Annex 3. Updated COT statement on a survey of mercury in fish and shellfish

Introduction

6.1 In 2002, the Committee reviewed the results of a Food Standards Agency (FSA) survey of the mercury levels in imported fish and shellfish and UK farmed fish and their products [1] and the provisional results of blood mercury levels in UK adults [2].

6.2 The Committee concluded that the Provisional Tolerable Weekly Intake (PTWI) of 3.3 µg/kg bw/week could be used in assessing methylmercury intakes by the general population. This PTWI was initially established by the Joint FAO/WHO Expert Committee on Food Additives and Contaminants (JECFA) in 1972 and confirmed on a number of occasions up to the year 2000, However, the 2000 JECFA PTWI was not considered adequate to protect against neurodevelopmental effects. The EPA reference dose of 0.1 µg/kg bw/day (0.7 µg/kg bw/week) was therefore applied for women who are pregnant, or who may become pregnant within the following year, or for breast-feeding mothers. The COT also noted that its conclusions should be reviewed following the JECFA evaluation of methylmercury in 2003. [3]

6.3 In June 2003, JECFA recommended that the PTWI for methylmercury should be reduced from 3.3 µg/kg bw/week to 1.6 µg/kg bw/week. The Committee has therefore reviewed its previous evaluation in the light of the new JECFA PTWI, also taking into account more recent data on fish consumption by adults. This statement on mercury in fish and shellfish supersedes COT statement 2002-04.

6.4 The FSA has asked a subgroup of members of the COT and the Scientific Advisory Committee on Nutrition (SACN) to provide combined advice on

the risks and benefits associated with fish consumption. The advice expressed in this COT statement therefore aims to protect the populations who are most susceptible to the risks of methylmercury, without being over-protective of individuals at lesser risk.

Background

6.5 The toxicity of mercury is dependent on whether it is inorganic, elemental or organic (e.g. methylmercury). Methylmercury affects the kidneys and also the central nervous system, particularly during development, as it crosses both the blood-brain barrier and the placenta [4]. Both neuro- and nephrotoxicity have been associated with acute methylmercury poisoning incidents in humans, and neurotoxicity, particularly in the developing fetus, has been associated with lower level chronic exposures.

6.6 Exposure of the general population to mercury can occur via inhalation of mercury vapour from dental amalgam fillings (elemental), or through the diet (methylmercury and inorganic mercury) [5]. Methylmercury in fish makes the most significant contribution to dietary exposure to mercury, although smaller amounts of inorganic mercury are present in other food sources. All forms of mercury entering the aquatic environment, as a result of man's activities or from geological sources, are converted into methylmercury by microorganisms and subsequently concentrated in fish and other aquatic species. Fish may concentrate the methylmercury either directly from the water or through consuming other components of the food chain. Methylmercury has a half-life of approximately 2 years in fish; thus, large older fish, particularly predatory species, will have accumulated considerably more methylmercury than small younger fish.

Previous COT evaluation

6.7 The COT previously considered the results of a survey of metals and other elements in marine fish and shellfish [6] published by the Ministry of Agriculture, Fisheries and Food (MAFF) in 1998. The survey examined a number of fish and shellfish species landed in the UK or imported from overseas ports including cod, haddock, herring, mackerel, lobster, mussels, crab and shrimps and samples of cod fish fingers. The survey also

produced estimates of the mean and 97.5th percentile dietary intakes of the elements surveyed.

6.8 The 1998 survey demonstrated that the levels of mercury in the fish and shellfish tested were low and that average and high level fish and shellfish consumers in the UK would not exceed the then current JECFA PTWI for methylmercury of 3.3 mg/kg bw/week, even assuming all the mercury in fish was in this form. The estimated mercury intake for the highest level consumer was 1.1 mg/kg bw/week including mercury intake from the rest of the diet. The main conclusion drawn from the survey was that "dietary intakes of the elements surveyed were below safe limits, where defined, and did not represent any known health risk even to consumers who eat large amounts of marine fish or shellfish".

International Safety Guidelines

Previous Joint FAO/WHO Expert Committee on Food Additives (JECFA) Evaluations

6.9 In 1972, JECFA established a PTWI of 5 mg/kg bw/week for total mercury, of which no more than two thirds (3.3 mg/kg bw/week) should be from methylmercury [7]. The PTWI of 3.3 mg/kg bw/week for methylmercury was subsequently confirmed in 1989 and 2000 [8,9]. The PTWI was derived from toxicity data resulting from poisoning incidents at Minamata and Niigata in Japan. In these incidents the lowest mercury levels associated with the onset of clinical disease in adults were reported to be 50 mg/g in hair and 200 mg/L in whole blood. Individuals displaying clinical effects, such as peripheral neuropathy, at these mercury levels were considered to be more sensitive than the general population, because there were a number of persons in Japan and other countries with higher mercury levels in hair or blood who did not experience such effects. However, the methods employed in determining the intake associated with toxicity, and the subsequent establishment of the PTWI are unclear.

6.10 In 1989, JECFA had noted that pregnant women and nursing mothers may be at greater risk than the general population to adverse effects from methylmercury. Therefore in its' 2000 re-evaluation of methylmercury, JECFA paid particular attention to possible effects of prenatal and

postnatal exposure, looking at large long-term prospective epidemiological studies conducted in the Seychelles Islands and the Faroe Islands. These studies attempted to identify the lowest dietary mercury exposure associated with subtle effects on the developing nervous system , , , . They followed the neurological development of the children by testing their learning and spatial abilities at a number of time-points during their childhood. A number of smaller studies were also considered.

6.11 JECFA compared the two main studies;

- The Faroe Islands cohort was tested up to the age of 7 years, whereas at the time of the JECFA evaluation, the Seychelles cohort had only been tested up to the age of 5.5 years.

- Exposure in the Seychelles was through consumption of a range of fish species with average mercury concentrations between 0.05 and 0.25 mg/kg. In the Faroe Islands, most of the population consumed fish at least three times a week and occasionally (approximately once per month) consumed pilot whale, which contains up to 3 mg/kg mercury. Pilot whale also contains high concentrations of polychlorinated biphenyls (PCBs), but a reanalysis of the data indicated that any effects seen in the Faroes cohort could not be attributed to confounding by the PCBs .

- The two studies used different methodology in assessing methylmercury exposure. The Seychelles study used maternal hair samples (approx. 9cm long), one taken shortly after birth to estimate methylmercury exposure during pregnancy and one taken 6 months later. The Faroe Islands study used cord blood and maternal hair (various lengths) taken at birth.

- The studies used different batches of tests to assess the effects of methylmercury on neurological development. The tests used in the Faroe Islands study examined specific domains in the brain (visual, auditory, etc.). The Seychelles study used tests of a more global nature, with each test examining a number of domains.

6.12 JECFA found that although the mean mercury exposures during pregnancy (assessed by maternal hair mercury) were similar[b], the results of these two studies were conflicting. In the Faroes study, regression analysis showed an association between methylmercury exposure and impaired performance in neuropsychological tests, an association that remained even after excluding the results of children with exposures associated with greater than 10 µg/g maternal hair mercury. However in the Seychelles study regression analysis identified no adverse trends, but increased maternal hair mercury was associated with a small statistically significant improvement in test scores on several of the developmental outcomes. The investigators noted that this could be due to beneficial nutritional effects of fish. A secondary analysis was performed where the results were split into sub-groups based on the maternal hair mercury level. Test scores in children with the highest mercury exposures (12 - 27 µg/g maternal hair) were not significantly different from the test scores in children with lowest exposure (< 3µg/g maternal hair).

6.13 A smaller study carried out in New Zealand on 6 year-old children used a similar batch of tests to the Seychelles study and had similar exposure to methylmercury, yet found methylmercury related detrimental effects on behavioural test scores. However there were possible confounding factors that may have influenced the results of the New Zealand study, such as the ethnic group and social class of the children studied.

6.14 Having considered all of the epidemiological evidence, JECFA concluded that it did not provide consistent evidence of neurodevelopmental effects in children whose mothers had hair mercury levels of 20 µg/g or less. Since there was no clear indication of a consistent risk, JECFA did not revise its' PTWI, but recommended that methylmercury should be re-evaluated when the latest evaluation of the Seychelles study and other relevant data become available[9].

[b] Seychelles: arithmetic mean 6.8 µg/g, range 0.5-26.7 µg/g;
Faroes: geometric mean, 4.27 µg/g, the upper mercury level in maternal hair is not clear from the reported data but may be as high as 70 µg/g.

Environmental Protection Agency (EPA)

6.15 In 1997 the US EPA established a reference dose of 0.1 µg/kg bw/day for methylmercury . This was based on a peak maternal hair mercury level during pregnancy of 11 µg/g, which was associated with developmental effects (e.g. late walking, late talking, mental symptoms, seizures) in children exposed *in utero* during a poisoning incident in Iraq in 1971.

6.16 In 2000, the US National Research Council (NRC) published a review of this EPA reference dose [26]. Following analysis of the data resulting from the available epidemiological studies, the NRC identified a benchmark dose lower confidence limit of 12 µg/g in maternal hair (corresponding to 58 µg/L in cord blood, assuming a ratio of hair:cord blood of 200:1). This was the lower 5% confidence limit of the lowest dose considered to produce a sufficiently reliable neurological endpoint (a 5% increase in abnormal scores on the Boston Naming Test [**]) in the Faroe Islands study. The NRC made a number of assumptions in deriving an estimate of methylmercury intake and included a composite uncertainty factor of 10, to account for interindividual variability and database insufficiencies, concluding that the reference dose of 0.1 µg/kg bw/day, as had previously been used by the EPA, was scientifically justifiable.

2003 JECFA Evaluation

6.17 At its 61st meeting in June 2003 , JECFA reviewed the new data from the Seychelles Child Development Study [18], re-analyses of the Faroes and New Zealand studies, epidemiological data from a number of small scale cross-sectional studies, and additional epidemiological data on reproductive toxicity, immunotoxicity, cardiotoxicity and general medical status.

[**] The Boston Naming Test is a neuropsychological test that assesses an individual's ability to retrieve a word that appropriately expresses a particular concern, for example naming an object portrayed by a simple line drawing.

6.18 The 9-year neurodevelopmental evaluations from the Seychelles study were performed using neurodevelopmental tests which, in contrast to the earlier assessments, allowed a direct comparison with the results of the Faroes Islands Study. The new data from the Seychelles study were consistent with results obtained at younger ages and provided no evidence for an inverse relationship between maternal methylmercury exposure and neurodevelopmental performance in infants. Additional analyses carried out on the Seychelles data from younger ages did not alter the conclusion that in the Seychelles population of frequent fish-consumers, no adverse effects of prenatal methylmercury exposure have been detected.

6.19 No new data were available from the Faroes Islands study. New analyses of the existing data did not support a role of occasional exposure to higher levels of methylmercury or polychlorinated biphenyls (PCBs) from consumption of whale-meat, in accounting for the positive associations in this study [19,20,14,21]. The additional epidemiological data from smaller cross-sectional studies on neurodevelopmental effects of methylmercury were reviewed. Because of the cross-sectional design and because adult hair mercury levels do not accurately reflect previous exposure during the critical period for neurodevelopmental effects, JECFA did not consider that the results from these studies could be used to form the basis of a dose response assessment.

6.20 JECFA noted that despite additional evidence of immunotoxicity, cardiotoxicity, and reproductive toxicity, neurotoxicity was still considered to be the most sensitive endpoint, and concluded that the PTWI should be based on studies of this endpoint. It was uncertainty about the possibility that significant immunotoxicity or cardiovascular effects could occur at levels below the neurodevelopmental benchmark dose that had led to the inclusion of an additional safety factor for database insufficiencies in the composite factor of 10 recommended by the NRC.

6.21 JECFA based its evaluation on the Seychelles and Faroe Islands studies. In the absence of a dose response analysis of the latest Seychelles data, the analysis of the data from younger ages was used since it was consistent with the latest data. Exposure associated with a maternal hair concentration of 15.3 µg/g mercury was identified as the no observed adverse effect level

(NOAEL) for the Seychelles study [22]. A benchmark dose lower confidence limit (BMDL) of 12 µg/g mercury in maternal hair was determined from the Faroes data [23,24,25,26,27]. This was viewed as a surrogate for the NOAEL.

6.22 Averaging the NOAEL and the BMDL resulted in a composite maternal hair concentration of 14 µg/g mercury reflecting exposure that was without effects in these study populations. Dividing by the average hair:blood ratio of 250 allowed conversion of the 14 µg/g in hair to a maternal blood mercury level of 56 µg/L. A pharmacokinetic model appropriate to pregnancy was then used to convert the blood mercury level to a steady-state daily ingestion of methylmercury of 1.5 µg/kg bw/day, which would be without appreciable adverse effects in the offspring of the Seychelles and Faroe Islands study populations. The model assumed a maternal blood volume of 7 L (9% of body weight) whereas the EPA used a value of 5 L and the NRC 3.6 L.

6.23 JECFA then applied a data-specific adjustment factor of 2 to allow for inter-individual variability in the hair:blood ratio, and a default uncertainty factor of 3.2 to account for inter-individual variability in the association between blood mercury concentration and intake. This resulted in a PTWI of 1.6 µg/kg bw/week, which JECFA considered to be sufficiently protective of the developing fetus. A factor for inter-individual variability in toxicodynamics was not required because the PTWI was based on studies in the most sensitive subgroup.

6.24 In its review, JECFA found no additional information that would suggest that the general population is at risk of methylmercury toxicity at intakes up to the previous PTWI of 3.3 µg/kg bw/week.

Survey of the mercury levels in fish

6.25 The 2002 FSA survey complemented the previous MAFF survey since it examined a wider range of fish, including imported exotic species of fish that have become more widely available on the UK market. These included shark, swordfish, marlin, orange roughy, red snapper and monkfish, as well as UK farmed fish such as salmon and trout [1].

6.26 Of the fish species covered by the survey, all but 3 species had mean mercury levels falling within the range 0.01 –0.6 mg/kg of fish. This range is in line with the levels defined by European Commission Regulation 466/2001 as amended by European Commission Regulation 221/2002 (0.5 mg of mercury/kg for fish in general and 1.0 mg mercury/kg for certain larger predatory species of fish including shark, swordfish, marlin, tuna and orange roughy).

6.27 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

6.28 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 NDNS [2].

6.29 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 (0.77µg/kg bw/day).

6.30 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

6.31 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

6.32 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 (mg/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 blood [10].

6.33 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 days [28].

6.34 Doherty and Gates [29] reported that the excretion rate of mercury in the suckling rodent is less than 1% of the adult excretion rate. Sundberg *et al*. 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 unknown [4].

6.35 The concentration of mercury in breast-milk is approximately 5% of the blood mercury concentration of the mother [28]. 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 mg/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

6.36 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.

6.37 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.

6.38 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.

6.39 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.

6.40 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 Spyker [32] 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.

6.41 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 development [31]. 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.

6.42 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.

6.43 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.

6.44 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 adults [4]. 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 widespread [4].

6.45 The longitudinal study in the Seychelles has attempted to examine the effects of postnatal exposure to methylmercury [12]. 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.

6.46 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

6.47 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 6.1). This table is a revised version of that which appears in the FSIS[1] 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).

6.48 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.

6.49 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 6.2), using portion sizes as recorded in the NDNS for fish consumption [36,37,38]. For comparative purposes similar estimates were made for canned tuna.

6.50 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.

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

6.52 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 µg/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

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

6.54 We *conclude* that the 2003 JECFA PTWI of 1.6 µg/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.

6.55 We *consider* that a guideline of 3.3 µg/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 µg/kg bw/week.

6.56 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 µg/kg bw/week.

6.57 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.

6.58 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 µg/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.

6.59 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.

6.60 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.

COT Statement 2003/06
December 2003

Table 6.1: Estimated mean and high level dietary intakes of mercury from salmon, prawns, canned tuna and the whole diet.

Consumer group	Mercury Intake - µg/kg bw/week [a]							
	Salmon [b]		Prawns [b]		Canned Tuna [b]		Whole Diet [c,d]	
	Mean	97.5%	Mean	97.5%	Mean	97.5%	Mean	97.5%
Infants	0.01	0.01	- [e]	- [e]	0.04	0.13	0.04	0.13
Toddlers	0.18	0.53 [f]	0.13	0.45 [f]	0.84	2.45	0.56	2.17
Young People aged 4 – 6	0.18	0.39 [g]	0.09	0.34 [f]	0.53	1.61	0.55	1.82
Young People aged 7 – 10	0.11	0.36 [f]	0.06	0.15 [f]	0.39	1.26	0.41	1.40
Young People aged 11 – 14	0.09	0.23 [g]	0.04	0.13 [f]	0.32	0.98	0.29	1.05
Young People aged 15 – 18	0.08	0.15 [g]	0.04	0.11	0.27	0.68	0.25	0.84
Adults	0.10	0.32	0.04	0.14	0.30	1.05	0.31	1.19
Adults – Women only	0.11	0.32	0.05	0.16	0.34	1.19	0.34	1.19

a) Consumption data for salmon, prawns and tuna are taken from the following sources:
   - 2002 National Diet and Nutritional Survey: adults aged 19 to 64 years. [38]
   - Food and Nutrient Intakes of British Infants Aged 6-12 Months. [35]
   - National Diet and Nutrition Surveys Children Aged 1.5 – 4.5 years. [37]
   - National Diet and Nutrition Survey: young people aged 4-18 years. Volume 1 report of the diet and nutrition survey. [36]

b) Mercury intake from eating the named fish only, for the mean and 97.5th percentile consumers.

c) Mercury exposure from the whole diet for individuals of the whole study population, including those that eat the named fish (taken from the 2000 Total Diet Study [39]). The whole diet mercury exposure does not equal the sum of the mercury exposures from the named fish and other foods in the typical UK diet.

d) The measurement of mercury does not distinguish between inorganic and organic mercury. Therefore although methylmercury is the major contributor to mercury intake from fish, the estimate of intake from the whole diet also includes inorganic mercury.

e) No infant consumption data were recorded for prawns in the Infant Survey.

f) Based on consumption data for fewer than 60 recorded consumers, therefore exposures to be regarded with caution.

g) Based on consumption data for fewer than 20 recorded consumers, therefore exposures to be regarded with extreme caution.

These estimates have been revised to incorporate up-to-date consumption and occurrence data for the rest of the diet from the TDS.

Table 6.2: Mercury intake from one weekly portion of shark, swordfish, marlin, fresh tuna or canned tuna.

Age group (years)	Body Weight (kg)	Av. Portion Size [a] (g)	Weekly mercury intake assuming one portion of fish per week [b] (µg/kg bw/week)				
			Shark	Swordfish	Marlin	Fresh Tuna	Canned Tuna
1.5 – 4.5	14.5	50	5.24	4.62	3.79	1.38	0.66
4 – 6	20.5	60	4.44	3.90	3.22	1.17	0.56
7 –10	30.9	85	4.17	3.69	3.04	1.10	0.52
11 – 14	48.0	140	4.44	3.92	3.21	1.17	0.55
15 – 18	63.8	105	2.51	2.21	1.82	0.66	0.31
Adults	70.1	140	3.04	2.68	2.20	0.80	0.38

a) The average portion size that each age group of the population would consume at a single meal event for fish consumption, as recorded in the following National Diet and Nutrition Surveys (NDNS):
   - 1995 National Diet and Nutrition Survey: Children aged one-and-a-half to four-and-a-half years [37].
   - 2000 National Diet and Nutrition Survey: young people aged 4 to 18 years [36].
   - 1990 The Dietary and Nutritional Survey of British Adults38.

b) This intake estimate does not include the intake from the rest of the diet, which is estimated to be 0.04 µg/kg bw/day (0.28 µg/kg bw/week) [39].

References

1. Food Standards Agency (2002): Mercury in imported fish and shellfish and UK farmed fish and their products. *Food Surveillance Information Sheet* **40/03**. http://www.food.gov.uk/science/surveillance/fsis-2003/fsis402003

2. The National Diet and Nutrition Survey (2000-2001): adults aged 19 to 64 years - Blood mercury results (unpublished).

3. COT (2002). 2002-04: COT statement on Mercury in Fish and Shellfish

4. Clarkson, T. W. (2002). The three modern faces of mercury. *Environ. Health Perspect*. **110** (1): 11-23

5. Clarkson T.W, Magos L. and Myers G.J. (2003), The toxicology of mercury – Current exposures and clinical manifestations. *N Engl J Med* **349**:1731-1737.

6. Ministry of Agriculture, Fisheries and Food (1998): Survey of the concentrations of metals and other elements in marine fish and shellfish. *Food Surveillance Information Sheet* **151** http://archive.food.gov.uk/maff/archive/food/infsheet/1998/no151/151fish.htm

7. WHO (1972). Evaluation of Mercury, Lead, Cadmium and the food additives Amaranth, Diethylpyrocarbonate and Octyl Gallate. FAO Nutrition Meetings Report Series, No. 51A: WHO Food Additives Series No. 4

8. WHO (1989). Toxicological evaluation of certain food additives and contaminants. Cambridge, Cambridge University Press. (WHO Food Additives Series, No. 24).

9. WHO (2000). Safety Evaluation of Certain Food Additives and Contaminants. WHO Food Additives Series 44

10. Grandjean, P., Weihe, P., White, R. F., Debes, F., Araki, S, Yokoyama, K., Murata, K., Sorensen, N., Dahl, R., Jorgensen, P. J. (1997). Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. *Neurotoxicol. Teratol*. **19**: 417-428

11. Crump, K.S., Van Landingham, C., Shamlaye, C., Cox, C., Davidson, P.W., Myers, G.J., Clarkson, T.W. (2000). Benchmark concentrations for methylmercury obtained form the Seychelles Child Development Study. *Environ. Health Perspect*. **108**: 257-263

12. Davidson, P.W., Myers, G., Cox, C., Axtell, C., Shamlaye, C., Sloane-Reeves, J., Cernichiari, E., Needham, L., Choi, A., Wang, Y., Berlin, M., Clarkson, T. W. (1998). Effects of prenatal and postnatal methylmercury exposure from fish consumption on neurodevelopment. Outcomes at 66 months of age in the Seychelles Child Development Study. *JAMA* **280**: 701-707

13. Myers, G. J., Davidson, P. W., Shamlaye, C. F. (1998). A review of methylmercury and child development. *Neurotoxicology* **19**: 313-328

14. Budtz-Jorgensen, E., Keiding N., Grandjean P. and White RF. (1999). Methylmercury neurotoxicity independent of PCB exposure. *Environmental Health Perspectives*, **107** (5): 236 – 237

15. Kjellstrom, T., Kennedy, P., Wallis, S., Stewart, A., Friberg, L., Lind, B., Witherspoon, P., Mantell, C. (1989). Physical and mental development of children with prenatal exposure to mercury from fish. Stage 2: Interviews and psychological tests at age 6. National Swedish Environmental Protection Board, Report 3642, Solna, Sweden

16. EPA (U.S. Environmental Protection Agency). (1997). Mercury Study Report to Congress. Vol. IV: An assessment of exposure to mercury in the United States. EPA-452/R-97-006. U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards and Office of Research and Development

17. National Research Council (2000), Toxicological effects of Methylmercury. National Academy Press, Washington, DC.

18. WHO (2003). Safety Evaluation of Certain Food Additives and Contaminants; Methylmercury. Summary and Conclusions of the 61st JECFA meeting. ftp://ftp.fao.org/es/esn/jecfa/jecfa61sc.pdf (07/10/2003)

19. Myers, G.J., Davidson, P.W., Coc, C., Shamlaye, C.F., Palumbo, D., Cernichiari, E., Sloane-Reeves, J., Wilding, G.E., Kost, J., Huang, L.S. and Clarkson, T.W. (2003). Prenatal methylmercury exposure from ocean fish consumption in the Seychelles Child development study. *The Lancet*. **361**: 1686-1692.

20. Grandjean, P., Weihe, P., Burse, V.W., Needham, L.L., Storr-Hansen, E., Heinzow, B., Debes, F., Murata, K., Simonsen, H., Ellefsen, P., Budtz-Jorgensen, E., Keiding, N. & White, R.F. (2001) Neurobehavioral deficits associated with PCB in 7-year-old children prenatally exposed to seafood neurotoxicants. *Neurotoxicol. Teratol*. **23**: 305-317.

21. Grandjean, P., Budtz-Jorgensen, E., Steuerwald, U., Heinzow, B., Needham, L.L., Jorgensen, P.J. & Weihe, P. (2003). Attenuated growth

of breast-fed children exposed to increased concentrations of methylmercury and polychlorinated biphenyls. *FASEB J*. **17**: 699-701.

22. Stewart, P.W., Reihman, J., Lonky, E.I., Darvill, T.J. & Pagano, J. (2003). Cognitive development in preschool children prenatally exposed to PCBs and MeHg. *Neurotoxicol. Teratol.* **25**: 11-22.

23. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for Mercury. 1999

24. Budtz-Jorgensen, F., Keiding, N. & Grandjean, P. (1999) Benchmark modeling of the Faroese methylmercury data. Final Report to US EPA, 1-13.

25. Budtz-Jorgensen, F., Grandjean, P., Keiding, N., White, R. & Weihe, P. (2000) Benchmark dose calculations of methylmercury-associated neurobehavioural deficits. *Tox. Lett*. 112-113, 193-199.

26. Budtz-Jorgensen, F., Keiding, N. & Grandjean, P. (2001) Benchmark dose calculation from epidemiological data. *Biometrics* **57**: 698-706.

27. Rice, D., Schoeny, R. & Mahaffey, K. (2003) Methods and rationale for the derivation of a reference dose for methylmercury by the U.S. EPA. *Risk Analysis* **23**: 107-115.

28. WHO (1976). Environmental Health Criteria 1. Mercury. United Nations Environment Programme and the World Health Organisation. Geneva

29. Doherty, R.A. and Gates, A.H. (1973). Epidemic human methylmercury poisoning; application of a mouse model system. *Paediatric Research*, **7(4)**: 319/91

30. Sundberg, J. Jonsson, S., Karlsson, M.O. and Oskarsson, A. (1999). Lactational exposure and neonatal kinetics of methylmercury and inorganic mercury in mice. *Toxicol. Appl. Pharmacol*. **154**: 160 – 169

31. Amin-Zaki, L., Majeed, M.A., Greenwood, M.R., Elhassani, S.B., Clarkson, T.W. and Doherty, R.A. (1981). Methylmercury poisoning in the Iraqi suckling infant: a longitudinal study over five years. *J. Appl. Toxicol*. **1(4)**: 210-214

32. Spyker, D.A, and Spyker J.M. (1977). Response model analysis of cross-fostering studies: Prenatal versus postnatal effects on offspring exposed to methylmercury dicyandiamide. *Toxicol. Appl. Pharmacol*, **40 (3)**: 1977 511-527

33. Grandjean, P., Weihe, P., Needham, L.L., Burse, V.W., Patterson, D.G., Sampson, E.J., Jorgensen, P.J., Vahter, M. (1995). Relation of a seafood diet to mercury, selenium, arsenic, and polychlorinated biphenyl and other organochlorine concentrations in human milk. *Environ. Res*. **71** (1): 29-38

34. Grandjean, P., Weihe, P., White, R.F. (1995a). Milestone development in infants exposed to methylmercury from human milk. *Neurotoxicol*. **16 (1)**: 27-33

35. Mills, A. & Tyler, H. (1992). Food and Nutrient Intakes of British Infants Aged 6-12 Months, HMSO

36. Gregory, J., Lowe, S., Bates, C.J., Prentice, A., Jackson, L.V., Smithers, G., Wenlock, R., and Farron, M. (2000). National Diet and Nutrition Survey: young people aged 4 to 18 years. Volume 1: Report of the diet and nutrition survey. London: TSO

37. Gregory, J., Collins, D.L., Davies, P.S.W., Hughes, J.M. and Clarke, P.C. (1995). National Diet and Nutrition Survey: Children aged one-and-a-half to four-and-a-half years. Volume 1: Report of the diet and nutrition survey. London, HMSO

38. Henderson L., Gregory J. and Swan, G. (2002). The National Diet and Nutrition Survey: adults aged 19 to 64 years. Volume 1: Types and quantities of foods consumed. TSO, UK.

39. Food Standards Agency (2004). 2000 Total Diet Study. *Food Surveillance Information Sheet* (to be published)