3.2 Methylmercury

205. While mainly focusing on methylmercury, this section also gives a few remarks on other organic mercury substances.

206. The compound dealt with most extensively in toxicological research in recent years is methylmercury. Like other alkylmercury compounds, the toxicity of methylmercury is much higher than that of inorganic mercury. Methylmercury is a potent neuro-toxin, hence human exposure to methylmercury is clearly unwelcome and should be regarded with concern. It is present worldwide in fish and marine mammals consumed by humans. Methylmercury is formed naturally (from anthropogenic and naturally released mercury) by biological activity in aquatic environments, and it is bio-magnified in the food chain, resulting in much higher concentrations in higher predatory fish and mammals than in water and lower organisms. Most of the total mercury concentrations in fish are in the form of methylmercury (close to 100 percent for older fish). Methylmercury has also been used deliberately as a pesticide/biocide (e.g. seed grain treatment), and this use gave rise to severe historical poisoning incidents in Iraq before 1960 and again in the early 1970's (US EPA, 1997).

207. Consumption of contaminated fish and marine mammals is the most important source of human exposure to methylmercury (WHO/IPCS, 1990; US EPA, 1997). The highest concentrations are found in large predatory fish like shark, king mackeral, swordfish and some large tuna (as opposed to the smaller tuna usually used for canned tuna), as well as in some freshwater fish like pike, walleye, bass, perch, and eels, and in mammals like seals and whales. Due to long-range atmospheric emission transport and ocean currents, methylmercury is also present in the environment far away from local or regional mercury sources. This implies that population groups particularly dependent on – or accustomed to – marine diets, such as the Inuits of the Arctic, as well as marine and freshwater fish-dependent populations anywhere else on the globe, are particularly at risk due to methylmercury exposure.

208. Methylmercury is highly toxic, and the nervous system is its principal target tissue. In adults, the earliest effects are non-specific symptoms such as paresthesia, malaise, and blurred vision; with increasing exposure, signs appear such as concentric constriction of the visual field, deafness, dysarthria, ataxia, and ultimately coma and death (Harada, 1995). The developing central nervous system is more sensitive to methylmercury than the adult. In infants exposed to high levels of methylmercury during pregnancy, the clinical picture may be indistinguishable from cerebral palsy caused by other factors, the main pattern being microcephaly, hyperreflexia, and gross motor and mental impairment, sometimes associated with blindness or deafness (Harada, 1995; Takeuchi and Eto, 1999). In milder cases, the effects may only become apparent later during the development as psychomotor and mental impairment and persistent pathological reflexes (WHO/IPCS, 1990; NRC, 2000). Studies from one population exposed to methylmercury from fish also suggest an association with increased incidence of cardiovascular system diseases (Salonen *et al.*, 1995, Rissanen *et al.*, 2000). From research on animals there is evidence of genotoxicity and effects on the immune system and the reproductive system.

209. Substantial parts of the descriptive text in this section were based on Pirrone *et al.* (2001) and to a lesser extent the submission from the Nordic Council of Ministers (sub84gov). Pirrone *et al.* (2001), mention that their presentation was largely based on previous reviews by WHO (WHO/IPCS 1990; 1991), IARC (IARC, 1993) and the US EPA (US EPA 1997; 2001b).

3.2.1 Neurological effects

210. In the most recent authorative evaluations of the toxicological effects of methylmercury (WHO/IPCS, 1990; NRC, 2000) it was concluded that the effects on the developing nervous system in unborn and newborn children are the most sensitive, well-documented effects judged from the evidence from human and animal studies. Such effects can take place even at exposure levels where the mother (through whom the children receive the mercury) remains healthy or suffers only minor symptoms due to mercury exposure (WHO/IPCS, 1990; Davis *et al.*, 1994, as cited by Pirrone *et al.*, 2001).

211. Methylmercury in our food is rapidly absorbed in the gastrointestinal tract and readily enters the brain. From the methylmercury poisoning episodes in Japan and Iraq it was known that the most severe effects take place in the development of the brain and nervous system of the unborn child (the fetus), but also severe effects on adults were observed. A series of large epidemiological studies have recently provided evidence that methylmercury in pregnant women's marine diets – even at low mercury concentrations (about 1/10 - 1/5 of observed effect levels on adults) – appears to have subtle, persistent effects on the children's mental development as observed at about the start of the school age (so-called cognitive deficits; NRC, 2000).

212. The Faroe Islands population was exposed to methylmercury mainly from pilot whale meat with relatively high concentration of methylmercury, around 2 mg/kg (US EPA, 2001b). The study of about 900 Faroese children showed that prenatal exposure to methylmercury resulted in neuropsychological deficits at 7 years of age (Grandjean *et al.*, 1997). The brain functions most vulnerable seem to be attention, memory, and language, while motor speed, visiospatial function, and executive function showed less robust decrements at increased mercury exposures. The mercury concentration in cord blood appeared to be the best risk indicator for the adverse effects, which were apparently only slightly affected by a large number of covariates examined. Special concern was expressed with respect to the impact of PCBs, which was present in the diet (in whale blubber) of these Faroese mothers. The results were roughly unchanged, however, when PCB levels were taken into account, and increased prenatal exposure to methylmercury appeared to enhance PCB toxicity (Grandjean et al., 2001). Developmental delays were significantly associated the methylmercury exposures, even if excluding the children whose mothers had hair mercury concentrations above 10 µg/g. Within the low exposure range, each doubling of the prenatal methylmercury exposure level was associated with a developmental delay of 1-2 months. On an individual basis the effects at these dose levels may not seem severe, but they may have severe implications on a population basis.

213. To put the level of exposures for methylmercury in perspective, for the most widely accepted non-lethal effect (neurodevelopmental effects), the benchmark dose (BMD) level is calculated to be 58 µg/l total mercury in cord blood (or 10 µg/g total mercury in maternal hair) using data from the Faroe Islands study of human mercury exposures (NRC, 2000; Budtz-Jorgensen *et al.*, 2000). This BMD level is the lower 95 percent confidence limit for the exposure level that causes a doubling of a 5 percent prevalence of abnormal neurological performance (developmental delays in attention, verbal memory and language) in children exposed *in-utero* in the Faroe Islands study. This dose level is estimated from actual test observations and analysis hereof, involving a number of scientifically based choices including statistic model and specific effect/test of effect used for evaluation. The 58 µg/l total mercury in cord blood and 10 µg/g total mercury in maternal hair are the tissue levels estimated to result from an average daily intake of about 1 microgram methylmercury per kilogram body weight per day (1 µg/kg body weight per day). By using an uncertainty factor of 10, this BMD level has been used to estimate safe exposure levels for humans (US EPA, 2001b; NRC, 2000; Pirrone *et al.*, 2001).

214. Another prospective study is ongoing in the Seychelles islands, where the methylmercury exposures are of similar extent. The fish consumption of pregnant women in the Seychelles is high, typically 10-15 meals per week (Shamlaye, 1995), while the mercury concentrations in the ocean fish consumed is lower (than the mercury concentrations in the pilot whale meat consumed by the Faroe Islands population), with a mean of 0.2-0.3 mg/kg (Cernichiari *et al.*, 1995). No effects on developmental tests up to 5.5 years of age were found to be associated with methylmercury exposure, as measured by hair-mercury in the pregnant mothers (Davidson *et al.*, 1998; Crump *et al.*, 2000; Myers *et al.*, 2000; Axtell *et al.*, 2000; Palumbo *et al.*, 2000). The main longitudinal study was started in 1989-1990 and comprised about 700 mother-child pairs. Maternal hair (mean about 7 µg/g) and child hair, but not cord-blood levels were used as markers of methylmercury exposure in this study. A reanalysis using raw scores rather than age standardized scores showed similar results. (Davidson *et al.*, 2001)

215. In addition, there is a study from New Zealand, suggesting an effect on the mental development of children at the age of 4 and 6-7 years. In a high-exposure group the average maternal hair-mercury was about 9 µg/g, and control groups were selected with lower exposure levels. In total, about 200 chil-

dren were examined at 6-7 years of age and a negative association was found between maternal hair-mercury and neuropsychological development of the children. Although carried out a decade earlier than the Seychelles and Faroe Islands studies (published as reports from the Swedish Environmental Protection Agency (Kjellstrom *et al.*, 1986; 1989)), inclusion of the findings from this study was considered appropriate by the US EPA in their recent assessment (US EPA, 2001b) given the similarities in study design and endpoints considered, and following a later analysis of data by Crump using a "benchmark dose" approach (Crump *et al.*, 1998).

216. Some cross-sectional studies using neuropsychological testing of older children in different settings (such as in the Amazonas and on the Madeira island), also found significant associations with mercury exposure (for a review, see US EPA, 2001b). As the relationship between mercury concentrations found in maternal hair, as well as in umbilical cord blood, and mercury concentrations in human diet is relatively well described (with some biological variation), it is possible to estimate corresponding levels of methylmercury doses in human diet, deemed to be safe. See section 4.2.1 on the use of such a risk evaluation tool.

217. The original epidemiological report of methylmercury poisoning involved 628 human cases that occurred in Minamata, Japan, between 1953 and 1960. The overall prevalence rate for the Minamata region for neurologic and mental disorders was 59 percent. Among this group 78 deaths occurred, and hair concentrations of mercury ranged from 50–700 μg/g. The most common clinical signs observed in adults were paresthesia, ataxia, sensory disturbances, tremors, impairment of hearing and difficulty in walking. Examination of the brains of severely affected patients that died revealed marked atrophy of the brain (55 percent normal volume and weight) with cystic cavities and spongy foci. Microscopically, entire regions were devoid of neurons, granular cells in the cerebellum, Golgi cells and Purkinje cells. Extensive investigations of congenital Minamata disease (children of exposed women) were undertaken, and 20 cases that occurred over a 4-year period were documented. In all instances the congenital cases showed a higher incidence of symptoms than did the cases wherein exposure occurred as an adult. Severe disturbances of nervous function were described, and the affected offspring were very late in reaching developmental milestones. Hair concentrations of mercury in affected infants ranged from 10 to 100 μg/g (Harada, 1995; 1997; Tsubaki and Takahashi, 1986; WHO/IPCS, 1990). In addition, later studies of patients with Minamata disease reported increased pain thresholds (an adverse effect) in the body and distal extremities (Yoshida *et al.*, 1992).

Symptoms and health effects of Minamata disease

The symptoms of Minamata disease include:

- sensory disorders in the four extremities (loss of sensation in the hands and feet);
- ataxia (difficulty in coordinating movement of hands and feet);
- narrowing of the field of vision;
- hearing impairment;
- impairment of faculties for maintaining balance;
- speech impediments;
- trembling of hands and feet; and
- disorders of the ocular movement.

In very severe cases, victims fall into a state of madness, lose consciousness and may even die. In relatively mild cases, the condition is barely distinguishable from other ailments such as headache, chronic fatigue and generalized inability to distinguish taste and smell.

When the first outbreaks of Minamata disease occurred, most patients exhibited a full set of severe symptoms. In 16 cases, the patient died within 6 months of the onset of symptoms, and in 1965 the mortality was 44.3 percent. Since then a large number of incomplete or mild cases, displaying an incomplete set of symptoms, have also been identified. (Minamata City, 2000)

Methylmercury poisoning in Minamata Bay, Japan

During the 1960/70's, the Minamata Bay mercury pollution problem received world-wide media attention, opening the world's eyes to the negative health effects of methylmercury and contributing to raising public awareness of the importance of environmental protection.

More than forty years ago, Minamata Bay in Japan was seriously polluted by wastewater containing methylmercury, formed as a by-product in the acetaldehyde synthesizing process of the local acetaldehyde chemical plant; 70-150 metric tons or more of mercury, mixed in the effluents from the factory, were discharged over a number of years into the Bay. The pollution affected the people of Minamata in the form of methylmercury poisoning, referred to as "Minamata disease", causing damage to the central nervous system in people eating large quantities of contaminated fish and shellfish from Minamata Bay. In addition, Congenital Minamata disease occurred, in which victims were born with a condition resembling cerebral palsy, caused by methylmercury poisoning of the fetus via the placenta when the mother consumed contaminated seafood during pregnancy. The disease, which was officially recognized on 1 May 1956, severely affected the local community and was a great burden to the city. Many people lost their lives or suffered from physical deformities and have had to live with the physical and emotional pain of "Minamata Disease" since.

After the cause of the disease was finally confirmed, a number of measures were gradually implemented to deal with the problems arising from the mercury pollution, ranging from regulation of the factory effluent, voluntary restrictions on harvesting of fish and shellfish from the Bay, installation of dividing nets in order to enclose the mouth of the Bay and prevent the spread of contaminated fish, to dredging of mercury-containing sediments in the Bay and appropriate deposit to contain the mercury-contaminated sludge. Finally, in October 1997, the dividing nets that had closed off the bay for 23 years were removed. After several studies confirming that mercury levels in fish were below regulatory levels and had remained so for three years, Minamata Bay was reopened as a general fishing zone and the Minamata Fisheries Co-op recommenced harvesting for the fish market (Minamata City, 2000).

The National Institute for Minamata Disease was formed to investigate the impacts of mercury contamination, and has contributed substantially to the knowledge of mercury toxicology and exposure both nationally and in other regions of the world since then.

The Ministry of Environment of Japan, in its report "Our Intensive Efforts to Overcome the Tragic History of Minamata Disease (JME, 1997)" concludes:
"From the incidence of Minamata Disease, Japan has learned a very important lesson on how activities that place priority on the economy, but lack consideration for the environment can cause grave damage to health and environment, and how it is difficult to recover from this damage later on. From the purely economic standpoint, too, a large amount of cost and a great deal of time are required to deal with such damages, and, when we compare these costs incurred vs. the cost of the measures that could have prevented the pollution, allowing such pollution is certainly not an economically advisable option. In our country, with the experience of suffering from disastrous damage by pollution including the Minamata Disease as a turning point, measures to protect the environment have made dramatic progress. But the sacrifices incurred on the way were truly huge, indeed. We sincerely hope that Japan's experience can be utilized as a vital lesson by other countries, that consideration is paid to the importance of the environment, and that pollution will be prevented without ever undergoing this kind of tragic pollution-related damage."

218. Several neurological signs and symptoms are among the cardinal features of high-dose exposures to methylmercury in adults. As no specific medical test is available to confirm the diagnosis of Minamata disease, cases were identified on the basis of a characteristic combination of symptoms (Harada, 1997; Uchino *et al.*, 1995). These included peripheral neuropathy, dysarthria, tremor, cerebellar ataxia, gait disturbance, visual-field constriction and disturbed ocular movements, hearing loss, disturbance of equilibrium, and subjective symptoms such as headache, muscle and joint pain, forgetfulness, and fatigue. Based on the assessment conducted by WHO/IPCS (1990), paresthesias in five percent of the adult population were judged to occur at hair mercury concentrations above 50 µg/g or blood mercury concentrations above 200 µg/l (WHO/IPCS, 1990). Later research provides some evidence of effects at lower concentrations on adults, see Lebel *et al.* (1998) below.

219. The predominant symptom noted in adults in the 1971 Iraqi poisoning incident was paresthesia, and it usually occurred after a latent period of from 16 to 38 days. In adults symptoms were dose-dependent, and among the more severely affected individuals ataxia, blurred vision, slurred speech and hearing difficulties were observed (Bakir *et al.*, 1973). Signs noted in the infants exposed during fetal development included cerebral palsy, altered muscle tone and deep tendon reflexes, as well as delayed developmental milestones. The mothers experienced paresthesia and other sensory disturbances but at higher doses than those associated with their children exposed *in utero* (during mothers pregnancy; Bakir *et al.*, 1973; WHO/IPCS, 1990; Al-Mufti *et al.*, 1976).

Mercury poisoning incidents in Iraq

Methyl- and ethylmercury poisonings occurred in Iraq following consumption of seed grain that had been treated with fungicides containing these alkylmercury compounds. The first outbreaks were caused by ethylmercury, and occurred in 1956 and 1959-1960, and about 1000 people were adversely affected. The second outbreak was caused by methylmercury and occurred in 1972. The number of people admitted to the hospital from the second outbreak with symptoms of poisoning has been estimated to be approximately 6,500, with 459 fatalities reported. Imported mercury-treated seed grains arrived after the planting season and were subsequently used as grain to make into flour that was baked into bread. Unlike the long-term exposures in Japan, the epidemic of methylmercury poisoning in Iraq was short in duration, but the magnitude of the exposure was high. Because many of the people exposed to methylmercury in this way lived in small villages in very rural areas (and some were nomads), the total number of people exposed to these mercury-contaminated seed grains is not known.

220. Lebel *et al.* (1998) found that abnormal performance on the Branches Alternate Movement Task (BAMT) was significantly associated with all measures of mercury exposure in adults from an Amazonian village, and abnormal visual fields were associated with mean and peak hair mercury concentrations. The authors state that the dose-related decrements in visual and motor functions were associated with hair mercury concentrations below 50 μg/g, a range in which clinical signs of mercury intoxication are not apparent. [1]

3.2.2 Cancer (neoplastic effects)

221. Studies were conducted on causes of death in populations in Minamata, Japan, with high exposures to methylmercury. The only clear indication of an increased cancer risk was in the most informative of these studies, in which excess mortality from cancer of the liver and of the oesophagus was found in the area with the highest exposure, together with an increased risk for chronic liver disease and cirrhosis. Consumption of alcoholic beverages was known to be higher than average in the area (IARC, 1993).

222. A cohort study of individuals in Sweden with a licence for seed disinfection with mercury compounds and other agents found no excess of brain cancer. Of the three Swedish case-control studies on exposure to mercury seed dressings and soft-tissue sarcomas, only one showed an odds ratio above unity. In all three studies the confidence intervals included unity. For malignant lymphomas, there was a slightly but nonsignificantly elevated odds ratio for exposure to mercury seed dressings, but other exposures had higher odds ratios and consequently, potential confounding factors (IARC, 1993).

223. Methylmercury chloride caused renal tumours in several studies in mice exposed through the diet, but not in rats. IARC judged that there is sufficient evidence for carcinogenicity of methylmercury

[1] The USA, in their comments to the first draft of this report (comm-24-gov), comment that in the Amazonian population, concurrent or previous exposure to metallic mercury vapour could not be entirely ruled-out, and there were other problems with nutrition, parasitism, and possible nutritional deficiencies in that population. Therefore, according to the US comments, other factors may have contributed to the neurological deficits reported; and the hair mercury concentration may thus be an inappropriate index for full attribution of the observed neurotoxicity.

chloride in experimental animals. In its overall evaluation for methylmercury compounds, where other relevant data were taken into consideration when making the overall evaluation, it concluded that methylmercury compounds are possibly carcinogenic to humans (group 2B) (IARC, 1993).

3.2.3 Renal effects (kidneys)

224. Renal toxicity has rarely been reported following human exposure to organic forms of mercury. The only evidence of a renal effect following ingestion of mercury-contaminated fish comes from a death-certificate review conducted by Tamashiro *et al.* (1986). They evaluated causes of death among residents of a small area of Minamata City that had the highest prevalence of Minamata disease using age-specific rates for the entire city as a standard. Between 1970 and 1981, the number of deaths attributed to nephritic diseases was higher than expected among women who resided in that region (mortality rate "SMR", 2.77; 95% CI, 1.02 – 6.02), but was within the expected range (mortality rate "SMR", 0.80; 95% CI, 0.17 – 2.36) among men who resided in this region.

3.2.4 Cardiovascular effects (heart and blood system)

225. Jalili and Abbasi (1961) described ECG (heart function) abnormalities in severely poisoned patients hospitalized during the Iraqi grain ethylmercury poisoning epidemic, and similar findings were reported in four family members who consumed ethylmercury-contaminated pork (Cinca *et al.*, 1979). Salonen *et al.* (1995) compared dietary intake of fish and mercury concentrations in hair and urine with the prevalence of acute myocardial infarction (AMI) and death from coronary heart disease or cardiovascular disease in a cohort of 1,833 Finnish men. Dietary mercury intake ranged from 1.1 to 95.3 µg per day (mean 7.6 µg per day). Over a 7-year observation period, men in the highest tertile (at or more than 2 µg/g) of hair mercury content had a two-fold higher risk (1.2 – 3.1) of AMI than men in the two lowest tertiles. A later follow-up (Rissanen *et al.*, 2000) showed a protective effect of omega-3 fatty acids with respect to acute coronary disease, which was, however, less evident in those with hair mercury at or above 2 µg/g. The authors concluded that a high mercury content in fish could reduce the protective effect of these fatty acids. A recent study by Sørensen *et al.* (1999) showed an association between prenatal exposure to methylmercury and cardiovascular function at age 7 in the children from the Faroe Islands, though this study was based on a single measurement per subject of blood pressure, with accompanying high uncertainty. Diastolic and systolic blood pressures increased by 13.9 and 14.6 mmHg, respectively, as cord-blood mercury concentrations rose from 1 to 10 µg/l. In boys, heart-rate variability, a marker of cardiac autonomic control, decreased by 47 percent as cord-blood mercury concentrations increased from 1 to 10 µg/l.

226. These studies suggest that even small increases in methylmercury exposures may cause adverse effects on the cardiovascular system, thereby leading to increased mortality. Given the importance of cardiovascular diseases worldwide, these findings need close attention and additional follow-up.

3.2.5 Genotoxicity

227. Skervfing (1974) found limited support for an association between chromosomal aberations and mercury in red blood cells in subjects consuming large amounts of contaminated freshwater fish. Wulf *et al.* (1986) reported an increased prevalence of sister chromatid exchange in humans who ate mercury-contaminated seal meat. However, information on smoking status and exposure to other heavy metals was not provided for those individuals, making interpretation of the study difficult. No increase in the frequency of sister chromatid exchange or numerical chromosomal alterations was detected in 16 subjects who ate fish caught from a methylmercury contaminated area in Colombia as compared to 14 controls (Monsalve and Chiappe, 1987). More recently, Franchi *et al.* (1994) reported a correlation between the prevalence of micronuclei in peripheral lymphocytes and blood mercury concentrations in a population of fishermen who had eaten mercury-contaminated seafood.