5. Summary of Data Reported and Evaluation

5.1 Exposure data

Mercury occurs at low concentrations in the Earth's crust, mainly in sulfide ores (cinnabar), from which it has been extracted for a variety of uses for many centuries. Common applications of metallic mercury are as a cathode in the electrolytic production of chlorine, in dental amalgams, in the extraction of gold from ore concentrates, in electrical equipment and in devices for measuring temperature and pressure. Mercury compounds have been used as fungicides in paints and on seeds and grains, as antiseptics, in electrical applications, and as catalysts and intermediates.

Table 17. Genetic and related effects of organomercury compounds in experimental systems

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Methylmercury chloride (80% Hg)				
BSD, *Bacillus subtilis rec* strains, differential toxicity	+	0	1000	Kanematsu *et al.* (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation (spot test)	-	0	NR	Kanematsu *et al.* (1980)
SA5, *Salmonella typhimurium* TA1535, reverse mutation (spot test)	-	0	NR	Kanematsu *et al.* (1980)
SA7, *Salmonella typhimurium* TA1537, reverse mutation (spot test)	-	0	NR	Kanematsu *et al.* (1980)
SA8, *Salmonella typhimurium* TA1538, reverse mutation (spot test)	-	0	NR	Kanematsu *et al.* (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation (spot test)	-	0	NR	Kanematsu *et al.* (1980)
EC2, *Escherichia coli* WP2, reverse mutation (spot test)	-	0	NR	Kanematsu *et al.* (1980)
ECR, *Escherichia coli* WP2 B/r, reverse mutation (spot test)	-	0	NR	Kanematsu *et al.* (1980)
SCG, *Saccharomyces cerevisiae*, gene conversion	-	0	NR	Nakai & Machida (1973) abstract
SCH, *Saccharomyces cerevisiae*, mitotic recombination	-	0	NR	Nakai & Machida (1973) abstract
SCH, *Saccharomyces cerevisiae* D7, mitotic recombination	-	0	10.0	Phipps & Miller (1982)
SCF, *Saccharomyces cerevisiae*, forward mutation	+	0	NR	Phipps & Miller (1983)
SCR, *Saccharomyces cerevisiae*, reverse mutation	-	0	NR	Nakai & Machida (1973) abstract
SCR, *Saccharomyces cerevisiae*, petite mutation	+	0	NR	Nakai & Machida (1973) abstract
SCR, *Saccharomyces cerevisiae*, petite mutation	-	0	10.0	Phipps & Miller (1983)
SCN, *Saccharomyces cerevisiae*, aneuploidy	?	0	NR	Nakai & Machida (1973) abstract
PLI, Water hyacinth (*Eichhornia crassipes*), micronuclei	+	0	0.1 (acute exposure)	Panda *et al.* (1988)
***, *Allium cepa*, spindle disturbances	+	0	1.0	Fiskesjö (1969)
***, Silkworm, aneuploidy	-		NR	Tazima (1974) abstract
DMN, *Drosophila melanogaster* aneuploidy (FIX system)	+		5.0	Osgood *et al.* (1991)
DMN, *Drosophila melanogaster* aneuploidy (ZESTE system)	-		100	Osgood *et al.* (1991)

Table 17 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Methylmercury chloride (contd)				
G9O, Gene mutation, Chinese hamster lung V79 cells, ouabain resistance, *in vitro*	+	0	0.32	Fiskesjö (1979)
G9H, Gene mutation, Chinese hamster lung V79 cells, 8-azaguanine resistance, *in vitro*	+	0	0.16	Fiskesjö (1979)
***, Micronucleus test, fish (*Lepomis macrochinus*) cells *in vitro*	+	0	0.08	Babich *et al.* (1990)
CIC, Chromosomal aberrations, Chinese hamster brain cells *in vitro*	+	0	NR	Kato (1976) abst.
***, Spindle disturbances, Indian muntjac fibroblasts *in vitro*	+	0	1.0	Verschaeve *et al.* (1984)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	0	0.016	Morimoto *et al.* (1982)
***, Spindle disturbances, human lymphocytes *in vitro*	+	0	0.4	Fiskesjö (1970)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	+	0	0.04	Kato (1976) abstract; Kato *et al.* (1976) abstract
***, Spindle disturbances, human lymphocytes *in vitro*	+	0	0.08	Tournamille *et al.* (1982)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	+	0	1.0	Verschaeve *et al.* (1985)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	+	0	0.12	Betti *et al.* (1992)
AIH, Aneuploidy, human lymphocytes *in vitro*	+	0	0.12	Betti *et al.* (1992)
SVA, Sister chromatid exchange, mouse fetal lung and liver cells *in vivo*	+		8.0, po × 1	Curle *et al.* (1987)
***, Micronuclei, newt (*Pleurodeles waltl*) larvae red blood cells, *in vivo*	+		0.012, in water × 12 days	Zoll *et al.* (1988)
***, Nuclear abnormalities, cat bone-marrow cells *in vivo*	+		0.008, po × 39 months	Miller *et al.* (1979)
***, Spindle disturbances, mouse fetal lung and liver cells *in vivo*	+		4.0, po × 1	Curle *et al.* (1983)
AVA, Aneuploidy, Syrian hamster bone-marrow cells *in vivo*	+		4.74, sc × 1	Watanabe *et al.* (1982)
***, Spindle disturbances, mouse fetal lung and liver cells *in vivo*	+		4.0, po × 1	Curle *et al.* (1987)
***, Spindle disturbances, killifish (*Fundulus heteroclitus*) embryos *in vivo*	+		0.04, in water	Perry *et al.* (1988)
CBA, Chromosomal aberrations, Syrian hamster bone-marrow cells *in vivo*	(+)		9.47, sc × 1	Watanabe *et al.* (1982)

Table 17 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Methylmercury chloride (contd)				
CBA, Chromosomal aberrations, rat bone-marrow cells *in vivo*	+		4.64, ip × 1	Li & Lin (1991)
AVA, Aneuploidy, Syrian hamster oocytes *in vivo*	-		9.47, sc × 1	Watanabe *et al.* (1982)
AVA, Aneuploidy, Syrian hamster bone-marrow cells *in vivo*	+		4.47, sc × 1	Watanabe *et al.* (1982)
COE, Chromosomal aberrations, Syrian hamster oocytes *in vivo*	-		9.47, sc × 1	Watanabe *et al.* (1982)
COE, Chromosomal aberrations, Syrian hamster oocytes *in vivo*	-		8.0, ip × 1	Mailhes (1983)
***, Chromosomal aberrations, newt (*Pleurodeles waltl*) larvae or embryos *in vivo*	+		0.04, in water × 4 days	Zoll *et al.* (1988)
COE, Chromosomal aberrations, rat embryo liver cells *in vivo*	+		1.52, ip × 1	Li & Lin (1991)
DLM, Dominant lethal mutation, male mice *in vivo*	-		5, po × 7 days	Khera (1973a)
DLM, Dominant lethal mutation, female mice *in vivo*	+		2.0, ip × 1	Verschaeve & Léonard (1984)
DLR, Dominant lethal mutation, male rats *in vivo*	+		2.5, po × 7 days	Khera (1973a)
DLR, Dominant lethal mutation, male rats *in vivo*	+		0.5, po × 90 days	Khera (1973a)
AVA, Aneuploidy, Syrian hamster oocytes *in vivo*	+		8.0, ip × 1	Mailhes (1983)
Methylmercury hydroxide [CH_3HgOH] (86% Hg)				
ACC, *Allium cepa*, chromosomal aberrations	+	0	0.05	Ramel (1969)
***, *Allium cepa*, spindle disturbances	+	0	0.05	Ramel (1969)
***, *Vicia faba*, spindle disturbances	+	0	0.02	Ramel (1972)
DMG, *Drosophila melanogaster*, meiotic crossing-over	-		4.3	Ramel (1972)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	(+)		4.3	Ramel (1972)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		8.6, diet	Magnusson & Ramel (1986)
***, *Drosophila melanogaster*, effect on radiation-induced chromosomal aberrations	-		4.3	Ramel (1972)
***, *Stethophyma grossum*, chromosomal aberrations	+		8 ng/animal	Klášterská & Ramel (1978)

Table 17 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Methylmercury hydroxide (contd)				
DMN, *Drosophila melanogaster*, aneuploidy	+		0.25, diet	Ramel & Magnusson (1969)
DMN, *Drosophila melanogaster*, aneuploidy	+		0.25, diet	Ramel & Magnusson (1979)
DMN, *Drosophila melanogaster*, aneuploidy	+		0.43, diet	Magnusson & Ramel (1986)
***, Spindle disturbances, Chinese hamster lung V79 cells *in vitro*	+	0	0.42	Önfelt (1983)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus, *in vitro*	–	0	0.16	Önfelt & Jenssen (1982)
DLM, Dominant lethal mutation, (SEC×C57Bl)F_1 male mice *in vivo*	(+)		7.4, ip × 1	Suter (1975)
DLM, Dominant lethal mutation, (101×C3H)F_1 male mice *in vivo*	–		7.4, ip × 1	Suter (1975)
Methylmercury acetate [$CH_3HgCO_2CH_3$] (73% Hg)				
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	183	Bruce & Heddle (1979)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	183	Bruce & Heddle (1979)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	183	Bruce & Heddle (1979)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	183	Bruce & Heddle (1979)
MVM, Micronuclei, B6C3F1 mouse bone-marrow cells *in vivo*	–		11.0, ip × 5	Bruce & Heddle (1979)
SPM, Sperm-head abnormalities, B6C3F1 mice *in vivo*	–		11.0, ip × 5	Bruce & Heddle (1979)
Methylmercury dicyandiamide [$CH_3HgNHC(NH)NHCN$] (67% Hg)				
***, *Allium cepa*, spindle disturbances	+	0	0.5	Ramel (1969)
DLM, Dominant lethal mutation, mice *in vivo*	–		2.0	Ramel (1972)
Ethylmercury chloride [CH_3CH_2HgCl]				
***, *Allium cepa*, spindle disturbances	+	0	0.4	Fiskesjö (1969)
***, Micronuclei, fish (*Lepomis macrochirus*) cells *in vitro*	+	0	0.08	Babich *et al.* (1990)
***, Spindle disturbances, human HeLa cells *in vitro*	+	0	1	Umeda *et al.* (1969)

Table 17 (contd)

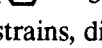
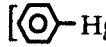
Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Bis(ethylmercury)hydrogen phosphate [$(CH_3CH_2Hg)_2HPO_4$]				
BSD, *Bacillus subtilis rec* strains, differential toxicity	-	0	14.4	Shirasu *et al.* (1976)
Butylmercury bromide [$(CH_3(CH_2)_3HgBr$]				
***, *Allium cepa*, spindle disturbances	+	0	0.2	Fiskesjö (1969)
Methoxyethylmercury chloride [$(CH_3O)CH_2CH_2HgCl$)]				
***, *Allium cepa*, spindle disturbance	+	0	0.63	Ramel (1969)
***, *Allium cepa*, spindle disturbances	+	0	2.0	Fiskesjö (1969)
DMN, *Drosophila melanogaster*, aneuploidy	-		20, diet	Ramel & Magnusson (1969)
DMN, *Drosophila melanogaster*, aneuploidy	-		2.5, larval diet	Ramel & Magnusson (1979)
G9O, Gene mutation, Chinese hamster lung V79 cells, ouabain resistance, *in vitro*	+	0	0.07	Fiskesjö (1979)
G9A, Gene mutation, Chinese hamster lung V79 cells, 8-azaguanine resistance, *in vitro*	+	0	0.07	Fiskesjö (1979)
***, Spindle disturbances, human lymphocytes *in vitro*	+	0	2.0	Fiskesjö (1970)
Phenylmercury chloride []				
BSD, *Bacillus subtilis rec* strains, differential toxicity	-	0	12.8	Shirasu *et al.* (1976)
***, Micronucleus test, fish (*Lepomis macrochirus*) cells *in vitro*	+	0	0.03	Babich *et al.* (1990)
***, Spindle disturbances, human HeLa cells *in vitro*	+	0	1.0	Umeda *et al.* (1969)
Phenylmercury hydroxide []				
PLM, *Anacharis canadensis*, mutation	+	0	6.8	MacFarlane & Messing (1953)

Table 17 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Phenylmercury hydroxide (contd)				
PLM, *Coleus blumei*, mutation	+	0	0.5	MacFarlane & Messing (1953)
PLM, *Raphanus sativus*, mutation	+	0	68	MacFarlane & Messing (1953)
PLM, *Ruppia maritima*, mutation	+	0	6.8	MacFarlane & Messing (1953)
PLM, *Zea mays*, mutation	+	0	6.8	MacFarlane & Messing (1953)
ACC, *Allium cepa*, chromosomal aberrations	+	0	6.8	MacFarlane (1956)
ACC, *Allium cepa*, chromosomal aberrations	+	0	0.24	Ramel (1969)
***, *Allium cepa*, spindle disturbances	+	0	0.16	Ramel (1969)
Phenylmercury nitrate []				
PLM, *Zea mays*, mutation	+	0	2.4	MacFarlane & Messing (1953)
ACC, *Allium cepa*, chromosomal aberrations	+	0	5.9	MacFarlane (1956)
Phenylmercury acetate []				
BSD, *Bacillus subtilis rec* strains, differential toxicity	–	0	12	Shirasu *et al.* (1976)
BSD, *Bacillus subtilis rec* strains, differential toxicity	+	0	200	Kanematsu *et al.* (1980)
DMN, *Drosophila melanogaster*, aneuploidy	(+)[b]		0.32	Ramel & Magnusson (1969)
Dimethylmercury [CH_3HgCH_3]				
***, *Physarum polycephalum* (slime mould), DNA fragments	+	0	500	Yatscoff & Cummins (1975)

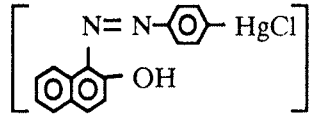
Table 17 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Dimethylmercury (contd)				
CIM, Chromosomal aberrations, mouse oocytes *in vitro*	+	0	10	Jagiello & Lin (1973)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	+	0	8.7	Betti *et al.* (1992)
AIH, Aneuploidy, lymphocytes *in vitro*	+	0	0.34	Betti *et al.* (1992)
COE, Chromosomal aberrations, mouse oocytes *in vivo*	-		140, iv × 1	Jagiello & Lin (1973)
Mercury-containing fungicides (denomination and composition as reported by authors)				
Panogen 5 (containing methylmercury dicyandiamide; Hg, 5 g/L)				
***, *Allium cepa*, spindle disturbances	+	0	0.05	Ramel (1969)
Panogen 8 (containing methylmercury dicyandiamide; Hg, 6.4 g/L)				
***, *Allium cepa*, spindle disturbances	+	0	0.16	Ramel (1969)
Panogen 15 (containing 2.3% methylmercury dicyandiamide; 1.54% Hg)				
***, *Vicia faba*, spindle disturbances	+	0	0.015	Ahmed & Grant (1972)
***, *Tradescantia* species, spindle disturbances	+	0	0.015	Ahmed & Grant (1972)
Ceresan (containing phenylmercury acetate; 1% Hg)				
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		200, diet, adult	Gayathri & Krishnamurthy (1985)
DML, *Drosophila melanogaster*, dominant lethal mutations	-		200, diet, adult	Gayathri & Krishnamurthy (1985)
Agrimax M (containing phenylmercury dinaphthylmethanedisulfonate; % Hg not known)				
***, *Avena sativa*, polyploidy	+	0	NR	Bruhin (1955)
***, *Crepis capillaris*, polyploidy	+	0	NR	Bruhin (1955)

Table 17 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Granosan (2% ethylmercury chloride [EMC] + 98% talc; 1.5% Hg)				Bruhin (1955)
***, *Crepis capillaris*, nuclear abnormalities	-	0	15	Kostoff (1940)
***, *Linum usitatissimum*, nuclear abnormalities	-	0	75	Kostoff (1940)
***, *Pisum sativum*, nuclear abnormalities	+	0	75	Kostoff (1939, 1940)
***, *Secale cereale*, nuclear abnormalities	+	0	15	Kostoff (1939, 1940)
***, *Triticum aegilopodes*, nuclear abnormalities	+	0	15	Kostoff (1939, 1940)
***, *Triticum durum*, nuclear abnormalities	+	0	15	Kostoff (1939, 1940)
***, *Triticum persicum*, nuclear abnormalities	+	0	15	Kostoff (1939, 1940)
***, *Triticum polonicum*, nuclear abnormalities	+	0	15	Kostoff (1939, 1940)
***, *Triticum vulgare*, nuclear abnormalities	+	0	15	Kostoff (1939, 1940)
Ceresan M[c] (containing ethylmercury *para*-toluenesulfonanilide)				
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		14.3, diet	Mathew & Al-Doori (1976)
Agallol 3 (containing methoxyethylmercury chloride; 3% Hg)				
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	-		600, diet, adult	Gayathri & Krishnamurthy (1985)
DML, *Drosophila melanogaster*, dominant lethal mutations	-		600, diet, adult	Gayathri & Krishnamurthy (1985)
Betoxin (containing 90% ethylmercury halogenide; % Hg not known)				
ACC, *Allium cepa*, chromosomal aberrations	+	0	NR	Fiskesjö (1969)
***, *Allium cepa*, spindle disturbances	+	0	NR	Fiskesjö (1'969)
New improved Ceresan (containing ethylmercury phosphate)				
PLC, *Zea mays*, chromosomal aberrations	+	0	NR	Sass (1937)

Table 17 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Azo dye				
Mercury orange (41% Hg) 				
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	103	Brown *et al.* (1978)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	103	Brown *et al.* (1978)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	103	Brown *et al.* (1978)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	103	Brown *et al.* (1978)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	103	Brown *et al.* (1978)

+, considered to be positive; (+), considered to be weakly positive in an inadequate study; –, considered to be negative; ?, considered to be inconclusive (variable responses in several experiments within an adequate study); 0, not tested

[a]LED, lowest effective dose; HID, highest ineffective dose. In-vitro tests, μg/ml; in-vivo tests, mg/kg bw. Doses given as concentration of element, not concentration of compound; NR, not reported; po, orally, by gavage; sc, subcutaneously; ip, intraperitoneally; iv, intravenously

[b]Statistically significant, but may be due to control values lower than those in other experiments

[c]Claimed to be responsible for two outbreaks of poisoning in 1956 and 1960 in Iraq

***Not displayed on profile

Workers are exposed to mercury by inhalation, principally to metallic mercury but also to inorganic and organic mercury compounds. Occupations in which the highest exposures occur include mercury mining, work in chloralkali and alkaline battery plants and production of devices for measuring temperature and pressure. Lower exposures have been measured for people employed in hospital laboratories and dental clinics. Exposures have been measured by both ambient air monitoring and biological monitoring.

Nonoccupational sources of exposure to mercury include food (methylmercury compounds, mainly in aquatic organisms) and dental amalgam fillings (metallic mercury). These exposure levels are usually lower than those typically detected in occupational settings.

5.2 Human carcinogenicity data

Metallic mercury and inorganic mercury compounds

A cohort study in a nuclear weapons factory in the USA on exposure to metallic mercury showed no difference in risk for lung cancer in exposed and unexposed subcohorts from the same factory. In a nested case–control study at two nuclear facilities in the USA, the risk for cancers of the central nervous system was not associated with estimated levels of exposure to mercury.

A cohort study of chloralkali workers in Sweden identified a two-fold, significant excess risk for lung cancer and some nonsignificant excess risks for cancers of the brain and kidney. Lung cancers also occurred in an almost two-fold excess in Norwegian chloralkali workers, whereas the numbers of cases of cancer of the brain and kidney were close to those expected. In both studies, asbestos and smoking were judged to be the main determinants of the excess risk for lung cancer.

In a study of male and female dentists and female dental nurses in Sweden, a two-fold risk for brain tumours was found in each of the three cohorts. No such risk appeared among dentists or medical and dental technicians in a US study of military veterans; these groups had excess risks for pancreatic and colon cancer, respectively. In an Australian case–control study of brain tumours and amalgam fillings, there was a decreased risk for gliomas and no effect was seen with regard to meningiomas.

The risk for lung cancer was found to be higher among individuals with silicosis who had been working in US mercury mines than in subjects with silicosis who had worked elsewhere. This finding was based on small numbers, however, and the confidence limits overlapped.

A case–control study in Italy indicated an excess risk for lung cancer among women in the felt-hat industry who had heavy exposure to mercury but also to arsenic.

In a population-based case–control study from Canada, risk for prostatic cancer was associated with exposure to mercury compounds in general and the risk for lung cancer with exposure to metallic mercury.

Organomercury compounds

Studies in Minamata, Japan, on causes of death in populations with high exposure to mercury included areas with a high prevalence of methylmercury poisoning. 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 cancer 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.

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.

5.3 Animal carcinogenicity data

Mercuric chloride was tested for carcinogenicity in two studies in mice, by oral gavage and by administration in the drinking-water; only the study by gavage was adequate for an evaluation of carcinogenicity. Mercuric chloride was also tested in one study in rats by oral gavage. In mice, a few renal adenomas and adenocarcinomas occurred in males only. In rats, a few renal adenomas occurred in females; there was a dose-related increase in the incidence of squamous-cell papilloma of the forestomach in males, and a few papillomas were seen in females. Dose-related hyperplasia of the forestomach was seen in both males and females.

Methylmercury chloride was tested for carcinogenicity in three studies in mice and two studies in rats by oral administration in the diet. In all three studies in mice, the incidence of renal adenomas and adenocarcinomas was increased in males. In the two studies in rats, no increase in tumour incidence was reported. In another study in mice given methylmercury chloride, a significant number of renal tumours was found in intact male mice and a few renal tumours were found in gonadectomized male and female mice that also received testosterone propionate; no renal tumour was found in male or female gonadectomized mice that did not receive testosterone propionate.

5.4 Other relevant data

After inhalation, about 70–80% of metallic mercury vapour is retained and absorbed. Little metallic mercury is taken up in the gastrointestinal tract, and less than 10% is absorbed. Metallic mercury passes into the brain and fetus. In the body, metallic mercury is oxidized to mercuric mercury, which binds to reduced sulfhydryl groups. The kidney is the main depository following exposure to both metallic and mercuric mercury. Mercuric mercury is eliminated mainly in urine and faeces; it is also excreted in milk. In humans, inorganic mercury compounds have two half-times: one lasts for days or weeks and the other much longer. Mercury concentrations in urine, blood and plasma are useful for biological monitoring.

Methylmercury compounds present in seafood are almost completely absorbed from the gastrointestinal tract and are distributed to most tissues. The methylmercury compounds bind to reduced sulfhydryl groups; a fraction is converted to mercuric mercury, the extent of

conversion differing among species. Methylmercury compounds are excreted mainly in the bile; in the intestine, some mercury is biotransformed into inorganic mercury compounds and excreted in the faeces. Methylmercury compounds pass into the fetus and are excreted in milk. In humans, methylmercury compounds have a single biological half-time of approximately two months. Concentrations in blood and hair are useful for monitoring exposure to methylmercury compounds.

Following intense exposure to metallic mercury vapour, lung damage occurs; gastrointestinal and renal tubular necrosis occur after ingestion of mercuric mercury. Long-term exposure to metallic mercury causes encephalopathy and renal damage; chronic exposure to mercuric mercury causes renal tubular damage. Immunologically based glomerulonephritis can occur. In rats, mercuric chloride may cause immunosuppression. Effects on the immune system vary considerably among rodent strains. Inorganic mercury is a cause of allergic contact dermatitis. The nervous system is the main target organ for methylmercury compounds, but interspecies differences exist; in some species, there are also effects on the kidney. Some selenium compounds affect the kinetics of inorganic and methylmercury compounds and have a protective effect against their toxicity.

In several studies of female dental assistants, no increased risk for spontaneous abortion or birth defects was seen. Parenteral administration of mercury salts to pregnant rodents induces fetal growth retardation, malformations and death; altered placental transport of nutrients may be involved. Methylmercury compounds induce adverse effects on human development—most notably microcephaly and deficits in neurological development. Similar effects have been shown in many laboratory species. The conceptus appears to be more sensitive than the maternal organism. The dose levels of methylmercury compounds that affect reproduction and development are generally lower than those of inorganic mercury and affect a wider range of end-points.

The findings of 14 studies of cytogenetic effects, such as sister chromatid exchange, micronucleus formation, structural chromosomal aberrations, aneuploidy and polyploidy, in peripheral lymphocytes of individuals exposed to metallic mercury and various mercury compounds are controversial and uncertain. Thus, four studies involving subjects exposed to methylmercury compounds from contaminated seal or fish meat were either inconclusive or indicated slight chromosomal effects. Nine studies in individuals exposed from occupational sources to metallic mercury, amalgams, alkyl- and arylmercury compounds or mercury fulminate gave either negative or borderline results, or the exact role of mercury in any positive result was uncertain. A slight yet significant increase in the frequency of sister chromatid exchange was observed in only one subset of children intoxicated with phenylmercury acetate used for disinfecting diapers.

Several organomercury compounds and fungicides containing organomercury compounds were assayed in a variety of short-term tests. Tests for unscheduled DNA synthesis, sister chromatid exchange, chromosomal aberrations and dominant lethal mutations in mammals *in vivo* gave conflicting results. Tests for clastogenicity in fish and amphibians gave more convincingly positive results. All studies of induction of c-mitosis (spindle disturbances), sister chromatid exchange, structural chromosomal aberrations and aneuploidy in cultured human lymphocytes gave positive results. The results of the majority of studies of the induction of forward mutations, c-mitosis and polyploidy in cultured

mammalian (non-human) cells were positive, and those of one study on micronucleus induction in cultured fish cells were also positive. In *Drosophila melanogaster* and other insects, the majority of mercury compounds induced sex-linked recessive lethal mutation and nondisjunction (aneuploidy) but did not induce dominant lethal mutation. The assessment of nuclear or mitochondrial DNA mutations, mitotic recombination and gene conversion in the yeast *Saccharomyces cerevisiae* led to conflicting results. Most of the few studies available in bacteria (investigating differential killing in *rec*$^-$ *Bacillus subtilis* or reversion in *his*$^-$ *Salmonella typhimurium* or *trp*$^-$ *Escherichia coli*) gave negative results.

There were fewer studies of inorganic mercury compounds (mostly mercuric chloride), and a minority compared inorganic and organic compounds. No experimental study was available on metallic mercury. As in studies with organomercury compounds, studies in rodents treated *in vivo* with mercuric chloride gave weakly positive results for dominant lethal mutation. Studies on the induction of chromosomal aberrations in rodents yielded conflicting results. One study on chromosomal effects in amphibians gave positive results for mercuric chloride and methylmercury chloride at similar doses. Chromosomal alterations were reported in cultured human lymphocytes. The dose of mercuric chloride required to induce sister chromatid exchange in cultured human lymphocytes was 5–25 times higher than those needed of methylmercury chloride. Mercuric acetate did not induce anchorage-independent growth in human cells. Five to ten times higher doses of mercuric chloride than methylmercury chloride were required to induce polyploidy. DNA damage has been induced repeatedly in mammalian cells by mercuric chloride. Although the information comes from single studies, this compound also induced sister chromatid exchange, chromosomal aberrations, aneuploidy (spindle disturbances) and enhancement of virus-induced morphological transformation. Unlike organomercury compounds, mercuric chloride failed to enhance the frequency of micronuclei in cultured fish cells. Mercuric chloride failed to enhance lethality in a DNA repair-deficient strain of *E. coli*.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of mercury and mercury compounds.

There is *inadequate evidence* in experimental animals for the carcinogenicity of metallic mercury.

There is *limited evidence* in experimental animals for the carcinogenicity of mercuric chloride.

There is *sufficient evidence* in experimental animals for the carcinogenicity of methylmercury chloride.

In making the overall evaluation, the Working Group took into account evidence that methylmercury compounds are similar with regard to absorption, distribution, metabolism, excretion, genotoxicity and other forms of toxicity.

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[1]For definition of the italicized terms, see Preamble, pp. 26-30.

Overall evaluation

Methylmercury compounds *are possibly carcinogenic to humans (Group 2B).*

Metallic mercury and inorganic mercury compounds *are not classifiable as to their carcinogenicity to humans (Group 3).*