association with test scores. It was suggested that this may be because a higher mercury level indicates a high fish intake and therefore a diet rich in n-3-polyunsaturated fatty acids and vitamin E, which have beneficial effects and may mask any subtle neurological deficits due to chronic low level exposure to methylmercury.

46. The risk is greater for women who are pregnant or likely to become pregnant within the following year because of the effects of methylmercury on the developing central nervous system of the fetus. There is uncertainty with respect to whether infants and young children are at greater risk of methylmercury toxicity whilst the central nervous system is still developing. The limited data available indicate that this is not the case for children but the possibility of increased sensitivity of infants cannot be discounted. Correlation of intakes by the breast-fed infant and the mother (paragraph 35) indicates that the methylmercury intake of the breast-fed infant is within the 2003 PTWI

of 1.6 µg/kg bw/week if the mother's intake is within the 2000 PTWI of 3.3 µg/kg bw/week.

Assessment of dietary exposure estimates

47. Dietary exposure to mercury was estimated for those fish species for which reliable consumption data were available^{35,36,37,38} (salmon, prawns and canned tuna) together with exposure from the rest of the diet. Dietary exposures to these fish were also calculated for adult women as this population group contains the most susceptible populations (Table 1). This table is a revised version of that which appears in the FSIS¹ as it incorporates the most up-to-date consumption and occurrence data available for the rest of the diet from the TDS. Of these fish, canned tuna provided the largest contribution to dietary mercury exposure for high level consumers. Total fish consumption by the high level consumer was equivalent to approximately five portions per week (688g).

48. The estimates of average and high level total dietary exposure for almost all age groups, from fish for which consumption data are available, are within the 2003 JECFA PTWI for methylmercury of 1.6 µg/kg bw/week, and not expected to be harmful. The mercury exposure from the whole diet in toddlers and young people aged 4-6 years who are high level consumers exceeds the 2003 PTWI of 1.6 µg/kg bw/week by between 13 and 26% but are well within the 2000 PTWI. The estimated intakes of toddlers who are high level consumers of canned tuna exceeds the 2003 PTWI by 50%, but again are within the 2000 PTWI. Children of this age (1.5-4.5 years) are likely to be less susceptible to neurodevelopmental effects. Therefore this exceedance of the 2003 PTWI is not likely to result in harmful effects.

49. Estimates were also made of the methylmercury intake resulting from consumption of one portion of shark, marlin, swordfish or fresh tuna, for which consumption data are not available (Table 2), using portion sizes as recorded in the NDNS for fish consumption^{36,37,38}. For comparative purposes similar estimates were made for canned tuna.

50. For adults, consumption of one weekly portion of shark, swordfish or marlin could result in a mercury intake in the range of 2.2 to 3.0 µg/kg bw/week, before considering intake from the rest of the diet (upper bound mean 0.28 µg mercury/kg bw/week, not all as methylmercury). Regular intake at this level during pregnancy, or in the year leading up to pregnancy could be associated with a risk of neurodevelopmental effects in the fetus. The methylmercury intake resulting from consumption of either two 140g portions of fresh tuna or four 140g portions of canned tuna would not be expected to result in neurodevelopmental effects.

51. Regular consumption of more than one portion of shark, swordfish or marlin per week could be associated with a risk of neurotoxicity in adults.

52. Dietary exposure of children is higher because their food intake is greater on a body weight basis. Regular consumption of one weekly portion of

shark, swordfish or marlin per week by children under the age of 14 could result in a methylmercury intake in the range of 3.0 to 5.2 $\mu\text{g}/\text{kg}$ bw/week, before considering intake from the rest of the diet. 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 any of the age groups.

Conclusions

53. We *note* that there has been no new information published to indicate that the 2000 PTWI of 3.3 $\mu\text{g}/\text{kg}$ bw/week is not sufficiently protective of the general population. We therefore *consider* that a methylmercury intake of 3.3 $\mu\text{g}/\text{kg}$ bw/week may be used as a guideline to protect against non-developmental adverse effects.

54. We *conclude* that the 2003 JECFA PTWI of 1.6 $\mu\text{g}/\text{kg}$ bw/week is sufficient to protect against neurodevelopmental effects in the fetus. This PTWI should be used in assessing the dietary exposure to methylmercury of women who are pregnant, and who may become pregnant within the following year.

55. We *consider* that a guideline of 3.3 $\mu\text{g}/\text{kg}$ bw/week is appropriate in considering intakes by breastfeeding mothers as the intake of the breast-fed infant would be within the new PTWI of 1.6 $\mu\text{g}/\text{kg}$ bw/week.

56. We *consider* the NDNS blood level data are reassuring with respect to average and high level consumption of fish. The adults surveyed had blood mercury levels indicating that 97.5% of the population had dietary intakes below 1.6 $\mu\text{g}/\text{kg}$ bw/week.

57. We *conclude* that average and high-level dietary exposure to methylmercury, resulting from the wide range of fish for which consumption data are available, is not likely to be associated with adverse effects in the developing fetus or at other life stages.

58. We *note* that consuming one weekly 140 g portion of either shark, swordfish or marlin would result in a dietary methylmercury exposure close to or above 3.3 $\mu\text{g}/\text{kg}$ bw/week in all age groups. We *consider* that this consumption could be harmful to the fetus of women who are pregnant or become pregnant within a year, but would not be expected to result in adverse effects in other adults.

59. We *note* that the mercury content of tuna is lower than that of shark, swordfish or marlin, but higher than that of other commonly consumed fish. We *consider* that 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.

60. We *recommend* that further research should include development of analytical methodology to allow direct measurement of methylmercury,

mechanistic studies to help elucidate population groups more at risk and research integrating the risks with nutritional benefits of fish consumption.

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