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 µg 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 µg/g and 10 µg/l) (Langworth *et al.*, 1992), but not in a recent study with somewhat lower exposure levels, urinary mercury 10-15 µg/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/m^3 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 occupationally 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 Enestrom 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/m^3 (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 Enestrom 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 0.6 mg/m^3.

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; Mabille *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; Rumbeiha *et al.*, 1992; Turner *et al.*, 1981 and WHO/IPCS, 1990.