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EVALUATION OF CERTAIN FOOD ADDITIVES AND CONTAMINANTS

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estimates of exposure from the different regional diets, similar results would be anticipated if other GEMS/Food regional diets were used in the scenario.

The Committee also estimated the effect on blood lead concentrations of long-term exposure to lead in the three models of regional diets, to illustrate the ranges of intake of lead under various assumptions. Long-term exposure was assumed to include that occurring in utero and for the first 10 years of life. As a conservative estimate, the Committee assumed that a dietary intake of $1\mu\text{g}/\text{kg}$ of body weight per day would result in an increase in blood lead concentration of $1\mu\text{g}/\text{dl}$, this being the upper estimate for infants, and that this relationship was valid during the long-term exposure period. This would correspond to an increase in blood lead concentration of $0.14\mu\text{g}/\text{dl}$ per μg of lead per kg of body weight per week. Using this assumption in combination with the ranges of values for high estimated dietary intake, the Expert Committee calculated that consumption of a diet containing lead at the limits proposed by the Codex Committee on Food Additives and Contaminants would result in an increase in blood lead concentration of $3\mu\text{g}/\text{dl}$. Consumption of diets containing lead at "typical" average or high concentrations would result in increases in blood lead concentrations of 0.3 and $0.6\mu\text{g}/\text{dl}$, respectively. The results shown in Table 4 provide confidence that the levels of lead that are found currently in foods would have negligible effects on the neurobehavioural development of infants and children. Nevertheless, the Committee stressed that a full risk assessment of dietary intake of lead should take into account other sources of exposure.

6.1.3 *Conclusions*

The Committee concluded that, overall, the concentrations of lead found currently in food would have negligible effects on intellectual development, but noted that foods with high lead content remain in commerce. The simulation model presented here could be used to evaluate the effects of any proposed regulatory interventions to reduce exposure to lead.

A toxicological monograph was prepared.

6.2 **Methylmercury**

The Committee first evaluated methylmercury at its sixteenth meeting (Annex 1, reference 30), when it established a PTWI of $300\mu\text{g}$ of total mercury per person, of which no more than $200\mu\text{g}$ should be present as methylmercury. At its twenty-second and thirty-third meetings (Annex 1, references 47 and 83), the Committee confirmed the PTWI of $200\mu\text{g}$ of methylmercury ($3.3\mu\text{g}/\text{kg}$ of body weight) for the general

Table 4
Decreases in intelligent quotient (IQ) associated with the concentration of lead in blood

Concentration of lead in blood (µg/dl)	Median decrement in IQ (95% confidence interval)
5	0.4 (0.0–1.5)
10	1.7 (0.5–3.1)
15	3.4 (1.1–5.0)
20	5.5 (1.6–6.9)

dose–response function generated, Table 4 shows the estimated net decreases in IQ for the median population at four values of blood lead concentration, with a range of uncertainty for each estimate.

Dose–response simulation

A simulation model was developed in which a dose–response component was added to the model of exposure described previously. This model was used to illustrate the net benefit of imposing limits on the levels of lead in food with respect to neurobehavioural development of children exposed to lead from dietary sources.

The studies that have associated exposure to lead with performance in behavioural tests were conducted in populations whose exposure to lead was relatively constant. In order to gauge the relative importance of shorter exposures, it was presumed that the net lifetime effect of lead on intellectual status (adult IQ) after a limited prenatal or postnatal exposure can be scaled relative to a period of 5–15 years, where the range represents the uncertainty associated with the adjustment.

The model was based on consumption patterns from a GEMS/Food Middle Eastern diet, assuming that the lead concentrations in food were typical of those in the USA and that non-dietary exposure roughly corresponded to that in the USA. In this hypothetical scenario, a decrement in IQ of 0.006 points (range of 0–0.06 points) was estimated for the population mean of children as a result of maternal exposure for 9 months. The procedure described above was used to adjust for the period of exposure. In a scenario in which the cereal grains in a regional diet contained 10 times higher lead levels than those used in the first model, the estimated decrement in IQ points attributable to exposure to lead was 0.02 points (range 0–0.1 points). A hypothetical intervention leading to a 50% reduction in the lead concentration of grain was estimated to reduce the decrement in IQ points to 0.011 points (range 0–0.08 points). Given the similarity in the

population. At its thirty-third meeting, the Committee noted that pregnant women and nursing mothers may be at greater risk than the general population from the adverse effects of methylmercury. The Committee considered the available data insufficient for it to recommend a specific methylmercury intake for this population group and recommended that more detailed studies be undertaken.

At its present meeting, the Committee reviewed information that had become available since the previous evaluation in order to estimate the risk associated with various levels of exposure. The PTWI was not reconsidered and was maintained at its present value.

6.2.1 *Intake*

Although methylmercury can occur in other foods, it is found primarily in fish. In other foods, mercury is present mainly as elemental mercury. The Committee noted the variation in levels of methylmercury in fish, both within and between species and also noted that fish from polluted waters usually have higher mercury levels than those from unpolluted waters. When intakes of total mercury were provided, the Committee assumed conservatively that all of the mercury was present as methylmercury.

A "typical" level of methylmercury must be established to permit estimation of intake from the GEMS/Food regional diets. A "typical" level should correspond to the average levels of intake by consumers and should therefore represent the usual levels in commonly consumed species of fish. The Committee concluded that levels based on estuarine fish, tuna or flake fillet would be appropriate for this purpose. For these analyses, the average concentrations found in tinned tuna and flake fillet were used to derive a range of estimates of regional intakes of methylmercury.

Data on the levels of mercury residues in food and/or assessments of mercury intake were submitted to the Committee by 25 countries representing the major regions of the world. The Committee used these data, together with the estimates of fish consumption in each of five regional GEMS/Food diets, to estimate typical methylmercury intakes of 0.3–1.1 $\mu\text{g}/\text{kg}$ of body weight per week, depending on the region. These values are based on the assumption that all fish and shellfish contain methylmercury at a concentration of 200 $\mu\text{g}/\text{kg}$. If all fish and shellfish that are consumed contain methylmercury at a concentration of 330 $\mu\text{g}/\text{kg}$, the intake would range from 0.5 to 1.8 $\mu\text{g}/\text{kg}$ of body weight per week.

The methylmercury intake of consumers in Australia, who were considered to have a high fish intake was estimated on the assumption

Table 5

Estimated intake of methylmercury from fish by consumers in the 95th percentile and comparison of the impact of three theoretical residue limits on intake levels^a

Residue limit ($\mu\text{g}/\text{kg}$ of fish)	Estimated intake of methylmercury ($\mu\text{g}/\text{kg}$ of body weight per week)		
	Children (2-5 years)	Women	Total
None	1.5	0.8	0.9
1000	1.4	0.7	0.9
500	1.4	0.6	0.8
200	0.8	0.4	0.5

^a Based on data from the USA.

that the fish contained methylmercury at a concentration of 200 or 640 $\mu\text{g}/\text{kg}$. The estimated intakes for consumers in the 95th percentile were 2.1 and 5.6 $\mu\text{g}/\text{kg}$ of body weight per week, respectively. As these values are based on the assumption that all fish contain methylmercury at these levels, they are highly conservative estimates of extreme levels of intake.

A probability analysis was conducted in the USA to provide a more realistic estimate of the intake of methylmercury by consumers in the 95th percentile, by taking into account the variation in both fish consumption and residue levels in the fish that are consumed. The analysis covered the entire distribution of fish consumption and methylmercury residues in fish. An estimate was also provided from a simulation model of the potential impact of establishing limits on intake of methylmercury, by repeating the analysis after excluding residue levels that exceeded theoretical regulatory limits of 1000, 500 or 200 $\mu\text{g}/\text{kg}$ of fish. The results of the analysis are presented in Table 5 for consumers in the 95th percentile in three population groups. These results suggest that the intake of the adult populations would be below the PTWI, providing individuals consumed fish containing "typical" levels of methylmercury.

The Committee also specifically evaluated the potential intake of children and infants. The GEMS/Food regional diets do not include separate estimates for children, but several countries provided estimates of the intake of mercury by children and infants. Comparison of the intake by adults and children in each country shows that children consume two to three times more mercury than adults per unit body weight. Nevertheless, the concentrations of mercury in the hair of children are similar to those in adult hair, indicating that children have similar body burdens to those of adults. Therefore, the higher

intakes of children would not necessarily result in an equivalent increase in risk, and, if children are no more sensitive than adults to methylmercury, the PTWI would be appropriate for both adults and children. In simulations conducted in the USA, children were found to have intakes below the PTWI. Although data were not available to permit equivalent analyses for other countries, the results can be expected to be similar, providing the methylmercury concentrations in fish and the levels of fish consumption are comparable to those in the USA.

6.2.2 *Pharmacokinetic data*

Studies of the kinetics of methylmercury showed that its distribution in tissues after ingestion is more homogeneous than that of other mercury compounds, with the exception of elemental mercury. The most important features of the distribution pattern of methylmercury are high blood concentrations, a high ratio of the concentrations in plasma to those in erythrocytes and high levels of deposition in the brain. Another important characteristic is slow demethylation, which is a critical detoxification step. Methylmercury and other mercury compounds have a strong affinity for sulfur and selenium. Although selenium has been suggested to provide protection against the toxic effects of methylmercury, no such effect has been demonstrated.

6.2.3 *Toxicity data*

A variety of effects have been observed in animals treated with toxic doses of methylmercury. Some of these, such as renal damage and anorexia, have not been observed in humans exposed to high doses. The primary tissues of concern in humans are those of the central nervous system, particularly the developing brain, and these have been the focus of epidemiological studies.

Methylmercury induces neurotoxicity in small rodents such as mice and rats at doses that usually also affect other organ systems. Moreover, the maternal dose that causes neurotoxic effects in offspring exposed in utero also results in maternal toxicity. The main neurotoxic effects are impairment of coordination and pathological changes in selected areas of the brain and spinal cord. Similar effects are seen in domestic animals. In cats, no difference in toxicity was observed between methylmercury naturally present in fish and methylmercury added to the diet.

Similar effects of methylmercury were observed in 4-year studies in non-human primates, in which the techniques used to detect neuronal damage included pathological and behavioural tests and investigations of the visual and auditory systems. Although the number of

animals included in these experiments was small, the NOEL was 10µg/kg of body weight per day (expressed as mercury and corresponding to a steady-state blood concentration of 0.4µg/l).

The clearance, half-life and blood concentrations of methylmercury at steady-state depend on the body surface area. On the basis of body weight, small animals are much less sensitive to methylmercury than are humans, while the sensitivity of non-human primates is similar to that of humans.

The two biomarkers used most frequently for quantifying the burden of methylmercury in the human body are blood and hair concentrations. Establishment of a quantitative relationship between exposure (daily intake) and concentrations in blood and hair began with a study of the effects of accidental consumption of grain treated with methylmercury fungicide in Iraq. Although the weight of evidence suggested that every 1µg/l increase in the blood concentration of methylmercury results in an increase in the hair concentration of 140–370µg/kg, in six of ten studies, the ratio of the hair: blood concentrations was 230–280. The Committee concluded that a ratio of 250 is a reasonable estimate of the ratio of the hair: blood concentrations. The approximate relationships between weekly intake and blood concentration of mercury at steady state indicate that intake of 1µg of mercury per kg of body weight per week in the form of methylmercury corresponds to a concentration of mercury of 10µg/l of blood and 2.5mg/kg of hair.

Since the Committee's previous consideration of methylmercury, a considerable amount of data have become available on the possible neurobehavioural effects of prenatal and postnatal exposure. The most relevant data are from two large prospective epidemiological cohort studies conducted in the Faroe Islands and the Seychelles, where large amounts of seafood are consumed. The prenatal exposure of the two cohorts to mercury appears to have been similar. The geometric mean concentration of mercury in the hair of mothers during pregnancy was 4.3µg/g (interquartile range 3–8µg/g) in the Faroe Islands and 6.8µg/g (interquartile range 0.5–27µg/g) in the Seychelles. In the Faroe Islands, the geometric mean concentration in umbilical cord blood was 23µg/l (interquartile range 13–41µg/l). In the study in the Faroe Islands, no association was seen between the extent of prenatal exposure to methylmercury and performance in clinical or neurophysiological tests, although significant decrements were observed in the children's scores in tests of functions such as fine motor skills, attention, language, visual-spatial skills and memory. Most of these associations were still apparent when the children whose mothers had had hair concentrations of mercury greater than 10µg/g were excluded from the analyses (representing 15% of the

total). No adverse effects associated with exposure to mercury were reported in the study in the Seychelles.

Several differences between the studies may have contributed to the apparent discrepancy between the findings. First, the children were evaluated for neurobehavioural end-points at different ages and using different tests. In the Faroe Islands, the first neurobehavioural evaluation was conducted when the children were 84 months (7 years) of age, whereas in the Seychelles, the children were assessed at 6, 19, 29 and 66 months of age. As the capabilities of young children change rapidly, the scores at different ages may reflect performance in qualitatively different types of tasks, and scores achieved by children of different ages cannot be compared easily. In addition, although early childhood development was assessed in both studies, different batteries of tests were used. In the Faroe Islands, the battery of tests focused on specific aspects of language, memory, fine motor function, attention and visual-spatial skills. In the Seychelles, the main test was a general test of development that included performance in many aspects of neurological function, although general tests of language, visual-spatial skills and academic achievement were also used. Even though some types of neurological function were assessed in both studies (e.g. language and memory), the differences in the specific tests used make the findings difficult to compare.

Secondly, the two study cohorts may differ with regard to exposure to other factors that can affect the neurobehavioural development of children. In the Faroe Islands, many potential confounding factors were addressed in the analysis, including exposure to polychlorinated biphenyls (PCBs). Pilot whale is the major source of both methylmercury and PCBs in this population, and PCBs are thought to adversely affect the neurodevelopment of children exposed prenatally. When PCBs were measured in samples of umbilical cord tissue (blood and plasma were not available) from one-half of the Faroe Islands cohort, the average PCB concentration in cord tissue lipids was lower than the concentration previously reported in breast milk lipids in the same population, indicating that cord tissue concentration may not be an appropriate indicator of the burden of PCBs. In the Seychelles, potential confounding exposures were not addressed, but it has been suggested that the finding that a higher intake of mercury was associated with higher scores in some tests of development is a result of nutritional factors or mitigating substances present in fish.

Thirdly, the intake patterns of the two cohorts may have differed. Most of the methylmercury consumed in the Faroe Islands is from pilot whale, which is eaten less frequently than fish but contains more mercury per serving. In contrast, the source of methylmercury in the

Seychelles is fish, which is consumed almost daily. Therefore, the intake of methylmercury in the Faroe Islands may be episodic, with high peak levels of intake. Although the effect of methylmercury on neurobehavioural development has generally been presumed to be a function of cumulative intake, short-term peak intake may also be important.

Further follow-up of these cohorts, with greater coordination between the study organizers, would be helpful for addressing some of the issues of assessment. For example, the cohort in the Seychelles was evaluated at 96 months with many of the same tests as were used in the Faroe Islands, and the results are expected to become available in the near future.

The Environmental Health Criteria monograph on methylmercury (13) cited the need "for epidemiological studies on children exposed in utero to levels of methylmercury that result in peak maternal hair mercury levels below 20µg/g, in order to screen for those effects only detectable by available psychological and behavioural tests". This proposal arose from an evaluation of data from the study in Iraq, which implied that adverse effects were associated with peak levels of 10–20µg/g of maternal hair.

6.2.4 *Conclusions*

The studies in the Faroe Islands and the Seychelles that were evaluated by the Committee did not provide consistent evidence of neurodevelopmental effects in the children of mothers whose intake of methylmercury yielded hair burdens of 20µg/g or less. The Committee could not evaluate the risks for the complex and subtle neurological end-points used in these studies that would be associated with lower intakes. In the absence of any clear indication of a consistent risk in these recent studies, the Committee recommended that methylmercury be re-evaluated in 2002, when the 96-month evaluation of the Seychelles cohort and other relevant data that may become available can be considered. The Committee noted that fish makes an important contribution to nutrition, especially in certain regional and ethnic diets, and recommended that its nutritional benefits be weighed against the possibility of harm when limits on methylmercury concentrations in fish or on fish consumption are being considered.

A toxicological monograph was prepared.

6.3 *Zearalenone*

Zearalenone is a heat-stable, non-steroidal estrogenic mycotoxin produced by several species of *Fusarium*. It has been implicated in

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Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study

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Abstract

Introduction Exposure to methylmercury (MeHg) before birth can adversely affect children's neurodevelopment. The most common form of prenatal exposure is maternal fish consumption, but whether such exposure harms the fetus is unknown. We aimed to identify adverse neurodevelopmental effects in a fish-consuming population.

Methods We investigated 779 mother-infant pairs residing in the Republic of Seychelles. Mothers reported consuming fish on average 12 meals per week. Fish in Seychelles contain much the same concentrations of MeHg as commercial ocean fish elsewhere. Prenatal MeHg exposure was determined from maternal hair growing during pregnancy. We assessed neurocognitive, language, memory, motor, perceptual-motor, and behavioural functions in children at age 9 years. The association between prenatal MeHg exposure and the primary endpoints was investigated with multiple linear regression with adjustment for covariates that affect child development.

Findings Mean prenatal MeHg exposure was 6.9 parts per million (SD 4.5ppm). Only two endpoints were associated with prenatal MeHg exposure. Increased exposure was associated with decreased performance in the grooved pegboard using the non-dominant hand in males and improved scores in the hyperactivity index of the Conner's teacher rating scale. Covariates affecting child development were appropriately associated with endpoints.

Interpretation These data do not support the hypothesis that there is a neurodevelopmental risk from prenatal MeHg exposure resulting solely from ocean fish consumption.