**Table 1.** Summary of the data for fish- and seafood product consumption and dietary intake of methylmercury (MeHg) from such foods according to the SCOOP task 3.2.11 for countries showing high and low intakes

| | The Netherlands | Portugal | Ireland | Greece | France | Norway |
|---|---|---|---|---|---|---|
| *Food consumption* | *(g/day)* *Mean (High)* | *(g/day)* *Mean (High)* | *(g/day)* *Mean (High)* | *(g/day)* *Mean (High)* | *(g/day)* *Mean (High)* | *(g/day)* *Mean (High)* |
| *- Fish and seafood*[1] | *10 (-)* | *50 (-)* | *20 (75)* | *41 (71)* | *35 (-)* | *80 (275)* |
| | | | | | | |
| *Intake of MeHg*[2] | | | | | | |
| **SCOOP: International dietary exposure**[3] | *µg MeHg/kg bw/week* | *µg MeHg/kg bw/week* | *µg MeHg/kg bw/week* | *µg MeHg/kg bw/week* | *µg MeHg/kg bw/week* | *µg MeHg/kg bw/week* |
| - Mean | 0.1 | 0.6 | 0.3 | 0.5 | 0.4 | 1.0 |
| - High[4] | | - | 1.0 | 0.9 | - | 3.5 |
| | | | | | | |
| **SCOOP: National dietary exposure**[5] | | | | | | |
| - Mean | <0.1 | 1.6 | <0.1 | 0.5 | 0.3 | 0.4 |
| - High | - | - | 0.4 | 2.2 | - | 1.8 |

[1] *Including fish, crustaceans, bivalves and molluscs*

[2] *Assuming that all mercury is methylmercury*

[3] *Estimated intake = Consumption of fish- and seafood products x 109 µg/kg food.*

[4] *High percentile represents 95th or 97.5th percentile of the distribution depending of the country considered*

[5] *Estimated intake = Consumption of fish- and seafood products x national data for the concentration of mercury.*

The SCOOP data showed that, although the population in Norway had the highest total consumption of fish and seafood products, the estimated high intake of methylmercury from these foods was lower in Norway than, for instance, in Greece. The reason for this is probably that the type of fish consumed in Norway consists of species, such as cod and saithe, which contain relatively low levels of methylmercury. The consumption of large predatory fish, which are at the top of the food chain such as swordfish and tuna, which all contain higher levels of methylmercury, may be significantly greater in countries in southern Europe.

***Refined intake assessment using national data***

A probabilistic analysis of the likelihood of exceeding the PTWIs was carried out using the French contamination data as reported to SCOOP in combination with the distribution of fish and seafood product consumption in France (Table 2).

The probability for a population to reach an exposure over the JECFA-PTWI and the U.S.-NRC limit was calculated using an empirical method, in which the individual consumption of each consumer of seafood products is multiplied by the mean level of contamination. The empirical probability is calculated as the number of subjects with an intake greater than 1.6 µg/week divided by the total number of subjects in the survey.

**Table 2.** Exposure assessment and probability of overstepping the tolerable intakes based on the distribution of consumption and fish contamination in France (Tressou *et al.*, 2004).

| Group | Number of subjects | Mean consumption | Mean exposure | 50th %ile | 97.5th %ile | Empirical probability of exceeding the PTWI (µg/kg bw/week) | |
|---|---|---|---|---|---|---|---|
| | | (g/week) | (µg/kg bw/week) | | | JECFA (1.6) | U.S.-NRC (0.7) |
| Children 3-6 years | 293 | 178 | 0.83 | 0.61 | 3.0 | 11.3% | 44% |
| Adults 25-34 years | 248 | 282 | 0.38 | 0.28 | 1.28 | 1.2% | 17% |

Children in the 3 to 6 year age group consume a greater amount of fish and seafood products than adults, when the consumption is expressed on a body weight basis. The calculated probabilities of exceeding the methylmercury exposure limits are therefore much higher for small children, who may then constitute a group with increased exposure.

It should be noted that these calculations were performed for a country in which fish and seafood products are consumed in relatively small amounts. For example, the consumption of fish at the 97.5$^{th}$ percentile intake in France is about 880 g per week/person corresponding to 125 g/day which is about one-half the amount consumed in Norway.

In addition, since the SCOOP-data were submitted, the Norwegian Food Safety Authority has made a more detailed intake calculation of mercury based on individual consumption figures for fish and seafood products and self-reported body-weight. The intake calculations were based on data on food consumption and the mean concentration of mercury in foods that were submitted to the SCOOP task. Instead of using single point estimates for food consumption (mean and 95$^{th}$ percentile), which was the case when assessing the mean and high intake of mercury for the SCOOP task, the new intake estimate was based on the distribution of the consumption values. This means that the individual consumption estimate for each species of fish and seafood products was multiplied with the concentration value for this particular fish species and seafood products. Subsequently, the intake of mercury from each of the fish and seafood products was totalled for each individual. The resulting distribution of the total intakes of all the participants was used to derive the mean and 95$^{th}$ percentile intake of mercury. The self-reported body weight of each participant was used in order to calculate the intakes expressed on a body weight basis.

Based on the distribution of the intake of mercury among the consumers of fish and seafood products (n=5696) the estimated intake of mercury was 1.0 µg/kg body weight per week (at the 95$^{th}$ percentile). Female participants of childbearing age (n=1565) had an estimated high intake of mercury (95$^{th}$ percentile), equal to the intake among the rest of the participants.

These estimates show a considerably lower high-level intake from fish and seafood products than the high international estimated exposure of 3.5 µg/kg body weight/week for Norway. This is mainly due to a lower concentration in the fish most commonly eaten in Norway (i.e. <50 µg/kg fish) than the mean concentration of 109 µg mercury/kg fish used when estimating the international intakes of the substance. However, the estimates are also lower than the SCOOP high national intake for Norway (1.8 µg/kg body weight/week). This may be explained by the methods used for estimating the exposure. As mentioned before, the SCOOP estimates were based on single points estimates for consumption (95$^{th}$ percentile) combined with single point estimates for concentration, which generates higher high-level intakes than when the distribution of individual intake estimates are used to derive high-level intake.

## Hazard Characterisation

### *Evaluations of methylmercury by the JECFA and by the U.S.-NRC*

In 1999, the fifty-third meeting of the JECFA reviewed information that had become available since its previous evaluation, particularly the information available on neurobehavioral development in children in the Faroe Islands and Seychelles. Because of the absence of any clear indication of a consistent risk in the epidemiology studies available at that time, the fifty-third meeting recommended that methylmercury should be re-evaluated at a subsequent meeting, in order to consider the 96-month evaluation of the Seychelles cohort and other relevant data that may have become available. The provisional tolerable weekly intake (PTWI) for methylmercury was not reconsidered and was maintained at the value established previously (200 μg of methylmercury equivalent to 3.3 μg per kg of body weight). This value was originally based on adverse effects in adults exposed during a poisoning outbreak in Iraq, and did not allow for the fact that the foetus could be more susceptible than the mature organism.

The sixty-first meeting of the JECFA in 2003 (JECFA, 2003) reviewed new data and analyses from the Seychelles Islands cohort and concluded that no adverse effects of prenatal methylmercury exposure had been detected in this cohort, in which intake occurs mainly from high levels of fish consumption. In contrast, neuropsychological deficits that correlated with the extent of methylmercury exposure have been detected consistently in a cohort of children in the Faroe Islands, in which intake occurs mainly from the consumption of whale meat. Stratifying analyses of the data from the Faroe Islands were used to allow for any confounding by possible neurotoxic effects of PCBs which are contaminants in whale blubber. The results from the two cohorts were combined in the JECFA evaluation, and the JECFA concluded that both were consistent with the absence of appreciable adverse effects in children born to mothers with hair concentrations of 14 μg mercury/g maternal hair. However, the Panel noted that this hair level was not a NOAEL in the data from the Faroe Islands. Information from other studies, including data from exposed cohorts in Iraq and New Zealand, were not incorporated quantitatively in the combined exposure-response assessment because these data were derived from smaller cohorts or differed substantially in study design.

The maternal hair concentration of 14 μg mercury/g was converted by the JECFA to a blood concentration using the average hair:blood ratio from a number of studies of Caucasian and Oriental subjects; the resulting maternal blood concentration (0.056 mg/L) was converted to a daily intake (1.5 μg/kg body weight) using an equation which incorporated the rate of elimination. Uncertainty factors were applied to allow for interindividual variability in the hair:blood ratio (2-fold) and in the rate of elimination ($10^{0.5}$ or 3.16-fold). Uncertainty factors for interindividual variability in (toxicodynamic) vulnerability or for incompleteness of the database were considered not to be necessary. Thus the PTWI was estimated as 1.6 μg/kg body weight/week ([1.5/6.32] μg/kg body weight/day). The JECFA considered that the available data for other effects, such as cardiotoxicity, were not conclusive and could not be used as a basis for estimating the PTWI.

As directed by the U.S. Congress, the U.S. Environmental Protection Agency (EPA) asked the U.S.-NAS to perform an evaluation of the toxicological effects of methylmercury and to prepare recommendations on the establishment of a scientifically appropriate methylmercury exposure reference dose (RfD) (NRC, 2000). The U.S.-NRC used benchmark dose level from the Faroes study (12 µg mercury/g maternal hair) and used a composite uncertainty factor of 10, to take into account interindividual variability and incompleteness of the data base, to derive an exposure limit of 0.1 µg/kg body weight per day or 0.7 µg/kg body weight per week. Further probabilistic modelling including the results of the three prospective studies (Faroe Islands, New Zealand, and Seychelles Islands) led basically to the same outcome. This limit agreed with the limit calculated previously by the U.S.-EPA on the basis of marked adverse effects in children prenatally exposed to methylmercury during a poisoning incident in Iraq, but the U.S.-NRC suggested that the justification should be based on the more recent epidemiological evidence on children exposed prenatally.

These risk assessments are based on studies of internal dose, as reflected by mercury concentrations in blood or hair. They have then been translated to average daily intake levels that can be compared with intake assessment included in the present opinion.

*Evaluation of methylmercury by the Scientific Panel on Contaminants in the Food Chain*

The Panel agrees with the JECFA and the U.S.-NRC evaluations that the developing brain should be considered the most sensitive target organ for methylmercury toxicity. The Panel also agrees with the JECFA that human risk assessment is possible on the basis of the prospective epidemiological studies on childhood development. However, an increasing body of data is now indicating that raised methylmercury exposure may augment the risk of cardiovascular morbidity and mortality (JECFA, 2003), but the complexity of the information available precludes a conclusion at this time.

There is a very large toxicity database from animal and epidemiology studies, and substantial complexity involved in assessing dose-response relationships from the available epidemiological data. In addition, the mathematical conversion of the exposure biomarker in the different cohorts into intake estimates depends on several assumptions, each associated with some degree of uncertainty. The Panel has noted that different approaches and uncertainty factors have been used in recent evaluations (e.g. the JECFA and the U.S.-NRC).

In interpreting the JECFA evaluation, several aspects should be kept in mind, which might lead to a lower exposure limit, such as the one determined by the U.S.-NRC. First, the benchmark dose level is a statistically defined point of deviation, and whether in the case of methylmercury it is consistent with a negligible adverse effect, as was concluded by the JECFA, will require careful and detailed consideration. Second, exposure assessment in epidemiological studies is always imprecise, since the exposure is not controlled *a priori*. In the case of methylmercury, calculation of the intake is complex because it is based on the conversion of biomarker data such as hair levels into daily intake. Imprecision in intake estimates may lead to underestimation of the true mercury effect and to an overestimation of the benchmark dose level. Third, epidemiology studies are associated with uncertainty because the effect of a single factor is ascertained in a situation where many covariates may affect the outcome. There are a large number of potential confounders in the main epidemiology studies on methylmercury, such as the source and pattern of methylmercury exposure, the nature of the populations, the influence of nutrition, and the presence of other pollutants such as PCBs, which make comparison of the studies and interpretation of the data difficult. Factors of potential relevance to the performance of children in neuropsychological tests, and that were not considered in the study reports include the possibility of an uneven distribution of parental consanguinity in isolated island populations which has been reported for the Faroe Islands and which could result in a depression of the performance of the children, and a number of other social, nutritional and environmental factors. All of these complexities need to be taken into account in evaluating the dose-response relationships and in assessing the adequacy of the uncertainty factors used in the recent evaluations.

The reduction of the PTWI for methylmercury by the JECFA at its latest meeting is justified because the new PTWI is based on the most susceptible lifestage, i.e. the developing foetus and intake during pregnancy, rather than on the general adult population, which was the basis for their previous evaluation. The recent evaluations by the JECFA and the U.S.-NRC considered several sources of uncertainties. The health based guidance values differed by a factor of two, and arose largely because of the different uncertainty factors used. Any refinement of the hazard characterisation for methylmercury will be dependent on resolution of a number of generic issues that have been raised above. The Panel recognises that this will require the establishment of working groups by the EFSA Scientific Committee.

**Risk characterisation**

Exposure evaluation based on the SCOOP data can be compared to the new PTWI of the JECFA. Comparison with the lower U.S.-NRC limit may offer additional guidance.

Fish and seafood products are important sources of energy, protein, and a variety of essential nutrients, such as vitamins, trace elements, and fatty acids. The nutrient contents vary between species, and dietary advice should seek to optimize the contribution of fish and seafood products to a healthy diet, while at the same time minimizing the exposure to contaminants, such as methylmercury.

Simplistic analyses of the data in the SCOOP report indicated that the international mean intake of methylmercury was below the PTWI established by the JECFA in 2003. Population-groups who frequently consume large predatory fish, such as swordfish, tuna, and halibut, may have a considerably higher intake of methylmercury and exceed the PTWI. Based on national data the highest average intake estimates were just at the PTWI and exceeded the U.S.-NRC exposure limit.

Analyses were done on national data sets in order to assess the probability of intakes above the PTWI established by the JECFA in 2003. The limited data available indicate that proportions of young children may exceed the PTWI when expressing exposure on a body weight basis. In addition, a percentage of adult populations with higher fish consumption would be predicted to have intakes above the PTWI. Nevertheless, the quality of data at European level is not sufficient to assess the size of these population groups.

## CONCLUSIONS AND RECOMMENDATIONS

The major source of methylmercury intake in humans is fish and seafood products. Specifically, large predatory fish which are at the top of the food chain, such as swordfish and tuna, which all contain higher levels of methylmercury, are significant sources of human exposure to methylmercury. Food sources other than fish and seafood products may also contribute mercury exposure, but mainly in the form of inorganic mercury that would not affect the current opinion on methylmercury.

The developing brain is the most sensitive target organ for methylmercury toxicity; *in utero* exposure is believed to be the critical period for methylmercury neurodevelopmental toxicity, although the duration of increased susceptibility may extent into postnatal development. To derive a PTWI, the JECFA used the data from two major epidemiological studies of foetal neurotoxicity performed in the Faroe Islands and the Seychelles Islands thereby basing its evaluation on the most sensitive population. The data from the SCOOP report indicate that the average intake of fish and seafood products in some countries may be close to the JECFA PTWI and, when compared to the previously established U.S.-NRC limit, some average intake levels may exceed this limit. Specific intake data for pregnant women are not available.

The data available in the SCOOP report do not allow reliable estimations of the intakes by high consumers in different populations. Because in some cases the estimated intakes based on the SCOOP report are close to or exceed the PTWI, specific intake studies, especially for women and children, should be performed on methylmercury. A more complete evaluation of exposures in Europe that includes data on internal dose levels would allow direct comparison of exposure with the dose-effect relationships, which are the basis for the hazard characterisation.

Mercury compounds serve no biological purpose in the human body. Methylmercury toxicity has been demonstrated at low exposure levels, and exposure to this compound should therefore be minimized, while recognizing that fish represents an important part of a balanced nutrition.

## DOCUMENTATION PROVIDED TO EFSA

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