

3 Toxicology

3.1 Overview

195. The toxicity of mercury depends on its chemical form, and thus symptoms and signs are rather different in exposure to elemental mercury, inorganic mercury compounds, or organic mercury compounds (notably alkylmercury compounds such as methylmercury and ethylmercury salts, and dimethylmercury). The sources of exposure are also markedly different for the different forms of mercury. For alkylmercury compounds, among which methylmercury is by far the most important, the major source of exposure is diet, especially fish and other seafood. For elemental mercury vapour, the most important source for the general population is dental amalgam, but exposure at work may in some situations exceed this by many times. For inorganic mercury compounds, diet is the most important source for the majority of people. However, for some segments of populations, use of skin-lightening creams and soaps that contain mercury and use of mercury for cultural/ritualistic purposes or in traditional medicine, can also result in substantial exposures to inorganic or elemental mercury.

196. While it is fully recognised that mercury and its compounds are highly toxic substances for which potential impacts should be considered carefully, there is ongoing debate on how toxic these substances, especially methylmercury, are. New findings during the last decade indicate that toxic effects may be taking place at lower concentrations than previously thought, and potentially larger parts of the global population may be affected. As the mechanisms of subtle toxic effects – and proving whether such effects are taking place – are extremely complex issues, a complete understanding has so far not been reached on this very important question.

Methylmercury

197. Of the organic mercury compounds, methylmercury occupies a special position in that large populations are exposed to it, and its toxicity is better characterized than that of other organic mercury compounds. Within the group of organic mercury compounds, alkylmercury compounds (especially ethylmercury and methylmercury) are thought to be rather similar as to toxicity (and also historical use as pesticides), while other organic mercury compounds, such as phenylmercury, resemble more inorganic mercury in their toxicity.

198. Methylmercury is a well-documented neurotoxicant, which may in particular cause adverse effects on the developing brain. Moreover, this compound readily passes both the placental barrier and the blood-brain barrier, therefore, exposures during pregnancy are of highest concern. Also, some 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, although yet to be confirmed, suggest that methylmercury exposures need close attention and additional follow-up. Moreover, methylmercury compounds are considered possibly carcinogenic to humans (group 2B) according to the International Agency for Research on Cancer (IARC, 1993), based on their overall evaluation.

Elemental mercury and inorganic mercury compounds

199. The main route of exposure for elemental mercury is by inhalation of the vapours. About 80 percent of inhaled vapours are absorbed by the lung tissues. This vapour also easily penetrates the blood-brain barrier and is a well-documented neurotoxicant. Intestinal absorption of elemental mercury is low. Elemental mercury can be oxidized in body tissues to the inorganic divalent form.

200. Neurological and behavioral disorders in humans have been observed following inhalation of elemental mercury vapour. Specific symptoms include tremors, emotional lability, insomnia, memory loss, neuromuscular changes, and headaches. In addition, there are effects on the kidney and thyroid.

High exposures have also resulted in death. With regard to carcinogenicity, the overall evaluation, according to IARC (1993), is that metallic mercury and inorganic mercury compounds are not classifiable as to carcinogenicity to humans (group 3). A critical effect on which risk assessment could be based is therefore the neurotoxic effects, for example the induction of tremor. The effects on the kidneys (the renal tubule) should also be considered; they are the key endpoint in exposure to inorganic mercury compounds. The effect may well be reversible, but as the exposure to the general population tends to be continuous, the effect may still be relevant.

Summary of effect levels

201. This chapter gives a brief presentation of the different adverse effects on human health from elemental (and inorganic) mercury, as well as methylmercury. To put the level of exposures for methylmercury in perspective, for the most widely accepted non-lethal adverse effect (neurodevelopmental effects), the United States (US) National Research Council (NRC, 2000) has estimated the benchmark dose (BMD) 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 (Grandjean *et al.*, 1997). This BMD level is the lower 95% confidence limit for the exposure level that causes a doubling of a 5% prevalence of abnormal neurological performance (developmental delays in attention, verbal memory and language) in children exposed *in-utero* in the Faroe Islands study. These are the tissue levels estimated to result from an average daily intake of about 1 µg methylmercury per kg body weight per day (1 µg/kg body weight per day).

202. Other adverse effects have been seen in humans with less reliability or at much higher exposures. For methylmercury, effects have been seen on the adult nervous system, on cardiovascular disease, on cancer incidence and on genotoxicity. Also, effects have been reported on heart rate variability and blood pressure in 7 year-old children exposed prenatally, and on cardiovascular mortality in adults. For elemental mercury and inorganic mercury compounds, effects have been seen on: the excretion of low molecular weight proteins; on enzymes associated with thyroid function; on spontaneous abortion rates; genotoxicity; respiratory system; gastrointestinal (digestion) system; liver; immune system; and the skin. Several detailed evaluations of response as a function of exposure that have been conducted are reviewed in Chapter 4. As this report presents the toxicity of mercury in summary only, the reviews, which the presentation was based on, have not been checked in the original references for correct quoting during the preparation of this report.

Dietary considerations

203. Fish are an extremely important component of the human diet in many parts of the world and provide nutrients (such as protein, omega-3 fatty acids and others) that are not easily replaced. Mercury is a major threat to this food supply. Certainly, fish with low methylmercury levels are intrinsically more healthful for consumers than fish with higher levels of methylmercury, if all other factors are equal.

204. There is limited laboratory evidence suggesting that several dietary components might reduce (e.g. selenium, vitamin E, omega-3 fatty acids) or enhance (e.g. alcohol) mercury's toxicity for some endpoints. However, conclusions cannot be drawn from these data at this time.

Explanation of some of the medical terms used in this chapter

Albuminuria: Albuminuria is a form of proteinuria.

Anaemia: Condition in which the number of red blood cells per unit volume of blood is decreased from normal, resulting in decreased oxygen-carrying capacity of the blood.

Ataxia: Wobbliness. Incoordination and unsteadiness due to the brain's failure to regulate the body's posture and regulate the strength and direction of limb movements.

Atrophy of the brain: Shrinkage/loss/waste of the brain.

Cardiovascular effect: Effect on the circulatory system, comprising the heart and blood vessels.

Cerebellar ataxia: Ataxia (see above) due to disease of the cerebellum.

Cerebrovascular: Related to blood vessels of the brain.

Creatinine: A chemical waste molecule that is generated from muscle metabolism and excreted in the urine. The concentration of creatinine in serum is used as a measure for the function of the kidneys. Mercury concentrations measured in urine samples are sometimes presented on the basis of the creatinine contents in the same urine sample (μg mercury/g creatinine) – rather than per volume of urine (μg mercury/l) – in order to eliminate the variation in water contents in urine.

Cystic cavities and spongy foci: Tissue abnormality with holes and spongy areas.

Diastolic and systolic blood pressures: Diastolic blood pressure is the pressure when the heart is extending (dilating) and filled with blood. Systolic blood pressure when the heart is contracting. (A blood pressure of 140/90 means that the systolic blood pressure is 140 and the diastolic blood pressure 90).

Dysarthria: Speech that is characteristically slurred, slow, and difficult to produce (and understand). The person with dysarthria may also have problems controlling the pitch, loudness, rhythm and voice qualities of their speech.

Glomerular proteinuria: Proteinuria (see below) due to dysfunction of the renal glomerulus (unit of the kidney).

Glomerulonephritis: A variety of nephritis (inflammation of the kidney) characterised by inflammation of the capillary loops in the glomeruli of the kidney. (The glomerulus is a functional unit of the kidney).

Interstitial pneumonitis: A form of pneumonia which involves the interstitial tissues (connective tissue) of the lung.

Ischemia: Local anaemia due to obstruction of the blood supply (e.g., narrowing of the arteries).

Ischemic heart disease: Heart disease because of local anaemia.

Micronuclei in peripheral lymphocytes: Small cell nucleus in the peripheral white blood cells.

Neoplastic effect: Has the effect of creating new cells that grow autonomously. A neoplasm is new and abnormal growth of tissue, which can be benign or malign (cancerous).

Nephritic/nephrotic syndrome: A disease of the kidneys that results in inflammation of the glomerulus (the portion of the kidney that filters the blood). A type of nephritis that is characterised by low serum albumin, large amount of protein in the urine and swelling (oedema).

Nephritis: Inflammation of the kidneys.

Nephrosis: Non-inflammatory, non-neoplastic disease of the kidney.

Paresthesia: An abnormal sensation, such as burning, pricking, tingling, or numbness that appears to have no objective cause.

Peripheral neuropathy: Degeneration of peripheral nerves (peripheral nerves are all nerves except the brain and the spinal cord).

Pneumonitis: Inflammation of the lungs secondary to viral or bacterial infection.

Proteinuria: More protein in the urine than normal (normal excretion is 150mg protein daily).

Renal tubule: Small structures in the kidney that filter the blood and produce the urine.

Stomatitis: Infection of the mucous membrane (the inside) of the mouth.

Tachycardia: A rapid heart rate, usually defined as greater than 100 beats per minute.

Tubular proteinuria: More protein in the urine than normal due to dysfunction of the renal tubules.

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 mackerel, 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 authoritative 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 re-opened 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 aberrations 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.

3.3 Elemental and inorganic mercury

228. While many sources of elemental mercury exist, a major exposure route of elemental mercury is dental amalgam. Other exposures to this mercury species are considered in general decline in Europe and most likely also in many other OECD countries. In these regions, methylmercury is considered the remaining exposure of most importance to humans. The national submissions to UNEP for this assessment indicate however that the exposures to elemental and inorganic mercury from local pollution, occupational exposure, certain cultural and ritualistic practices, and some traditional medicines may vary considerably between countries and regions in the world, and that these exposures are significant in some areas.

229. The following presentation of toxic effects of elemental and inorganic mercury is based on a presentation prepared by Pirrone *et al.* (2001), and was edited slightly for this report. Pirrone *et al.* (2001), mention that their presentation was largely based on previous reviews by WHO (WHO/IPCS, 1990; 1991), IARC (IARC, 1993), and US EPA (US EPA, 1997; 2001b). Also, some information was obtained from the recent IPCS report (WHO/IPCS, 2002).

230. Signs and symptoms observed in mercury vapour poisoning differ depending on the level and duration of exposure. Most studies have been performed in occupationally exposed subjects, but there are also some data from accidents in the general population, and on low-level exposure from dental amalgams. The latter subject has been widely discussed and reviewed (US Public Health Service, 1993; Clarkson, 2002; WHO/IPCS, 2002).

3.3.1 Neurological effects

231. As reviewed by the US EPA (1997), the reports from accidental exposures to high concentrations of mercury vapours (Aronow *et al.*, 1990; Fagala and Wigg, 1992; Taueg *et al.*, 1992), as well as studies of populations chronically exposed to potentially high concentrations (Ehrenberg *et al.*, 1991; Roels *et al.*, 1982; Sexton *et al.*, 1978) have shown effects on a wide variety of cognitive, sensory, personality and motor functions. In general, symptoms have been observed to subside after removal from exposure. However, persistent effects (tremor, cognitive deficits) have been observed in occupationally exposed subjects 10-30 years after cessation of exposure (Albers *et al.*, 1998; Kishi *et al.*, 1993; Mathiesen *et al.*, 1999; Letz *et al.*, 2000).

232. Studies of workers exposed to elemental mercury vapour have reported a clear increase in symptoms of disfunction of the central nervous system at exposure levels greater than 0.1 mg/m^3 (Smith *et al.*, 1970) and clear symptoms of mercury poisoning at levels resulting in urinary mercury greater than $300 \text{ } \mu\text{g}$ in a 24-hour urine sample (Bidstrup *et al.*, 1951). Several studies, however, have shown evidence of neurotoxicity at approximately 2- to 4-fold lower concentrations. Self-reported memory disturbances, sleep disorders, anger, fatigue, and/or hand tremors were increased in workers chronically exposed to an estimated air concentration of 0.025 mg/m^3 (approximately equal to urinary and blood mercury levels of about $25 \text{ } \mu\text{g/g}$ and $10 \text{ } \mu\text{g/l}$) (Langworth *et al.*, 1992), but not in a recent study with somewhat lower exposure levels, urinary mercury 10-15 $\mu\text{g/g}$ (Ellingsen *et al.*, 2001).

233. Objective measures of cognitive and/or motor function in exposed populations have shown significant differences from unexposed controls (Ehrenberg *et al.*, 1991; Liang *et al.*, 1993; Roels *et al.*, 1982). In the study by Langworth *et al.* (1992), there were, however, no objective findings in neuropsychological tests or tremor recordings. This was also mainly the case in the study by Ellingsen *et al.* (2001), although there were possibly some exposure-related effects. Tremor was reported at long-term exposure to relatively low concentrations of mercury vapour (Fawer *et al.*, 1983; Chapman *et al.*, 1990), and mild tremor may constitute an early adverse effect (Biernat *et al.*, 1999; Netterstrøm *et al.*, 1996). Several studies failed, however, to show an increase of tremor at low-level exposure (Roels *et al.*, 1989; Langworth *et al.*, 1992; Ellingsen *et al.*, 2001).

234. In a recent assessment of all studies on the exposure-response relationship between inhaled mercury vapour and adverse health effects, IPCS concluded that several studies consistently demon-

strate subtle effects on the central nervous system in long-term occupational exposures to mercury vapour at exposure levels of approximately 20 µg/m³ or higher (WHO/IPCS, 2002).

3.3.2 Renal effects (kidneys)

235. The kidney is, together with the central nervous system, a critical organ for exposure to mercury vapour. Elemental mercury can be oxidized in body tissues to the inorganic divalent form. The kidney accumulates this inorganic mercury to a larger extent than most other tissue with concentrations in occupationally unexposed groups typically of 0.1 – 0.3 µg/g (Drasch *et al.*, 1996; Barregard *et al.*, 1999; Hac *et al.*, 2000; Falnoga *et al.*, 2000). The critical kidney mercury concentration is not known, but levels in subjects with ongoing occupational exposure may be about 25 µg/g (Kazantzis *et al.*, 1962; Borjesson *et al.*, 1995; Barregard *et al.*, 1999).

236. High exposure may cause (immune-complex mediated) glomerulonephritis with proteinuria and nephritic syndrome. This has been shown at occupational exposures (Kazantzis, 1962; Tubbs *et al.*, 1982), as well as after use of mercury-containing ointment or skin-lightening creams (Becker *et al.*, 1962; Kibukamusoke *et al.*, 1974), but the reported cases are relatively few. Therefore, a specific genetic susceptibility is probably needed for a frank nephritis to develop. For a review, see Eneström and Hultman (1995).

237. More common at high exposure is proteinuria, glomerular (albumin) as well as tubular (low molecular weight proteins). Albuminuria is, however, generally not seen at exposure levels resulting in urinary mercury below 100 µg/g creatinine (Buchet *et al.*, 1980; Roels *et al.*, 1982; 1989; Langworth *et al.*, 1992; Barregard *et al.*, 1997; Ellingsen *et al.*, 2000).

238. Effects on the renal tubules, as demonstrated by increased excretion of low molecular proteins, have been shown at low-level exposure, and may constitute the earliest biological effect. This effect was previously shown at occupational exposure with urinary mercury of about 35 µg/g creatinine, equivalent to long-term exposure to air levels of 25-30 µg/m³ (Barregard *et al.*, 1988; Langworth *et al.*, 1992; Cardenas *et al.*, 1993). In a recent report by Ellingsen *et al.* (2000), such an effect was also shown in workers with urinary mercury of about 10 µg/g creatinine. Ongoing research (Wastensson G, personal communication, 2001, as quoted by Pirrone *et al.*, 2001) appears to support the finding of low-level effects in Swedish chlor-alkali workers at levels in the range of 5 µg/g creatinine, which is only slightly higher than that found in the general population. On the other hand, the possible long-term implications of tubular proteinuria are still unclear (Jarup *et al.*, 1998). For example, Ellingsen *et al.* (1993a) have suggested that some renal effects may be reversible after a long enough period of time, and Frumkin *et al.* (2001) have concluded from their research that “no strong associations were demonstrated with neurological or renal function or with porphyrin excretion.”

239. Among male European mercury miners an increased mortality was observed from nephritis and nephrosis (mortality rate “SMR” 1.55, 95 % CI 1.13-2.06) (Boffetta *et al.*, 2001), whereas this was not shown among chlor-alkali workers (Barregard *et al.*, 1990; Ellingsen *et al.*, 1993).

240. The IPCS recently concluded (WHO/IPCS, 2002), based on existing studies, that adverse effects on the kidney usually occur at exposures higher than those inducing neurophysiological effects. Also, although a large number of serious and even fatal intoxications (often suicides or suicide attempts) have been described after ingestion of inorganic mercury compounds, data from humans does not allow identification of lowest harmful or non-adverse exposure levels, especially in long-term exposure. From studies on experimental animals, a No-Adverse-Effect Level (NOAEL) of 0.23 mg/kg per day was identified (US ATSDR, 1999; WHO/IPCS, 2002).

3.3.3 Cancer (neoplastic effects)

241. Data on the carcinogenicity of metallic mercury and its inorganic compounds mainly come from studies on cancer occurrence in occupational populations, including dentists, nuclear weapon

manufacturers, chlor-alkali workers and miners. Previous data are summarized in reviews (IARC, 1993; Boffetta *et al.*, 1993).

242. In 1993, IARC evaluated metallic mercury and inorganic mercury compounds and found that there was inadequate evidence in experimental animals for carcinogenicity of metallic mercury and limited evidence in experimental animals for carcinogenicity of mercuric chloride. In its overall evaluation, it concluded that metallic mercury and inorganic mercury compounds are not classifiable (group 3) with respect to carcinogenicity in humans (IARC, 1993).

243. Citing a number of studies of occupational mercury exposure, including studies done after the IARC evaluation in 1993, Pirrone *et al.* (2001) concludes that lung cancer is the only cancer form, which seems to be consistently increased among various groups of workers exposed to metallic and inorganic mercury. The main difficulty in the interpretation of the data on lung cancer is the possible co-exposure to other lung carcinogens, in particular arsenic (in the fur industry), radon and silica (among miners). An additional limitation is the almost universal lack of data on tobacco smoking. The fact that no increase was found in a large group of European mercury miners not exposed to quartz (Boffetta *et al.*, 1998) argues against the hypothesis that mercury vapour may cause lung cancer. There is no suggestion of a consistent increase of any other neoplasm, including brain and kidney cancers, in these populations.

3.3.4 Respiratory effects

244. Respiratory toxicity in humans following exposure to elemental mercury vapours has been characterized by pulmonary edema and congestion, coughing, interstitial pneumonitis and respiratory failure (Bluhm *et al.*, 1992; Taueg *et al.*, 1992; WHO/IPCS, 1991). Barregard *et al.* (1990) and Ellingsen *et al.* (1993) found no associations between mortality from respiratory disease and mercury exposure among workers exposed to mercury in the chlor-alkali industry, although the power of the studies were low. Merler *et al.* (1994) found no excess mortality of respiratory disease in men (mortality rate “SMR”, 0.67; 95% CI, 0.35 – 1.14) exposed to mercury in the fur hat industry. This was also true for mercury miners, except for pneumoconiosis (Boffetta *et al.*, 2001).

3.3.5 Cardiovascular effects (heart and blood system)

245. Signs of cardiovascular toxicity in humans after acute exposure to elemental mercury include tachycardia, elevated blood pressure and heart palpitations (Bluhm *et al.*, 1992; Snodgrass *et al.*, 1981; Soni *et al.*, 1992, Wossmann *et al.*, 1999). Intermediate-duration exposure to elemental mercury vapours produced similar effects (i.e., tachycardia and elevated blood pressure) (Fagala and Wigg, 1992; Foulds *et al.*, 1987). Piikivi (1989) demonstrated a positive correlation between heart palpitations and urinary mercury concentrations in workers from a chlor-alkali plant but also “found only a tendency for a subtle reduction of cardiovascular reflex responses and a slight increase of subjective symptoms, but no significant autonomic dysfunction associated with the low levels of exposure.” Nevertheless, it is unclear from the available scientific literature whether the effects on cardiovascular function are due to direct cardiac toxicity or to indirect toxicity (e.g., due to effects on neural control of cardiac function) of elemental mercury. Barregard *et al.* (1990) showed that Swedish chlor-alkali workers had increased mortality due to ischemic heart disease and cerebrovascular disease. However, there were no such findings in Norwegian chlor-alkali workers (Ellingsen *et al.*, 1993a). Nonetheless, the IPCS (2003) and US ATSDR (1999) have recently reported that acute inhalation exposure to high concentrations of elemental mercury vapour from the heating of elemental/inorganic mercury resulted in increased blood pressure and palpitations. Exposures of longer durations due to spills or occupational exposures have also been reported to result in increased blood pressure and increased heart rate (WHO/IPCS, 2002; US ATSDR, 1999).

246. Among European mercury miners, increased mortality from hypertension (SR 1.46, 95 % CI 1.08-1.93) and from heart diseases (other than ischemic disease) have been reported (mortality rate “SMR”, 1.36, 95 % CI 1.20-1.53), and these effects increased with time since first employment and

with estimated cumulative mercury exposure. But, findings were not consistent among countries. Also, no increase was shown for ischemic heart disease or cerebrovascular diseases (Boffetta *et al.*, 2001).

247. Statistically significant increases of approximately 5 mmHg in both systolic and diastolic blood pressure were found in 50 volunteers with dental amalgam when compared to an age- and sex-matched control group (average age approximately 22 years) without mercury amalgam fillings. Potential confounding differences between the two groups, such as life-style and body mass, were not discussed. Significantly decreased hemoglobin and hematocrit, and increased mean corpuscular hemoglobin concentration were also found compared to controls without dental amalgams (Siblerud, 1990, as cited in WHO/IPCS, 2002).

3.3.6 Gastrointestinal (digestive system) and hepatic (liver) effects

248. The most common sign of frank mercury poisoning is stomatitis, which is usually reported following acute, high concentration exposure to elemental mercury vapours (Bluhm *et al.*, 1992; Snodgrass *et al.*, 1981). Other commonly reported gastrointestinal effects include nausea, vomiting, diarrhea and abdominal cramps (Bluhm *et al.*, 1992; Lilis *et al.*, 1985; Sexton *et al.*, 1978; Snodgrass *et al.*, 1981; Vroom and Greer, 1972). However, no increased mortality from the digestive system was observed in European mercury miners (Boffetta *et al.*, 2001).

3.3.7 Effects on the thyroid gland

249. The thyroid may accumulate mercury with continued exposure to elemental mercury (Kosta *et al.*, 1975; WHO/IPCS, 1991; Falnoga *et al.*, 2000). It has been shown that moderate occupational exposure affects a particular enzyme system in the thyroid at urinary mercury levels of 15-30 µg/g creatinine – the same levels as those associated with reports of minor effects on the central nervous system and the kidneys (Barregard *et al.*, 1994; Ellingsen *et al.*, 2000). A recent study (Ellingsen *et al.*, 2000) compared thyroid function in 47 chlor-alkali workers exposed to mercury vapours for an average of 13.3 years with 47 “referents.” The median serum concentration of reverse triiodothyronine (T3) was statistically significantly higher in the exposed group compared to the referents. Also, the free thyroxine (T4)/free T3 ratio was higher in the highest exposed subgroups compared with referents. The enzyme deiodinase responsible for the deiodination of thyroxine (T4) to triiodothyronine (T3), a seleno-enzyme, seems to be affected. However, Ellingsen *et al.* (2000) also reported that the “overall function of the thyroid gland as assessed by measuring TSH and the thyroid hormones appears to be maintained in the workers exposed to low levels of elemental mercury.”

3.3.8 Effects on the immune system

250. The ability of mercury to induce immune-mediated disease has been thoroughly investigated in mice and rats experimentally exposed to inorganic mercury compounds, in most studies divalent mercury, but also mercury vapour. The type of response depends on the strains, some of them being susceptible to autoimmune disease and some being resistant. It is therefore assumed that the genotype is probably important also for the potential immunological effects in humans. For a review, see Eneström and Hultman (1995) and Sweet and Zelikoff (2000). Some studies in humans occupationally exposed to moderate levels of elemental mercury reported changes in biochemistry of the immune response system (see Pirrone *et al.*, 2001).

3.3.9 Effects on the skin (dermal)

251. Exposure to elemental mercury vapours for acute or intermediate duration may result in a response known as acrodynia or “pink disease”, which is characterized by peeling palms of hands and soles of feet, excessive perspiration, itching, rash, joint pain and weakness, elevated blood pressure and tachycardia (Fagala and Wigg, 1992; Karpathios *et al.*, 1991; Schwartz *et al.*, 1992). Also, rash and stomatitis have been reported after high inhalation exposures (Bluhm *et al.*, 1992; Barregard *et al.*, 1996).

3.3.10 Reproductive and developmental effects

252. A study of the pregnancies of Polish dental professionals showed a high frequency of malformations of a nonspecified nature (Sikorski *et al.*, 1987). In contrast, a study of Swedish dental professionals found no increases in malformations, abortions, or stillbirths (Ericsson and Källén, 1989). An increase in low birth weight infants was noted in the offspring of female dental nurses (Ericsson and Källén, 1989); however, in this same study similar effects were not observed for either dentists or dental technicians, and socioeconomic factors may have contributed to the effects observed.

253. Studies of occupational exposure indicate that exposure to elemental mercury may affect human reproduction. Possible effects are increased spontaneous abortions, congenital anomalies, and reduced fertility among women.

254. In occupational exposure studies, paternal exposure to metallic mercury does not appear to cause infertility or malformations (Alcser *et al.*, 1989; Lauwerys *et al.*, 1985). However, a study of pregnancy outcomes among the wives of 152 mercury-exposed men revealed an increased incidence of spontaneous abortions (Cordier *et al.*, 1991). Preconception paternal urinary mercury concentrations above 50 µg/l were associated with a doubling of the spontaneous abortion risk. Elghancy *et al.* (1997) compared the pregnancy outcomes of 46 mercury-exposed workers to those of 19 women who worked in nonproduction areas of the same factory. Women exposed to inorganic mercury had a higher rate of births with congenital anomalies. Concentrations were up to 0.6 mg/m³.

255. However, no significant differences in stillbirths or miscarriage rates were noted between the two groups of women. Also, no increase in spontaneous abortions was observed among dental assistants (potentially exposed to mercury vapour) in a historical prospective study of pregnancy outcomes among women in 12 occupations (Heidam, 1984). Similarly, no relationship between the amalgam fillings prepared per week and rate of spontaneous abortions or congenital abnormalities was observed in a postal survey in California (Brodsky *et al.*, 1985). No excess in the rate of still births or congenital malformations was observed among 8,157 infants born to dentists, dental assistants, or technicians, nor were the rates of spontaneous abortions different from the expected values (Ericsson and Källén, 1989). Rowland *et al.* (1994), however, found that the probability of conception among female dental hygienists who prepared more than 30 amalgams per week and had at least five poor hygiene practices when handling mercury was only 63 percent of that among unexposed controls. Women with lower exposures, however, were more fertile than unexposed controls. A large study conducted in Norway compared reproductive success rates among 558 female dental surgeons with those of 450 high-school teachers (Dahl *et al.*, 1999). They concluded that exposure to mercury, benzene, and chloroform was not associated with decreased fertility except for a possible mercury effect on the last pregnancy of multiparous dental surgeons.

3.3.11 Genotoxicity

256. Two occupational studies (Anwar and Gabal, 1991; Popescu *et al.*, 1979) reported on workers inhaling inorganic mercury; the data were inconclusive regarding the clastogenic activity of inorganic mercury. Workers involved in the manufacture of mercury fulminate (Hg[OCN]₂) had a significant increase in the incidence of chromosomal aberrations and micronuclei in peripheral lymphocytes when compared to unexposed controls (Anwar and Gabal, 1991). There was no correlation between urinary mercury levels or duration of exposure to the increased frequency of effects; the study authors concluded that mercury may not have been the clastogen in the manufacturing process. In a study by Popescu *et al.* (1979), 18 workers exposed to a mixture of mercuric chloride, methylmercuric chloride and ethylmercuric chloride had significant increases in the frequency of acentric fragments. Barregard *et al.* (1991) demonstrated a correlation between cumulative mercury exposure and induction of micronuclei among a group of chlor-alkali workers, suggesting a possible genotoxic effect. Other studies did not observe genotoxic effects among workers exposed to mercury vapour (Vershaeve *et al.*, 1976, 1979; Mabile *et al.*, 1984).

3.4 Interactions – possible confounding effects of certain nutrients

257. The evidence is inconclusive and uncertain on the possible effects of various nutrients in relation to mercury toxicity. Nonetheless, limited evidence suggests that diet and nutrition may potentially reduce or enhance the toxicity of mercury, depending on dietary patterns and specific substances in the diet. Thus, nutritional status and dietary interactions might potentially affect the outcome of mercury studies, either by influencing the toxicity of mercury or by having effects on the endpoints measures. Some limited evidence suggests that protective effects of some nutrients (such as selenium, vitamin E, omega-3 fatty acids) might possibly reduce potentially harmful effects of mercury. Other components of the diet (such as ethanol) might possibly enhance toxicity of mercury. Also, mal-nourishment might possibly affect study results either by directly reducing the sensitivity of an endpoint tested or by exacerbating the effects of mercury and thereby increasing the sensitivity to mercury toxicity. Other nutritional factors such as iron or folate deficiencies that disrupt neuronal development might also possibly influence the impact of mercury.

258. Moreover, in studies of mercury toxicity to humans, other pollutants in the diet (such as PCBs) may prevent obtaining clear information on mercury toxicity. This is particularly the case when investigating more subtle toxic effects at low exposure levels, and much effort has been given to eliminating the misinterpretation of results due to such so-called “confounders.” More information on possible interactions of nutrients and other components of food can be found, among others, in the following references: Block, 1985; Bulat *et al.*, 1998; Chalon *et al.*, 1998; Chapman and Chan, 2000; Drasch *et al.*, 1996; Falnoga *et al.*, 2000; Goyer, 1997; Kling *et al.*, 1987; McNeil *et al.*, 1988; NRC, 2000; Petridou *et al.*, 1998; Rowland *et al.*, 1986; Rumbelha *et al.*, 1992; Turner *et al.*, 1981 and WHO/IPCS, 1990.