



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

UPDATED COT STATEMENT ON A SURVEY OF MERCURY IN FISH AND SHELLFISH

Introduction

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 products¹ and the provisional results of blood mercury levels in UK adults².

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

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.

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

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 placenta⁴. 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. 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

7. The COT previously considered the results of a survey of metals and other elements in marine fish and shellfish⁶ 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.

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 µg/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 µg/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

9. In 1972, JECFA established a PTWI of 5 µg/kg bw/week for total mercury, of which no more than two thirds (3.3 µg/kg bw/week) should be from methylmercury⁷. The PTWI of 3.3 µg/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 µg/g in hair and 200 µg/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.

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 ^{10,11,12,13}. 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.

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 ¹⁴.
- 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.

12. JECFA found that although the mean mercury exposures during pregnancy (assessed by maternal hair mercury) were similar⁸, 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).

13. A smaller study carried out in New Zealand on 6 year-old children¹⁵ 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.

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 available⁹.

Environmental Protection Agency (EPA)

15. In 1997 the US EPA established a reference dose of 0.1 µg/kg bw/day for methylmercury¹⁶. 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.

16. In 2000, the US National Research Council (NRC) published a review of this EPA reference dose²⁶. 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

⁸ 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.

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

17. At its 61st meeting in June 2003¹⁷, JECFA reviewed the new data from the Seychelles Child Development Study¹⁸, 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.

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.

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.

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.

^{**} 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.

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 study²². 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.

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.

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.

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

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 trout¹.

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).