資料 No. 2－1

JECFA/61/SC

Food and Agriculture Organization of the United Nations

World Health Organization

JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES
Sixty-first meeting
Rome, 10-19 June 2003

SUMMARY AND CONCLUSIONS （抜粋）

A meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was held in Rome, Italy, from 10 to 19 June 2003. The purpose of the meeting was to evaluate certain food additives and contaminants.

Mrs Inge Meyland, Senior Scientific Adviser, Institute of Food Research and Nutrition, Danish Veterinary and Food Administration, Søborg, Denmark, served as Chairman and Professor Ron Walker, Emeritus Professor of Food Science, School of Biomedical and Life Sciences, University of Surrey, Guildford, England served as Vice-Chairman.

Dr Manfred Luetzow, Food Quality and Standards Service, Food and Nutrition Division, Food and Agriculture Organization of the United Nations, and Dr Sam Page, International Programme on Chemical Safety, World Health Organization, served as joint secretaries.

The present meeting was the sixty-first in a series of similar meetings. The tasks before the Committee were (a) to elaborate further principles for evaluating the safety of food additives and contaminants; (b) to evaluate certain food additives and flavouring agents; (c) to review and prepare specifications for selected food additives and flavouring agents; (d) to evaluate a water-treatment agent; (e) to evaluate a nutritional source for iron; and (f) to evaluate certain contaminants.

The report of the meeting will appear in the WHO Technical Report Series. Its presentation will be similar to that of previous reports, namely, general considerations, comments on specific substances, and recommendations for future work. An annex will include detailed tables (similar to the tables in this report) summarizing the main conclusions of the Committee in terms of acceptable daily intakes (ADIs) and other toxicological recommendations. Information on specifications for the identity and purity of certain food additives examined by the Committee will also be included.

The participants in the meeting are listed in Annex 1. Further information required or desired is listed in Annex 2. Items of a general nature that contain information that the Committee would like to disseminate quickly are included in Annex 3 and 4.

Toxicological monographs or monograph addenda on most of the substances that were considered will be published in WHO Food Additives Series No. 52.

New and revised specifications for the identity and purity of the compounds will be published in FAO Food and Nutrition Paper Series 52, Addendum 11.

More information on the work of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) is available at:

www.fao.org/es/esn/jecfa/index_en.stm

www.who.int/pcs/jecfa/jecfa.htm

Toxicological recommendations and information on specifications

8. Contaminants

Contaminant	Tolerable intake and other toxicological recommendations
Cadmium	Provisional tolerable weekly intake (PTWI) of 7 μg/kg bw (maintained)
Methyl mercury	Provisional tolerable weekly intake (PTWI) of 1.6 μg/kg bw

Annex 1

Sixty-first meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)

Rome, 10-19 June 2003

Members

Dr Christopher E. Fisher, Hatfield, Herts, UK

Dr David G. Hattan, Food and Drug Administration, College Park, MD, USA

Dr Yoko Kawamura, National Institute of Health Sciences, Tokyo

Dr Paul M. Kuznesof, Food and Drug Administration, College Park, MD, USA

Dr Inge Meyland, The Danish Veterinary and Food Administration, Ministry of Food, Agriculture and Fisheries, Søborg, Denmark *(Chairman)*

Dr Gérard Pascal, Institut National de la Recherche Agronomique (INRA), Paris, France

Dr Madduri Veerabhadra Rao, Central Laboratories Unit, U.A.E. University, Al Ain, United Arab Emirates

Dr Josef Schlatter, Food Toxicology Section, Swiss Federal Office of Public Health, Zürich, Switzerland

Dr Gerrit J.A. Speijers, National Institute of Public Health and Environmental Protection (RIVM), Bilthoven, The Netherlands

Ms Elizabeth Vavasour, Food Directorate, Health Canada, Ottawa, Ontario, Canada

Dr Philippe Verger, National Institute for Agricultural Research, SAFE Consortium on food safety, Brussels, Belgium

Prof Ronald Walker, School of Biomedical and Life Sciences, University of Surrey, Guildford, Surrey, United Kingdom *(Vice-Chairman)*

Dr Harriet Wallin, National Food Agency, Helsinki, Finland

Dr Donald Brian Whitehouse, Bowdon, Cheshire, UK

Secretariat

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Dr Angelika Tritscher, Department Quality and Safety Assurance, Nestlé S.A., Lausanne, Switzerland, *(WHO Temporary Adviser)*[*]

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[*] Appointed WHO Joint Secretary

Annex 4

The Committee reviewed new data for cadmium and methyl mercury and took note of additional submissions related to these contaminants. This section of the report will be edited extensively before its formal publication. This draft is being made available so that the information is disseminated quickly, particularly for use by the Codex Committee on Food Additives and Contaminants and for consideration by interested third parties.

Cadmium

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Methylmercury

Methylmercury was previously evaluated at the sixteenth, twenty-second, thirty-third and fifty-third meetings of JECFA (Annex 1, reference *144*). At the latter meeting, the Committee reaffirmed the previously established Provisional Tolerable Weekly Intake (PTWI) for methylmercury of 200 μg (3.3 μg per kg of body weight) for the general population, but noted that the fetus and infants may be at a greater risk of toxic effects. The Committee concluded that data from studies undertaken in the Seychelles and Faroe Islands, which were evaluated at the fifty-third 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. The Committee recommended that methylmercury be re-evaluated in a subsequent meeting in order to consider the analysis of the eight-year neurodevelopmental evaluations of the Seychelles cohort and other relevant data that might become available. The Committee noted that fish make an important nutritional contribution to the diet, especially in certain regional and ethnic diets, and recommended that when considering setting limits for methylmercury concentration in fish or on fish consumption, nutritional benefits should be weighed against the possibility of adverse effects. Studies published since the fifty-third meeting were considered at the present meeting.

Observations in animals

In its previous assessment, the Committee reviewed an extensive collection of experimental data which indicated that the developing nervous system, particularly in non-human primates, is a sensitive target for methylmercury.

In all experimental animal species evaluated, methylmercury is readily absorbed (up to 95%) following oral exposure. Methylmercury effectively crosses both the blood–brain barrier and the placenta, resulting in higher levels of mercury in the fetal than the maternal brain. The major route of methylmercury elimination is in the bile and faeces, with neonatal animals having a lower excretory capacity than adults. Experimental evidence indicates a possible protective effect of selenium against some aspects of methylmercury toxicity, but results are conflicting.

Ataxia, paralysis, loss of coordination, and hind limb crossing are common neurological signs of methylmercury exposure in rodents. Changes in behaviour, decreased activity, and deficiencies in learning and memory are also observed. In rodents, methylmercury neurotoxicity usually becomes evident at doses that also affect other organ systems. Neurotoxic effects observed in non-human primates are consistent with the symptoms of Minamata disease, the syndrome observed in humans poisoned with methylmercury via the consumption of contaminated seafood. The nature and severity of symptoms are dependent on dose and duration of exposure, as well as developmental stage. From a mechanistic perspective, methylmercury exposure *in vitro* disrupts intracellular calcium homeostasis, induces reactive oxygen species and oxidative DNA damage, and inhibits axonal morphogenesis and cell cycle progression in neuroepithelial cells.

In rodents, treatment of pregnant females with methylmercury induces abortions, increases fetal resorption and malformations, and reduces offspring viability. Methylmercury also affects the rodent immune system, inducing reduced mast cell function and, at high oral doses, decreased spleen and thymus cell viability.

Observations in humans

At its fifty-third meeting, the JECFA noted that methylmercury can induce toxic effects in several organ systems (nervous system, kidney, liver, reproductive organs), and the present Committee confirmed that neurotoxicity is considered the most sensitive endpoint. In humans, indices of neurotoxicity include neuronal loss, ataxia, visual disturbances, impaired hearing, paralysis and death. Both the central and peripheral nervous systems exhibit signs of methylmercury-induced damage.

Information about the neurotoxicity of chronic fetal exposure to low doses of methylmercury has come primarily from epidemiological studies of populations in which fish consumption is relatively high. The results of neurodevelopmental assessments of the Seychelles Child Development Study cohort at 8 years of age are consistent with results obtained at younger ages, and provide no evidence for inverse associations between maternal methylmercury exposure and neurodevelopment in children. Many of the neuropsychological test instruments included in the battery were the same as those used in the Faroe Islands cohort study and which had been observed to be associated, in 7-year-old children, with biomarkers of prenatal methylmercury exposure. In addition, further analyses of data from the assessments of the Seychellois children that were conducted at 5.5 years of age have been published, which include the application of alternative statistical approaches, the adjustment for additional potential confounding factors, and more detailed evaluation of specific test scores. The results of these analyses did not alter the conclusion that in this population of frequent fish-consumers, no adverse effects of prenatal methylmercury exposure have been detected.

No new data from the main Faroe Islands study were available. Additional analyses of the assessments conducted at seven years of age were carried out to explore the issue of age- and test-dependent variation on susceptibility to methylmercury. Analyses were also conducted to evaluate the extent to which the methylmercury-associated neuropsychological deficits in this cohort are attributable to episodes of higher methylmercury exposure during pregnancy (associated with whale-meat meals), residual confounding due to concomitant exposure to PCBs, and methylmercury-associated effects on children's visual function. The analyses did not support a role for any of these factors in accounting for the positive associations in this study.

In a second smaller cohort assembled in the Faroe Islands (182 infants), prenatal methylmercury exposure was found to be inversely related to newborn neurological status and to postnatal growth at 18 months of age. The association was still present after adjusting for exposure to 28 PCB congeners and 18 organochlorine pesticides or their metabolites.

A small number of new epidemiological studies of neurodevelopment were reported, although these were cross-sectional rather than prospective in design, involved much smaller sample sizes than either the Seychelles or Faroe Islands studies, and, in most cases, higher methylmercury exposures. A cross-sectional study of adult neurotoxicity reported significant mercury-associated neurobehavioural deficits in a sample in which the current hair-mercury level of all participants was below 15 mg/kg. Because of the cross-sectional design of this study and because an adult's hair-mercury level does not accurately reflect past levels during the critical exposure period for neurodevelopment, the Committee considered that these results could not form the basis of a dose–response assessment.

Additional epidemiological studies have addressed issues such as reproductive toxicity, immunotoxicity, cardiotoxicity, and general medical status. With regard to reproductive toxicity, a methylmercury-associated decrease in the ratio of male:female births in the area of Minamata City during the period of peak pollution was reported, but the ratio subsequently returned to control levels. In a case–control study, higher blood mercury levels were found among infertile than fertile couples. With respect to cardiotoxicity, in a cohort study, hair-mercury levels of 2 mg/kg or greater were associated with a doubling of the risk of suffering an acute myocardial infarction and, over a 4-year follow-up interval, with increased atherosclerotic disease. The results of two large case–control studies investigating

mercury exposure and coronary heart disease were in conflict with one another, however, one study reporting significantly higher toenail-mercury levels in cases than in controls whereas the other reported similar toenail-mercury levels in both groups. In the latter study, half the participants were dentists and had levels of toenail-mercury that were twice as high as those of non-dentists, suggesting that much of their exposure was to metallic mercury rather than to methylmercury. In another study, high fish consumption, the primary route of methylmercury exposure, was associated with an increased risk of stroke, but no biomarkers of mercury exposure were measured. The Committee determined that the available evidence on the potential cardiotoxicity of methylmercury is not conclusive, but noted that further studies are needed. With regard to general health status, the rates of liver disease, renal disease, and diabetes mellitus were not significantly increased as a function of proximity to Minamata Bay, although the frequencies of many neurological and neuromuscular symptoms were higher.

Dose–response assessments

The Committee concluded that neurotoxicity resulting from *in utero* exposure should be considered to be the most sensitive health outcome for methylmercury toxicity. A number of dose–response assessments have been conducted using the data from the three major epidemiological studies of fetal neurotoxicity, conducted in the Faroes Islands, Seychelles Islands, and New Zealand. These assessments were based on evaluations made of children at 7 years of age in the Faroes Islands study, 5.5 years of age in the Seychelles Islands study, and 6 years of age in the New Zealand study. A comprehensive dose–response assessment using the data from the evaluations of the children in the Seychelles Islands study at 8 years of age has not yet been reported, but the study results were similar to those obtained at 5.5 years of age. Mercury in maternal hair and/or cord blood served as the primary biomarkers of *in utero* exposure to methylmercury in the Faroe Islands and Seychelles Islands studies. Based on a consideration of numerous publications, the Committee confirmed the validity of these biomarkers for both short-term (blood) and longer-term (hair) intake of methylmercury.

The maternal hair-mercury concentration corresponding to a no observed effect level (NOEL) for neurobehavioural effects was identified for the Seychelles Islands study, and a mathematical analysis of the concentration–response relationship was used to determine a benchmark dose lower confidence limit (BMDL) for the Faroes Islands and New Zealand studies. The Committee noted that one child (of the 237) in the New Zealand study sample had a large impact on the BMDLs. The maternal hair-mercury level for this child was 86 mg/kg, more than four times the next highest maternal-hair mercury level in the study sample. Including this observation produced BMDLs of 17 to 24 mg/kg, while omitting it produced BMDLs of 7.4 to 10 mg/kg. Because of uncertainty about which set of BMDLs is most valid, the Committee decided to base the evaluation only on the Faroe Islands and Seychelles Islands studies. The Committee noted, however, that including the New Zealand study did not materially alter the conclusions of the evaluation.

Table: Estimates of maternal hair concentrations associated with the NOEL/BMDL for neurotoxicity associated with in utero exposure

Study	N	NOEL/ BMDL
Faroes	917	12 mg/kg maternal hair[1]
Seychelles	711	15.3 mg/kg maternal hair[2]
Composite		14 mg/kg maternal hair

[1] Budtz-Jorgensen et al., 1999, 2000, 2001; U.S. National Research Council, 2000; Rice et al., 2003

[2] U.S. ATSDR, 1999

The Committee used the average from the two studies, 14 mg/kg maternal hair-mercury, as an estimate of the level in maternal hair reflecting exposures that would be without appreciable adverse effects in the offspring in these two study populations.

Calculation of the steady-state ingestion (µg/kg bw/day) of methylmercury from a maternal hair-mercury concentration requires two steps to be taken into account; conversion of the concentration in maternal hair to that in maternal blood, and conversion of the maternal blood concentration into maternal intake.

The ratio of the concentration of methylmercury in hair to that in blood has been determined in a number of studies, using samples from different study groups and with a variety of analytical methods. The mean hair:blood ratios reported in different studies were mostly in the range 140-370. The Committee used a value of 250 to represent the overall average ratio. The concentration of methylmercury in maternal blood that would be without appreciable adverse effects in the offspring was calculated to be 0.056 mg/L, determined by dividing a maternal hair concentration of 14 mg/kg by the hair:blood ratio of 250.

In humans, the steady state mercury concentration in blood can be related to the average daily intake using a one-compartment model that incorporates refinements (U.S. NRC, 2000) to the original WHO (1990) formula 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)

The Committee used values appropriate to conversion during pregnancy, because this is considered to be the vulnerable life stage. Despite an elimination half-life for methylmercury of approximately two months, the maternal body burden at term would be determined largely by intakes in the second and third trimesters of pregnancy.

Using this equation, the Committee determined that a steady-state daily ingestion of methylmercury of 1.5 μg/kg bw/day would result in the concentration in maternal blood estimated to be without appreciable adverse effects in the offspring in these two study populations.

Dietary intake

The fifty-third meeting of the JECFA in 1999 re-evaluated the safety of methylmercury-contaminated foods, and fish in particular. The re-evaluation included consideration of information on potential intake submitted by numerous national bodies. For most populations, fish is the only significant source of methylmercury in food. Generally, concentrations are below 0.4 mg/kg, but fish at the highest trophic levels may contain methylmercury above 5 mg/kg. Older and larger predatory fish species and certain marine mammals contain the highest levels of methylmercury.

At the current meeting, the committee updated its evaluations of national intakes and the use of biomarkers of exposure for methylmercury, including intake information submitted by Australia, France, Japan, New Zealand, and Slovakia. The Committee also evaluated information published in the literature between 1997 and 2003 concerning levels of mercury and methylmercury in various fish species as well as analyses of methylmercury intake in populations consuming large amounts of fish (>100g/p/d). The committee noted that overall methylmercury levels in fish species were similar to those analysed at the fifty-third meeting and therefore concluded that the analyses of exposure conducted at the fifty-third meeting remain current. These estimates range from 0.3-1.5 μg/kg bw/week for the 5 regional GEMS/Food diets and from 0.1 to 2.0 μg/kg bw/week for numerous nationally-reported diets.

Evaluation

The Committee evaluated new information that became available since methylmercury was considered at the fifty-third JECFA meeting. This information included results of studies performed in laboratory animals and humans, and epidemiological studies investigating possible effects of prenatal methylmercury exposure on child neurodevelopment. Neurodevelopment was considered to be the most sensitive health outcome, and *in utero* exposure the most sensitive period of exposure.

The calculations referred to in the dose response assessment used average values for each parameter, and did not allow for inter-individual variability in either the hair:blood ratio or in the elimination rate constant in the above equation. Potential human variability was taken into account by the application of adjustment or uncertainty factors. In choosing the factors to apply to this intake estimate, the Committee considered the following:

1. Neurodevelopment is a sensitive health outcome, and *in utero* exposure is the critical period for methylmercury neurodevelopmental toxicity. Furthermore, the two study samples represent diverse populations. Therefore, no uncertainty factor is needed to account for variation in vulnerability among subgroups.

2. The available data on the hair:blood ratio show both inter-study and inter-subject variability. No population-specific data on hair:blood ratios are available for the Faroe Islands or Seychelles Islands populations. The majority of published study means are within a range of 140 to 370. Few data were available to the Committee on the range of individual hair:blood ratios. The ratios reported for human individuals in a limited number of studies were in the range 137–585. These individual ratios would include any analytical errors. The ratio from the overall average of 250 to the highest study mean was 1.5 (370/250), while the ratio to the highest individual value was 2.3 (585/250). The Committee concluded that the available data on the distribution of individual ratios were not adequate for derivation of a chemical-specific adjustment factor, and decided to apply a factor of 2 to the overall

average of 250 to allow for the likely inter-individual variability, which is indicated by the differences in study means and by the limited available individual data.

3. Inter-individual pharmacokinetic variability should be taken into account when converting the steady-state concentration of mercury in maternal blood to an estimate of daily intake. As limited pharmacokinetic data specific to the study populations used in this assessment were available, the Committee recommended the use of a combined uncertainty factor of 3.2 (100.5) (WHO, 1999) to account for the total human inter-individual variability for dose reconstruction (converting maternal blood concentration to a steady-state dietary intake).

A steady-state intake of 1.5 µg methylmercury/kg bw/day was estimated to represent the exposure that would be expected to be without appreciable adverse effects in children. A total factor of 6.4 (2 x 3.2) was applied to this figure to derive a PTWI of 1.6 µg/kg bw. This PTWI is considered sufficient to protect the developing fetus, the most sensitive subgroup of the population.

Pending reduction in uncertainty associated with various aspects of the derivation of the steady-state intake from maternal hair, the Committee concluded that the uncertainty factor could be refined and possibly reduced. The Committee also reaffirmed its position that fish are an important part of a balanced nutritious diet and that this has to be appropriately considered in public health decisions when setting limits for methylmercury concentrations in fish. The Committee considered whether a PTMI rather than a PTWI for methylmercury should be developed but deferred this decision pending the outcome of the Joint FAO/WHO Project to Update the Principles and Methods for the Risk Assessment of Chemicals in Food.