codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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DISCUSSION PAPER ON THE GUIDELINE LEVELS FOR METHYLMERCURY IN FISH

Prepared by the European Community with the assistance of Australia, Cuba, Canada, India, Italy, Japan, Korea, New Zealand, South Africa, Spain, Sweden, Thailand, United Kingdom, USA, Consumers International and WHO[1]

BACKGROUND

1. The 36th session of the Codex Committee on Food Additives and Contaminants (CCFAC) established a working group led by the European Community, with assistance from Australia, Canada, France, India, Italy, Japan, Kenya, South Africa, the USA and Consumers International to prepare a discussion paper on methylmercury in fish. The discussion paper would consider the possible need to revise the guideline levels on methylmercury in fish and would examine other possible risk management options.

2. At the 37th Session of the CCFAC, the Committee agreed that a working group led by the European Community, with the assistance of Australia, Cuba, Canada, India, Italy, Japan, Korea, New Zealand, South Africa, Spain, Sweden, Thailand, United Kingdom, USA, Consumers International and WHO, would revise the Discussion Paper to consider methods of analysis of methylmercury, the elaboration of Terms of Reference for an Expert Consultation on risks and benefits of fish consumption and the elaboration of a possible request to the Joint FAO/WHO Expert Committee on Food Additives (JECFA)[2].

INTRODUCTION

3. On 10 June 2003, JECFA revised its risk assessment on methylmercury in fish (1). JECFA adopted a lower Provisional Tolerable Weekly Intake (PTWI) of 1.6 µg/kg body weight, based upon the most vulnerable life stage, the developing foetus. In 2000, JECFA had confirmed the previously established PTWI of 3.3 µg/kg body weight for the general population, but highlighted that the foetus and infant may be at a greater risk of toxic effects and recommended a re-evaluation when further data from one of the key studies are available. .

4. Codex guideline levels for methylmercury are set at 1 mg/kg for predatory fish and 0.5 mg/kg for all other fish. In view of evidence that consumers might sometimes reach or even exceed the PTWI, including pregnant and breast-feeding women, it is necessary to review the risk management measures and options available to the Codex Alimentarius.

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[1] Members of the electronic working group have got limited time to contribute to the elaboration of this discussion paper. Contributions submitted have been included in this final version.

[2] ALINORM 05/28/12, § 203

5. Mercury occurs in the environment from natural sources, but also as a result of atmospheric deposition and pollution from man's activities. It accumulates in the aquatic food chain, including in fish and seafood, largely as methylmercury, which is the form of toxicological concern. Mercury is also present in other foods, although most occurs as inorganic mercury and levels of methylmercury tend to be very low. Dietary inorganic mercury is poorly absorbed into the body from the gastro-intestinal tract and so is of less toxicological concern than methylmercury. To reduce dietary exposure to methylmercury requires risk management on its presence in fish and fishery products.

TOXICOLOGY

6. Methylmercury is toxic, particularly to the nervous system. JECFA (1) concluded that methylmercury can induce toxic effects in several organ systems (nervous system, kidney, liver, reproductive organs) and that neurotoxicity is the most sensitive endpoint. In humans, neurotoxic effects of excessive methylmercury exposure include neuronal loss, ataxia, visual disturbances, impaired hearing, paralysis and death. The developing brain is thought to be the most sensitive target organ. High methylmercury intake by pregnant women has been linked to adverse effects in neurological developmental in children. *In utero* exposure is believed to be the critical period for methylmercury neurodevelopmental toxicity. However, the duration of increased susceptibility may extend into postnatal development (2), for example during the first few years of life when the brain is developing and growing rapidly.

7. In 2000, JECFA confirmed the previously established PTWI of 3.3 µg/kg body weight per week for methylmercury for the general population, whereas the PTWI established in 2003 was 1.6 µg/kg body weight per week, based on the most sensitive sub-group of the population, the developing foetus. In December 2003, the UK Committee on Toxicity (3) indicated that the JECFA PTWI of 3.3 µg/kg body weight remained sufficiently protective against non-developmental effects and was relevant for those not falling in the most vulnerable sub-populations. The lower PTWI is considered relevant for developmental effects. This covers the groups highlighted by JECFA, the foetus and infants, and possibly further into postnatal development for young children.

8. The 2003 JECFA assessment based its assessment on two major epidemiology studies, investigating the relationship between maternal exposure to mercury and impaired neurodevelopment in their children. These were performed in the Faroe Islands (4) and the Seychelles (5, 6), both regions where consumption of fish and seafood (and marine mammals in the Faroe Islands) is high in the local communities. Adverse effects on neurodevelopment were reported in the Faroe Islands study, but not in the Seychelles Islands study. The reasons for the different findings are unclear. To include the underlying uncertainty the JECFA combined data from both studies in its risk assessment.

9. A follow-up study in the Faroe Islands indicated effects on neurodevelopment in the children 14 years later (7). There is also some indication, albeit with much scientific uncertainty, on possible links with cardiovascular disease. A study in the Faroe Islands reported weaker heart rate variability, a risk factor for cardiovascular disease, in children 14 years of age that had been exposed (largely pre-natal) to higher levels of mercury (8). This area needs further investigation.

10. In addition to the international risk assessment of JECFA, it is prudent also to bear in mind the conclusions of relevant risk assessments conducted elsewhere. For example, a previous evaluation by the United States (US) National Research Council (NRC) in 2000 recommended an intake limit of 0.7 µg/kg body weight per week (9), lower than that of JECFA. In the European Union (EU), the European Food Safety Authority (EFSA) considered data in relation to both the JECFA and NRC recommendations (2). EFSA highlighted that the differences in the JECFA and NRC safety thresholds were largely due to different uncertainty factors used and concluded that the NRC assessment can offer additional guidance relevant to risk managers. The varying safety factors used and the lack of quantitative risk assessment make it difficult to conclude further on the actual risk.

11. Methylmercury is scheduled for re-evaluation at the 67th meeting of JECFA in particular to clarify the current PTWI for population subgroups, to assess scientific evidence of relevance of direct exposure to infants and small children (prenatal vs. postnatal exposure, including breast feeding) and to evaluate the impact of the current Codex guideline levels on methylmercury exposure and risk (10).

OCCURRENCE IN FOOD

12. Available data collected on mercury in fish are largely for total mercury rather than methylmercury. However, in most fish methylmercury can contribute more than 90% of the total mercury content. Therefore, total mercury generally can be a good indicator of methylmercury. Methylmercury can accumulate in some types of fish more than others. Key factors include the age, size, natural environment and food sources. Fish that are more likely to accumulate higher levels of methylmercury are larger, longer-living and predatory species. It is often difficult to conclude which individual species has been tested, as data are often reported for general varieties of fish. Examples of varieties found to contain high levels include shark (all species), swordfish/ broadbill (*Xiphias gladus*), marlin (*Makaira species*, *Tetrapturus species)* and orange roughy (*Hoplostethus atlanticus)*. Some species of tuna can also contain high levels, such as big eye *(Thunnus obesus)*, blue fin *(Thunnus thynnus)* and albacore tuna *(Thunnus alalunga)*, although the average concentrations tend to be significantly lower than in the fish varieties listed above. Pike (*Esox lucius)*, tilefish (*Caulolatilus princes)* and king mackerel (*Scomberomous cavalla)* from certain geographic locations can also contain relatively high levels of mercury. Mercury levels in canned tuna are often lower than in fresh tuna, largely due to the species or because smaller-sized fish are used. Skipjack tuna *(Katsuwonus pelamis)* is often canned and this variety tends to contain lower levels of mercury. However, species with higher levels may also be canned, such as albacore tuna (*Thunnus alalunga)* known as canned 'white' tuna in some countries including the US).

13. Summaries of occurrence data are given below, in particular highlighting some common findings of high mercury levels.

a) In the US, 3730 fish samples tested for total mercury were reported by FDA, largely from the FDA Monitoring Programme 1990-2003 (11). Fish species containing high, mid-range and low levels of mercury were identified.

Highest levels were found in king mackerel (213 samples, mean 0.73 mg/kg, maximum 1.67 mg/kg), shark (351 samples, mean 0.99 mg/kg, maximum 4.54 mg/kg), swordfish (605 samples, mean 0.97 mg/kg, maximum 3.22 mg/kg) and tilefish (60 samples, mean 1.45 mg/kg, maximum 3.73 mg/kg).

In the mid-range, mean levels of mercury were generally below 0.5 mg/kg in 23 varieties of fish and shellfish (only grouper and orange roughy were above). The maximum levels were often near or above 1 mg/kg. Of 131 samples of fresh/ frozen tuna the mean was 0.38 mg/kg and maximum 1.3 mg/kg, whereas for 179 samples of canned albacore tuna the mean was 0.35 mg/kg and maximum 0.85 mg/kg. Other US data reported by Consumers International found levels of mercury in canned albacore tuna to be higher, with a mean value of 0.51 mg/kg.

Low levels of mercury were reported in 33 other fish varieties, the highest mean level being 0.12 mg/kg for canned 'light' tuna.

b) In Canada, in 2002 a study of mercury in 244 samples of fish and shellfish (12) reported high levels in swordfish (mean 1.82 mg/kg, maximum 3.85 mg/kg), shark (mean 1.26 mg/kg, maximum 2.73 mg/kg), marlin (mean 1.43 mg/kg, maximum 3.19 mg/kg), fresh and frozen tuna (mean 0.93 mg/kg, maximum 2.12 mg/kg), canned tuna (mean 0.15 mg/kg, maximum 0.59 mg/kg). The lowest mean level was found in oysters at 0.01 mg/kg. A further study (13) highlighted the proportion of methylmercury to total mercury in relevant fish species, finding 51 to 63 % in marlin (3 samples), 46 to 94% in shark (12 samples), 43 to 76% in swordfish (10 samples), 61 to 94% in tuna (13 samples) and 30 to 79% in canned tuna (37 samples). Unpublished data from the Canadian Food Inspection Agency on mercury in more than 70 varieties of fish found levels exceeding 1 mg/kg in species additional to those above, including grouper (27 samples, mean 0.34 mg/kg, maximum 1.12 mg/kg), sablefish (77 samples, mean 0.36 mg/kg, maximum 1.20 mg/kg), escolar (16 samples, mean 0.54 mg/kg, maximum 1.56 mg/kg) and dogfish (a type of shark) (70 samples, mean 0.63 mg/kg, maximum 1.29). The lowest levels were found in shellfish and salmon, mostly well below 0.1 mg/kg.

c) In the EU, mercury occurrence data were collected as part of a scientific co-operation task for an assessment of dietary intake (14). Monitoring samples of fish and fishery products were taken over varying periods from 1992 to 2002. Data were all for total mercury and had been collected using different methods in different Member States, including pre-merged data in some cases. Overall the data indicated that most fish species and shellfish tend to contain mercury well below the Codex guideline levels of 0.5 mg/kg in general and 1 mg/kg in large predatory fish (similar to the EU maximum levels (15)), although high values of 1.0 mg/kg to 5.8 mg/kg were reported for some fish varieties. Species containing high levels included shark, swordfish, pike and tuna. The provisional data were used by EFSA in its risk assessment on mercury, published in February 2004 (2). EFSA concluded that, by disaggregating the sample data for approximately 15000 samples, the average level of mercury in each fish sample would have been 0.109 mg/kg.

Enforcement activities in the EU have identified samples of fish exceeding the maximum levels. During the period from 2001-2004, the Member States notified the EU Rapid Alert System on 117 occasions of fish exceeding the respective maximum levels. 63 notifications were for swordfish (1.1 to 11.4 mg/kg), 22 for shark (1.1 to 3.8 mg/kg), 11 for tuna (1.1 to 1.7 mg/kg), 5 for marlin (1.2 to 1.8 mg/kg) and 16 for other species (0.6 to 3.6 mg/kg).

d) In Spain, 1954 samples of fish and seafood from different catching areas of the world were analysed for total mercury in 2001 and 2002. Of these, 377 samples were grouped by different tuna species. Many samples of albacore, yellowfin, bigeye and bluefin tuna were above 0.5 mg/kg, sometimes above 1.0 mg/kg. Of 106 samples of bigeye tuna 20% contained mercury above 1.0 mg/kg. Skipjack tuna contained lower levels although 9 of 70 samples were above 0.5 mg/kg (maximum 0.77 mg/kg). Another variety found to contain high levels was the rosy soldier fish, all 7 samples contained above 0.5 mg/kg, with 3 samples above 1 mg/kg.

e) In the UK, a survey in July 2003 (16) reported high mean levels of methylmercury in shark (1.5 mg/kg), swordfish (1.4 mg/kg), marlin (1.1 mg/kg), orange roughy (0.6 mg/kg) and fresh tuna (0.4 mg/kg). The maximum levels in these species were all above 1 mg/kg, except for orange roughy. Fish containing mid-range levels, with means below 0.5 mg/kg included canned tuna (mean = 0.19 mg/kg), halibut (mean 0.29 mg/kg), hoki (mean 0.19), monkfish (mean 0.20). Low levels, with mean values not exceeding 0.1 mg/kg, were found in sardine, pilchard, salmon, anchovy, trout, sea bass, sea bream, pollack, mussels, prawns and squid.

f) Levels of mercury in Nordic freshwater fish (mainly pike, perch, trout and char) in more than 1500 lakes were reported, comparing lakes of different regions (17). Mercury levels were highest in some low-altitude lakes, with levels exceeding 0.5 mg/kg in fish from up to 80% of lakes. The presence of the mercury resulted largely from atmospheric deposition of mercury over large geographical areas. Studies of sports fish in the Canadian lakes have identified that in remote lakes, where fish grow large slowly over a long period of time, fish can accumulate higher levels of mercury than similar sized fish that grow faster in high nutrient lakes (18). These studies highlight the need for global-scale measures to reduce mercury emissions to the atmosphere (19).

g) National surveillance on mercury in fish conducted in Japan (20) included 5619 samples and 320 species. The proportion of methylmercury in pacific blue marlin was found to be lower than in other marlin, as demonstrated in 22 samples. Total mercury levels were mean 1.16 mg/kg and maximum 9.30 mg/kg, whereas methylmercury levels were mean 0.19 mg/kg and maximum 0.69 mg/kg). In other species, the mean mercury concentrations were > 0.5 mg/kg in alfonsino (97 samples, mean 0.67 mg/kg, maximum 2.18 mg/kg), blue fin tuna (123 samples, mean 0.73 mg/kg, maximum 6.10 mg/kg), swordfish (44 samples, mean 0.97 mg/kg, maximum 1.71 mg/kg), big eye tuna (88 samples, 0.74 mg/kg, maximum 3.10 mg/kg) and blue shark (30 samples, mean 0.54 mg/kg, maximum 0.81 mg/kg).

EXPOSURE

14. Using occurrence data and information on consumption of fish, calculations on dietary intake of methylmercury have been made. JECFA reported estimates close to and sometimes exceeding the PTWI of 1.6 µg/kg body weight. Values ranged from 0.3 to 1.5 µg/kg body weight per week for the five regional GEMS/Food diets and from 0.1 to 2.0 µg/kg body weight per week for numerous nationally-reported diets. Further recent examples of national and regional findings are given below.

a) Estimates of dietary exposure to mercury in the EU were made by the European Commission (14) and EFSA (2). The estimated intakes of mercury in the EU varied by country, depending on the amount and the type of fish consumed. National average exposures to mercury from fish and seafood products were between 1.3 and 97.3 µg/week, corresponding to below 0.1 to 1.6 µg/kg body weight per week (assuming a 60 kg adult body weight). Assuming total mercury to roughly represent methylmercury in fish, the highest average intake estimates were just at the PTWI and exceeded the NRC recommendation. However, people who eat a lot of fish, the high level consumers, could exceed the JECFA PTWI. The range of exposure to methylmercury for high level consumers was estimated to be 0.4 to 2.2 µg/kg body weight per week.

   Data from Norway indicated that intake overestimates for methylmercury can be made where the main fish species consumed are those with relatively low concentrations. Comparison with other EU data showed that the population in Norway had the highest total consumption of fish and seafood products. However, the estimated intake of methylmercury was lower in Norway than in southern European countries. The likely reason was that the type of fish consumed in Norway consists of species containing relatively low levels (such as cod and saithe). The consumption of top predatory fish containing higher levels of methylmercury may be significantly greater in southern countries of Europe.

   EFSA performed a probabilistic analysis of data from France, which indicated that children are more likely to exceed the PTWI than adults. However, this result is possibly skewed because the types of fish often eaten by children in the EU, such as white fish in fish sticks/ fish fingers, are generally lower in mercury. Nevertheless, tuna is also popular in the diet of children and this can contain higher levels. EFSA highlighted the need to investigate the consumption of various fish species by women of child bearing age and young children. Such data and specific intake studies would allow refining of the risk assessment for these vulnerable groups of the population.

b) The UK Committee on Toxicity (3) indicated that 97.5% of adults had blood mercury levels corresponding to dietary intake below the PTWI of 1.6 µg/kg body weight per week. 2.5% had levels corresponding to exposure above the PTWI, in a nation that eats relatively small amounts of fish. In countries that eat more fish there are likely to be higher proportions of consumers that exceed the PTWI. Dietary intake estimates for different sub-populations in the UK showed that high level consumers (97.5%ile) of two groups were shown to exceed the PTWI, toddlers (1.5 to 4.5 years of age) and young children (4 to 6 years of age) (16). Also, the PTWI was exceeded for high level consumers of canned tuna. The highest value was for high level consumption of canned tuna by toddlers (2.45 µg/kg body weight per week). Theoretical intake from consumption of shark, swordfish, marlin and fresh tuna was calculated, based upon single, average sized portions, containing their respective average levels of methylmercury. For shark, swordfish or marlin these single portions would contribute up to 47% of the PTWI. For fresh tuna the contribution was up to 12 % of the PTWI. Therefore, if more is eaten or if higher than average levels of mercury are present this could compromise the PTWI.

c) Amounts of fish consumed in Australia were reported by Food Standards Australia and New Zealand (FSANZ) (21). Mean amounts of fish eaten by women 16 to 44 years of age were 95 g/day finfish and 65 g/day canned fish. High level consumption was 265 g/day finfish and 155 g/day canned fish. Mean amounts eaten by children 2 to 6 years of age were 60 g/day finfish and 40g/day canned fish. High level consumption was 140 g/day finfish (no high value recorded for canned fish). Therefore, for example, for finfish the mean weekly consumption for the vulnerable sub-populations is 665 g for women of childbearing age and 420 g for young children. These mean values are relatively high and if large predatory fish are included the PTWI easily could be reached or exceeded. The high level consumers can clearly exceed the PTWI.

FSANZ calculated that for a 66 kg woman 16 to 44 years of age, the JECFA PTWI is roughly 105 µg/week. Using orange roughy as an example, on average with 540 µg/kg mercury, the PTWI would be reached in 194 g orange roughy. One average adult serving of 150 g would therefore give a dietary intake approaching the PTWI.

d) In the US, a study of mercury levels in hair showed that for frequent fish consumers the mean hair mercury levels were 3-fold higher in women and 2-fold higher for children compared with non-consumers (22). A study of blood mercury levels in children and women of child-bearing age found that the entire study population had exposures that were well below estimates of no observed effect levels that were derived on the basis of the Faroe Islands study (23). A previously developed exposure model was used to assess the effectiveness of various advisory scenarios on minimizing methylmercury exposure in the US. This exposure model was developed to predict levels of mercury in blood in women of child-bearing age in the US, based on the frequency of seafood consumption, the amount of seafood consumed per serving and the types of seafood consumed. The predictability of the model was confirmed via the use of National Health and Nutrition Examination Survey (NHANES) blood mercury data. Simulations for various advisory scenarios were developed on the basis of limitations on total consumption of seafood, elimination of the consumption of certain species altogether, and/or a combination of both. In the baseline model, the median (uncertainty) estimates for the 50th, 95th and 99th per capita population percentiles were 1.25, 8.2 and 16.1 ppb blood mercury, respectively. After restriction of seafood consumption to no more than 12 ounces per week, the median estimates for the 50th, 95th and 99th per capita population percentiles were 1.2, 6.8 and 10.6 ppb blood mercury, respectively. Elimination of methylmercury-containing species, with average concentrations above 0.6 mg/kg, resulted in very modest decrements in blood mercury levels, in comparison with either the baseline or the reduced consumption scenarios. These results suggest that strategies to reduce methylmercury exposure by reducing the amount of fish consumed (e.g. 12 ounces per week) are more effective at reducing high intakes than are strategies intended to change the types of fish consumed (24).

e) Estimations of dietary exposure in Canada (25) found that average intakes of mercury by women of child-bearing age were up to 0.21 µg/kg body weight per week and for children of 1 to 4 years of age up to 0.35 µg/kg body weight per week. These levels are considerably lower than the PTWI. For fish found to contain high levels of mercury, intake estimations found that by consuming fresh and frozen tuna, marlin, swordfish or shark once a month or less, the dietary intakes of total mercury by women of child-bearing age (averaged over 1 month) and children would be below the PTWI (12).

f) In Japan, the results of a total diet study for mercury under the normal dietary conditions showed an estimated average daily intake of total mercury to be 8.4 µg/person from 1994 to 2003. This value is below the re-evaluated PTWI of JECFA.

15. In general, consumers who eat average amounts of varied fishery products are not likely to be exposed to unsafe levels of methylmercury. However, people who eat appreciably more than average amounts of certain types of fish are more likely to exceed the recommended safety thresholds. Mercury toxicity in high consumers has been reported (26). In particular, based upon monitoring data, population groups who frequently consume top predatory fish, such as shark, swordfish and some species of tuna, may have a considerably higher intake of methylmercury and exceed the PTWI. Protective measures based on 'average' levels of seafood consumption may not protect those individuals at most risk. Considerations are necessary on how to ensure safe levels of exposure of the vulnerable groups of the population, i.e. pregnant women, infants, young children and people who eat a lot of fish.

16. It is possible to eat modest amounts of fish containing mercury up to 1 mg/kg and to keep dietary exposure below the PTWI, although at this level the remainder of the diet should not contain any significant further contribution to avoid exceeding the PTWI. For example, the PTWI of 1.6 µg/kg body weight equals 96 µg/week for an average 60 kg adult. This amount would be present in 96 g of fish containing 1 mg/kg methylmercury. Swordfish, shark, marlin and pike from some locations can often contain such a level. To comply with the PTWI, it would be necessary to eat no more than 96 g of fish with this level per week, with no other intake of methylmercury.

ANALYTICAL METHODS

17. Most mercury in fish (up to above 90%) is methylmercury and analyses around the world generally have been done on total mercury content. Analysis for total mercury is easier, requires less expertise and equipment and is more economical than analysing for methylmercury. However, the hazard of concern is methylmercury and chemical analyses and surveillance should be conducted on this form as well as total mercury. This need is highlighted by the findings in Canada and Japan showing that methylmercury may contribute less towards the total mercury content in some fish (see paragraph 11 (b) and (g) above).

18. Methods available for measuring the methylmercury content of environmental samples were reviewed in 1998 (27) and a summary of observations on errors encountered and their resolution was given for a variety of these in 1999 (28). In 2005, state-of-the-art methods available for the determination of methylmercury in fish specifically were described and compared within the frame of a Comité International des Poids et Mesures (CIPM) Pilot Study organised by the Institute for Reference Materials and Measurements from the European Commission (29). These methods are summarised in Annex 1. Some of them are more completely presented throughout different publications (30, 31, 32, 33, 34, 35, 36, 37, 38). The CIPM study showed that laboratories worldwide are potentially able to supply accurate results for methylmercury at mg/kg level in fish-type matrices within ± 10 % uncertainty.

19. Typically, methods for analysing methylmercury involve chemical processing steps, which may be separate or concomitant, to digest the sample matrix and to extract methylmercury in either its original form, or derivatised (essentially, alkylation in the aqueous phase and butylation by the Grignard reaction) to a form suitable for separation and detection. The analyte, which is liquid extracted or trapped on a solid-phase, can be further separated from the matrix and other mercury species by gas or liquid chromatography (GC or LC).

20. A commonly investigated challenge for analysis is the complete recovery of methylmercury without changing speciation information (i.e. the loss of methylmercury and its creation from inorganic mercury in the sample). Amongst other factors, this is dependent on the digestion and derivatisation reagents used. Decomposition of methylmercury using alkaline digestion or during acid leaching with nitric acid and, to a lesser extent, hydrochloric acid was reported.

21. An example of a relatively simple GC method, with proven robustness for measuring methylmercury in fish is described in references 29 and 37. Samples are digested in a heated mixture of potassium hydroxide and methanol, the mixture is cooled, buffered and sodium tetra-ethylborate is added to transform mercury species to volatile dialkyl derivatives. These are purged from solution by a flow of inert gas and are trapped on an adsorbent material, then heated to desorb the species onto a GC column. The LC method described in references 29 and 35 is more complex but also less prone to alteration of mercury speciation as it is based on enzymatic extraction. The methylmercury complex is diluted with mobile phase to ensure compatibility with LC separation conditions. Degradation of derivatised compounds by elevated temperatures is also avoided, as LC is not normally operated over 80 ºC in contrast to GC.

22. The vaporisation of mercury atoms by chemical reduction, cold vapour generation, is a proven approach that allows mercury detection by atomic fluorescence or absorption spectrometry. These are element-specific detectors, with the high sensitivity required to measure methylmercury at the levels found in natural samples, which are most commonly coupled to the species separation apparatus. Beside, inductively coupled plasma mass spectrometry (ICP MS) detection is widely considered to be the state-of-the-art, and it offers the possibility to use species specific isotope dilution (SS-ID) calibration. IDMS, which is regarded as the most robust calibration strategy for speciation because it does not require quantitative control of the methylmercury species all the way through the analytical process, was made much easier to implement due to the availability of a certified, isotopically enriched methylmercury reference material. Modern GC-electron impact (EI)-MS instrumentation, which now demonstrates sufficient sensitivity for the detection of mercury species in trace amounts, also permits SS-IDMS.

23. The CIPM study (29) also showed that, despite improvements in methodology and instrumentation, unanticipated problems with methylmercury measurements in fish do occur and method validation is necessary. For this purpose, the recommendations from ISO/IEC17025 (39) include the participation to inter laboratory comparisons and the analysis of reference materials. Materials including fish, shellfish and marine sediment are available with certified contents of methylmercury, from a number of organisations around the world.

RISK MANAGEMENT OPTIONS TO REDUCE DIETARY EXPOSURE TO METHYLMERCURY

24. It has been demonstrated that fish can contain levels of methylmercury that may contribute significantly towards recommended safety thresholds for dietary intake. Risk management strategies tend to focus on ways of reducing potential exposure through consumption of fish. Setting maximum levels, giving advice to consumers and environmental action to lower contamination are the main approaches that have been developed.

A) Maximum levels

25. Codex guideline levels are already set for methylmercury, 1 mg/kg for predatory fish and 0.5 mg/kg for other species of fish (CAC/GL 7-1991). However, no clear guidance is provided which fish species should be included in the category of predatory fish.

26. Other examples of maximum levels and guideline levels set for total mercury include the following.

a) In the EU, legislation sets maximum levels for mercury in fishery products (15). 1 mg/kg mercury applies to certain listed species and 0.5 mg/kg in other fish and fishery products. In view of the levels of mercury often detected in fish, the scope to further reduce the maximum levels has been considered to be limited. Alternative additional measures for protecting the vulnerable groups have been considered necessary, such as consumer advice.

b) Maximum levels of 1 mg/kg for species known to contain high levels of mercury and 0.5 mg/kg for all other species of fish (also applicable to crustaceans and molluscs) are prescribed in Australia and New Zealand (FSANZ, 21).

c) In Canada, there is a guideline of 0.5 mg/kg total mercury in the muscle of fish (40). This guideline is applicable to all fish sold at retail except for the following three predatory fish varieties: shark, swordfish and fresh/frozen (but not canned) tuna.

d) In Japan, the provisional maximum levels have been established for certain fish species (marlin, swordfish, tuna, and skipjack tuna), fresh water fish (except lake-fish) and deep-sea fish (including rockfish species, alfonsino, blue-cod, and sharks). The maximum level is 0.4 mg/kg as total mercury (calculated as 0.3 mg/kg as methylmercury). If the content of total mercury in a fish sample exceeds the maximum level, such fish sample will be removed from the market under the guidance of the respective regional government.

27. The CCFAC agreed at its 37th session that the revision of the guideline levels would require more comprehensive consideration in order to take account of all factors related to the consumption of fish, in particular, risks and benefits and that in the meantime the existing guideline levels for methylmercury in fish (CAC/GL 7-1991) can be retained with the understanding that enforcement can be performed by determination of total mercury as a screening method (for facilitation/monitoring). Methylmercury needs only to be determined for verification purposes[3].

28. In order to improve the application of the current guideline levels, it could be appropriate to identify which species are to be considered as predatory fish. Such a list should include the commercial and important recreational fish species which might, taking into account age, length, weight and catching area (location), contain methylmercury content above 0.5 ppm.

B) Consumer advice

29. Since the revised PTWI of JECFA was adopted in 2003, much new and revised consumer advice on fish consumption in relation to methylmercury content has been developed around the world. The general message has been essentially similar, with national and regional considerations reflected in the fish species highlighted. However, the presentation of the advice can differ. Some recommendations include safe amounts for consumption, whereas others also include advice for vulnerable groups to avoid eating certain species. It is important to note that these advisories have been developed without the benefit of quantitative risk assessment and the likely effect of consuming fish above the advised levels is unknown.

a) In the US, the FDA and EPA issued joint advice on mercury in fish, focusing on women who may become pregnant, pregnant women, nursing mothers and young children (11). Three recommendations for the target groups of women include: do not eat shark, swordfish, king mackerel or tilefish because they contain high levels of mercury; eat up to 12 ounces a week of a variety of fish and shellfish that are lower in mercury (e.g. shrimp, canned light tuna, salmon, pollack and catfish); check local advisories about fish caught in local rivers, lakes and coastal areas (if no local advice available, consume up to 6 ounces per week locally caught fish but no other fish). The same advice applies when feeding fish to young children, but recommends smaller portions. Guidance is also given on different types of tuna. Albacore 'white' tuna and fresh tuna steaks tend to have higher levels of mercury and a maximum consumption of 6 ounces per week is advised, compared with 12 ounces for canned 'light' tuna. (Note: 1 ounce = 28.35 grammes.)

b) In the EU, the European Commission has issued specific advice for vulnerable groups (14). This has been distributed through EU-wide public health channels to help ensure that the information reaches the target audience. The note contains advice on fish consumption for women who might become pregnant, who are pregnant or breastfeeding and for young children. It advises that these consumers should not eat more than one small portion (below 100 g) per week of large predatory fish, such as swordfish, shark, marlin and pike, and that if they eat this portion, they should not eat any other fish during this period. It also advises that they should not eat tuna more than twice per week. EU consumers are also advised to pay attention to any more specific advice given by national authorities in light of local or regional consumption characteristics.

[3] ALINORM 05/28/12, § 202

Several Member States of the EU have issued specific national advice, including limiting the frequency of consumption of particular predatory fish, such as swordfish, marlin, pike and tuna. In some cases the advice is even to avoid eating certain species of predatory fish. For example, the UK Food Standards Agency published advice for consumers (41) in response to the scientific advice of the UK Scientific Advisory Committee on Nutrition and the Committee on Toxicity on the benefits and risks of fish consumption (42). In relation to mercury, the UK advises women who are pregnant or planning to get pregnant to avoid eating shark, swordfish or marlin. Also to limit the amount of tuna eaten to no more than two tuna steaks (weighing about 140 g when cooked, or 170 g raw) or four medium-size cans of tuna a week (with a drained weight of about 140 g per can). This advice is based upon levels of mercury found in tuna on the UK market, however, in other EU countries, such as Spain, higher levels of mercury have been found in canned tuna products.

Other than the highlighted vulnerable groups, the general population can also be affected. Following the UK COT approach, that 3.3 µg/kg body weight per week remains relevant for the general population other than the most at risk groups (3), it would be possible to double the amount of fish considered safe for consumption if containing 1 mg/kg mercury e.g. 200 µg swordfish or shark per week. The FSANZ guidance also follows this separate PTWI approach (21).

c) FSANZ advises pregnant women, women planning pregnancy and young children to limit their intake to no more than 1 serving per fortnight of shark (flake) or billfish (swordfish/ broadbill and marlin) and no other fish that fortnight, or 1 serving per week of orange roughy/ deep sea perch or catfish and no other fish that week, or 2-3 servings per week of any other fish and seafood (1 serving for women 16 to 44 years of age = 150g, for children up to 6 years = 75g). At the same time, the nutritional value of fish is highlighted, being low in saturated fats, a source of protein, vitamins and minerals, such as vitamin D and iodine and omega-3 fatty acids. Although swordfish contain omega-3 fatty acids, other fish containing high levels but lower levels of mercury are recommended as they can be more frequently consumed (mackerel, silver warehou, atlantic salmon, canned salmon, tuna in oil, herrings and sardines). FSANZ advises 2-3 servings per week of these species or 1 serving per week or per fortnight for large predatory fish such as shark (flake) or billfish (swordfish/ broadbill and marlin) and no other fish that week

For tuna, the recommendation is 2-3 servings, canned or fresh per week. Canned tuna is often from smaller fish, less than 1 year old with lower levels of mercury, therefore can be eaten more often. However, the species of tuna also is important, for example canned albacore tuna is likely to contain higher levels of mercury than skipjack tuna.

For the rest of the population, FSANZ advises 1 serving per week or per fortnight for large predatory fish such as shark (flake) or billfish (swordfish/ broadbill and marlin) and no other fish that week, or 2-3 servings per week of any other fish and seafood (one serving = 150 g)

d) In Canada, three varieties of fish are excluded from the guideline of 0.5 mg/kg total mercury, shark, swordfish, and fresh/frozen (but not canned) tuna (40). These fish are the subject of a consumer advisory that recommends that Canadians limit consumption of shark, swordfish and fresh and frozen tuna to one meal per week. Pregnant women, women of child-bearing age and young children should eat no more than one meal per month of these fish. The advisory does not apply to canned tuna. Health Canada is currently reviewing both its mercury in fish guideline and the consumer advisory to determine whether changes are required.

e) In Japan, the advice is given to pregnant women (20) to limit consumption of certain fish and shellfish

- up to 80 g per 2 months for Bottlenose dolphin *(Tursiops truncates)*;
- up to 80 g per 2 weeks for Short-finned pilot whale (*Globicephala macrorhynchus)*;
- up to 80 g per week for Alfonsino *(Beryx splendens)*, Swordfish *(Xiphias gladus)*, Bluefin tuna *(Thunnus thynnus)*, Bigeye tuna *(Thunnus obesus)*, Finely-striate Buccinum *(Buccinum striatissimum)*, Baird's beaked whale *(Berardius bairdii)* and Sperm whale *(Physeter macrocephalus)*;
- up to 160 g per week for Yellowback Seabream *(Dentex tumifrons)*, Marlin *(Makaira species, Tetrapturus species)*, Hilgendorf saucord, *(Helicolenus hilgendorfii)* Southern bluefin tuna *(Thunnus maccoyii)*, Blue shark *(Prionace glauca)* and Dall's porpoise *Phocoenoides dalli)*.

The above advice has been published on 2nd November 2005 in accordance with the tolerable weekly intake for methylmercury in pregnant women which has been established by the Japanese Food Safety Commission (48).

30. Mercury can affect all of the population and consideration must be given to different vulnerable groups. Advice for consumption by women can help to protect the foetus and infants during breastfeeding, but less detailed advice has been given specifically for consumption by young children. More detailed advice would appear to be necessary for parents of children, for example up to 6 years of age (although the risk assessment information is not clear regarding an age cut-off for the main period of risk to neurodevelopment). In addition, advice is needed to help inform high consumers of fish in the general population. A 'traffic light' approach using red, yellow, green-light listings is an example of a possible way to indicate which fish varieties tend to contain high, medium and low amounts of mercury. This approach has been developed in the US State of Wisconsin (43). Another approach, developed in the US State of Minnesota, is the 'Smart Fish Calculator' whereby consumers can input their body weight and the variety of fish that they wish to eat, and receive the calculated safe amount that can be eaten (44). It is important to note that information from focus groups on the uptake of advice in the US has indicated that consumer advisories can be misinterpreted to cause people to substantially limit or even eliminate fish consumption, even when the advisory indicates they need not do so. This is an area for further study.

31. Regarding the possibility of effects on cardiac health (7), this is an area where further investigation and further risk assessment is needed to inform any further considerations for risk management.

International consumption advice

32. Information and guidance on mercury and fish consumption has been developed in some countries, but not in many others. To make available international advice would help facilitate national-level education on this issue world-wide. Different predominant fish species are eaten in different regions of the world and local or national advice would be the most accurate way to provide clear information to consumers. However, general international advice could be used by all countries as a basis to develop more specific regional consumer advice where necessary.

33. Based upon risk assessment findings and available information on methylmercury in fish, it might be possible to formulate a rough guide as a starting point. For example, in general alignment with existing national and regional advisories, international advice could indicate for women who might become pregnant, women who are pregnant and women who are breastfeeding to either avoid or not eat more than one 100 g per week of certain large predatory fish or other fish known to often contain mercury at levels close to or above 1 mg/kg. Such fish include shark, billfish (swordfish, marlin) and may include pike, tilefish and king mackerel depending on the region. If they eat this portion they should not eat any other fish during this period. For fresh tuna, attention should be paid to the species and to national or local advice. Parents should be aware that this advice also applies to young children. In different countries consumers should pay attention to any specific advice from national authorities in light of local information on mercury in fish and fishery products.

34. Certain difficulties arising from this approach need to be considered. The advice would need to be sufficiently general to avoid conflict with national provisions. The risks of adverse effects, such as limiting public health and nutritional benefits would need to be carefully considered. Moreover, difficulty arises in defining which fish contain high amounts of mercury. Data are limited world-wide and often similar common names are used to describe different fish in different regions of the world. For example, bass is used to describe a range of different fish species. Freshwater bass and sea bass can contain widely different levels, large freshwater bass tending to have higher levels and sea bass tending to be low. Generic names can cover wide taxonomic groups, such as catfish. In Australia, ‘catfish’ has been highlighted to sometimes contain high amounts of mercury, whereas in US ‘catfish’ is listed as containing low methylmercury. This example highlights the importance that general advice on varieties of fish is clear and as far as possible unequivocal world-wide.

35. Listing fish varieties shown to generally contain low levels of methylmercury also can be important, in addition to listing fish with high levels. This could help to give consumers a balanced view. A negative list alone could result in consumers taking precautionary action and avoiding all fish, in case they choose species high in mercury. This can result in a lost source of nutrients to the diet. However any list that will be elaborated should be accompanied by a statement that the list is for guidance only and that there can be variations in methylmercury content depending on geographic variation.

36. Consumer advice on this issue is an important tool for risk management. To manage the risks from contaminants in food, risk managers have generally used guideline levels, limits, maximum levels, action levels and other guidance values. However, recommending limits on the amounts of mercury present in fish is insufficient alone to guarantee safe levels of dietary intake, particularly in view of the difficulty to sufficiently lower the limits. International advice on methylmercury could be developed to give nations a platform on which to formulate and send clear, consistent messages to consumers. Simple, carefully structured messages would be necessary, although more detailed advice also could be available for people motivated to find out more.

37. How to disseminate consumer advice on mercury needs careful consideration, particularly as this approach relies upon effective uptake by consumers, which is not easy. Past experience on risk communication and risk perception indicates that any message about risk, including content, format or context needs to be developed specifically for a well-defined target audience if it is to have a good chance of success. Nevertheless, all adults should have access to dietary advice, particularly women and parents of young children. It is important to ensure that advice would reach these target groups on a continual basis. To achieve this, effective strategies are needed. Points of sale, eating establishments, labelling and via public health professionals are possibilities. An example of thorough communication on the risks from mercury in fish has been developed in the US State of Wisconsin (18, 43). This largely responds to high level consumers and high levels of mercury that can be found in sports fish, caught and eaten in local communities. A considerable amount of specific information, pictures, posters and leaflets, giving details of which fish contain high, medium or low amounts of mercury, has been published and distributed, with high penetration of awareness within the population.

38. This is a challenge needing an open-minded approach, to identify and develop the best ways to help educate and inform consumers at international level. Also, it is important that advice does not have the adverse effect of discouraging healthy consumption of fish. Experts in communicating with consumers should assist in developing the necessary advice. It might be necessary to develop combined advice, also to include other relevant contaminants in fish. During its 38th session, CCFAC will host a workshop on ‘risk communication as a management tool for contaminants in food’, with the aim to exchange views on risk communication strategies and to explore the scope for the development of a worldwide general guidance for risk communication. At the workshop the importance of risk communication will be highlighted and topics such as communication on risk assessment and communication on risk management, the role of the media in risk communication will be addressed. Two case studies on consumption advice will be presented (acrylamide and methylmercury).

39. Following the establishment by JECFA at its sixty-first meeting in 2003 of the PTWI of 1.6 µg/kg body weight per week for methylmercury, WHO and FAO have been concerned about the possible adverse impact that this hazard characterisation may have on the health and nutritional status, particularly those populations living in developing countries where fish is a major source of food. The uncertainties in the hazard characterisation as well as considerations of other risks and benefits associated with fish consumption suggest that it would be appropriate to provide risk managers with additional guidance in interpreting risk/benefit assessment and in deciding on a risk management option appropriate for their countries.

40. Therefore, WHO, in cooperation with FAO, has developed a document, which has been discussed at a workshop held in Geneva from 10-12 January 2006, on the application of risk analysis to methyl mercury in fish to provide guidance to risk managers on balancing the risks and benefits of fish consumption and to offer some guidance on developing practical risk communication considerations for target groups, such as pregnant women (47). The guidance provided in the document should be viewed in conjunction with the JECFA assessment, other national guidance, as well as assessments that have been conducted balancing the risk and benefits of fish consumption. The document will be completed with the outcome of the re-evaluation of methylmercury which will take place at the 67th JECFA meeting in June 2006 (see § 11)

C) Environmental measures

41. A global programme to reduce environmental emissions of mercury is being developed by the United Nations Environment Programme (UNEP) (19). Global reductions in environmental emissions of mercury would help to lower the background levels of mercury in the water systems, thereby lowering the levels of mercury available to accumulate in fish. Lower levels of methylmercury in fish would then be easier to attain to help ensure that consumers do not exceed safety thresholds for dietary intake. However it should also be noted that mercury in the environment can be of natural origin (e.g. volcanic). In these situations, the scope to reduce environmental levels is very limited.

CONCLUSIONS

42. The levels of methylmercury that occur in some fish species can lead to consumers exceeding the JECFA PTWI recommendations. Quantitative risk assessment is lacking and would help to clarify the significance of the effects of such levels of dietary intake. Also, further epidemiology studies would help to resolve discrepancies between the findings of the major studies which have been used for the risk assessment on methylmercury. Nevertheless, in view of dietary intakes above the recommended safety guideline, risk management measures are needed, particularly to help protect the most vulnerable groups of the population, the developing foetus, infants and young children, but also other individuals who eat a lot of fish that may contain significant levels of methylmercury. Due to the important role that fish play in diets world-wide, it is important that further developed risk management measures would take a balanced approach, taking into account the dietary benefits of fish and avoiding the risk of overreaction by consumers.

43. Assessments balancing the risks and the benefits of fish consumption have already been performed. Examples thereof are (non-exhaustive)

- In 2004, in the UK the Scientific Advisory Committee on Nutrition (SACN) and the Committee on Toxicity (COT) brought together in a report the nutritional considerations on fish consumption and the toxicological considerations on the contaminants in fish. The nutritional benefits were weighed against the risks and coherent dietary advice for the public on the consumption of fish, in particular to oily fish was developed (45).
- In 2005, the Scientific Panel on contaminants in the Food Chain from the European Food Safety Authority conducted a scientific assessment of the health risks related to human consumption of wild and farmed fish (46). In this assessment advice is provided on the safety and nutritional contribution of wild and farmed fish. The Panel further recommends the development of a consistent and agreed methodology for carrying out quantitative assessments of risks and benefits related to food consumption
- In 2006, the WHO, in cooperation FAO, conducted a workshop in Geneva to discuss and elaborate the document “Application of risk analysis to methylmercury in fish” providing advice to risk managers on balancing the risks due to the presence of methylmercury and benefits of fish consumption and offering some guidance on developing practical risk communication considerations for target groups, such as pregnant women (47).

There is a need to have a worldwide Expert Consultation to consider comprehensively the risks and benefits of fish consumption.

44. Limiting the presence of methylmercury in fish is one possible approach to reduce dietary exposure. However, to further lower the Codex guideline levels would appear to be unrealistic, without compromising a large proportion of certain varieties of fish. Alternative measures have included education and advice on consumption of fish. This approach has been developed by several nations, to help the vulnerable members of the population become aware of the risks, particularly focusing on women that may become pregnant, women who are pregnant, women who are breast-feeding and young children.

45. Effective risk management relies upon communication and reaction. It cannot rely upon guideline levels alone, in particular in this case. In view of the difficulty to lower the guideline levels for methylmercury in fish and acknowledging the nutritional benefits of fish in the diet, it is necessary to investigate the extent to which international guidance and targeted consumption advice could be provided for the vulnerable groups of the population.

46. In order to have an exchange of views on risk communication strategies as a management tool for contaminants in food, CCFAC will host a workshop on this subject at its 38th session. During this workshop an exchange views on risk communication strategies and the scope for the development of a worldwide general guidance for risk communication will be explored. At the workshop the importance of risk communication will be highlighted and topics such as communication on risk assessment and communication on risk management, the role of the media in risk communication will be addressed.

RECOMMENDATIONS

47. To specify the list of fish species that may be considered as predatory fish. Such a list should include the commercial and important recreational fish species which might, taking into account age, length, weight and catching area (location), contain methylmercury content above 0.5 ppm.

48. To request data for comparison of levels of methylmercury with total mercury in different fish species. Further development on analytical methods to detect methylmercury is necessary to widen the accessibility of such methods, particularly in view of evidence that proportions of methylmercury to total mercury may be lower in some species.

49. To organise an Expert consultation to assess comprehensively the risks and benefits of fish consumption with the following proposed terms of reference:

<u>Assessment of the risks associated with the consumption of fish:</u>

- To identify and to consider the contaminants of possible concern which are present in fish (methylmercury, dioxins, PCBs, brominated flame retardants, lead, cadmium etc.).
- To describe the pattern of contamination of the different contaminants in the relevant fish species fish groups such as predatory fish, oily fish.
- To identify vulnerable groups of the population who might be at higher risk than the average consumer (e.g. infants, young children, pregnant women, high consumers).
- To provide guidance to countries on ways to identify regions where people are more likely to be exposed to high levels of contaminants because of differences in nutritional behaviour or local contamination.

<u>Assessment of the benefits of fish consumption:</u>

- To consider and review the evidence on the beneficial nutritional factors of eating fish (e.g. source of protein and essential nutrients such as vitamin D, iodine and omega-3 fatty acids).

<u>Comparison of the risks and benefits of fish consumption:</u>

- To develop a methodology and identify data necessary for carrying out quantitative assessments of risks and benefits related to fish consumption.
- To weigh nutritional benefits against the possibility of adverse effects taking into consideration all groups in the population, and if possible allowing quantitative comparisons of human health risks and benefits of fish consumption.

50. In addition the Expert Consultation could provide advice on the possibility to apply this methodology to food groups other than fish.

51. To investigate the possibility to provide international guidance on risk communication advice for vulnerable groups of the population on the consumption of fish, particularly for species known to frequently contain high levels of methylmercury. Also, to consider listing species of fish known to contain consistently lower levels of methylmercury independent from catching areas to help consumers make informed choices. A general model would be helpful for national governments to develop more specific advice to cover regional and local needs. Coherent dietary advice should be developed for the public on consumption of fish taking into account all contaminants of relevance and total dietary exposure. Consumer advice should not have the adverse effect of discouraging healthy consumption of fish.

52. To encourage Codex member countries to promote measures at national and international levels to reduce mercury pollution into the environment (for example, contributing towards the mercury initiative of the United Nations Environment Programme).

ANNEX 1

Comparison of state-of-the-art analytical methods as reported in 2005 in reference 29

Participant		Calibration	Sample mass (g)	Spike addition	Digestion → Extraction → Derivatisation	Separation/ detection	References
1	BKAE-ET	SA	0.25	n/a	KOH, MeOH/US, 70°C → phenylation → SPME headspace	GC/CV-AFS	30
2	EC-JRC-IRMM	1x ID	0.18	H	$HCl_{(Conc.)}$ → NaOH, DDTC, toluene/C, 20°C → Grignard butylation	GC/ICP-MS	31
3	ENEA	1x ID	0.20	IM	6 M HCl, toluene extraction/US → back extraction with cysteine → phenylation → $CuSO_4$, hexane extraction	GC/EI-MS	-
4	FGI	EC	0.40	n/a	KOH, MeOH/HP, 70-80°C → buffer/ethylation → purge and trap (carbotrap)	GC/CV-AFS	32
5	IAEA-MEL	EC	0.20	n/a	KOH, MeOH/O, 75°C → ethylation	GC/CV-AFS	-
6	JSI	SA	0.40	n/a	H_2SO_4, KBr, $CuSO_4$, CH_2Cl_2 → separation and evaporation of CH_2Cl_2 to aqueous phase → ethylation	GC/CV-AFS	33
7	LCABIE	1x ID	0.40	IM	TMAH/open focussed MW, 3 min at 40 W → buffer, propylation → *i*-octane extraction	GC/ICP-MS	34
8	LGC	2x ID	0.40	H	Protease Type XIV, Buffer, Mercaptoethanol, trypsin / RI, 37°C 24 hr → dilution in LC mobile phase	LC/ICP-MS	35
9	NIST	1x ID	0.40	IM	Acetic acid/ MW, 3 min → phenylation → SPME headspace	GC/EI-MS	-
10	NMIJ	2x ID	0.25	H	TMAH/US 3h → 6 M HCl, toluene → buffer, phenylation	GC/ICP-MS	-
11	NRCC	1x ID	0.4	H	KOH, MeOH/MaS, 20°C → buffer, propylation → SPME headspace	GC/ICP-DF-SD-MS	30, 36
12	TU	1x ID	0.02	IM	KOH, MeOH/HP, 60°C → ethylation	GC/ICP-MS	37
13	UO	2x ID	0.45	IM	HCl, NaCl/MaS, 20°C → propylation	GC/EI-MS	-
14	UU	1x ID	0.30	IM	TMAH/MaS, 20°C → extraction as DDTC complex to toluene → Grignard butylation	GC/ICP-MS	38

Key: EC = external calibration; SA = standard additions; 1x ID = Direct species-specific isotope dilution; 2x ID = Double species-specific isotope dilution; IM = immediately prior to digestion; H = some hours (2-16) prior to digestion; PD = post-sample digestion; C = centrifugation; HP = hot plate; MaS = manual shaking; MW = microwave irradiation; O = oven; RI = rotating incubator; US = ultrasounds; GC = capillary gas chromatography; LC = Liquid Chromatography; CV-AFS = Cold Vapour Atomic Fluorescence Spectrometry; DF-SD = Double Focussing Single Detector; ICP = Inductively Coupled Plasma; EI = Electron Impact; MS = Mass Spectrometry. Acronyms given in column 2 represent institutions participating in the comparison; full details are given in reference 29.

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