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# Safety evaluation of certain food additives and contaminants

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

**METHYL MERCURY**  
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IPCS — International Programme on Chemical Safety

## **METHYLMERCURY (addendum)**

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Explanation .....	270
Biological data .....	271
Biochemical aspects .....	271
Absorption, distribution and excretion .....	271
Toxicological studies .....	272
Reproductive and developmental toxicity .....	272
Relevance of studies of developmental toxicity in rodents to risk assessment in humans .....	273
Observations in humans .....	274
Prenatal exposure and neurodevelopment .....	274
Neurodevelopment and postnatal exposure to methylmercury in human milk during infancy .....	278
Neurodevelopment and exposure to methylmercury during childhood .....	279
Methylmercury exposure and cardiovascular function in the young .....	281
Methylmercury exposure and neurological effects in adults .....	282
Methylmercury exposure and cardiovascular effects in adults .....	284
Dose–response assessments .....	286
Risk–benefit analyses .....	287
Dietary intake .....	291
Biomarkers of exposure .....	291
Relationships between various biomarkers of exposure .....	291
Cord tissue as a biomarker of exposure .....	291
Blood methylmercury concentrations in childhood .....	295
Blood mercury concentrations in women of childbearing age .....	296
Biomarkers of co-exposure to other environmental contaminants .....	296
Consumption of fish and whale and exposure to methylmercury .....	297
Consumption of other foods and exposure to methylmercury .....	299

The effect of GLs for methylmercury on exposure and risk .....	299
The nature of GLs .....	300
Data submitted to the Committee .....	300
The impact of risk management options on exposure .....	305
Comments .....	307
Vulnerability of the embryo and fetus .....	307
Vulnerability of the infant and child .....	307
Vulnerability of adults .....	308
Impact of current GLs for methylmercury in fish on exposure and risk .....	308
Evaluation .....	309
References .....	310

## 1. EXPLANATION

Methylmercury was evaluated by the Committee at its sixteenth, twenty-second, thirty-third, fifty-third and sixty-first meetings (Annex 1, references 30, 47, 83, 143 and 166). At its sixty-first meeting, the Committee established a new provisional tolerable weekly intake (PTWI) of 1.6 µg/kg bw, after considering information that had become available since its fifty-third meeting. This information included the results of studies performed in laboratory animals and humans, and epidemiological studies of the possible effects of prenatal exposure to methylmercury on child neurodevelopment. Neurodevelopment was considered to be the most sensitive health outcome and development in utero the most sensitive period of exposure. Calculation of the PTWI was based on an average benchmark-dose level or no-observed-effect level (BMDL or NOEL) of 14 mg/kg (14 µg/g) for mercury in maternal hair in the studies of neurodevelopmental effects in cohorts of children from the Faroe Islands and the Seychelles. The concentration of mercury in maternal hair was calculated to be equivalent to a maternal blood methylmercury concentration of 0.056 mg/l (56 µg/l), which was calculated to arise from a daily intake of methylmercury of 1.5 µg/kg bw. The PTWI was derived by dividing this intake by a total uncertainty factor of 6.4 to give a value of 1.6 µg/kg bw. The PTWI established in 2003 was considered to be sufficient to protect the developing embryo and fetus, the most sensitive subgroup of the population. The new value of 1.6 µg/kg bw was a revision of the previous PTWI of 3.3 µg/kg bw, and the latter value should be considered as withdrawn.

After the establishment of this new PTWI, based on maternal–fetal exposure, Codex Commission on Food Additives and Contaminants (CCFAC) at its Thirty-seventh Session in 2005 (Codex Alimentarius Commission, 2005) considered a discussion paper on guideline levels (GLs) for methylmercury in fish. CCFAC noted that the Joint Expert Committee on Food Additives (JECFA) usually sets a single health-based guidance value for the whole population, which is protective for the most sensitive part of the population; however, in the case of guidance values based on developmental end-points, this may be overly conservative for some parts of the population. CCFAC further commented that in specific cases JECFA might consider setting separate values for subgroups of the population. This request to clarify the

PTWI for methylmercury in this context was considered by the Committee at its present meeting, taking into account relevant earlier and recent studies. The following issues were addressed:

- Clarification of the relevance of the PTWI of 1.6 µg/kg bw for different subgroups of the population;
- Assessment of the scientific evidence on the relevance of direct exposure to methylmercury to neurodevelopment in infants and young children;
- The impact of current GLs for methylmercury in fish on exposure and risk.

Descriptions of additional papers relevant to prenatal risks, published since the last review in 2004, are included for completeness.

## **2. BIOLOGICAL DATA**

### **2.1 Biochemical aspects**

#### *2.1.1 Absorption, distribution and excretion*

Details regarding the absorption and distribution of methylmercury in various species of experimental animals have been previously provided (Annex 1, reference 144). Briefly, methylmercury is effectively absorbed from the gastrointestinal tract and readily crosses the placenta and blood–brain barrier. Concentrations in the fetal blood and brain are generally greater than the corresponding maternal concentrations at parturition.

Recent analyses/assessments have further indicated that methylmercury tends to concentrate in the fetus. The relationship between mercury in erythrocytes and plasma fatty acid composition in 63 pairs of Japanese mothers and fetuses (umbilical cord blood) at delivery was recently reported. The geometric mean concentration of mercury in fetal erythrocytes was 13.4 ng/g, which was significantly higher than that in maternal erythrocytes (8.41 ng/g). The average ratio of mercury in fetal/maternal erythrocytes was 1.6 (range, 1.1 to 2.2). This suggests individual differences in methylmercury concentration ratios between maternal and fetal circulations at delivery. A significant correlation was observed between maternal and fetal concentrations of n-3 polyunsaturated fatty acids (PUFA) ( $r = 0.37$ ,  $p < 0.01$ ) and between concentrations of mercury in fetal erythrocytes and PUFA in fetal plasma ( $r = 0.35$ ,  $p < 0.01$ ). These results confirm that methylmercury and PUFA, which originated from fish consumption, transferred from maternal to fetal circulation (Sakamoto et al., 2004a).

The transport of methylmercury from maternal blood into human milk is less efficient than the transport across the blood–brain and blood–placenta barriers, and methylmercury concentrations in human milk are known to be very low (Skerfving, 1988; Oskarsson et al., 1995, 1996). Exposure of rodent offspring to methylmercury via lactation is lower than exposure in utero, with milk : blood ratios of the order of 0.03–0.2 (Annex 1, reference 144). Observations of decreasing concentrations of inorganic mercury in maternal blood during breastfeeding suggest that mercury may be excreted in human milk (Vahter et al., 2000); however the relevance of this

observation to methylmercury excretion via human milk is uncertain because of the kinetic differences between the two forms of mercury.

## **2.2 Toxicological studies**

### *2.2.1 Reproductive and developmental toxicity*

Since polychlorinated biphenyls (PCBs) and methylmercury both occur as contaminants in some marine species and because co-exposure to PCBs was an issue in the studies in humans in the Faroe Islands, further studies were carried out to investigate the interactions of PCBs and methylmercury in development (Roegge et al., 2003; Widholm et al., 2004).

In the first study, the effect of pre- and postnatal exposure to PCBs and/or methylmercury on motor function was examined. Groups of at least 15 female Long-Evans rats (aged 60 days) were assigned to each of four exposure groups: (1) PCBs only, dissolved in corn oil and fed on a wafer cookie at 6 mg/kg bw per day; (2) methylmercury only, given at 0.5 µg/ml in the drinking-water (giving an average exposure of 41.90 µg/kg bw per day before mating and 58.90 µg/kg bw per day during gestation); (3) PCBs + methylmercury at the same doses; and (4) a control group given wafer cookies containing corn oil and pure drinking-water). It should be noted that the study was conducted in three cohorts spaced 6 months apart, with animals being assigned to the treatment groups evenly across each cohort. Mating commenced 28 days after the start of dosing and treatment continued for 66 days during mating, pregnancy and lactation until the offspring were aged 16 days. The offspring were weaned at age 21 days. The dams showed no overt signs of toxicity and there was no effect of treatment on length of gestation, dam body or liver weight, litter size or percentage of live births. The offspring of the groups exposed to PCBs or PCBs + methylmercury showed signs of toxicity, including significantly lower body weights, increased liver- and brain : body weight ratios and lower thymus : body weight ratio at age 21 days. After weaning and up to age 63 days, body weights were significantly reduced by 5–11% in the group exposed to PCBs and by 11–15% in the group exposed to PCB + methylmercury. Body weight was unaffected in the group exposed to methylmercury at up to age 63 days, but after this time, average body weight in this group was 7% lower than that of the controls, while average body weight in groups exposed to PCBs or PCBs + methylmercury was reduced by 8% and 11% respectively. Starting at age 60 days, one male and one female from each litter were tested over the next 4 weeks on three motor tasks that involved cerebellar function. Function measure by ability to traverse a rotating rod showed significant impairment in offspring exposed to PCBs + methylmercury, while offspring exposed to PCBs only were also impaired but not significantly. In the vertical-rope climb task, females exposed to methylmercury only were slightly impaired compared with controls, the difference being statistically significant on the third day of the 3 days of testing. In the parallel-bars test, males exposed to methylmercury only made significantly fewer hindlimb slips than did controls. There were no other significant effects of treatment in these two tests (Roegge et al., 2003).

In a further publication, describing the same experiment, one male and one female from each litter in the four treatment groups were tested on a spatial

alternation task at age 110 days. This test was chosen because it assesses both memory and learning and has previously been shown to be sensitive to disruption by PCBs. Methylmercury alone caused no overt toxicity. On the spatial alternation task, animals exposed to PCBs and/or methylmercury showed impaired function relative to controls. Specifically, there were significant reductions in non-cued alternation training in the groups treated with methylmercury only or PCBs + methylmercury, and reductions in delayed spatial alternation in the groups treated with PCBs only or methylmercury only. The group treated with PCBs + methylmercury showed a reduction of similar magnitude in delayed spatial alternation but the difference was not statistically significant because of variability within the group. Exposure to PCBs did not potentiate the effects of exposure to methylmercury. The authors concluded that the delays were indicative of either an associative or attentional impairment, rather than an effect on memory (Widholm et al., 2004).

Following up on earlier studies in which deficits in vision, hearing and fine motor control were observed during middle age in monkeys exposed to methylmercury at 50 µg/kg bw per day from birth to age 7 years or exposed at 10, 25 or 50 µg/kg bw per day in utero and after birth for 4–4.5 years (Rice & Gilbert, 1982, 1990; Rice & Hayward, 1999; Rice, 1999), a further study was conducted by the same group to examine the effects of methylmercury when exposure was limited to the prenatal period. To prevent postnatal exposure, the offspring were separated from their mothers at birth and reared separately. The mothers showed no overt signs of toxicity during gestation. Offspring of monkeys exposed orally to methylmercury at doses of 0, 50, 70 or 90 µg/kg bw per day before and throughout pregnancy were tested at 11–14.5 years of age on a visual contrast sensitivity task. There were 9, 8, 2 and 2 offspring in the 0, 50, 70 and 90 µg/kg bw per day groups, respectively. Monkeys exposed prenatally to methylmercury showed a significant loss of contrast sensitivity, particularly for higher frequency visual images. The degree of impairment was not related to maternal or newborn methylmercury body burden or clearance and in almost half the exposed animals function was unimpaired (Burbacher et al., 2005).

### *2.2.2 Relevance of studies of developmental toxicity in rodents to risk assessment in humans*

Although there are a number of studies in rodents that have addressed the issue of prenatal vs postnatal exposure, the utility of these studies to address the question of vulnerability of humans at different life stages is limited. The period during which brain growth is most rapid (brain growth spurt) during development occurs postnatally during the first 3 weeks of life in rats, while it occurs prenatally during the third trimester of gestation in humans (Dobbing & Sands, 1979; Rice & Barone, 2000). It has therefore been suggested that rats exposed to methylmercury postnatally during lactation could be used as models—at least with respect to the brain growth spurt—for human prenatal exposure during the last trimester. For example, administration of methylmercury during the postnatal phase only in rats (Wakabayashi et al., 1995) has resulted in central nervous system lesions that are similar to those of human fetal Minamata disease (Takeuchi, 1982), while prenatal administration of methylmercury to rats does not produce the same spectrum of

damage to the central nervous system as in humans exposed prenatally (Kakita et al., 2000a; 2000b; 2001).

However, there are known toxicokinetic differences between rodents and humans with regard to methylmercury (Annex 1, reference 144) that preclude simple extrapolation. In addition, a more recent study indicated that the postnatal rat receiving methylmercury via maternal milk may not be a suitable model for exposure of humans in the third trimester of gestation because blood and brain concentrations of methylmercury decline rapidly during the suckling period (Sakamoto et al., 2002a). The same group has shown that if methylmercury is administered directly to suckling rats via a micropipette, rather than via maternal milk, then the postnatal rat may serve as a useful model for exposure in humans during the third trimester (Sakamoto et al., 2004b).

## 2.3 Observations in humans

### 2.3.1 Prenatal exposure and neurodevelopment

Cognitive development was investigated at age 1 year in a prospective cohort study of 233 infants born to mothers with generally low levels of exposure to mercury during pregnancy, in Krakow between 2001 and 2003. Samples of maternal and umbilical cord blood were taken at delivery. Cognitive function in the infants was assessed by Bayley Scales of Infant Development (BSID-II), mental and motor scales. Fish consumption in grams per week, assessed by questionnaire during pregnancy, was related to both maternal blood and cord blood mercury concentrations. The method of preparation of the fish (smoked, fried, roasted or grilled) had no effect on maternal blood levels of mercury. The geometric mean for maternal whole blood total mercury concentrations at delivery was 0.55 µg/l (range, 0.10–3.40) and for cord blood was 0.88 µg/l (range, 0.10–5.00), with a significant correlation between maternal and cord blood values. These values are consistent with published values from other countries. One hundred and ninety-seven infants showed normal development on the Bayley mental and motor scales and 36 showed delayed motor or psychomotor performance, with a significant difference between the mean psychomotor development Index for the two groups. There were no significant differences between the two groups in the proportions of mothers breastfeeding for given time intervals (< 25, 26–38, 39–51 and > 52 weeks). For the group of infants with normal developmental scores, the geometric mean for maternal blood mercury was significantly lower than that of the group with delayed development (0.52 µg/l; 95% confidence interval [CI] 0.46–0.58; and 0.75 µg/l; 95% CI, 0.59–0.94, in normal and delayed groups respectively). Cord blood mercury concentrations were also lower in the normal group (0.85 µg/l; 95% CI, 0.78–0.93 and 1.05 µg/l; 95% CI, 0.87–1.27, in normal and delayed groups respectively), but the significance was borderline ( $p = 0.070$ ). The relative risk (RR) for delayed performance increased more than three-fold (RR = 3.58; 95% CI, 1.40–9.14) if the cord blood mercury concentration was greater than the median value of 0.80 µg/l. Similar analysis for mercury concentrations in maternal blood showed a significantly increased risk for delayed performance (RR = 2.82; 95% CI, 1.17–6.79) if maternal blood mercury concentration was greater than the median value of 0.50 µg/l (Jedrychowski et al., 2005).

The association between maternal fish consumption during pregnancy, umbilical cord mercury concentrations, child fish consumption and development were assessed in 7421 British children born in Bristol in 1991–1992 (part of the Avon Longitudinal Study of Parents and Children (ALSPAC) study). At age 15 months, a parent-completed assessment, based on the MacArthur Communicative Development Inventory (MCDI), assessed the children's vocabulary, comprehension and social activity. When the child was aged 18 months, the parents administered an adaptation of the Denver Developmental Screening Test (DDST) which screens for developmental differences in language, social skills, fine and gross motor skills. Eighty-eight percent of the mothers ate fish during pregnancy, and of these, 80% ate fish at least once a week. Higher mean developmental assessment scores were associated with a modest but consistent increase in maternal fish intake during pregnancy, particularly for the MCDI comprehension score. Tests for trend were significant for all measures except social skills in the DDST. These associations were not altered by the child's fish intake, but the child's intake at age 6 and 12 months was independently associated with an increase in all of the neurodevelopment scores except the language score in the DDST. Breastfeeding did not confound these relationships. Other potentially confounding factors (first born, female sex, higher home-observation-for-measurement of the environment (HOME) scores, higher maternal education, mother abstaining from alcohol during pregnancy) did not modify the relationship between maternal fish intake and neurodevelopment. Maternal fish intake was associated with wet weight umbilical cord mercury concentrations, but overall, umbilical cord concentrations were low in this population (median 0.01 µg/g, with only 33 cord concentrations being ≥ 0.1 µg/g) and when umbilical cord mercury concentrations were divided into quartiles, there was no association between the quartiles and the developmental scores. These concentrations are considerably lower than that reported to be the median for umbilical cords in the Faroe Islands cohort (Dalgard et al., 1994), which was 0.3 µg/g dry weight, equivalent to around 0.04 µg/g when adjusted to a wet weight value, based on a water content of 85–90%. These results indicate that these low levels of prenatal exposure are not associated with developmental effects and that, when fish is not significantly contaminated with mercury, fish intakes during pregnancy and lactation may be beneficial for development (Daniels et al., 2004).

A further statistical analysis has been undertaken of previously reported neurodevelopmental test data obtained at age 5.5 years in the Seychelles Child Development Study (SCDS) (Davidson et al., 1998). Linear measurement error models were used to correct bias resulting from unknown errors of measurement in data in order to obtain unbiased slope estimates that better approximate the true relationship between exposure and outcome. Reanalysis using the measurement-error-model approach indicated that adjustment for measurement errors in prenatal exposure and other explanatory variables had no appreciable effect on the original results (Huang et al., 2003).

Another further statistical analysis of the data from the SCDS at age 9 years has also been published. In the original analysis of the data at age 9 years (Myers et al., 2003), which has been reviewed previously by this Committee (Annex 1, reference 167), conventional linear regression models were used to analyse the data concerning prenatal exposure to methylmercury via maternal fish consumption



and neurodevelopmental test scores. Such models assume a linear relationship between exposure and outcome. However, if the true relationship between exposure and outcome were nonlinear, other statistical models would be more appropriate. Accordingly, the data from the SCDS gathered at age 9 years has been re-analysed using semi-parametric additive modelling with different degrees of smoothing to explore whether nonlinear effects of prenatal exposure were present. From the original 21 end-points yielded by the neurodevelopmental tests on 643 children, they selected the six end-points with a two-tailed  $p$  value of less than 0.2. A nonlinear effect was identified with the smoother model on adjusted results for only one end-point, the grooved pegboard dominant hand. It suggested no effect of exposure up to a maternal hair total mercury concentration of 12  $\mu\text{g/g}$ , but a slight effect above 12  $\mu\text{g/g}$ . However, the authors noted that there were fewer data points above a maternal hair concentration of 12  $\mu\text{g/g}$  and the curves were estimated with less precision. In the new analysis, the overall effect for prenatal exposure to total mercury was also significant ( $p = 0.04$ ), while the overall effect in the previous linear analysis (Myers et al., 2003) was not ( $p = 0.08$ ). The significant associations found in the previous linear analysis (adverse effect on grooved pegboard non-dominant hand in males and a beneficial effect on the Connors Teacher Rating Scale) remained significant in this new analysis. The authors concluded that this reanalysis confirms the findings of their previous linear regression analysis, with little evidence for adverse effects from prenatal methylmercury exposure in the Seychelles cohort, but that it does reveal a possible adverse effect in the uppermost exposure range at greater than 12  $\mu\text{g/g}$  for maternal hair mercury (Huang et al., 2005). The authors further note that this possibility is consistent with the World Health Organization (WHO) analysis of the data from the Iraq poisoning incident, which also suggested a threshold for adverse effects on the offspring in the range of 10–20  $\mu\text{g/g}$  for maternal hair mercury as a biomarker for prenatal exposure (WHO, 1990).

In the SCDS main study, at age 19 months, enhanced Motor Developmental Index scores were associated with increasing exposure to methylmercury in groups of caregivers with higher intelligence quotient (IQ) at several levels of family income. A similar analysis of the evaluations at 66 months to determine whether the modifying influences of social and environmental factors were consistent with those previously observed was performed. Children in the cohort ( $n = 711$ ) were evaluated for cognitive ability (McCarthy Scales of Children's Abilities), language development (Preschool Language Scale), drawing and copying (Bender Gestalt Test), scholastic achievement (the Woodcock-Johnson Test of Achievement), and behaviour (the Child Behavior Checklist). Interactions between prenatal exposure to methylmercury and caregiver intelligence, socioeconomic status, home environment, and sex were examined by multiple regression analysis. The median prenatal exposure to methylmercury as measured by concentrations in maternal hair was 5.9  $\mu\text{g/g}$ , with a range of 0.5–26.7  $\mu\text{g/g}$ . Prenatal exposure interacted with sex, one or more social or environmental covariates for general cognitive ability, overall language ability, and pre-arithmetic achievement. The effects were not consistent across either endpoints or covariate categories. The authors determined that a consistent pattern of effect modification was not observed, suggesting that the any statistically significant results were due to chance (Davidson et al., 2004).

The Faroe Islands cohort underwent detailed neurobehavioral examination at age 14 years. Prenatal exposure to methylmercury was determined by analyses of cord blood, cord tissue, and maternal hair. Of the 1010 living cohort members, 878 were available for examination. Eighteen participants with neurological disorders were excluded. The neuropsychological test battery was designed based on the same criteria as applied at the examination at age 7 years. Multiple regression analysis was carried out and included adjustment for confounders. Indicators of prenatal methylmercury exposure were significantly associated with deficits in finger tapping speed, reaction time on a continued performance task, and cued naming. Postnatal exposure to methylmercury had no discernible effect. These findings are similar to those obtained at age 7 years, and the relative contribution of mercury exposure to the predictive power of the multiple regression models was also similar. An analysis of the test score difference between results at age 7 and 14 years suggested that mercury-associated deficits had not changed between the two examinations. Exposure to methylmercury was significantly associated with deficits in motor, attention, and verbal tests. According to the authors, the effects on brain function associated with prenatal exposure to methylmercury appear to be multi-focal and permanent (Debes et al., 2006).

The associations between maternal fish intake during pregnancy and maternal hair mercury at delivery with visual brain processing among 135 mother–infant pairs was assessed in a prospective study of pregnancy and child cohorts in the United States of America (USA). Infant cognition by the percent novelty preference on visual recognition memory testing at age 6 months was determined. Maternal fish consumption averaged 1.2 servings per week during the second trimester. Mean maternal hair total mercury was 0.5  $\mu\text{g/g}$ , with 10% of samples exceeding 1.2  $\mu\text{g/g}$ . Mean visual recognition memory score was 59.8 with a range of 10.9–92.5. Higher fish intake was associated with higher infant cognition, after adjusting for participant characteristics using linear regression. The association strengthened after adjustment for maternal hair mercury concentration. For each additional weekly fish serving, offspring visual recognition memory score was 4.0 points higher. An increase of 1  $\mu\text{g/g}$  in hair mercury concentration was associated with a visual recognition memory decrement of 7.5 points. Visual recognition memory scores were highest among infants of women who consumed more than two weekly servings of fish but had hair mercury concentrations of less than or equal to 1.2  $\mu\text{g/g}$  (Oken et al., 2005).

In a similar study, the impact of long-term exposure to PCBs and methylmercury on visual brain processing in Canadian Inuit children was assessed. Concentrations of total mercury in blood and PCB 153 in plasma were measured at birth and again at the time of testing in 102 children of preschool age. Relationships between contaminants and pattern-reversal visual evoked potentials were assessed by multivariate regression analyses, taking into account several potential confounding variables. The possible protective effects of selenium and n-3 PUFA against toxicity caused by methylmercury and PCBs were also investigated. Results indicate that exposure to methylmercury and PCB from consumption of fish and sea mammals were associated with alterations in responses to visual evoked potentials, especially delays in the latency of the N75 and of the P100 components. In contrast, the concomitant intake of n-3 PUFA was associated with a shorter latency of the

P100. No significant interactions between nutrients and contaminants were found. Significant associations were found with concentrations of neurotoxicants in blood samples collected at the time of testing at preschool age (Saint-Amour et al., 2006).

The effects of prenatal and postnatal long-term exposure to mercury, polychlorinated PCBs and lead on the neuromotor development of preschool children was assessed in a study of 110 preschool Canadian Inuit children. Blood mercury, PCBs and lead concentrations were measured in cord blood and at the time of testing. Gross motor functions were evaluated and a neurological examination was performed. Fine neuromotor performance was assessed using quantitative measures of postural hand tremor, reaction time, sway oscillations, as well as alternating and pointing movements. Potential covariates were documented including demographic and familial characteristics, other prenatal neurotoxicants (alcohol, tobacco) and nutrients (selenium, n-3 PUFA). Hierarchical multivariate regression analyses were performed, controlling for significant covariates. Gross motor development was not linked to prenatal exposures. However, significant associations were observed between blood lead concentration at testing time and changes in reaction time, sway oscillations, alternating arm movements and action tremor. Negative effects of PCBs on neuromotor development were not clearly observed, neither were the potential beneficial effects of n-3 PUFA and selenium. Increased action tremor amplitude was related to blood mercury concentrations at testing time, which corroborates an effect reported among adults (Després et al., 2005).

In order to assess the association between mercury exposure in children with autistic spectrum disorder, a cross-sectional cohort study was performed over a 5-month period in 2000 to compare the hair and blood mercury concentrations of children with this disorder ( $n = 82$ ; mean age, 7.2 years) and a control group of normal children ( $n = 55$ ; mean age, 7.8 years). There was no difference in the mean mercury concentrations. The mean blood mercury concentrations for the autistic and control groups were 19.5 and 17.7 nmol/l, respectively ( $p = 0.15$ ), and the mean hair mercury concentrations of the autistic and control groups were 2.26 and 2.07 ppm, respectively ( $p = 0.79$ ). These results indicate that there is no causal relationship between mercury as an environmental neurotoxin and autism (Ip et al., 2004a).

### *2.3.2 Neurodevelopment and postnatal exposure to methylmercury in human milk during infancy*

Details of the critical studies of neurodevelopment from the Seychelles and the Faroe Islands underlying the establishment of the PTWI of 1.6  $\mu\text{g}/\text{kg}$  bw in 2004 have been described previously (Annex 1, reference 167). Since then, further studies have been published that are relevant to the question of the possible additional role of postnatal exposure to methylmercury via human milk in contributing to the neurobehavioural changes.

Earlier observations from the Faroe Islands cohort where the length of breastfeeding showed a positive correlation with mercury concentration in the hair of the infants at age 12 months, indicated that, in addition to prenatal exposure, exposure also took place through human milk (Grandjean et al., 1994). In spite of

this, it was noted that breastfed children reached their developmental milestones before formula-fed children (Grandjean et al., 1995), suggesting an overall beneficial effect of human milk, despite the contamination with mercury. When examined in a series of neurobehavioural tests, in one test (reflecting attention) worse performance at age 7 years was associated with increased hair mercury concentrations at age 12 months, irrespective of whether the children were breastfed or not, but paradoxically, performance on a test of language skills increased with increasing hair mercury concentrations at age 12 months (Grandjean et al., 1999). The picture is further complicated by the observation, derived from a meta-analysis of available studies, that breastfeeding in general is associated with improvements in neurological and cognitive development across all ages from 6 months to 15 years and carries greater benefits in children of low birth weight (Anderson et al., 1999).

The role of breastfeeding on neuropsychological performance at age 7 years was examined in the Faroe Islands cohort of 905 children who had relatively high prenatal exposures to mercury. They compared the influence of breastfeeding exclusively for 0–4 months with breastfeeding for more than 4 months as well as total months of breastfeeding until weaning (0–6 months or > 6 months). All except 7.7% of the children were breastfed and 61% were exclusively breastfed for 0–4 months. The breastfeeding period exceeded 6 months for 55% of the children; of these only 5% were exclusively breastfed for more than 6 months, the remainder received other food in addition to human milk. Children who were breastfed longer (both exclusively and in total) performed slightly better on most neuro-psychological tests before adjustment for confounders (e.g. sex of child, parents professionally trained, father employed at examination, child in day care, etc). This effect was reduced after adjustment for these confounders, but children breastfed exclusively for more than 4 months or for longer in total still performed slightly better on most tests, with significantly better scores on the Boston Naming Test and Wechsler Intelligence Scale for Children—Revised, Block Designs. After further adjustment for cord-blood mercury and child hair mercury, the results were unaffected, except for the Boston Naming Test where the difference became non-significant. Adjusting for exposure to PCBs did not affect the associations found. Children who were not breastfed at all generally performed less well on most tests than those that were breastfed. The authors however, acknowledge the difficulty of differentiating between prenatal and postnatal exposure to mercury, because very few children in the cohort were not breastfed and most children were exposed to mercury both prenatally and early postnatally. Thus, in this cohort with relatively high prenatal exposure and demonstrated adverse effects from that exposure, breastfeeding was not associated with any deficit in neuropsychological performance at age 7 years, although breastfeeding appeared to be not as beneficial as previously reported by other investigators in non-exposed populations (Jensen et al., 2005).

### *2.3.3 Neurodevelopment and exposure to methylmercury during childhood*

In the re-analysis of the Seychelles (SCDS) data by Huang et al. (2003), described earlier in the section on prenatal exposure, the influence of postnatal exposure on neurodevelopment at age 5.5 years was also re-evaluated. Application

of linear measurement error models did not alter the significance levels for several beneficial effects compared with previous linear regression analysis (Davidson et al., 1998).

Murata et al. (2004) have studied the influence of exposure to methylmercury on brainstem auditory evoked potentials (BAEP) in children from the Faroe Islands cohort. A total of 878 children (87%) from the original cohort were given a thorough paediatric examination at age 14 years, hair samples were taken and analysed for mercury and BAEPs were determined in 859 of the children. Their hair mercury concentrations were increased compared with the previous examination of these children at age 7 years, as published previously (Budtz-Jørgensen et al., 2004); at age 14 years, geometric mean hair-mercury concentrations were 0.96 (range, 0.02–9.7)  $\mu\text{g/g}$  compared with 0.60 (range, 0.04–7.5)  $\mu\text{g/g}$  at age 7 years. However, these were still less than one quarter of the concentration in maternal hair at the time of their birth, which was 4.22 (range, 0.2–39.1)  $\mu\text{g/g}$ . Audiometry results generally showed normal hearing, but in accordance with their findings on the BAEP test at age 7 years (Grandjean et al., 1997), latencies of BAEP peaks III and V and especially the I–III interpeak interval were delayed in association with prenatal exposure to methylmercury, as measured by cord blood values. The delay was about 0.012 ms when cord blood mercury concentration doubled. The regression coefficients for the delay in latencies were approximately halved at age 14 years compared with age 7 years, suggesting that there may be some degree of compensation. More recent exposure, as measured by hair concentrations at age 14 years, was associated with a prolongation of the III–V interpeak interval. This change was not associated with prenatal exposure to methylmercury and analysis for exposure to PCBs did not affect the results.

The authors note that all these effects are subtle and not nearly as marked as the changes in BAEP that occur in disease states such as multiple sclerosis, acoustic neuroma or diabetes mellitus. They also comment that previous calculations based on the most sensitive end-point from all their neuropsychological evaluations on this cohort, using a benchmark response of 5%, indicate a benchmark dose (BMD) lower 95% confidence limit (BMDL derived from the BMD) of about 10  $\mu\text{g/g}$  for maternal hair, but the postnatal BMDL for the prolonged III–V interpeak interval is approximately one half of that. The authors acknowledge that the statistical uncertainties are such that the difference may not necessarily reflect the relative toxic potentials of prenatal and postnatal exposures. They also acknowledge that the postnatal exposure estimates were limited and may not necessarily represent the magnitude of exposure at susceptible time windows. Moreover, biomarkers of prenatal and postnatal exposure were highly associated. However, since biomarkers of prenatal and postnatal exposure were associated with effects on different peaks and/or peak intervals, this indicates that the differential effects of pre- and postnatal exposure may be robust. The authors conclude that the significance of postnatal methylmercury exposure needs to be documented further in independent studies with more frequent exposure assessments, but that the results suggests vulnerability to neurotoxicity attributable to methyl mercury may extend into the teenage period.

### 2.3.4 Methylmercury exposure and cardiovascular function in the young

To ascertain whether heart function in childhood is affected by exposure to methylmercury, the Faroese birth cohort was examined at age 7 and 14 years. Blood pressure, heart rate variability (HRV) and brainstem auditory evoked potentials (BAEPs) (see above) were measured. Mercury concentrations were determined in cord blood as the measure of prenatal exposure and in the child's hair as a measure of recent exposure. HRV, which reflects the continuous changes in central control of cardiac autonomic balance, was partitioned into its individual components by spectral analysis and the results expressed in terms of high frequency (HF) and low frequency (LF) components. HF components reflect parasympathetic activity and LF components reflect sympathetic activities. A doubling of prenatal methylmercury exposure was associated with significant decreases of about 6.7% in LF, mainly at 7 years of age, and in HF, mainly at 14 years of age. The coefficient of variation of the electrocardiograph R-R interval was also significantly decreased with increasing prenatal exposure to methylmercury at age 7 years and at 14 years. No discernible effect of methylmercury on blood pressure was apparent at age 14 years. Decreased LF was associated with increased latency of the BAEP peak III, but adjustment for prenatal and postnatal exposure substantially attenuated this correlation. The authors concluded that prenatal exposure was associated with decreased sympathetic and parasympathetic modulation of the HRV at age 14 years. The authors hypothesised that both the delay in one of the BAEP latencies and the effects on HRV parameters may be caused by underlying neurotoxicity of methylmercury to brainstem nuclei. The authors speculate on the possible clinical significance of the observed changes, citing clinical studies in adults showing that decreased vagal (parasympathetic) tone is associated with an increased risk of sudden cardiac arrest and coronary artery disease (Grandjean et al., 2004a).

In a similar study to that described above, the subclinical effects of prenatal exposure to methylmercury from fish consumption on the cardiac autonomic function were assessed in 136 Japanese children aged 7 years. In the children, cord tissue methylmercury concentration (range, 0.017–0.367, median, 0.089 µg/g) was not significantly correlated with hair total mercury at 7 years of age (range, 0.43–6.32, median, 1.66 µg/g). The principal finding was that prenatal exposure to methylmercury, as measured by cord tissue methylmercury concentration, was associated with decreased vagal modulation of cardiac autonomic function, in agreement with the findings in the Faroe Islands cohort at age 14 years. These associations remained after correcting for possible confounders such as age and sex. Hair mercury concentration was not significantly correlated with any cardiac autonomic indicators. The authors concluded that these findings suggest that prenatal exposure to methylmercury at a median of estimated maternal hair mercury concentration at parturition of 2.24 µg/g, may be associated with reduced parasympathetic activity and/or sympathovagal shift (Murata et al., 2006). The Committee noted that this is about six times lower than the value used to derive the PTWI in 2003.

### 2.3.5 Methylmercury exposure and neurological effects in adults

Monoamine oxidase (MAO) regulates biogenic amine concentration in the brain and peripheral tissue and is known to be a molecular target of mercury compounds in animal models. Blood platelet MAO-B activity may reflect MAO function in the central nervous tissue. The relationship between platelet MAO-B and mercury exposure (blood and hair) in fish-eating adults ( $n = 127$ ) living along the St Lawrence River in Canada was assessed. A significant negative association was observed between platelet MAO-B activity and blood mercury concentration, but not with hair mercury concentrations. Multiple linear regression analysis demonstrated that blood mercury and heavy smoking were associated with reduced platelet MAO activity in the total population. The reduction in MAO-B activity appeared to be associated with blood mercury concentrations of greater than  $3.4 \mu\text{g/l}$  (75th percentile). These results suggest that MAO-B activity in blood platelets may be a useful biomarker to assess the biochemical effects of exposure to mercury (Stamler et al., 2006).

Two groups of 22 Italian adult male subjects who were frequent consumers of tuna and 22 controls were examined in a cross-sectional field study. The assessment included neurobehavioral tests of vigilance and psychomotor function and hand tremor measurements. Mercury in urine and serum prolactin were measured in all exposed subjects and controls, while measurements of the organic component of mercury in blood (O-Hg) were available for only 10 exposed and six controls. Mercury in urine was significantly higher among exposed subjects (median,  $6.5 \mu\text{g/g}$  of creatinine; range, 1.8–21.5) than controls (median,  $1.5 \mu\text{g/g}$  of creatinine; range, 0.5–5.3). The median blood concentrations of O-Hg were  $41.5 \mu\text{g/l}$  among the tuna-fish eaters and  $2.6 \mu\text{g/l}$  in the control group. Both mercury in urine and O-Hg were significantly correlated with the quantity of fish consumed per week. The neurobehavioral performance of subjects who consumed tuna fish regularly was significantly worse on colour word reaction time, digit symbol reaction time and finger tapping speed. After accounting for education level and other covariates, the multiple stepwise regression analysis indicated that O-Hg concentration was most significantly associated with individual performance on these tests, accounting for about 65% of the variance in test scores (Carta et al., 2003).

An annual follow-up involving multiple health examinations in about 1500 persons of age 40 years or more took place near Minamata City each summer from 1984 to 2004. Case-control studies were designed to estimate the role of risk factors for various health issues using geographical differences. The results of the study are summarized as follows. There were no significant differences in the prevalence of diseases associated with Minamata disease. Subjective complaints, which were related not only to neurological but also to general complaints, were consistently much more common in the polluted area than in the control area. Five percent of the inhabitants who were not certified as patients with Minamata disease had a high predicting index of Minamata disease and therefore could have been affected by methylmercury poisoning. No significant differences with respect to activities of daily living by residential area were observed. It is important to take into consideration mental stress not only from the physical effects but also from the secondary social damage experienced in these areas in making a differential diagnosis of Minamata disease (Futatsuka et al., 2005).

The thresholds of touch and two-point discrimination of residents near the Shiranui Sea and patients with Minamata disease were examined using the quantifiable instruments. Patients with Minamata disease could perceive the stimulation of touch although their touch thresholds were significantly increased in comparison with those of the control group. Their touch thresholds increased at the proximal extremities and the trunks as well as at the distal extremities. The evenly distributed increases at both distal and proximal parts indicated that the persistent somatosensory disturbances were not caused by the injuries to their peripheral nerves. The thresholds of two-point discrimination, which are associated with the function of the somatosensory cortex, increased at both forefingers and the lip in both groups. Apraxia limb kinetics, astereognosis and disorder of active sensation, which are all associated with damage to the somatosensory cortex, were detected in the patients with Minamata disease. The authors concluded that the persisting somatosensory disorders after discontinuation of exposure to methylmercury were induced by diffuse damage to the somatosensory cortex (Ninomiya et al., 2005).

A psychophysical study of tactile sensation to evaluate the somatosensory abilities was conducted in subjects living in a methylmercury-polluted area around Minamata City, Japan. Control subjects and methylmercury-exposed subjects with and without numbness were included in the study groups. A history of exposure to methylmercury was taken and a neurological examination was performed. Aluminum-oxide abrasive papers were used as stimuli in a psychophysical sensory examination of fine-surface-texture discrimination. Difference thresholds from 3  $\mu\text{m}$  were calculated by the two-alternative, forced-choice technique. Difference thresholds in control subjects were also calculated. The difference threshold was 6.3  $\mu\text{m}$  in exposed subjects with sensory symptoms, 4.9  $\mu\text{m}$  in exposed subjects without sensory symptoms, and 2.7  $\mu\text{m}$  in control subjects. Acuity of fine-surface-texture discrimination was disturbed not only in subjects with clinical complaints of hand numbness, but also in subjects without hand numbness who lived in the district where methylmercury exposure occurred. Sensory testing using a psychophysical test of fine-surface-texture discrimination in this population suggests that the number of individuals affected by methylmercury exposure in the polluted area was greater than previously reported (Takaika et al., 2004).

Neurological symptoms and signs of Minamata disease were assessed in another Japanese study by assessing neurological signs and symptoms temporally using multiple logistic regression analysis. The severity of predictive index in the study population declined over a 25 year period. Only a few patients showed aggravation of neurological findings, which were caused by complications such as spinocerebellar degeneration. Patients with chronic Minamata disease who were older than age 45 years had several concomitant diseases, so that their clinical pictures were complicated. It was difficult to statistically differentiate chronic Minamata disease based on sensory disturbance alone (Uchino et al., 2005).

A cross-sectional analysis was used to determine the effect of mercury concentrations on neurobehaviour in 474 subjects in the Baltimore Memory Study, a longitudinal study of cognitive decline in people aged 50 to 70 years. Total mercury in whole blood samples was analysed and multiple linear regression was used to examine its associations with neurobehavioral test scores. Twenty scores from 12 neurobehavioral tests were considered. The median blood mercury concentration



was 2.1 µg/l. After adjustment for covariates, increasing blood mercury was associated with worse performance on Rey complex figure delayed recall, a test of visual memory. However, increasing blood mercury concentrations were associated with better performance on finger tapping, a test of manual dexterity. Overall, the authors concluded that this study did not provide strong evidence that blood mercury concentrations are associated with worse neurobehavioral performance in this population of older urban adults (Weil et al., 2005).

### *2.3.6 Methylmercury exposure and cardiovascular effects in adults*

The association between mercury in blood and 24-h blood pressure in four groups of healthy subjects was assessed. The following describes the subjects in each group: group 1, Danes living in Denmark consuming European food; group 2, Greenlanders living in Denmark consuming European food; group 3, Greenlanders living in Greenland consuming European food; and group 4, Greenlanders living in Greenland consuming mainly traditional Greenlandic food. Mercury concentrations in blood were highest in Greenlanders and increased when they lived in Greenland and consumed traditional Greenlandic food (group 1: 2.2 µg/l (median), group 2: 4.8 µg/l, group 3: 10.8 µg/l, and group 4: 24.9 µg/l). The 24-h blood pressure was the same in all three groups of Greenlanders. However, 24-h diastolic blood pressure was significantly lower (71 vs 76 mm Hg) and 24-h pulse pressure was significantly higher (54 vs 50 mm Hg) among Greenlanders in comparison with Danes. Mercury in blood was significantly and positively correlated to pulse pressure (the difference between systolic and diastolic pressure). The differences in pulse pressure were undoubtedly due to the lower diastolic blood pressure noted in the Greenlanders (Pedersen et al., 2005).

The cross-sectional relationship between total blood mercury concentration and blood pressure was assessed in a representative sample of 1240 women, aged 16–49 years, from the National Health and Nutrition Examination Survey (NHANES) 1999–2000 in the USA. No overall association was found between blood mercury and blood pressure in multivariate models. Data by dietary fish intake was stratified resulting in 759 consumers of fish and 481 nonconsumers. Total blood mercury concentrations averaged 2.3 µg/l for the consumers and 0.8 µg/l for the nonconsumers. For each 1.3 µg/l (interquartile distance) increase in blood mercury, systolic blood pressure significantly increased by 1.83 mm Hg (95% CI, 0.36–3.30) among nonconsumers. A similar pattern was seen for diastolic blood pressure, although it was nonsignificant. No significant effects of blood mercury concentrations on blood pressure were seen among consumers of fish. While no adverse effect on blood pressure of mercury exposure at background levels was present when considering all study participants, an adverse association was present among young and middle-aged women who did not consume fish. The authors speculated that fish consumption may counter the effects of mercury on blood pressure regulation (Vupputuri et al., 2005).

Three Amazonian villages of the Tapajos Basin were studied in relation to fish mercury concentrations, mercury in hair (fish consumption) and erythrocytes, body mass index (body weight/height squared, kg/m<sup>2</sup>), and blood pressure. The mean concentrations of mercury in fish were higher in predatory (578.6 ng/g) than in non-predatory species (52.8 ng/g). Overall, only 26% of concentrations of

mercury in fish were greater than 500 ng/g, and only 11% were greater than 1000 ng/g. There was no systematic trend in concentrations of mercury in fish from rivers with a history of gold-mining activities. The biomarker of fish consumption (hair mercury) was significantly associated with erythrocyte mercury ( $r = 0.5181$ ;  $p = 0.0001$ ). There was a trend of lower increase in blood pressure with age among consumers with a higher consumption. Summary clinical evaluation did not detect neurological complaints compatible with mercury intoxication (paraparesis, numbness, tremor, balancing failure), but endemic tropical diseases such as clinical history of malaria showed a high prevalence (55.4%). Fish is an abundant natural resource, important in the native diets, that has been historically consumed without perceived problems and can easily be traced through hair mercury. The authors concluded that exposure to methylmercury in freshwater fish is a less important health issue than endemic infectious diseases such as malaria and lack of basic medical services (Dorea et al., 2005b).

The incidence of myocardial infarction and death from all causes was reported during 24 years of follow-up of a prospective cohort study of 1462 women in Gothenberg, Sweden. There were a total of 87 cases of myocardial infarction, of which 39 died and 253 all-cause deaths. At baseline of the prospective study (1968–1969), sera from participants were collected and stored for future research. The sera samples were analysed for mercury concentrations in 1992–1993, and the correlation between mercury concentrations and disease or death was examined. An inverse correlation, though not statistically significant, was detected for myocardial infarction ( $p = 0.10$  adjusted for age and  $> 0.20$  when adjusted for age and education) and also for death ( $p = 0.09$ ). A statistically significant inverse correlation between serum mercury and death was found when the correlation was adjusted for both age and education. No correlation coefficients were provided in the paper (Ahlqwist et al., 1999).

A case–control study nested within a larger ongoing prospective programme on cardiovascular disease and diabetes prevention was conducted in northern Sweden. Participants in the prospective programme had responded to health surveys and donated blood samples in 1994 that were stored for future research. From these participants, persons with first myocardial infarction with sufficient blood sample and without cancer ( $n = 78$ ) were selected as cases, and persons matched by age, sex, date of health survey ( $\pm 1$  year) and geographical region to the cases were selected as controls ( $n = 156$ ). The average time to onset of first myocardial infarction for the cases after responding to the health survey was 18 months. The case–control study examined the association between first myocardial infarction and concentration of mercury in erythrocytes, as well as glutathione peroxidase in erythrocytes (Ery-GSH-Px) and plasma concentrations of n-3 PUFA eicosapentaenoic and docosahexaenoic acids (P-PUFA), which the researchers considered to be biomarkers of fish intake. Fish consumption assessed by questionnaire was also evaluated. The results of the study showed a marginally significant inverse association between myocardial infarction and erythrocyte mercury in the univariate analysis. When the range of values for erythrocyte mercury (0.5 to 67 ng Hg/g erythrocytes) was divided into tertiles ( $< 3$ , 3–6, and  $> 6$  ng Hg/g erythrocytes), the odds ratio for the highest vs lowest tertile was 0.43 (95% CI, 0.19–0.95). Erythrocyte mercury was found to be significantly correlated with reported weekly fish consumption. P-PUFA also showed an inverse association with myocardial

infarction and was significantly correlated with reported weekly fish consumption. No association between myocardial infarction and Ery-GSH-Px was detected. When erythrocyte mercury and P-PUFA and their interaction were analysed in a multivariate model that adjusted for smoking and body mass index, there was a significantly lower risk of myocardial infarction for the group that had both high erythrocyte mercury and high P-PUFA (OR = 0.16, 95% CI, 0.04–0.65) (Hallgren et al., 2001).

The correlation of hair mercury concentration with the risk of acute coronary events and cardiovascular and all-cause mortality was assessed in a study of men from eastern Finland. The population-based prospective Kuopio Ischaemic Heart Disease Risk Factor Study cohort of 1871 Finnish men aged 42 to 60 years and free of previous coronary heart disease or stroke at baseline was used. During an average follow-up time of 13.9 years, 282 acute coronary events and 132 cases of cardiovascular disease, 91 cases of coronary heart disease, and 525 all-cause deaths occurred. Men with hair mercury content within the highest third of the range (i.e. > 2.03 µg/g) had an adjusted 1.60-fold (95% CI, 1.24–2.06) risk of acute coronary event, 1.68-fold (95% CI, 1.15–2.44) risk of cardiovascular disease, 1.56-fold (95% CI, 0.99–2.46) risk of coronary heart disease, and 1.38-fold (95% CI, 1.15–1.66) risk of any death compared with men in the lower two thirds. High mercury content in hair also attenuated the inverse correlations of docosahexaenoic acid plus docosapentaenoic acid concentration with these cardiovascular risk factors (Virtanen et al., 2005).

The five epidemiological studies of mercury concentrations in adults in relation to cardiovascular disease or death are shown in [Table 1](#). Three of these studies are described in this monograph (Virtanen et al., 2005; Hallgren et al., 2001; Ahlqwist et al., 1999) and two (Guallar et al., 2002; Yoshizawa et al., 2002) in the previous monograph on methylmercury prepared by the Committee at its sixty-first meeting (Annex 1, reference 166). One study (Salonen et al., 1995) in the previous monograph is not shown in the table because it concerns the same cohort of men in Eastern Finland as that described by Virtanen et al. (2005), with longer follow-up.

As the table demonstrates, the studies are not directly comparable owing to different biomarkers for ascertaining total mercury concentrations, i.e. hair, erythrocytes, toenails or serum. Two of the five studies (Virtanen et al., 2005; Guallar et al., 2002) found an increased risk of acute coronary event or myocardial infarction with higher mercury concentrations; one study (Hallgren et al., 2001) found a decreased risk of myocardial infarction with higher concentrations of mercury (the authors consider mercury concentrations to be a biomarker for fish consumption in this study); and the other two studies (Yoshizawa et al., 2002; Ahlqwist et al., 1999) did not show a statistically significant association between myocardial infarction and mercury concentrations. The reason for the differences in findings across studies and population groups is not clear but suggests that the evidence for the association between cardiovascular disease and methylmercury exposure is preliminary.

### 2.3.7 Dose–response assessments

Exposure misclassification always constitutes an issue in dose–response relationships concerning epidemiology studies in humans. In additional work, the Faroese research team (Grandjean et al., 2005) considered the issue of imprecision

in analyses of mercury in cord blood and maternal hair. Laboratory imprecision for both chemical analyses was less than 5% coefficient of variation. Factor analysis and structural equation analysis were applied to assess the full extent of the imprecision. Calculated total imprecision exceeded the known laboratory variation: the coefficient of variation was 28–30% for the cord blood mercury concentration and 52–55% for the maternal hair mercury concentration. These findings illustrate that measurement error may be underestimated if judged solely on the basis of the ability of the laboratory to reproduce the data with check analysis. Adjustment by sensitivity analysis is meaningful only if realistic measurement errors are applied (Grandjean et al., 2004b; Budtz-Jørgensen et al., 2004).

### 2.3.8 Risk–benefit analyses

When exposure recommendations are developed for foods that potentially have both harmful and beneficial qualities, a balance must be struck between the associated risks and benefits to optimize public health. Although quantitative methods are commonly used to evaluate health risks, such methods have not been generally applied to evaluating the health benefits associated with environmental exposures. A quantitative method for risk–benefit analysis has been used by several groups of investigators that allows for consideration of diverse health end-points (e.g. neurodevelopment, cardiovascular) that differ in their impact (i.e. duration and severity), using dose–response modelling by estimating the number of quality-adjusted life years saved.

To demonstrate the usefulness of this method, the risks and benefits of fish consumption were evaluated using a single health risk and health benefit end-point. The benefits of eating fish were defined as the decrease in mortality caused by myocardial infarction, and risk was defined as the increase in neurodevelopmental delay (i.e. delay in talking) resulting from prenatal exposure to methylmercury. Using the proposed framework, the net health impact of eating fish was estimated either in a whole population or in a population of women of childbearing age and their children. It was demonstrated that across a range of concentrations of methylmercury in fish (0–1 mg/kg) and a range of fish consumption levels (0–25 g/day), neurodevelopmental effects in the general population, including the embryo and fetus in women of childbearing age, would have to be weighed 6 times more and 250 times less than the cardiovascular benefits, when identifying optimal levels of fish consumption. These methods have the potential to evaluate the merits of other public health and risk management programmes that involve trade-offs between risks and benefits (Ponce et al., 2000).

As part of the effort to quantitatively integrate the benefits of fish consumption and the risks of exposure to methylmercury, the Harvard Center for Risk Analysis convened expert panels to quantify the net impact of changes in fish consumption by the US population of consumers. This included estimates of the effects on prenatal cognitive development, mortality from coronary heart disease, and stroke. Study weights were assigned to account for statistical precision, relevance of three end-point domains (general intelligence, verbal ability, and motor skills) to prediction of IQ, and age at evaluation. Eight randomized controlled trials comparing cognitive development in controls and in children who had received supplementation with n-3

**Table 1. Epidemiological studies on the association between cardiovascular disease or death with mercury concentrations in adults**

Author/Country	Study design	Study participants	Ascertainment of mercury concentration	Disease or death	Results
Guallar et al. (2002) Eight European countries and Israel	Case-control	Cases: 684 men Controls: 724 men	Toenail Hg (toenails collected after MI, occurrence of MI, analysed in 1991-1992)	First acute MI	Range in toenail Hg concentrations: 0.14 to 0.57 µg/g (authors presented averages in control patients across study centres) Adjusted OR for MI: highest quintile of Hg compared with lowest quintile: 2.16 (95% CI, 1.09-4.29)
Yoshizawa et al. (2002) USA	Case-control within prospective cohort study	Cases: 470 men Controls: 464 men matched on age and smoking status	Toenail Hg (toenails collected before the onset of CHD, analysed in 1987)	CHD	Toenail Hg concentration in controls: range: 0.03-14.6 µg/g mean (SD): dentists: 0.91 (1.47) µg/g others: 0.45 (0.40) µg/g Adjusted OR for CHD: highest quintile of Hg compared with lowest quintile in dentists: 0.97 (95% CI, 0.63-1.50)
Hallgren et al. (2001) Sweden	Case-control within a prospective cohort study	Cases: 78 men and women	Hg in erythrocytes (blood samples stored in 1985 for future	First MI	Adjusted OR for CHD: highest quintile of Hg compared with lowest quintile, excluding dentists: 1.27 (95% CI, 0.62 to 2.59) Range of erythrocyte Hg concentration: 0.6-67 ng/g erythrocytes Adjusted OR for MI:

Author/Country	Study design	Study participants	Ascertainment of mercury concentration	Disease or death	Results
Ahlqwist et al. (1999) Sweden <sup>a</sup>	Prospective cohort study of women	Controls: 156 men and women, matched for age, sex, date and geographic location 1462 women, enrolled in 1968–1969	research purposes, analysed 1998 Serum Hg (blood samples collected in 1968–69, then 1980–81 for future research; mostly used earlier samples)	MI ( $n = 87$ , 39 died); all-cause death ( $n = 253$ )	intermediate Hg (3–6 ng/g) compared with lowest Hg (< 3 ng/g): 0.9 highest Hg (> 6 ng/g) compared with lowest Hg (< 3 ng/g): 0.4 (95% CI, 0.19–0.95) An inverse, but not statistically significant correlation between serum Hg and MI was found A statistically significant inverse correlation between serum Hg and death from all causes was found after adjusting for age and education
Virtanen et al. (2005) Eastern Finland	Prospective cohort study of men, 14 year follow-up	1871 men who were free of CVD at baseline (1984–1989)	Hair Hg (hair collected before onset of disease or death, analysed in 1992–1993)	Acute CE ( $n = 282$ ); death from CVD ( $n = 132$ ), death from CHD ( $n = 91$ ), all-cause death ( $n = 525$ )	Hair Hg concentration: mean: 1.9 µg/g; range: 0–15.7 µg/g Adjusted RR for acute CE: middle third of Hg compared with lowest third: 1.1 highest third of Hg compared with lowest third: 1.7* Adjusted RR for CVD death: middle third of Hg compared with lowest third: 0.7 highest third of Hg compared with lowest third: 1.3 Adjusted RR for CHD death:

Author/Country	Study design	Study participants	Ascertainment of mercury concentration	Disease or death	Results
					middle third of Hg compared with lowest third: 0.6 highest third of Hg compared with lowest third: 1.2 Adjusted RR for any death: middle third of Hg compared with lowest third: 0.9 highest third of Hg compared with lowest third: 1.3* *range of 95% CI above 1.0

<sup>a</sup>This study also examined the incidence of stroke ( $n = 77$ ), diabetes ( $n = 77$ ), and cancer ( $n = 208$ ).

CE: coronary event; CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; Hg: mercury; MI: myocardial infarction; OR: odds ratio; RR: relative risk.

PUFA (seven studies of formula supplementation and one study of maternal dietary supplementation) were aggregated. The results of this part of the analysis estimated that increasing maternal intake of docosahexaenoic acid by 100 mg/day increases child IQ by 0.13 points (Cohen et al., 2005b). The other major component of this assessment considered the impact of prenatal exposure to methylmercury on cognitive development. This analysis aggregated results from three major prospective epidemiology studies (from the Faroe Islands, Seychelles and New Zealand) to quantify the association between prenatal methylmercury exposure and cognitive development as measured by IQ. The outcome of this analysis demonstrated that prenatal exposure to methylmercury sufficient to increase the concentration of mercury in maternal hair at parturition by 1 µg/g decreased IQ by 0.7 points. This paper identified important sources of uncertainty influencing this estimate, and concluded that the plausible range of values for this loss is 0 to 1.5 IQ points (Cohen et al., 2005a).

The final integration of the quantitative consideration of risk and benefit showed that substituting fish with high methylmercury concentrations for fish containing less methylmercury in the diet of women of childbearing age would result in developmental benefits and few negative impacts. However, if women of childbearing age instead decrease overall fish consumption, there is a substantial reduction in benefits. If other adults reduce fish consumption, the net public health impact is negative. This analysis clearly shows that in considering the risk of any environmental contaminant in a food such as fish without a thorough and robust consideration of countervailing nutritional risks can result in unintended negative public health consequences (Cohen, et al., 2005c).

### **3. DIETARY INTAKE**

#### **3.1 Biomarkers of exposure**

##### *3.1.1 Relationships between various biomarkers of exposure*

The epidemiological studies have used various biomarkers of exposure, such as the concentrations in blood, hair or cord tissue, making immediate comparisons between studies difficult. [Table 2](#) compares the mean ratios between various biomarkers, based on recent publications, to assist in exposure comparisons between studies. The data in the table are for methylmercury unless otherwise stated.

##### *3.1.2 Cord tissue as a biomarker of exposure*

In the Faroe Islands study, the main biomarkers of exposure to methylmercury, i.e. the total mercury concentrations in cord blood and maternal hair obtained at parturition from 447 births, were compared. Umbilical cord tissue mercury was found to correlate closely with mercury in cord blood. Regression analyses showed that the cord dry-weight concentration of mercury was almost as good a predictor of methylmercury-associated neuropsychological deficits at age 7 years as was the concentration of mercury in cord blood. The authors noted that



mercury in cord blood is almost entirely in the methylated form and concluded that analysis of cord tissue can be used as a valid measure of prenatal exposure to methylmercury (Grandjean et al., 2005).

The relationship between total mercury and methylmercury concentrations among umbilical cord tissue and other tissues as biomarkers of fetal exposure to methylmercury were studied in a Japanese cohort. A total of 116 paired samples were collected in three Japanese districts. Total mercury was measured in hair and cord, while methylmercury was measured in cord tissue and blood and in maternal blood. More than 90% of the mercury in cord tissue, cord blood, and maternal blood was methylmercury. Total mercury and methylmercury in cord blood was about two times higher than in maternal blood. A strong correlation was found between total mercury and methylmercury in cord tissue and between cord tissue total mercury and methylmercury and cord blood mercury (Sakamoto, et al., 2006).

#### *Biomarkers of exposure via human milk*

A study in rats has shown that exposure during lactation is less than during gestation and that brain mercury concentrations decline during lactation. Ten female Wistar rats were given a diet containing methylmercury at a concentration of 5 mg/kg of diet (approximately equivalent to 0.32 mg/kg bw per day) before mating and during gestation and lactation. Offspring were provided with the same diet as their mothers after weaning. All treated offspring matured, with normal body-weight gain and without overt physical signs. They exhibited locomotor and behavioural deficits at age 5–6 weeks and histopathological changes in the brain postnatally that are typical of prenatal exposure to methylmercury in rats. At birth, blood and brain mercury concentrations in the offspring were 33 and 4.5  $\mu\text{g/g}$ , respectively, concentrations that were approximately 1.5-fold those of their mothers. At weaning at age 30 days, blood and brain mercury concentrations in the offspring had declined to 12 and 1  $\mu\text{g/g}$ , respectively (Sakamoto et al., 2002a).

In a subsequent study, the same group evaluated the time course of changes in brain total mercury concentrations after prenatal and postnatal exposure to methylmercury via the maternal diet. Female Wistar rats were given access ad libitum to a diet containing methylmercury at a concentration of 5 mg/kg of diet (approximately equivalent to 0.32 mg/kg bw per day), and when blood mercury concentrations had almost reached a plateau, after 8 weeks, they were mated. They continued on the same diet with access ad libitum during gestation and lactation until postnatal day 20. Maternal blood concentrations were lower during pregnancy than at mating, but blood mercury concentrations in the offspring were twice as high as in the mothers on the day of birth. Postpartum, maternal blood concentrations were higher on day 10 and 20 of lactation, comparable with the values observed at mating. During suckling, blood concentrations of mercury in the offspring declined rapidly and progressively. The offspring showed no overt signs of toxicity. Fetal brain mercury concentrations were around 4–4.5  $\mu\text{g/g}$  on days 18, 20, and 22 of gestation and at birth, which was about 1.5–2 times higher than corresponding brain concentrations in the mothers. Postnatally, brain mercury concentrations in the offspring declined rapidly to about one tenth of that observed at birth; mercury concentrations in offspring liver also mirrored the pattern of the brain concentrations (Pan et al., 2004).

**Table 2. Relationship between common biomarkers of exposure to methylmercury**

Sample	Concentration <sup>a</sup>	Comparison (corrected for different units) <sup>b</sup>	Mean ratio	Reference
Maternal blood at delivery <sup>c</sup>	0.45 µg/l	—	—	Björnberg et al. (2005)
Cord blood <sup>c</sup>	0.99 µg/l	Maternal blood at delivery	2.2	Björnberg et al. (2005)
Infant blood at age 4 days	1.10 µg/l	Maternal blood at delivery	2.4	Björnberg et al. (2005)
Milk at age 4 days (total mercury) <sup>d</sup>	0.29 µg/l	Maternal blood at delivery	0.64	Björnberg et al. (2005)
Cord blood	22.6 µg/l	—	5.4	Budtz-Jorgensen et al. (2004)
Maternal hair (full length) (total Hg)	4.22 µg/g	Cord blood	187 <sup>e</sup>	Budtz-Jorgensen et al. (2004)
Blood at age 7 years (total Hg)	1.93 µg/l	—	—	Budtz-Jorgensen et al. (2004)
Hair at age 7 years (total Hg)	0.6 µg/g	Blood at age 7 years	310 <sup>f</sup>	Budtz-Jorgensen et al. (2004)
Blood at age 14 years (total Hg)	3.81 µg/l	—	—	Budtz-Jorgensen et al. (2004)
Hair at age 14 years (total Hg)	0.96 µg/g	Blood at age 14 years	252 <sup>g</sup>	Budtz-Jorgensen et al. (2004)
Cord blood (total Hg)	22.4 µg/l	—	—	Grandjean et al. (2005)
Maternal hair (full length) (total Hg)	4.17 µg/g	Cord blood	187	Grandjean et al. (2005)
Cord tissue (wet weight) (total Hg)	0.025 µg/g	Cord blood	1.1	Grandjean et al. (2005)
Cord tissue (dry weight) (total Hg)	0.21 µg/g	Cord blood	9.4	Grandjean et al. (2005)
Maternal blood (total Hg)	0.52 µg/l	—	—	Jedrychowski et al. (2005)
Cord blood (total Hg)	0.85 µg/l	Maternal blood	1.6	Jedrychowski et al. (2005)

Hg: mercury.

<sup>a</sup> Mean or median as reported.

<sup>b</sup> Assumes that 1 l of blood or milk = 1 kg.

<sup>c</sup> The corresponding concentrations of inorganic mercury were 0.09 µg/l in both maternal and neonatal infant blood

<sup>d</sup> The concentrations in milk correlated with maternal blood inorganic mercury concentrations; other data have shown a correlation between the concentrations in milk and the number of maternal amalgam fillings (Da Costa et al., 2005).

<sup>e</sup> The published mean ratio based on paired data was 370.

<sup>f</sup> The published mean ratio based on paired data was 370.

<sup>g</sup> The published mean ratio based on paired data was 264.

The same group has examined the contribution of mercury exposure via human milk to methylmercury concentrations in human infants, in order to evaluate the relative risks of fetal vs postnatal exposure, based on total mercury concentrations in erythrocytes. Seven pairs of maternal and infant blood samples were compared at parturition and 3 months after parturition. Six of the mothers consumed fish two or three times per week and the other mother once a week. Five infants were reared on human milk only and two were reared on human milk, supplemented with milk formula from age 4 weeks and 6 weeks. At parturition, erythrocyte mercury concentrations were higher in umbilical cord (geometric mean, 0.011  $\mu\text{g/g}$ ) than in the mothers (0.007  $\mu\text{g/g}$ ), with a strong correlation between the two. During the period of breastfeeding, all the infants showed declines in their erythrocyte mercury concentrations, reaching a geometric mean value of 0.006  $\mu\text{g/g}$  at age 3 months. Mercury concentrations in human milk (geometric mean, 0.21  $\text{ng/g}$ ) were about 20% of those in maternal plasma; there were significant correlations between concentrations of mercury in maternal plasma and in milk, and between concentrations of mercury in maternal erythrocytes and in milk, as was also reported by Skerfving (1988) and Oskarsson et al. (1996). The study authors attributed the decline in infant erythrocyte mercury to the low amounts of mercury in human milk and the rapid growth rate of the infant. Noting the correlations between maternal blood concentrations and the concentrations of mercury in human milk, the authors concluded that there need be no concerns about breastfeeding if the concentrations of methylmercury to which the offspring is exposed are low enough during gestation to avoid adverse effects on the fetus (Sakamoto et al., 2002b).

A more recent study confirmed that exposure to methylmercury is higher in the fetus than in the breastfed infant. Twenty Swedish mothers with limited consumption of fish (especially of species potentially high in mercury) and few amalgam fillings were studied, together with their infants. Exposure to mercury was low. Methylmercury and inorganic mercury were measured in the blood of the mothers and their infants at delivery and when the infants were aged 4 days and 13 weeks. Total mercury was measured in human milk collected at 4 days, 6 weeks and 13 weeks after delivery. At delivery, infant blood methylmercury concentrations were highly correlated with maternal blood concentrations, although infant blood concentrations were more than twice as high as maternal ones. The concentrations of methylmercury in infant blood declined markedly during the 13 weeks after birth from a median of 1.1  $\mu\text{g/l}$  at age 4 days to 0.38  $\mu\text{g/l}$  at 13 weeks. Total mercury concentrations in human milk decreased significantly from postnatal day 4 (median, 0.29  $\mu\text{g/l}$ ) to postnatal week 6 (median, 0.14  $\mu\text{g/l}$ ), but did not change thereafter. Total mercury concentrations in human milk did not correlate with maternal blood methylmercury concentrations but did correlate significantly with methylmercury concentrations in infant blood at 13 weeks. Conversely, total mercury concentrations in human milk did correlate significantly with maternal blood inorganic mercury concentrations but did not correlate with inorganic mercury concentrations in infant blood at 13 weeks. From these results the study authors concluded that exposure to both forms of mercury is higher before birth than during the breastfeeding period. Also, that although inorganic mercury is more easily transported from maternal blood into human milk than methylmercury,

methylmercury contributes more than inorganic mercury to postnatal exposure, probably because it is more readily absorbed by the infant gastrointestinal tract (Björnberg et al., 2005).

The same authors (Björnberg et al., 2005) also discuss the potential of the breastfeeding infant to excrete methylmercury. They consider it to be limited because demethylating bacteria do not appear in the infant gut until after weaning (Rowland et al., 1983). Consequently, methylmercury would be reabsorbed via the enterohepatic circulation. They found the marked decline in infant blood methylmercury concentrations during breastfeeding surprising and they recommended that further studies were needed on total excretion of methylmercury in the infant. Although they did note that the decline could be partly related to the rapidly increasing body weight and decrease in erythrocyte volume fraction in the infant postnatally, they may not have considered other factors. These include the higher affinity of methylmercury for fetal haemoglobin (IPCS, 1990; Stern & Smith, 2003), the decline in concentrations of mercury in human milk during the breastfeeding period, and the possibility of uptake of methylmercury by various tissues, including the brain. Together all these factors could contribute significantly to the marked decline of methylmercury concentrations in infant blood (Björnberg et al., 2005).

A study of mercury concentrations in samples of colostrum from human milk from urban mothers and from mothers married to fishermen in Taiwan, did not find any significant difference between the two groups, despite higher fish consumption in the wives of fishermen. The geometric mean values (and ranges) for total mercury concentrations were 2.02 (0.24–9.35)  $\mu\text{g/l}$  in 56 urban mothers and 2.04 (0.26–8.62)  $\mu\text{g/l}$  in 12 fishermen's wives, values that are comparable to previously published measurements made in other countries. Some of the urban mothers consumed more shellfish and raw fish (sushi and sashimi) meals than the fishermen's wives. The authors estimated that breastfeeding contributed 96.3–99.6% of the total mercury exposure of infants, the remainder coming from air (inhalation) or water (dermal exposure). The concentrations of mercury in colostrum corresponded to mercury intakes of around 0.3  $\mu\text{g/kg bw}$  per day for urban babies, assuming intakes of 1.04  $\mu\text{g/day}$  and body weights of about 3.5 kg (Chien et al., 2006).

### 3.1.3 Blood methylmercury concentrations in childhood

The concentrations of methylmercury in hair and whole blood have been followed in the children in the Faroe Islands cohort, for whom the prenatal exposure and neurodevelopmental findings have been described and discussed in detail elsewhere (Annex 1, reference 167). This study was designed to further elucidate the relationship between blood and hair biomarkers for methylmercury exposure, whole blood and hair mercury concentrations in the children at age 7 and 14 years. These children were exposed both prenatally and postnatally via maternal consumption and subsequently direct consumption of fish and whale. Although questionnaire information was obtained at both ages about the frequency of whale dinners, information on this aspect of the study was not reported. The biomarker data showed that postnatal exposure of the children was substantially lower than their prenatal exposure. The geometric means (and ranges) for whole blood mercury concentrations were 1.93 (0.3–12.6) and 3.81 (0.3–39.8)  $\mu\text{g/l}$  at age 7 and

14 years, respectively, compared with cord blood concentrations of 22.6 (0.9–351)  $\mu\text{g/l}$ . Similarly, hair mercury concentrations were 0.60 (0.04–7.5)  $\mu\text{g/g}$  and 0.96 (0.02–9.7)  $\mu\text{g/g}$  at age 7 and 14 years, respectively, compared with values for full-length maternal hair at the time of birth of 4.22 (0.2–39.1)  $\mu\text{g/g}$  (Budtz-Jørgensen et al., 2004).

Total blood mercury has been measured in children aged 1–5 years in the USA, as part of NHANES since 1999. The findings confirm that blood mercury concentrations in young children usually are below levels of concern. During 1999–2002, the geometric mean (and 95th percentile) of total blood mercury concentrations was 0.33  $\mu\text{g/l}$  (2.21  $\mu\text{g/l}$ ). In almost all cases, inorganic mercury was not detectable in blood, indicating that total blood mercury mostly reflected exposure to organic mercury, especially methylmercury (Centers for Disease Control and Prevention, 2004).

### 3.1.4 *Blood mercury concentrations in women of childbearing age*

The NHANES has measured blood mercury concentrations in women of childbearing age in the USA since 1999. The findings confirm that the blood mercury concentrations in this population usually are below levels of concern. During 1999–2002, the geometric mean (and 95th percentile) of total blood mercury concentrations for all women of childbearing age was 0.92  $\mu\text{g/l}$  (6.04  $\mu\text{g/l}$ ). As for children, almost all inorganic blood mercury concentrations were undetectable, indicating that total blood mercury mostly reflected exposure to methylmercury (Centers for Disease Control and Prevention, 2004).

The NHANES for the years 1999–2002 was also used to obtain population estimates of blood mercury concentrations among women of childbearing age classified as belonging to the 'other' racial/ethnic group (Asian, Pacific Islander, native American, and multiracial). Blood mercury concentrations in this group ( $n = 140$ ) were compared with those among all other women participants ( $n = 3497$ ), classified as Mexican American, non-Hispanic black, non-Hispanic white, and 'other' Hispanic. An estimated 16.6% of the group designated as Asian, Pacific Islander, native American, and multiracial had blood mercury concentrations of greater than 5.8  $\mu\text{g/l}$ . Among the remaining NHANES participants, 5.1% had blood mercury concentrations greater than 5.8  $\mu\text{g/l}$  (Hightower et al., 2006).

### 3.1.5 *Biomarkers of co-exposure to other environmental contaminants*

The studies from the Faroe Islands have not found a significant interaction between exposure to methylmercury and co-exposure to PCBs with respect to neurodevelopment. The extent of co-exposure has been documented in recent publications, showing that exposure to PCBs in the Faroese population are generally higher than those reported elsewhere in Europe and North America, and that there is also exposure to other persistent organic pollutants, such as polybrominated diphenyl ethers (PBDEs).

Concentrations of hydroxylated polychlorinated biphenyls (OH-PCBs), PCBs and PBDEs in serum and milk samples from pregnant Faroese women and serum samples from their 7-year-old children were studied to determine the possible impact of the consumption of fatty fish and whale blubber on the body burdens of

environmental contaminants. High concentrations of OH-PCBs and PCBs were found in some of the serum samples, the respective ranges being 19–1800 ng/g lipid weight and 150–22 000 ng/g lipid weight. The relative congener distributions were similar to those observed elsewhere. 4-Hydroxy-2,2,3,4,5,5,6-heptachlorobiphenyl was the most abundant OH-PCB metabolite in all samples analysed, with four other OH-PCB congeners as the dominant metabolites. More than 25 additional OH-PCBs were detected. Maternal serum was dominated by 2,2',4,4'-tetrabromodiphenyl ether (BDE-47), while 2,2',4,4',5,5'-hexabromodiphenyl ether (BDE-153) prevailed in the children's serum 7 years later. PBDE was present in serum of both mothers and children up to 3 and 6 ng/g lipid weight, respectively. Concentrations of the 18 PCB congeners analysed in the children's serum averaged about 60% of that in their mothers, with median concentrations for both being greater than 1 µg/g lipid weight and with similar PCB congener patterns. Serum concentrations of OH-PCBs from the mothers and their children showed ranges of 1.8–36 ng/g wet weight and 0.49–22 ng/g wet weight, respectively, with nearly all OH-PCB congener concentrations being lower in the children. In milk samples OH-PCBs were present in trace amounts only, at levels of approximately 1% of the PCB concentrations. PBDE concentrations showed a clear increase over time, and their concentrations in human milk are among the highest reported so far from Europe, with results of individual samples ranging from 4.7 to 13 ng/g lipid weight. The PBDE concentrations were similar in both mothers and their children. This study confirmed the presence of high concentrations of organohalogen substances in the Faroese population (Fangstrom et al., 2002, 2005a, 2005b).

In a follow-up study of the main birth cohort in the Faroe Islands study, data were collected by questionnaire on potential predictors of persistent organic pollutant concentrations, such as duration of breastfeeding and blubber consumption. Exposure to PCBs (37 congeners), to *p,p'*-dichlorodiphenyl trichloroethane (*p,p'*-DDT) and its primary degradate *p,p'*-dichlorodiphenyl dichloroethylene (*p,p'*-DDE) was assessed from in utero until age 14 years, using 316 umbilical cord samples, 124 serum samples collected from participants at approximately age 7 years, and 795 serum samples collected from participants at age 14 years. Measurements of more highly chlorinated PCB congeners made on individuals' serum samples collected at age 7 and 14 years were highly correlated. Concentrations at age 7 years were generally two to three times higher than at age 14 years. Umbilical cord tissue PCB concentrations were correlated with PCB concentrations in serum samples at age 7 and at age 14 years. Duration of breastfeeding and consumption of blubber were significant predictors of serum PCB concentrations at age 7 and 14 years. Multivariate analyses showed that breastfeeding duration was the primary contributor to serum concentrations of PCBs at age 7 years, and blubber consumption was the primary contributor at age 14 years. Thus although consumption of pilot whale blubber appears to be a significant source of methylmercury and of PCBs, human milk is only a significant source for PCBs (Barr et al., 2006).

### 3.1.6 Consumption of fish and whale and exposure to methylmercury

After an official recommendation in the Faroe Islands that women should abstain from eating pilot whale because of mercury contamination, a survey was carried out to obtain information on dietary habits and hair samples for mercury

analysis. A letter was sent to all 1180 women aged 26–30 years who resided within the Faroes, and the women were contacted again 1 year later. A total of 415 women responded to the first letter; the second letter resulted in 145 repeat hair samples and 125 new responses. Questionnaire results showed that Faroese women, on average, consumed whale meat for dinner only once every second month, but the frequency and meal size depended on the availability of whale in the community. The geometric mean hair-mercury concentration at the first survey was higher in districts with available whale than in those without (3.03 vs 1.88  $\mu\text{g/g}$ ;  $p = 0.001$ ). The concentration of mercury also depended on the frequency of whale meat dinners and on the consumption of dried whale meat. The 36 women who did not eat whale meat at all had a geometric mean hair-mercury concentration of 1.28  $\mu\text{g/g}$ . At the time of the second survey, the geometric mean had decreased to 1.77  $\mu\text{g/g}$  ( $p < 0.001$ ), although whale was now available in all districts. In comparison with previously published data on hair-mercury concentrations in pregnant Faroese women, these results document substantially lower exposures as well as a further decrease temporally associated with the issue of stricter dietary advice (Weihe et al., 2005).

Fetal exposure to mercury was determined in 308 women in the Hawaii Islands by measuring concentrations of mercury in cord blood and analysing the association with fish consumption during pregnancy. Of the 308 women who were enrolled, 275 completed a dietary survey. The mean mercury concentration in cord blood was 4.82  $\mu\text{g/l}$ . A significant relationship was noted between the amount of fish consumed during pregnancy and elevated mercury concentrations in cord blood (Sato et al., 2006).

The impact of fish consumption on the nutritional status of Indian children of eastern Amazonia has been evaluated. Weight-for-height Z score was measured, and hair mercury was determined in 203 children (age < 10 years) in three villages. There was significantly higher consumption of fish in Kayabi children (16.6  $\mu\text{g/g}$ , as measured by hair mercury concentration) than in children of the villages of Missao-Cururu (4.8  $\mu\text{g/g}$ ) and Kaburua (2.9  $\mu\text{g/g}$ ). Mean weight-for-height Z scores of -0.27, -0.22, and 0.40 were noted for Kayabi, Missao-Cururu and Kaburua villages, respectively. There was no significant correlation between weight-for-height Z score and total hair mercury concentration (Dorea et al., 2005a).

The relationship between dietary habits and exposure to mercury was studied in a cohort of Chinese children. The hair and blood mercury concentrations of children aged more than 3 years were studied. Sociodemographic data, dietary habits of the past 6 months, and other risk factors for environmental mercury exposure were collected from the 137 Chinese children (mean age, 7.2 years) recruited. The mean hair mercury concentration was 2.2  $\mu\text{g/g}$  and the mean blood mercury concentration was 17.6 nmol/l (3.8  $\mu\text{g/l}$ ). There was a strong correlation ( $r = 0.88$ ) between hair and blood mercury concentrations. Frequency of fish consumption correlated with hair ( $r = 0.51$ ) and blood ( $r = 0.54$ ) mercury concentrations. For those children who consumed fish more than three times per week, hair and blood mercury concentrations were twice as high as in those who consumed fish one to three times per week, and three-fold higher than in those who never consumed fish. Both blood and hair (i.e. tissue) mercury concentrations of children in Hong Kong were elevated and correlated with the frequency of fish consumption (Ip et al., 2004b).

In the 1999–2000 NHANES, 1250 children aged 1 to 5 years and 2314 women aged 16 to 49 years were selected to participate in the survey. The data gathered are based on analysis of cross-sectional data for the non-institutionalized, US household population and are considered to be nationally representative. The survey consisted of interviews conducted in participants' homes and standardized health examinations conducted in mobile examination centres. Household interviews, physical examinations, and blood-mercury concentration assessments were performed on 705 children (response rate, 56%) and 1709 women (response rate, 74%). Blood mercury concentrations were approximately three times higher in women than in children. The geometric mean concentration of total blood mercury was 0.34 µg/l in children and 1.02 µg/l in women. Geometric mean mercury concentrations were almost four times higher among women who had eaten three or more servings of fish in the past 30 days compared with women who ate no fish in that period (1.94 µg/l vs 0.51 µg/l) (Schober, 2003).

Exposure to mercury was also assessed in 838 US children, aged 1–5 years, and 1726 women, aged 16–49 years, using hair mercury analysis during the 1999–2000 NHANES. The association of hair mercury concentrations with sociodemographic characteristics and fish consumption was reported. Geometric mean hair mercury was 0.12 µg/g in children, and 0.20 µg/g in women. Among frequent fish consumers, geometric mean hair mercury concentrations were three times higher for women (0.38 vs 0.11 µg/g) and twice as high for children (0.16 vs 0.08 µg/g) compared with non-consumers. Hair mercury concentrations were associated with age and frequency of fish consumption (McDowell et al., 2004).

### *3.1.7 Consumption of other foods and exposure to methylmercury*

The use of fish meal as a source of protein for poultry and swine may lead to exposure to methylmercury in addition to that which arises from the consumption of fish. A study in Sweden measured concentrations of inorganic mercury and methylmercury in blood in 9 men and 18 women, aged 20–58 years, who stated that they had consumed no fish for a period of 2 years or more. Participants answered a food-frequency questionnaire and reported number of dental amalgam fillings. Methylmercury concentrations in blood were very low. A significant association between the number of dental amalgam fillings and the inorganic mercury concentration in blood was found. Total hair mercury concentration was significantly associated with methylmercury in blood, but not with the inorganic mercury (Lindberg et al., 2004).

## **3.2 The effect of GLs for methylmercury on exposure and risk**

CCFAC at its Thirty-seventh Session (Codex Alimentarius Commission, 2005) asked the Committee to consider the impact on exposure and risk of the current GLs for methylmercury in fish, set at 1 mg/kg for predatory fish, and 0.5 mg/kg for non-predatory fish.<sup>1</sup>

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<sup>1</sup> See [http://www.codexalimentarius.net/download/standards/21/CXG\\_007e.pdf](http://www.codexalimentarius.net/download/standards/21/CXG_007e.pdf)



### 3.2.1 *The nature of GLs*

Previous meetings of the Committee have considered the dietary impact of limits for other contaminants on exposure. For instance, differing GLs for aflatoxin M<sub>1</sub> and ochratoxin A were evaluated by the Committee at its fifty-sixth meeting in 2001 (Annex 1, reference 152). In each of these examples, the effect of setting limits was found to be minimal, only affecting exposure at the extreme tail of the intake distributions. It has been noted at previous meetings of the Committee that using GLs to influence exposure is, in general, not effective until a large fraction of the affected commodity has been withdrawn from the marketplace.

A GL is risk management tool set to protect a consumer of an affected food from exposure to a toxic dose of a substance. For substances with acutely toxic effects, GLs that are enforced can limit exposure. However, when the toxic effect of a substance results from long-term exposure, GLs will have a much smaller protective effect as the consumer will be exposed to the substance at the mean level of its distribution in the affected food<sup>2</sup>. The shape of the distribution of the levels of the substance in affected food will determine the extent of impact of a GL on exposure. The further the GL is set from the average of the distribution, the smaller the impact that GL will have on exposure.

In responding to the CCFAC request concerning the dietary impact of GLs for methylmercury, the Committee noted that no alternatives to the current GLs are under consideration. The situation is complex as many fish species are consumed as food and the terms predatory and non-predatory species have not been clearly defined. These terms are primarily used to designate fish that are higher on the food chain from those lower on the chain. In practice, non-predatory species are those typically containing low average concentrations of methylmercury and predatory species are those with higher average concentrations. This is owing to the bioaccumulation of methylmercury, especially in larger, older fish. Another complicating factor is the presumed non-random nature of consumer choice among fish species, thus fish eaters will experience some weighted average of mercury concentrations across species. Because of the nature of mercury accumulation in different species, GLs will have differing impacts on individual species, and thus on overall exposure based on the individual's choices.

Default assumptions were required for this analysis of the dietary impact of GLs. The Committee chose to compare the current situation with a scenario where no GLs are in effect or are enforced.

### 3.2.2 *Data submitted to the Committee*

The Committee received dossiers containing total mercury and/or methylmercury levels in finfish and/or shellfish from France, Japan, and the United Kingdom (UK), and obtained additional analytical data from the USA and from the published literature. Each of the dossiers contained analyses on individual samples. Additionally, two papers were reviewed from the USA and France, which considered

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<sup>2</sup> This assumes that the portions consumed over a lifetime are of approximately the same magnitude, as would be expected for a primary food in the diet.

**Table 3. Data on total mercury in finfish, from the UK**

<i>Mean values:</i>				
Samples		Mean (mg/kg)	No. of samples	
All samples		0.25	282	
< 1.0 mg/kg		0.14	263	
< 0.5 mg/kg		0.09	240	
<i>Values within species</i>				
Species	No. of samples	Mean (mg/kg)		% Reduction
		All samples	Violative samples removed	
<i>&gt; 1.0 mg/kg</i>				
Shark	5 of 5	1.52	0.00	100
Tuna	1 of 74	0.25	0.23	8
Swordfish	11 of 17	1.36	0.43	68
Marlin	2 of 4	1.09	0.51	53
<i>&gt; 0.5 mg/kg</i>				
Shark	5 of 5	1.52	0.00	100
Tuna	11 of 74	0.25	0.17	32
Swordfish	13 of 17	1.36	0.22	84
Orange roughy	6 of 6	0.60	0.00	100
Halibut	2 of 8	0.29	0.19	34
Ice fish	1 of 1	0.66	0.00	100
Marlin	3 of 4	1.09	0.41	62

United Kingdom (2006) Dossier on fish mercury concentrations submitted to the Committee. UK, United Kingdom

risk management options for controlling exposure to methylmercury (Carrington, 2004; Crépet, 2005).

#### *Data from the UK*

The dossier from the UK (Food Standards Agency) contained analytical results on total mercury from 336 samples, comprising 282 finfish and 54 shellfish, collected in 1999–2002. Because the maximum concentration found in shellfish was only 0.25 mg/kg, one half the GL for non-predatory fish, they will not be considered further. The only species found to contain total mercury at concentrations greater than 1.0 mg/kg were shark, swordfish, marlin, and tuna. Three additional species, orange roughy, halibut, and Atlantic icefish, were found to contain total mercury at concentrations greater than 0.5 mg/kg (Table 3).

**Table 4. Data on total mercury in finfish, from France**

<i>Mean values:</i>				
Samples		Mean (mg/kg)	No. of samples	
All samples		0.099	1254	
< 1.0 mg/kg		0.089	1245	
< 0.5 mg/kg		0.077	1219	
<i>Values within species</i>				
Species	No. of samples	Mean (mg/kg)		% Reduction
		All samples	Violative samples removed	
<i>&gt; 1.0 mg/kg</i>				
Tuna	2 of 64	0.32	0.28	12
Shark	1 of 16	0.43	0.31	28
Barracuda	5 of 14	0.85	0.59	31
Ray	1 of 23	0.16	0.09	44
<i>&gt; 0.5 mg/kg</i>				
Tuna	13 of 64	0.32	0.21	34
Shark	4 of 16	0.43	0.23	47
Barracuda	10 of 14	0.85	0.23	73
Ray	1 of 23	0.16	0.09	44
Rainbow trout	1 of 604	0.05	0.05	0
Marine fish	5 of 91	0.18	0.16	11
Ling	1 of 14	0.26	0.24	8

France (2006) Dossier on fish mercury concentrations submitted to the Committee.

#### *Data from France*

The dossier submitted by France contained analytical results on total mercury from 1661 samples; 1254 finfish and 407 shellfish, collected in 1998–2002. Because the maximum concentration found in shellfish was only 0.43 mg/kg, 80% of the GL for non-predatory fish, shellfish were not considered further. The only species found to contain mercury at concentrations greater than 1.0 mg/kg were shark, tuna, barracuda, and ray. Three additional species were found to contain mercury at concentrations greater than 0.5 mg/kg—rainbow trout, marine fish, and ling (Table 4).

#### *Data from the USA*

The information received from the USA contained analytical results on total mercury from 952 samples, comprising 903 finfish and 49 shellfish, collected in 2002–2005. The maximum concentration found in shellfish was 0.30 mg/kg, which

**Table 5. Data on total mercury in finfish, from the USA**

<i>Mean values:</i>				
Samples		Mean (mg/kg)	No. of samples	
All samples		0.27	903	
< 1.0 mg/kg		0.25	885	
< 0.5 mg/kg		0.19	780	
<i>Values within species:</i>				
Species	No. of samples	Mean (mg/kg)		% Reduction
		All samples	Violative samples removed	
<i>&gt; 1.0 mg/kg</i>				
Swordfish	10 of 14	1.33	0.72	46
Tuna	3 of 531	0.26	0.26	0
Grouper	2 of 30	0.45	0.40	11
Snapper	1 of 26	0.18	0.14	22
Bass	1 of 52	0.32	0.28	13
Sable fish	1 of 2	0.64	0.22	66
<i>&gt; 0.5 mg/kg</i>				
Swordfish	13 of 14	1.33	0.16	88
Tuna	54 of 531	0.26	0.22	15
Grouper	8 of 30	0.45	0.29	36
Snapper	1 of 26	0.18	0.14	22
Bass	9 of 52	0.32	0.21	34
Sable fish	1 of 2	0.64	0.22	66
Orange roughy	17 of 29	0.54	0.40	26
Weakfish	4 of 24	0.24	0.16	33
Blackfish	6 of 6	0.61	0.00	100
Char	2 of 26	0.08	0.04	50
Bluefish	6 of 30	0.35	0.31	14
Halibut	1 of 14	0.23	0.21	9
Tilefish	1 of 14	0.13	0.11	15

United States (2006) Private communication on fish mercury concentrations made to the Committee.

is 60% of the GL for non-predatory fish; these results were not considered further. The only species found to contain mercury at concentrations greater than 1.0 mg/kg were swordfish, tuna, sablefish, bass, and snapper. Seven additional species, orange roughy, bluefish, blackfish, weakfish, char, halibut, and tilefish, were found to contain mercury at concentrations greater than 0.5 mg/kg (Table 5).

*Data from Japan*

The information received from Japan contained aggregated analytical results on total mercury and methylmercury from 227 fish species (including marine mammals) and shellfish. There were 6707 samples (1146 from marine mammals) and 918 shellfish, collected in 2003–2005. The fish species found to contain total mercury at concentrations greater than 1.0 mg/kg were dolphin (marine mammal), whale (marine mammal), tuna, alfonsino (related to red snapper), swordfish, porpoise (marine mammal), bluefish, halibut, and grouper. Additionally, the following species were found to have samples containing total mercury at concentrations greater than 0.5 mg/kg: rockfish, bluefish, snapper, marlin, stargazer, shark, sablefish, thornyhead, saucord, flounder, yellowtail, fusiliner, seaperch, brotula, sea bream, mackerel, and John Dory. Because these data were aggregated, it is not possible to determine the number of samples or the percentage within a species that exceeded either of the two limits. However, the species that contained mercury at average concentrations of greater than 1.0 mg/kg were dolphin, whale, marlin, porpoise (all marine mammals), and grouper. The species containing mercury at average concentrations greater than 0.5 mg/kg were swordfish, snapper, alfonsino, and shark.

Methylmercury concentrations were also measured in many of the samples. Species found to contain methylmercury at concentrations greater than 1.0 mg/kg were dolphin, whale, tuna, alfonsino, and swordfish. Yellowtail, seaperch, grouper, shark, sablefish, thornyhead, flounder, snapper, marlin, porpoise, saucord, marlin, rockfish, bluefish, and stargazer were found to have samples containing methylmercury at concentrations greater than 0.5 mg/kg. Again, because these were aggregated data, it was not possible to determine the number of samples or the percentage within each species above either of the two limits.

Individual sample raw data were submitted for a number of species known to contain higher levels of mercury. These were tuna, marlin, swordfish, alfonsino, sablefish shark, red snow crab, and the finely-striated buccinum, a gastropod. Of the 501 individual samples measured, 53 (11%) were found to contain total mercury at greater than 1.0 mg/kg, with 208 (40%) greater than 0.5 mg/kg. The average mercury content of this sub-sample was 0.54 mg/kg. Exclusion of the samples containing mercury at greater than 1.0 mg/kg reduces the average for the remaining samples to 0.42 mg/kg, while exclusion of all samples containing mercury at greater than 0.5 mg/kg lowers the average to 0.27 mg/kg.

The dossier from Japan contained data on the consumption of fish and fish species known to be high in mercury (Table 6). The data were compiled in 2001 and 2002. Overall mean consumption of fish was found to be approximately 80 g/person per day, with consumption at the 90th percentile being approximately 170 g/person per day. It is important to note that, with the exception of tuna, both canned and fresh (approximately 40% eaters), no species is consumed by more than 5% of the population surveyed, with all except bream species being consumed by less than 1% of the survey population. Intakes and percentages of eaters were not significantly different for the population subgroups, women aged 19–45 years, and all women aged more than 20 years.

**Table 6. Data on total mercury in fish and marine mammals, from Japan**

Species of fish or marine mammal consumed	All people who ate fish or marine mammals				
	Average (g/day)	50th percentile (g/day)	90th percentile (g/day)	95th percentile (g/day)	No. of people
Average for all fish	82.7	72.0	168.0	208.1	18839
Blue marlin and striped marlin	69.8	70.0	100.0	138.5	135
Alfonsino	79.2	71.0	133.3	160.0	144
Shark species	76.3	64.0	125.0	125.0	6
Bream species	56.2	43.7	105.0	140.0	708
Tuna species	26.3	18.8	65.3	100.0	6043
Big-eye	88.0	76.0	125.0	250.0	38
Marine mammals	94.1	82.0	150.0	250.0	17
Canned tuna	21.6	17.5	50.0	60.0	1461

Japan (2006) Dossier on fish mercury concentrations submitted to the Committee.

### 3.2.3 The impact of risk management options on exposure

The Committee considered two recent publications that dealt directly with the present analysis. A paper from the USA evaluated exposure scenarios based on curtailing or removing exposure to mercury from fish species known to contain mercury at typically high levels (Carrington, 2004). This paper used food intake data from the USA with mercury analyses of domestic (USA) and imported seafood. The scenarios evaluated exposure based on limits on seafood consumption of 6, 12 or 18 ounces per week, replacing fish containing mercury at high concentrations with fish containing mercury at intermediate or low concentrations, and considered exposure when no limits on consumption were necessary, but when fish containing mercury at high concentrations were excluded from the diet. These scenarios bracket the advice given to seafood consumers in the USA concerned with reducing exposure to mercury<sup>3</sup>. Fifty-one types of finfish and nine shellfish were included. Of these, 11 finfish had maximum mercury concentrations greater than 1.0 mg/kg. Gulf tilefish was the only type to have a mean concentration greater than 1.0 mg/kg. Additionally, shark, swordfish, king mackerel, grouper, and orange roughy had mean mercury concentrations greater than 0.5 mg/kg. Water loss on preparation and market share were also taken into consideration in the exposure modelling.

<sup>3</sup> The advice issued in the USA concerning mercury recommends that pregnant women (or those planning on becoming pregnant) avoid consuming shark, swordfish, king mackerel, and tilefish, and include up to 12 ounces per week of a variety of other fish in their diets.

The paper concludes: "In general, reducing overall fish consumption appears to have more impact on the overall population distributions than reducing or eliminating levels of high-level mercury species only." With respect to the current analysis, reducing or eliminating high-level mercury species is more drastic than simply removing fish of those species in which the GL is exceeded, which simply reduces the mean of the remaining distribution of mercury levels in those species.

A second paper, published in 2005, considers the question in the current analysis, the effect of enforced GLs on exposure, and the effect of excluding or limiting predatory fish intake, as in the analysis by Carrington et al., discussed above (Crépet, 2005). In this publication, exposure to methylmercury was determined using French data on food intake and analyses of fish and fishery products available in the French marketplace. Mean mercury contamination levels from 89 individual food items (from a total of 2818 individual analyses) containing fish were used and combined with appropriate 7-day average food intakes for the 89 items. Correction factors (0.84 for finfish, 0.36 for shellfish and 0.43 for molluscs) were applied to convert total mercury analyses to methylmercury levels in each food. Actual body weights from surveyed consumers in the food intake survey were used.

In one scenario, all predatory fish containing mercury at concentrations greater than 1.0 mg/kg and all non-predatory fish (includes all shellfish and molluscs) with mercury concentrations greater than 0.5 mg/kg were excluded and the mean mercury concentration of the food type was recalculated. In this scenario, 2.3% of predatory fish samples, tuna, shark, swordfish, rays, and marlin, would be excluded. In a second scenario, all fish containing mercury at concentrations greater than 0.5 mg/kg were excluded. In this scenario, 8.8% of predatory fish samples would be excluded. In the first scenario, only 27 fish food types had their mean mercury concentration lowered by the exclusion, most by less than 15%. The largest reduction, of 42%, was for fried, simmered, or oven-baked skate. The second, more drastic scenario resulted in the further lowering of the mean methylmercury concentration of 18 fish food types, but did not lower the mean of any food type not affected by the conditions of the first scenario.

Methylmercury exposures in each scenario were calculated for children aged 3–6 years and 7–10 years, and for women of childbearing age, as were the probabilities of exceeding the PTWI of 1.6  $\mu\text{g}/\text{kg}$  bw (Annex 1, reference 166). In the first scenario, there were no significant differences between the probabilities of exceeding the PTWI from compliance with the GLs or baseline (no GLs). In the second scenario, for children aged 3–6 or 7–10 years there were also no significant differences in the probabilities of exceeding the PTWI, but the difference for women of childbearing age did reach significance (4.4% for no GLs vs 0.6 for a uniform GL of 0.5 mg/kg). The authors note that the impact of reducing exposure to predatory fish would be greater for women of childbearing age because products derived from predatory fish make up a larger proportion of their diets than in the case of children, and is a larger vector of exposure for those that would exceed the PTWI (23% for children vs 70% for women).

## 4. COMMENTS

### 4.1 *Vulnerability of the embryo and fetus*

The Committee noted that the new toxicokinetic, toxicological and epidemiological studies available since its previous evaluation in 2003 further confirmed the embryo and fetus as the most vulnerable stage of life with respect to the adverse effects of methylmercury. The new data do not suggest the need for revision of the previously established PTWI of 1.6 µg/kg bw, with respect to maternal intakes and this life stage.

### 4.2 *Vulnerability of the infant and child*

In reviewing the available studies relevant to risk assessment for infants and young children exposed after birth via human milk and via the diet in general, the Committee noted that few studies have attempted to separate the potential effects of postnatal exposure to methylmercury from the known neurodevelopmental effects of prenatal exposure.

There is clear evidence from the concentrations of mercury in human milk and in the blood of infants that, compared with exposure in utero, postnatal exposure to methylmercury is considerably lower in infants who are breastfed and, similarly, postnatal exposure is lower in those that are formula-fed. The Faroe Islands study reported earlier developmental milestones in breastfed compared with formula-fed infants and lack of any independent association between breastfeeding and neurological deficits at age 7 years. The study authors suggested that breastfeeding is beneficial even in a population with a relatively high prenatal exposure to methylmercury because of maternal consumption of fish and whale. This suggestion is compatible with other extensive data showing that breastfeeding per se offers benefits for cognitive development.

It is clear from the earlier major poisoning incidents in Japan and Iraq that methylmercury did cause neurotoxicity when exposure of children was limited to the postnatal period. However, the incidents do not give much insight into the question of whether children may be more vulnerable than adults to exposure at low levels, since in most cases there was prenatal as well as postnatal exposure to methylmercury and the exposures were very high. Similarly, while monkeys exposed to methylmercury from birth to early adulthood (age 7 years), but not exposed in utero, showed deficits in fine motor control (clumsiness) beginning in middle age and restrictions in visual fields during old age, the exposure levels in those studies, at 50 µg/kg bw per day, were high relative to dietary exposures in humans. Data from the Faroe Islands have suggested a subtle but measurable effect of postnatal exposure on latency in a single interpeak interval in brainstem auditory evoked potentials measured at age 14 years. The health significance of this observation, if any, remains unclear.

Knowledge of human brain development raises the theoretical possibility of continuing vulnerability to neurodevelopmental effects from postnatal exposure to methylmercury, but there is no clear evidence on this. For example, the influence of exposure to methylmercury on synaptogenesis, which continues well into



adolescence in humans, is not known. However, in rats given methylmercury as a single, high, oral dose at 8 mg/kg bw administered by gavage during the late fetal period, synaptogenesis had been shown to be affected. Similarly, both neuronal myelination and remodelling of the cortex of the brain occur postnatally in humans and have a protracted time course, continuing through adolescence until about age 17 years, but again there was no evidence as to whether exposures to methylmercury at low levels might affect these potentially vulnerable processes.

In summary, there are insufficient data from the studies previously reviewed by the Committee and the more recent studies reviewed at the present meeting to draw conclusions regarding the vulnerability of infants and children to methylmercury. It is clear that they are not more vulnerable than the embryo and fetus, but the information available to date does not enable any firm conclusions to be drawn on whether infants and children, including adolescents, are more, or less, vulnerable than adults.

#### **4.3 Vulnerability of adults**

For adults, the previously established PTWI of 3.3 µg/kg bw, which was revised in 2003, was regarded by the Committee in 1988 at its thirty-third meeting (Annex 1, reference 83) as adequate to take account of neurotoxicity, excluding developmental neurotoxicity; the Committee at its present meeting considered that this remained the case. Concerning other health aspects, the Committee gave further consideration to previous and more recent studies on methylmercury exposure and cardiovascular findings and concluded that the weight of evidence at the current time did not indicate an increased risk of adverse cardiovascular events. The Committee also noted that fish consumption in general is associated with cardiovascular benefits.

#### **4.4 Impact of current GLs for methylmercury in fish on exposure and risk**

The Committee evaluated the impact of current Codex GLs for methylmercury in fish (predatory fish, 1.0 mg/kg; non-predatory fish, 0.5 mg/kg) on exposure and risk. Submissions were received from France, Japan, and the UK, and additional information on the distribution of mercury and methylmercury in various fish species was obtained from the USA. Additionally, two recent publications concerning risk management options for the control of exposure to methylmercury were considered by the Committee.

Previous Committees have noted that excluding foodstuffs containing a contaminant at a concentration that is at the high end of a log-normal distribution of concentrations is not an effective method for reducing overall exposure to that contaminant in the general population. Large proportions of foodstuffs must be excluded from the market before the average exposure to the contaminant is significantly reduced. The data from France, Japan, the UK and the USA reviewed at this meeting support this conclusion for methylmercury in fish. In each of those countries, the total market—and hence the total distribution of methylmercury in seafood—is dominated by species that do not contain a high concentration of mercury. If it were the case that seafood consumers randomly chose from the total

market over their lifetime, their mean level of exposure to methylmercury in seafood would not be substantially reduced by excluding fish containing methylmercury at concentrations greater than the GLs of 1.0 mg/kg for predatory fish and 0.5 mg/kg for non-predatory fish, and the numbers of individuals exposed to methylmercury at intakes greater than the PTWI would not be lowered significantly.

For individual consumers whose preferred choice of fish comprises species that are known to accumulate methylmercury at higher concentrations, exclusion from their diets of all fish found to exceed the GLs may significantly limit their total exposure to methylmercury. The information submitted by France, the UK and the USA showed that excluding fish samples found to contain methylmercury at concentrations greater than the current Codex GLs would reduce the mean concentration of methylmercury in those species by 30–100% in fish available on the market. This would, however, be at the cost of removing the majority of samples of those species from the market. The French analysis suggests that the impact of those exclusions on an individual's intake of methylmercury may not be great, as the percentage of women exceeding the PTWI for methylmercury would only be reduced significantly if all fish containing methylmercury at concentrations greater than 0.5 mg/kg (one half of the GL for predatory species) were removed from their diets, while the percentage of children aged 3–10 years with exposures greater than the PTWI would still not be significantly reduced.

In other populations (e.g. Japan, where the mean consumption of seafood in the population is higher than that in France, the UK or the USA), exclusion from the population diet of all fish exceeding the Codex GLs may have a greater impact on the percentage of individuals with exposures greater than the PTWI. It was not possible from the data submitted by Japan to determine the percentage of samples in the Japanese market that exceeded the current Codex GLs for each marine species, and therefore, not possible to estimate the extent or significance of any reduction in exposure to methylmercury resulting from the removal of such fish from the market. The species containing the highest concentrations of methylmercury are not consumed by large percentages of the Japanese population, suggesting that GLs would not be very effective in reducing the overall number of vulnerable individuals in the population who would have exposures greater than the PTWI.

## **5. EVALUATION**

At its present meeting, the Committee made it clear that the previous PTWI of 3.3 µg/kg bw had, in fact, been withdrawn in 2003. The Committee confirmed the existing PTWI of 1.6 µg/kg bw, set in 2003, based on the most sensitive toxicological end-point (developmental neurotoxicity) in the most susceptible species (humans). However, the Committee noted that life stages other than the embryo and fetus might be less sensitive to the adverse effects of methylmercury.

In the case of adults, the Committee considered that intakes of up to about two times higher than the existing PTWI of 1.6 µg/kg bw would not pose any risk of neurotoxicity in adults, although in the case of women of childbearing age, it should be borne in mind that intake should not exceed the PTWI, in order to protect the embryo and fetus.

Concerning infants and children aged up to about 17 years, the data did not allow firm conclusions to be drawn regarding their sensitivity compared with that of adults. While it was clear that they are not more sensitive than the embryo or fetus, they might be more sensitive than adults because significant development of the brain continues in infancy and childhood. Therefore, the Committee could not identify a level of intake higher than the existing PTWI that would not pose a risk of developmental neurotoxicity for infants and children.

The Committee had previously noted that fish makes an important contribution to nutrition, especially in certain regional and ethnic diets. The present Committee recommended that the known benefits of fish consumption need to be taken into consideration in any advice aimed at different subpopulations. Risk managers might wish to consider whether specific advice should be given concerning children and adults, after weighing the potential risks and benefits. The Committee was unable to offer any further advice in this regard since it is not within its remit to examine the beneficial aspects of fish consumption. The Committee also noted that the relative benefits of fish consumption will vary from situation to situation, depending on, for instance, the species of fish consumed and the relative nutritional importance of fish in the diet.

The Committee concluded that the setting of GLs for methylmercury in fish may not be an effective way of reducing exposure for the general population. The Committee noted that advice targeted at population subgroups that might be at risk from methylmercury exposure could provide an effective method for lowering the number of individuals with exposures greater than the PTWI.

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