

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

MERCURY IN FISH AND THE NEW JECFA PTWI FOR METHYLMERCURY

Introduction

1. In 2002 the COT considered the levels of mercury in fish and the risks to consumers, and agreed that its conclusions should be reviewed following the evaluation of methylmercury by the Joint Expert Committee on Food Additives and Contaminants of the World Health Organisation and the Food and Agriculture Administration (JECFA).
2. This JECFA review took place in June 2003, resulting in recommendation of a new, lower provisional tolerable weekly intake (PTWI) of 1.6 µg/kg bw/week. The Committee is asked to consider its previous conclusions on mercury in fish in light of the revised JECFA PTWI for methylmercury.

Background

3. In 2002, the COT considered the results of a survey of mercury concentrations in imported fish and shellfish and UK farmed fish and their products, blood mercury levels of adults from the 2000 adults national diet and nutrition survey (NDNS) and estimates of mercury intake. The Committee reviewed the relevant safety guidelines for methylmercury (the predominant form of mercury present in fish) and the toxicological and epidemiological information on which these guidelines were based. The statement published containing the COT conclusions is attached at Annex A.
4. The COT concluded that women who are pregnant or breastfeeding and women who may become pregnant within the following year should be considered to be at higher risk of methylmercury toxicity because of the risk of neurotoxicity to the developing foetus and neonate. The COT considered that that the JECFA PTWI for methylmercury of 3.3 µg/kg bw/week was sufficiently protective for the general population, but not for these higher risk groups. Therefore the dietary exposure of the higher risk groups was compared with the US Environmental Protection Agency (EPA) reference dose of 0.1 µg/kg bw/day (0.7 µg/kg bw/week), which was based on subtle neurological effects seen in children exposed to low levels of mercury *in utero*.

The revised JECFA PTWI

5. Methylmercury was previously evaluated at the 16th, 22nd, 33rd and 53rd meetings of JECFA (WHO 1972, 1976, 1989, 2000). At the latter meeting, JECFA reaffirmed the previously established PTWI for methylmercury of 3.3 µg/kg bw/week for the general population, but noted that the fetus and infants may be at a greater risk of toxic effects. It concluded that data from studies undertaken in the Seychelles and Faroe Islands, which were evaluated at the 53rd meeting, did not provide consistent evidence concerning the neurodevelopmental effects on children of mothers whose methylmercury intakes resulted in hair-mercury burdens of 20 mg/kg and below. Adverse effects on neurodevelopment were reported in the Faroes Island studies, but not in the Seychelles Islands study. However, different neurobehavioural assessment methods had been used for the different cohorts.

6. JECFA recommended that methylmercury be re-evaluated at a subsequent meeting in order to consider the analysis of the 8-year neurodevelopmental evaluations of the Seychelles cohort and other relevant data that might become available. At its 61st meeting in June 2003, JECFA reviewed the new data from the Seychelles Child Development Study (Myers *et al.*, 2003), 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 outcome of the discussions at the 61st meeting is attached at Annex B, and the results of the Seychelles study at 9 years are attached at Annex C.

7. The 9-year neurodevelopmental evaluations from the Seychelles study were performed using a batch of neurodevelopmental tests which, in contrast to the earlier assessments, allowed 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 neurodevelopment 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.

8. 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 (Grandjean *et al.* 2001 and 2003; Budtz-Jorgensen E, *et al.* 1999; Stewart *et al.* 2003). 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 level did not accurately reflect past levels of exposure during the critical exposure period for neurodevelopment, JECFA did not consider that the results from these studies could be used to form the basis of a dose response assessment.

9. JECFA noted that despite additional evidence of immunotoxicity, cardiotoxicity, and reproductive toxicity, neurotoxicity was still considered to be the most sensitive endpoint, and that the PTWI should be based on studies of this endpoint.

Derivation of the PTWI

10. 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 maternal hair concentration of 15.3 mg/kg mercury was identified as the no observed adverse effect level (NOAEL) for the Seychelles study (U.S. ASTDR 1999). A benchmark dose lower confidence limit (BMDL) of 12 mg/kg mercury in maternal hair was determined from the Faroes data (Budtz-Jorgensen, F *et al.*, 1999, 2000, 2001; National Research Council, 2000; Rice *et al.*, 2003). This was viewed as a surrogate for the NOAEL.

11. Averaging the NOAEL and the BMDL resulted in a composite maternal hair concentration of 14 mg/kg 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 mg/kg in hair to a blood mercury level of 56 µg/L.

12. Previous JECFA evaluations assumed that daily methylmercury intake at steady state for a 70kg person (in µg/day) was equivalent to the blood mercury level (in µg/L). Thus a blood level of 56 µg/L would have corresponded to an intake of 56 µg/day and therefore 0.8 µg/kg bw/week in a 70kg person. In its 2003 evaluation, JECFA used a one compartment pharmacokinetic model similar to that used by the National Research Council (NRC 2000). Using this model with parameters appropriate to pregnancy indicated that the blood mercury level of 56 µg/L would be associated with a steady-state daily ingestion of methylmercury of 1.5 µg/kg bw/day. This was considered to be without appreciable adverse effects in the offspring of the Seychelles and Faroe Islands study populations. The formula used was as follows:

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

Where:

C = mercury concentration in blood (µg/L)
b = elimination rate constant (0.014 days⁻¹)
V = Blood volume (9% of bw – pregnant female)
A = Fraction of the dose absorbed (0.95)
f = the absorbed fraction distributed to the blood (0.05)
bw = body weight (65 kg for pregnant female)
d = dose (µg/kg bw/day)

13. 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.

14. 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.

Previous COT discussion of the new JECFA PTWI

15. In 2003, the Committee produced a statement on the levels of 12 metals in infant foods (COT, 2003). The Committee noted that the new lower JECFA PTWI for methylmercury of 1.6 µg/kg bw/week is intended to be protective of both the general population and the high-risk groups, and therefore it could be used in assessing the dietary exposure of infants to mercury. The Committee is now invited to consider whether this conclusion can be extended to other subgroups of the population.

Additional information

Toxicological information

16. The Secretariat has conducted a literature search of papers on methylmercury published during 2003 conducted using 'Medline' and 'Toxline' in order to ensure that all the relevant information had been considered. No new information was identified either in the JECFA review, or subsequently, to indicate that the general population was not adequately protected by the former PTWA of 3.3 µg/kg bw/week.

Dietary exposure to mercury

17. At this meeting, the Committee is presented with data on analysis of metals and other elements in the 2000 Total Diet Study (Agenda item 7, paper TOX/2003/39). The estimates of dietary exposure to mercury are presented in Table 1 and have been incorporated into estimates of total dietary exposure to mercury below. Not all of the mercury in food is in the form of methylmercury.

Table 1: Estimated dietary exposure to mercury from the 2000 Total Diet Study

Population Group	Estimated dietary exposure ($\mu\text{g}/\text{kilogram}$ bodyweight/week) ^{1,2,3}	
	Mean	High-level
Adults	0.21-0.28	0.84-0.91
Toddlers (1.5-4.5 years)	0.42-0.49	1.82-1.89
Young people (4-18 years)	0.28-0.35	1.05-1.12
Elderly (free living)	0.26-0.29	0.83-0.85
Elderly (Institutional)	0.21-0.28	0.77-0.84
“Vegetarians” (including fish-eaters)	0.21	1.12

Notes

1. Exposures have been estimated from a range (lower - upper bound) of mean concentrations and these have been included as ranges where they apply.
2. The exposure to mercury by the average and high level (97.5%) consumer for all foods combined is not equal to the sum of the exposure from the individual food. It refers to the dietary exposure by a consumer consuming one or any combination of the foods containing the metal. These values are derived from a distribution of the individual consumer's consumption patterns with regards to the individual foods.
3. Consumption data for each population group taken from the relevant NDNS (Gregory 1995, 2000; Henderson 2002; Finch 1998; MAFF 1998).

Intakes of mercury from fish consumption

18. Since the previous COT discussion, the new National Diet and Nutrition Survey (NDNS) of adults aged 19-64 has been published, and shows an increase in fish consumption by women (Henderson *et al.*, 2002). Therefore the new consumption data have been used to revise the intakes of mercury for adult women for those fish for which consumption data are available. These data are presented in Table 2 and have been considered by the joint SACN/COT subgroup as part of the ongoing review of the risks and benefits of fish consumption (see <http://www.sacn.gov.uk/fish.htm>). These consumption data were also used by the Food Standards Agency in formulating advice on fish consumption based on the COT statement.

Table 2: Estimated dietary intakes of mercury by female consumers¹ of Salmon, Prawns and Tuna (based on 2001 consumption data)

Fish Type	Mean mercury Concentration (mg/kg)	Consumption of named fish (g/ kg bw/day) ²		Intake (mg/kg bw/week) ³			
				From named fish only		Total dietary	
				Mean	97.5 %ile	Mean	97.5 %ile
Fresh Salmon	0.050	0.29	0.90	0.11	0.29	0.39	0.57
Prawns	0.048	0.14	0.45	0.05	0.15	0.33	0.43
Canned Salmon	0.032	0.29	0.90	0.07	0.20	0.35	0.48
Canned Tuna	0.19	0.22	0.76	0.29	0.98	0.57	1.26

Notes:

1. Consumption data taken from *Dietary and Nutritional Surveys of British Adults. 2000-2001* (Henderson et al., 2002)
2. The total consumption by the mean and 97.5th percentile consumer for each fish type combined is not equal to the sum of the consumption from the individual fish types. It refers to a consumer consuming one or any combination of each fish type.
3. The intake from the rest of the diet is taken as the mean adult intake for the normal UK diet, as estimated from the 2000 TDS (mercury = 0.28 µg/kg bw/week). The total intake will include an element of double counting because each fish type included in the survey will also have contributed to the mean intake estimated from the TDS.

19. The Secretariat has prepared a working paper (Annex D – to be tabled), which once finalised by the Committee will supersede the previous statement on mercury in fish and shellfish (COT 2002-04). The working paper incorporates the information from the previous statement with the updated exposure assessments, and takes into account the new, lower JECFA PTWI in the evaluation.

Questions on which the views of the Committee are sought

20. Members are invited to comment on the new information and to consider the following questions:

- i. Should the new JECFA PTWI of 1.6 µg/kg bw/week be applied to the whole population?
- ii. Alternatively, in view of the nutritional benefits of fish, would it be appropriate for the Food Standards Agency to refer to the former PTWI of 3.3 µg/kg bw/week when assessing the risks of methylmercury toxicity in the general population, and the new JECFA PTWI of 1.6 µg/kg bw/week when assessing the risks of neurodevelopmental effects in the unborn or newborn baby? It is proposed that this approach could be used as a risk management option in advising on fish consumption.
- iii. If Members agree with the suggestion at question (ii), comments are invited on the working paper in Annex D

**Secretariat
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2002-04 COT Statement on Mercury in Fish and Shellfish.

This document is also available at the following page of the FSA web-site:
<http://www.food.gov.uk/multimedia/pdfs/COTmercurystatement.PDF>

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Summary of the JECFA evaluation of methylmercury taken from the summary report of the 61st JECFA meeting held in June 2003.

This summary is also available at:

<ftp://ftp.fao.org/es/esn/jecfa/jecfa61sc.pdf>

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This paper contains the results of the latest evaluation of the Seychelles Child Development Study.

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Working Paper: Mercury in fish and Shellfish.

This Annex will be circulated at a later date.

Once finalised the working paper will supersede the current COT Statement on Mercury in Fish and Shellfish (2002-04)

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