MERCURY AND MERCURY COMPOUNDS

1. Exposure Data

1.1 Chemical and physical data and analysis

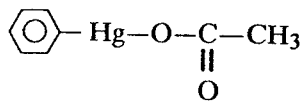
1.1.1 *Synonyms, trade names and molecular formulae*

Synonyms, trade names and molecular formulae for mercury and certain mercury compounds are presented in Table 1. The list of mercury compounds is not exhaustive, nor are those compounds necessarily the most commercially important mercury-containing substances; it includes the mercury compounds for which data on carcinogenicity are considered in this volume.

Table 1. Synonyms (Chemical Abstracts Service [CAS] names are in italics), trade names and atomic or molecular formulae of mercury and mercury compounds

Chemical name	CAS Reg. No.[a]	Synonyms and trade names	Formula
Mercury metal	7439-97-6 (8030-64-6; 51887-47-9; 92355-34-5; 92786-62-4; 123720-03-6)	Colloidal mercury; hydrargyrum; liquid silver; quecksilber; quicksilver	Hg
Mercuric acetate	1600-27-7 (6129-23-3; 7619-62-7; 19701-15-6)	*Acetic acid, mercury (2+) salt*; bis(acetyloxy)mercury; diacetoxymercury; mercuri, diacetic acid; mercury acetate; mercuric diacetate; mercury diacetate	$Hg(O-\overset{O}{\overset{\|}{C}}-CH_3)_2$
Mercuric chloride	7487-94-7	Abavit B; bichloride of mercury; Calochlor; corrosive sublimate; corrosive mercury chloride; CRC; dichloromercury; mercuric bichloride; mercuric chloride; mercuric dichloride; mercury bichloride; *mercury chloride*; mercury(2+) chloride; mercury(II) chloride; mercury dichloride; mercury perchloride; Sublimate; Sulem	$HgCl_2$
Mercuric oxide	21908-53-2 (1344-45-2; 8028-34-0)	Mercuric oxide (HgO); mercury monoxide; mercury oxide; *mercury oxide (HgO)*; mercury(II) oxide; mercury(2+) oxide; red mercuric oxide; santar; yellow mercuric oxide	HgO

Table 1 (contd)

Chemical name	CAS Reg. No.[a]	Synonyms and trade names	Formula
Dimethylmercury	593-74-8	Methyl mercury	$(CH_3)_2Hg$
Methylmercury chloride	115-09-3	Caspan; *chloromethylmercury*; mercury methyl chloride; methylmercuric chloride; methylmercury monochloride; monomethyl mercury chloride	CH_3ClHg
Phenylmercury acetate	62-38-4 (1337-06-0; 8013-47-4; 61840-45-7; 64684-45-3)	*Acetato-O-phenylmercury*; acetatophenylmercury; acetatophenylmercury; acetic acid, phenyl mercury derivative; (acetoxymercurio)benzene; acetoxyphenylmercury; mercuriphenyl acetate; phenylmercuric acetate; phenylmercury(II) acetate	

[a]Replaced CAS Registry numbers are shown in parentheses

1.1.2 *Chemical and physical properties of the pure substances*

Selected chemical and physical properties of mercury and of the mercury compounds covered in this monograph are presented in Table 2.

Mercury (also called quicksilver because of its liquid state at room temperature) was known as early as 1000 BC. The discovery in 1938 of 1 kg of the metal in 2500-year-old sand layers on the eastern coast of Greece indicates that mercury was used in the extraction of gold at an early date. Mercury was mentioned about 200 BC in India as well as in China (Han dynasty). As early as 1556 AD, five different methods for extracting mercury from its ores were reported (Simon *et al.*, 1990).

Inorganic mercury exists in three oxidation states: 0 (metallic), +1 (mercurous) and +2 (mercuric); mercurous ions usually occur as dimers (Hg^{2+}). The mercurous and mercuric states form numerous inorganic and organic chemical compounds. Organomercury compounds are those in which mercury is attached covalently to at least one carbon atom (Aylett, 1973; Simon *et al.*, 1990; WHO, 1990, 1991).

In its elemental form, mercury is a dense, silvery-white, shiny metal, which is liquid at room temperature and boils at 357 °C. At 20 °C, the vapour pressure of the metal is 0.17 Pa (0.0013 mm Hg). A saturated atmosphere at 20 °C contains 14 mg/m^3 (Simon *et al.*, 1990).

Mercury compounds differ greatly in solubility: for example, in water, the solubility of metallic mercury is 60 µg/L at 25 °C, 250 µg/L at 50 °C and 1100 µg/L at 90 °C (Simon *et al.*, 1990); the solubility of mercurous chloride is 2 mg/L at 25 °C and that of mercuric chloride is 69 g/L at 20 °C (Lide, 1991). Methylmercury chloride is more soluble in water than mercurous chloride by about three orders of magnitude, owing to the very high solubility of the methylmercury cation in water. Certain species of mercury, including metallic mercury and the halide compounds of alkylmercury compounds, are soluble in non-polar solvents

Table 2. Chemical and physical properties of mercury and mercury compounds

Chemical name	Relative atomic/ molecular mass	Melting-point (°C)	Typical physical description	Density	Solubility
Mercury metal	200.59	– 38.87	Silvery-white, heavy, mobile, liquid metal	13.546 (20 °C)	Soluble in nitric acid, sulfuric acid upon heavy boiling, lipids, pentane; insoluble in dilute hydrochloric, hydrobromic and hydroiodic acids, water (2 µg/L at 30 °C), ethanol, diethyl ether, cold sulfuric acid
Mercuric acetate	318.7	178–180 (decomposes)	White crystals or crystalline powder	3.27	Soluble in water (250 g/L at 10 °C), ethanol, acetic acid
Mercuric chloride	271.50	276	Colourless, rhombic, odourless, crystal or white powder	5.44 (25 °C)	Soluble in water (69 g/L at 20 °C), methanol, ethanol, amyl alcohol, acetone, formic acid, acetic acid, the lower acetate esters, diethyl ether, benzene, glycerol; slightly soluble in carbon disulfide and pyridine
Mercuric oxide	216.6	500 (decomposes)	Yellow or red, *ortho*-rombic, odourless crystalline powder	11.14	Insoluble in water (53 mg/L at 25 °C), soluble in acids; insoluble in ethanol, diethyl ether, acetone, alkali, ammoniac
Dimethylmercury	230.66	NR	Colourless liquid with a sweet odour	3.19 (20 °C)	Soluble in ethanol and diethyl ether; insoluble in water
Methylmercury chloride	251.10	167–168	White crystalline solid with a disagreeable odour	4.06	Slightly soluble in water
Phenylmercury acetate	336.75	150	White to cream-coloured, small, odourless, lustrous crystalline solid (prism, powder, leaflet)	2.4	Soluble in ethanol, benzene, glacial acetic acid, acetone, ammonium acetate, chloroform, diethyl ether; slightly soluble in water (4.37 g/L) at 25 °C)

From Aylett (1973); Lide (1991); Alfa Products (1990); Budavari (1989); Sax & Lewis (1987); Drake (1981); Singer & Nowak (1981); Worthing (1987); Strem Chemicals (1992). NR, not reported

(WHO, 1991). Mercury vapour is more soluble in plasma, whole blood and haemoglobin than in distilled-water or isotonic saline (Hursh, 1985).

Mercury forms monovalent and divalent compounds with the halogens fluorine, chlorine, bromine and iodine. It also forms monovalent and divalent compounds with sulfur. From the biochemical point of view, the most important chemical property of mercuric mercury and alkylmercury compounds may be their high affinity for sulfhydryl groups (Simon *et al.*, 1990; WHO, 1991).

The main volatile mercury species in air is metallic mercury, but dimethylmercury may also occur. Mercury compounds such as mercuric chloride and methylmercury hydroxide are also relatively stable in fresh water, including snow, rain and standing and flowing water. $HgCl_4^{2-}$ is the dominant form of mercury in seawater (WHO, 1991).

1.1.3 *Technical products and impurities*

Metallic mercury—purities: triple-distilled grade, ≥ 99.99% (4N); ACS reagent grade, 99.995–99.9995%; electronic grade, 99.9998%; ultra-high purity grade, 99.99999–99.999999% (Alfa Products, 1990; CERAC, Inc., 1991; Aldrich Chemical Co., 1992; Strem Chemicals, 1992; Atomergic Chemetals Corp., undated; D.F. Goldsmith Chemical & Metal Corp., undated); impurities (%): Ag, 0.0001; Fe, 0.00005; Pb, 0.00001; Cu, 0.00001; Cd, 0.00001; Zn, 0.00005 (Janssen Chimica, 1990).

Mercuric acetate—purities: 97–99.9%; ACS reagent grade, ≥ 98% (Janssen Chimica, 1990; CERAC, Inc., 1991; Aldrich Chemical Co., 1992; Strem Chemicals, 1992).

Mercuric chloride—purities: ACS reagent grade, 99%; 99.9–99.9995%; impurities (%): Fe, 0.002; Pb, 0.002; Cu, 0.002; Ca, max. 0.002 (Janssen Chimica, 1990; CERAC, Inc., 1991; Aldrich Chemical Co., 1992; Strem Chemicals, 1992).

Mercuric oxide—purities: high-purity, 99.999%; ACS grade (yellow or red), 99% (CERAC, Inc., 1991; Aldrich Chemical Co., 1992).

Dimethylmercury— purities, 95–98% (Aldrich Chemical Co., 1992; Strem Chemicals, 1992)

Methylmercury chloride—purity: ≥ 95% (Alfa Products, 1990)

Phenylmercury acetate—purities: 97–97.5%; practical, US Pharmacopeia and National Formulary grades (Janssen Chimica, 1990; Aldrich Chemical Co., 1992; Strem Chemicals, 1992; D.F. Goldsmith Chemical & Metal Corp., undated). Some of the trade names associated with phenylmercuric acetate include: Agrosan D; Agrosan GN5; Algimycin; Aligimycin 200; Anticon; Antimucin WBR; Antimucin WDR; Bufen; Bufen 30; Caswell No. 656; Cekusil; Celmer; Ceresan; Ceresol; Contra Creme; Dyanacide; Femma; FMA; Fungicide R; Fungitox OR; Gallotox; Hexasan; HL-331; Hostaquick; Intercide 60; Intercide PMA 18; Kwiksan; Lerophyn; Leytosan; Liquiphene; Lorophyn; Meracen; Mercron; Mercuron; Mergal A 25; Mersolite; Mersolite 8; Mersolite D; Metasol 30; Neantina; Norforms; Nuodex PMA 18; Nylmerate; Pamisan; Panomatic; Phenmad; Phix; PMA; PMA 220; PMAC; PMAcetate; PMAL; PMAS; Programin; Purasan-SC-10; Puraturf 10; Quicksan; Quicksan 20; Riogen; Ruberon; Samtol; Sanitized SPG; Sanitol; Sanmicron; Scutl; SC-110; Seed Dressing R; Seedtox; Setrete; Shimmerex; Spor-Kl; Spruce Seal; Tag; Tag 331; Tag Fungicide; Tag HL-331; Trigosan; Troysan 30; Troysan PMA 30; Verdasan; Volpar; Zaprawa Nasienna R; Ziarnik

Impurities of mercury compounds that are the subjects of other monographs are lead (IARC, 1987a) and cadmium (this volume, p. 119).

1.1.4 *Analysis*

Selected methods for the determination of mercury in various media are presented in Table 3. Other methods have been reviewed (WHO, 1990, 1991).

Table 3. Methods for the analysis of mercury in various media

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Air	Collect on Hydrar sorbent; desorb with nitric then hydrochloric acids	CVAA	0.03 µg/sample	Eller (1989)
Drugs	Digest in water–hydrochloric acid–nitric acid; heat; cool; add potassium dichromate	AAS	NR	Helrich (1990a)
Liquid waste, groundwater	Digest with sulfuric and nitric acids; add potassium permanganate and potassium persulfate solutions; heat; cool; reduce with sodium chloride–hydroxylamine sulfate; add stannous sulfate and aerate	CVAA	0.2 µg/L	US Environmental Protection Agency (1986a) (Method 7470); Helrich (1990b)
		AAS	NR	
Soil, sediment, solid and semisolid waste	Digest with distilled water and aqua-regia; heat; cool; add potassium permanganate and heat; cool; add sodium chloride–hydroxylamine sulfate; or digest as above	CVAA	0.2 µg/L	US Environmental Protection Agency (1986b) (Method 7471)
Blood, urine	Reduce inorganic and organic mercury to Hg^0 with reducing agents (e.g., $SnCl_2$); estimate organic mercury as difference between total and inorganic	CVAA	0.5 µg/L	Magos & Clarkson (1972)
	Reduce total mercury with sodium borohydride; enrich with an amalgamation device (Au/Pt gauze)	CVAA	0.3 µg/L urine or blood	Angerer & Schaller (1988)
Blood, urine, hair, tissues	Automated form of the method of Magos and Clarkson (1972)	CVAA	2.5 µg/kg	Farant *et al.* (1981)

Abbreviations: CVAA, flameless cold vapour atomic absorption spectroscopy; AAS, flame or flameless atomic absorption spectroscopy; NR, not reported

The original 'dithizone' method has been replaced by atomic absorption spectrometry, neutron activation analysis, atomic fluorescence spectrometry, inductively coupled plasma emission spectrometry and spark source spectrometry. Cold vapour atomic absorption is the most popular and reliable technique. Metallic mercury and inorganic mercury compounds and organomercury compounds in biological and environmental specimens are converted by

reducing agents (tin chloride, cadmium chloride–tin chloride, sodium borohydride) to metallic mercury and released as mercury vapour, which is either pumped directly through the quartz cell of the atomic absorption spectrophotometer or analysed after amalgamation on a silver–platinum gauze. The organic mercury content of the sample is given by the difference between total and inorganic compounds. For routine analysis, especially for blood and urine samples, the total mercury content is determined using sodium borohydride as the reducing agent, avoiding time-consuming decomposition of the samples (Angerer & Schaller, 1988).

The neutron activation procedure for analysis in urine is regarded as the most accurate and sensitive procedure and is usually used as the reference method (WHO, 1991).

Helrich (1990a) described several methods (atomic absorption spectrometry, gravimetry, titrimetry) for the determination of mercury and mercury compounds in various forms of drugs (solutions of organomercury compounds, ointments, calomel tablets, tablets containing purgative drugs). Helrich (1990c) described methods (flameless atomic absorption spectrometry, colorimetric dithizone) for the determination of mercury in food and fish and gas chromatographic methods for the determination of methylmercury compounds in fish and shellfish. Helrich (1990d) described methods (volatilization, precipitation, titrimetry, gravimetry) for the determination of mercury in organomercury seed disinfectants.

Pre-analytical and analytical procedures involve the risk of losing mercury from the sample, or contamination. Owing to the small amounts of mercury (in nanogram or even sub-nanogram ranges) in specimens, especially of biological materials, careful quality control must be undertaken. Control materials (blood and urine) are commercially available for intralaboratory quality control, and national and international intercomparison programmes are offered for external quality control. Reference materials covering the range of samples obtained for monitoring are commercially available for both environmental and biological samples (see WHO, 1991); however, the available control materials for daily use and reference materials do not cover the demand for different mercury species.

(a) Metallic mercury

Analytical methods for mercury in air can be divided into instant reading methods and methods with separate sampling and analysis stages. One direct ('instant') reading method is based on the 'cold vapour atomic absorption' technique, which measures the absorption of mercury vapour by ultraviolet light at a wavelength of 253.7 nm. Most of the atomic absorption spectroscopy procedures have a detection limit in the range of 2–5 $\mu g/m^3$ mercury (WHO, 1991).

Another direct reading method employed increasingly is a special gold amalgamation technique, which has been used in a number of studies to evaluate the release of metallic mercury vapour into the oral cavity from amalgam fillings (WHO, 1991). The method is based on an increase in the electrical resistance of a thin gold film after absorption of mercury vapour. The detection limit is 0.05 ng mercury (McNerney *et al.*, 1972).

In an analytical method based on separate sampling and analysis, air is sampled in two bubblers in series containing sulfuric acid and potassium permanganate. The mercury is subsequently determined by cold vapour atomic absorption. With this method, the total mercury in the air, and not just mercury vapour, can be measured. Another sampling

technique involves solid absorbents. Amalgamation techniques using gold have been shown to collect mercury vapour efficiently (WHO, 1991).

Air can be sampled for the analysis of mercury by static samplers or by personal monitoring (WHO, 1991). In a comparison of results obtained using static samplers and personal samplers, the latter yielded higher time-weighted average concentrations than the former in most work places (Roels *et al.*, 1987).

(*b*) *Mercuric chloride and mercuric acetate*

A dual-stage differential atomization atomic absorption technique was developed to allow speciation of 10 mercury-containing compounds, including mercuric chloride and mercuric acetate, in aqueous solution and biological fluids (Robinson & Skelly, 1982).

(*c*) *Methylmercury compounds*

Gas chromatography is usually used for selective measurement of methylmercury compounds and other organomercury compounds, particularly in fish tissues. An alternative approach is to separate methylmercury compounds from inorganic mercury compounds by volatilization, ion exchange or distillation and to estimate them by nonselective methods (e.g. atomic absorption) (WHO, 1990).

(*d*) *Phenylmercury acetate*

Phenylmercury acetate was determined in pharmaceutical products by reverse-phase high-performance liquid chromatography of a morpholinedithiocarbamate derivative. The method is specific and sensitive and has been used to determine a number of phenylmercury salts in pharmaceutical products (Parkin, 1987).

1.2 Production and use

1.2.1 *Production*

Worldwide production data for mercury are presented in Table 4. Over the last 10 years, production figures have changed only slightly. Current production in the USA is approximately 53% of the potential capacity: Because of reduced demand, many mines and smelting plants are no longer operating or have greatly cut back production. A large proportion of Mexican production has been exported to Brazil and Argentina. China claims to have the largest mercury resources in the world; most of the Chinese production is exported to the USA. Italy, once a large producer of mercury, now imports it from Algeria and Yugoslavia. The Almadén mercury mine in Spain accounted for 90% of the total output of the European Economic Community for many years, and most of the production has been exported to Belgium, France, Luxembourg and the USA. Whereas in 1986 the former USSR exported most of its mercury, almost the entire production is now reserved for domestic use (Simon *et al.*, 1990; WHO, 1991).

(*a*) *Metallic mercury*

All mercury ores are relatively low-grade, the average mercury content being about 1%. Mercury ores lie close to the Earth's surface, so that the required mining depth is about 800 m

Table 4. Worldwide production of mercury (tonnes)

Country	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991
Algeria	1049	1055	506	841	877	386	828	587	795	690	773	690	586	637	431
China[a]	700	600	700	800	800	800	850	800	800	850	900	940	880	800	700
Czechoslovakia	183	196	171	159	153	151	144	152	158	168	164	168	131	126	120
Dominican Republic	18	17	21	6	3	2	4	2	1	NR	< 0.5	< 0.5	< 0.5	NR	NR
Finland	22	39	46	75	67	71	65	80	130	147	147	130	159	141	125
Germany	99	84	91	56	76	53	NR	NR	NR	NR	NR	NR	NR	NR	NR
Italy	14	3	NR	3	252	159	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mexico	333	76	68	145	240	295	221	384	264	345	124	345	651	735	720
Russia[a]	2200	2000	2000	1800	1700	1700	1700	1600	1600	1500	1650	2300	2300	2100	1900
Spain	926	1020	1116	1721	1560	1540	1416	1520	1539	1471	1553	1716	1380[a]	425[a]	450
Turkey	162	173	163	154	204	246	162	182	226	262	202	97	197	60	60
USA	974	834	1018	1058	962	888	864	657	570	470	34	379	414	NR	NR
Former Yugoslavia	108	NR	NR	NR	NR	NR	52	72	88	75	67	70	51	37	30
Total[b]	6788	6097	5900	6818	6894	6291	6306	6036	6171	5978	5906	6835	6749	5061	4536

From Simon *et al.* (1990); Reese (1992a). NR, not reported

[a]Estimated values

[b]Totals may not add up because some values are estimates.

at most. The most important ore for mercury extraction is α-mercuric sulfide (red) (cinnabar, cinnabarite). The ore is heated with lime in retorts or furnaces to liberate the metal as vapour, which is cooled in a condensing system to form metallic mercury. Other methods include leaching of ores and concentrates with sodium sulfide and sodium hydroxide and subsequent precipitation with aluminium or by electrolysis; alternatively, mercury in ore is dissolved in a sodium hypochlorite solution, the mercury-laden solution is then passed through activated carbon to absorb the mercury, and the activated carbon is heated to produced metallic mercury. The latter methods are, however, no longer used (Drake, 1981; Simon *et al.*, 1990).

Industrial waste containing mercury also contributes to its production. The majority of plants using chloralkali electrolysis employ liquid mercury cathodes, resulting in residues containing 10% mercury or more. In addition to this major secondary source, mercury batteries, mercury fluorescent tubes, electrical switches, thermometer breakage and obsolete rectifiers should be regarded as sources of mercury. Scrap material and industrial and municipal wastes and sludges containing mercury are treated in much the same manner as ores to recover mercury. Scrap products are first broken down to liberate metallic mercury or its compounds. Heating in retorts vaporizes the mercury which, upon cooling, condenses to high-purity metallic mercury. Industrial and municipal sludges and wastes may be treated chemically before roasting (Drake, 1981; Simon *et al.*, 1990). Although the overall production of mercury has decreased over the last 20 years, sufficient potential uses, and therefore secondary sources, remain for the foreseeable future owing to the unique properties of the metal (Simon *et al.*, 1990).

Most of the metallic mercury on the market is 4N material (99.99% mercury). The most common purification methods include: *Dry oxidation*—with this method, readily oxidizable constituents such as magnesium, zinc, copper, aluminium, calcium, silicon and sodium can be removed by passing air or oxygen through the liquid metal; the oxides that form have a lower density than mercury and float on its surface, where they can be removed by filtration, scooping or by removing the mercury from the bottom. *Wet oxidation*—in an aqueous medium, mercury is dissolved by adding nitric, hydrochloric or sulfuric acid (see IARC, 1992) with dichromate, permanganate or peroxide to oxidize impurities; the aqueous solution can be separated from the mercury by decanting, and traces of water can be removed with calcium oxide. *Electrolytic refining*—perchloric acid containing mercuric oxide serves as the electrolyte. *Distillation*—mercury can be evaporated under atmospheric pressure or *in vacuo*; elements with a lower vapour pressure than mercury can be separated in this way. In many cases, mercury must be distilled repeatedly to achieve the desired purity (Simon *et al.*, 1990).

(*b*) *Mercuric acetate*

Mercuric acetate is produced by dissolving mercuric oxide in dilute acetic acid and concentrating the resulting solution (Simon *et al.*, 1990).

(*c*) *Mercuric chloride*

Mercuric chloride is prepared by the direct oxidation of mercury with chlorine gas, the same method (chamber method) that is used to prepare mercurous chloride, except that, for

mercuric chloride, an excess of chlorine gas is used to ensure complete reaction to the higher oxidation state; the reaction is carried out at temperatures > 300 °C. The escaping sublimate vapour is condensed in cooled receivers, where it settles as fine crystals. Excess chlorine is absorbed by sodium hydroxide in a tower; a very pure product results from use of this method (Singer & Nowak, 1981; Simon *et al.*, 1990).

Mercuric chloride can also be prepared from other mercury compounds. For example, if mercuric sulfate is heated in the dry state with sodium chloride, the evolving mercuric chloride vapour can be condensed to a solid in receivers (Simon *et al.*, 1990).

(*d*) *Mercuric oxide*

Mercuric oxide can be prepared *via* the anhydrous route by reaction of mercury and oxygen at 350–420 °C under oxygen pressure or by thermal decomposition of mercury nitrates at about 320 °C. Production *via* the wet route, by precipitation, is more important commercially: The oxide is precipitated from solutions of mercuric salts by addition of caustic alkali (usually mercuric chloride solutions with sodium hydroxide). Whether the yellow or the red form is obtained depends on the reaction conditions: Slow crystal growth during heating of mercury with oxygen or during thermal decomposition of mercurous nitrate leads to relatively large crystals (i.e. the red form); rapid precipitation from solution gives finer particles (i.e. the yellow form) (Simon *et al.*, 1990).

(*e*) *Dimethylmercury*

The reaction of methyl iodide with mercury–sodium amalgam gives dimethylmercury (Drake, 1981).

(*f*) *Methylmercury chloride*

Organomercury compounds can be synthesized by reaction of Grignard reagents with mercury halides. In order to obtain pure products, the mercury salt and the Grignard reagent must contain the same anion (R is an aromatic or aliphatic group and X is a halogen):

$$RMgX + HgX_2 \rightarrow RHgX + MgX_2$$

Organic mercury compounds can also be produced by the reaction of sulfinic acids (RSO_2H) or their sodium salts with mercury halides (Simon *et al.*, 1990).

(*g*) *Phenylmercury acetate*

Phenylmercury acetate is prepared by refluxing a mixture of mercuric acetate and acetic acid in a large excess of benzene (see IARC, 1987b), in what is generally referred to as a 'mercuration reaction'. The large excess of benzene is necessary because more than one hydrogen on the benzene ring can be replaced. The technical grade of phenylmercury acetate contains about 85% pure compound; the remaining 15% is di- and tri-mercurated products, which are less soluble than phenylmercury acetate and are removed by recrystallization. The product is isolated after distillation of excess benzene and acetic acid (Singer & Nowak, 1981).

1.2.2 *Use*

(*a*) *Metallic mercury*

The patterns of use of mercury in Germany and in the USA in different periods are presented in Tables 5 and 6. A major use of mercury is as a cathode in the electrolysis of sodium chloride solution to produce caustic soda and chlorine gas (chloralkali industry). About 50 tonnes of liquid metal are used in each of these plants. In most industrialized countries, stringent procedures have been taken to reduce losses of mercury. Mercury is used widely in the electrical industry (in lamps, arc rectifiers and mercury battery cells), in domestic and industrial control instruments (in switches, thermostats, barometers) and in other laboratory and medical instruments. Another use of liquid metallic mercury is in the extraction of gold from ore concentrates or from recycled gold articles (Kaiser & Tölg, 1984; Sax & Lewis, 1987; Budavari, 1989; Agency for Toxic Substances and Disease Registry, 1989; Simon *et al.*, 1990; WHO, 1991).

Table 5. Use patterns for mercury in Germany (%)

Use category	1973	1976	1979	1982	1985
Chloralkali industry	37	32	28	18	23
Catalysis	13	3	8	7	2
Paints, dyes	6	4	3	1	< 1
Pesticides	9	9	11	2	5
Electrical engineering	8	13	14	21	36
Control instruments and apparatus construction	4	3	4	7	4
Chemicals and reagents	7	14	14	21	None
Medicine	7	8	8	9	13
Miscellaneous	9	14	10	14	17
Total (tonnes)	346	325	313	257	182

From Simon *et al.* (1990)

Table 6. Use patterns for mercury in the USA (%)

Use category	1985	1987	1990	1991	1992
Electrical	64	56	35	33	29
Chloralkali industry	14	12	33	33	34
Paint	9	10	15		
Industrial and control instruments	6	6	7	34	37
Other	7	16	10		

From Carrico (1985, 1987); Reese (1990, 1991, 1992b)

WHO (1991) estimated that, in industrialized countries, about 3% of the total consumption of mercury is in dental amalgams. Dental amalgam is a mixture of mercury with a silver–tin alloy. Most conventional amalgams consist of approximately 45–50% mercury, 25–35% silver, 2–30% copper and 15–30% tin. In industrialized countries, the alloy with mercury is now mixed in sealed capsules and applied in the prepared tooth cavity, where excess amalgam (< 5%) is removed immediately before or during condensation of the plastic mix. The amalgam begins to set within minutes of insertion and must therefore be carved to a satisfactory anatomical form within that period of time. Polishing with rotating instruments can take place after 24 h. Amalgam has been used extensively as a tooth-filling material for more than 150 years and accounts for 75–80% of all single tooth restorations. It has been estimated that each US dentist in private practice uses an average of 0.9–1.4 kg of amalgam per year (Sax & Lewis, 1987).

(*b*) *Mercuric acetate*

Mercuric acetate is used in the synthesis of organomercury compounds, as a catalyst in organic polymerization reactions and as a reagent in analytical chemistry (Singer & Nowak, 1981; Simon *et al.*, 1990).

(*c*) *Mercuric chloride*

Mercuric chloride is an important intermediate in the production of other mercury compounds, e.g. mercurous chloride, mercuric oxide, mercuric iodide, mercuric ammonium chloride and organomercury compounds. It is also used as a catalyst in the synthesis of vinyl chloride, as a depolarizer in dry batteries and as a reagent in analytical chemistry. It has a minor importance as a wood preservative and retains some importance as a fungicide. Other uses (e.g. as a pesticide or in seed treatment) have declined considerably (Simon *et al.*, 1990).

(*d*) *Mercuric oxide*

Red mercuric oxide in particular has become increasingly important commercially in the production of galvanic cells with mercuric oxide anodes in combination with zinc or cadmium cathodes. These cells are distinguished from other systems in that their voltage remains constant during discharge: they are used mainly as small, button-shaped batteries, e.g. for hearing devices, digital watches, exposure meters, pocket calculators and security installations. Additional uses of mercuric oxide are in the production of mercury[II] salts, by treatment with the corresponding acids, and as a reagent in analytical chemistry. Its importance as an additive to antifouling paint for ships and in medicine (e.g. for eye ointment) has decreased (Simon *et al.*, 1990).

(*e*) *Dimethylmercury*

Dimethylmercury is an environmental contaminant that finds limited use as a laboratory reagent (Budavari, 1989; WHO, 1990).

(*f*) *Phenylmercury acetate*

The primary use for phenylmercury acetate has been in latex paint; it is used at low levels as a preservative and at higher levels to protect the dry film from fungal attack or mildew. It

can be used for these purposes in other aqueous systems, such as inks, adhesives and caulking compounds. Phenylmercury acetate is also used as the starting material in the preparation of many other phenylmercury compounds, which are generally prepared by double-decomposition reactions with the sodium salts of the desired acid groups in aqueous solution. It is also used as a slimicide in paper mills, as a catalyst for the manufacture of certain polyurethanes, as a research chemical (Singer & Nowak, 1981; Sax & Lewis, 1987; Budavari, 1989; Campbell *et al.*, 1992), in contraceptive gels and foams, as a preservative (including in shampoos: see IARC, 1993), as a disinfectant and as a denaturant in ethanol.

(*g*) *Other mercury-containing compounds*

A number of mercury-containing compounds have been used as topical antiseptics (mercuric iodide, mercuric cyanide, ammoniated mercuric chloride, merbromin [mercurochrome] and merthiolate) and as fungicides, mildewcides, insecticides and germicides (mercurous chloride, phenylmercury oleate, phenylmercury propionate, phenylmercury naphthenate, phenylmercury lactate, phenylmercury benzoate and phenylmercury borate) (Singer & Nowak, 1981; Sax & Lewis, 1987; Budavari, 1989; Simon *et al.*, 1990). A number of alkylmercury compounds are also used as fungicides in the treatment of seed grains (ethylmercury chloride, ethylmercury *para*-toluenesulfonanilide, ethylmercury acetate, ethylmercury 2,3-dihydroxypropyl mercaptide, bis[methylmercury]sulfate, methylmercury dicyandiamide and methoxyethylmercury acetate or chloride) (Greenwood, 1985; Sax & Lewis, 1987). Mercuric fulminate is used as a detonator in explosives (Singer & Nowak, 1981).

Mercury-containing creams and soaps have long been used by dark-skinned people in some regions to obtain a lighter skin tone. The soaps contain up to 3% mercuric iodide, and the creams contain up to 10% ammoniated mercury. Both the soap and the cream are applied to the skin, allowed to dry and left overnight (WHO, 1991).

1.3 Occurrence

1.3.1 *Natural occurrence*

Metallic mercury occurs as a part of the Earth's natural geochemistry, comprising 50 μg/kg of the Earth's crust. It is 62nd in order of abundance (Aylett, 1973). It is found in the form of the sulfide, as cinnabar ore, which has an average mercury content of 0.1–4%; it is also present in the form of geodes of liquid mercury and as impregnated schist or slate. The major source of atmospheric mercury is suggested to be degassing of the Earth's crust and the oceans (Lauwerys, 1983; Berlin, 1986; WHO, 1990).

Methylmercury compounds are formed in aquatic and terrestrial environments from the methylation of metallic mercury and mercuric mercury. Methylation is likely to occur in bacteria in sediments of sea- or lakebeds. The methylmercury compounds formed are accumulated by aquatic organisms, and dimethylmercury gases are formed by degradation and released into the air. Dimethylmercury can be decomposed in the atmosphere by acidic rainwater to monomethylmercury compounds and thus re-enter the aquatic environment (Berlin, 1986). Little is known about the quantitative aspects of these cycles, and the local load of methylmercury compounds can be increased considerably by anthropogenic sources (Clarkson *et al.*, 1988a; WHO, 1990).

1.3.2 *Occupational exposures*

Approximately 70 000 workers in the USA are regularly exposed to mercury (Campbell *et al.*, 1992). Table 7 lists some potential occupational exposures to the various forms of mercury. Mercury vapour is the commonest form to which workers are exposed in industries such as mining and processing of cinnabar ore and the chloralkali industry, where brine is electrolysed in mercury cells in which the cathode is a flowing sheet of liquid mercury. The manufacture and use of liquid mercury-containing instruments constitute another source of occupational exposure to mercury vapour through breakage, spillage or careless handling. Dental personnel are exposed to mercury vapours through the preparation of dental amalgams (Stokinger, 1981; Clarkson *et al.*, 1988b).

Table 7. Products, industries and jobs in which there is potential occupational exposure to mercury

Metallic mercury	Inorganic mercury compounds	Organomercury compounds
Dental medicine	Disinfectants	Bactericides
Batteries	Paints and dyes	Embalming preparations
Barometers	Explosives	Paper manufacture
Boiler makers	Fireworks manufacture	Farmers
Calibration instruments	Fur processing	Laundry and diaper services
Caustic soda production	Ink manufacture	External antiseptics
Carbon bush production	Chemical laboratory workers	Fungicides
Ceramics	Percussion caps and detonators	Insecticides manufacture
Chloralkali production	Spermicidal jellies	Seed handling
Ultrasonic amplifiers	Tannery workers	Wood preservatives
Direct current meters	Wood preservatives	Germicides
Infrared detectors	Tatooing materials	
Electrical apparatus	Taxidermists	
Electroplating	Vinyl chloride production	
Fingerprint detectors	Embalming preparations	
Silver and gold extraction	Mercury vapour lamps	
Jewellery	Antisyphilitic agents	
Fluorescent, neon, mercury arc lamps	Thermoscopy	
	Silvering of mirrors	
Manometers	Photography	
Paints	Perfumery and cosmetics	
Paper pulp manufacture	Acetaldehyde production	
Photography		
Pressure gauges		
Thermometers		
Semiconductor solar cells		

From Campbell *et al.* (1992)

Mixed exposure to aerosols of organic or inorganic mercury compounds also occurs: Chlorine in combination with mercury vapour, produced in chloralkali industries, forms mercuric chloride aerosols. Another source of occupational exposure is in pathology labo-

ratories, where mercuric chloride is used with formalin as a histological fixative. Exposure to aerosols of methyl- and ethylmercury compounds has been described in connection with the manufacture and use of mercuric salts and during seed treatment (Berlin, 1986). Disinfectant manufacturers, fungicide manufacturers, seed handlers, farmers, lumberjacks, pharmaceutical industry workers and wood preservers may be exposed to organomercury compounds (Campbell *et al.*, 1992).

Data on exposure to mercury in air and the results of biological monitoring in various industries and occupations are described below and summarized in Tables 8 and 9 (pp. 258–260). It should be noted that the concentrations of mercury detectable in the general working environment are generally lower than those to which individual workers are exposed, as detected by personal air sampling. This is due to the fact that mercury can accumulate on the clothes, hair and skin of workers, creating a situation which has been called 'micro-environmental exposure'. In a Belgian manufacturing plant, mercury concentrations in the general work environment were between 8 and 88 μg/m^3, while personal samples from the workers showed concentrations ranging from 16 to 680 μg/m^3 (see Ehrenberg *et al.*, 1991).

Biological monitoring of people occupationally exposed to mercury vapours and inorganic mercury compounds, by measuring mercury in urine and blood mercury, reflects recent exposure. Occupational and environmental exposure to methylmercury compounds can be estimated from blood mercury levels. Mercury in hair can be used as an indicator of environmental exposure to methylmercury compounds but not for monitoring exposure to metallic mercury and inorganic mercury compounds (Elinder *et al.*, 1988).

(*a*) *Chloralkali plants*

Exposures in chloralkali plants have been reviewed (WHO, 1976). In recent studies, covering mainly Swedish plants, average urinary mercury concentrations of 50–100 μg/L were reported (WHO, 1991).

In a study in the USA and Canada of 567 male workers in 21 chloralkali plants, the mean atmospheric concentration of mercury was 65 μg/m^3 (SD, 85); in 12 plants, the time-weighted average concentration was 100 μg/m^3 or less, while in the remainder some employees were exposed to higher concentrations. At an ambient air concentration of 100 μg/m^3, the concentration in blood was about 60 μg/L and that in urine about 200 μg/L. In 117 control subjects, blood mercury concentrations were lower than 50 μg/L; in 138 controls, urinary mercury concentrations were generally less than 10 μg/L (corrected to specific gravity) (Smith *et al.*, 1970).

The airborne concentrations of mercury in a chloralkali plant in Italy were between 60 and 300 μg/m^3; the mean urinary concentration in 55 workers exposed for 11.5 ± 8.8 years in cell preparation rooms was 158 μg/L (range, 0–762 μg/L) and that in 17 workers exposed to mercury irregularly for 15.2 ± 10.7 years was 40.3 μg/L (range, 0–96 μg/L) (Foà *et al.*, 1976).

The atmospheric concentrations of mercury in a chloralkali plant in Sweden in 1975 were 64 μg/m^3 (range, 36–112 μg/m^3); the mean blood mercury concentration in 13 workers employed for 0.5–5.5 years was 238 nmol/L (47.6 μg/L), and the mean urinary concentration in the same subjects was 808 nmol/L (range, 369–1530 nmol/L) [161 μg/L; range, 74–306 μg/L]. Two years later, after improvement of the ventilation systems in the plant, the mean concentrations of mercury were 22.6 (range, 15–43) μg/m^3 in air, 92 nmol/L

(18.4 μg/L) in blood and 196 (range, 117–327) nmol/L [39.2 μg/L; range, 23–65 μg/L] in urine in a group of 16 workers who had been employed for one to seven years (Lindstedt *et al.*, 1979).

Exposure to mercury in a chloralkali plant in Sweden was studied during ordinary maintenance work and in workers hired for a special repair task during a temporary production shutdown. A group of 14 normal maintenance workers were exposed to mean air concentrations of mercury of 65 μg/m^3 (range, 24–123 μg/m^3) and had a mean blood mercury concentration of 73 nmol/L, ranging from 45 to 150 nmol/L [14.6 μg/L; range, 9–30 μg/L], and a mean urinary concentration of 32 nmol/mmol (57.2 μg/g) creatinine (range, 16–43 nmol/mmol; 28.6–76.9 μg/g). The 16 special repair workers were exposed to a mean air concentration of 131 μg/m^3 (range, 38–437 μg/m^3) and had a mean blood mercury concentration of 148 nmol/L, ranging from 85 to 240 nmol/L [29.6 μg/L; range, 17–48 μg/L), and a mean urinary mercury concentration of 6.1 nmol/mmol (10.9 μg/g) creatinine (range, 4.7–8.7 nmol/mmol; 8.4–15.5 μg/g) (Sällsten *et al.*, 1992).

In an epidemiological study of 1190 workers in eight Swedish chloralkali plants (described in detail on p. 271), biological monitoring data indicated a substantial reduction in exposure to mercury with time, from about 200 μg/L in urine during the 1950s to 150 μg/L in the 1960s and less than 50 μg/L in 1990 (Barregård *et al.*, 1990). In another Swedish chloralkali plant, the average levels of mercury in air were 25–50 μg/m^3 throughout the 1980s. The mean concentrations of mercury in 26 male workers were 252 nmol/L (50.4 μg/L) in urine, 48 nmol/L (9.6 μg/L) in plasma and 78 nmol/L (15.6 μg/L) in erythrocytes, and those in 26 unexposed workers were 19 nmol/L (3.8 μg/L) in urine, 7.5 nmol/L (1.5 μg/L) in plasma and 33 nmol/L (6.6 μg/L) in erythrocytes (Barregård *et al.*, 1991). The mean concentrations of mercury in 1985–86 in another group of 89 chloralkali workers in Sweden, who had been exposed for 1–45 years, were 55 nmol/L (11 μg/L) in blood, 45 nmol/L (9 μg/L) in serum and 14.3 nmol/mmol (25.5 μg/g) creatinine in urine. The concentrations in a control group of 75 non-occupationally exposed workers were 15 nmol/L (3 μg/L) in blood, 4 nmol/L (0.8 μg/L) in serum and 1.1 nmol/mmol (1.95 μg/g) creatinine in urine (Langworth *et al.*, 1991).

In chloralkali plants, exposure to asbestos can occur during various maintenance operations (Barregård *et al.*, 1990; Ellingsen *et al.*, 1993).

(*b*) *Thermometer production*

In 1979, exposure to metallic mercury vapour was studied in a small thermometer factory in Israel with generally inadequate engineering and hygiene arrangements. The mean mercury concentrations in five workers exposed to 50–99 μg/m^3 were 299 nmol/L (59.8 μg/L) in urine and 105 nmol/L (21 μg/L) in blood; those in three workers exposed to 100–149 μg/m^3 were 449 nmol/L (89.8 μg/L) in urine and 122 nmol/L (24.4 μg/L) in blood; and those in seven workers exposed to 150–200 μg/m^3 were 628 nmol/L (125.6 μg/L) in urine and 143 nmol/L (28.6 μg/L) in blood (Richter *et al.*, 1982).

Concentrations of mercury were measured in four thermometer plants in Japan: The air concentrations ranged from 25 to 226 μg/m3; those of inorganic mercury compounds in blood ranged from 80 to 1150 nmol/L (16–230 μg/L); those of metallic mercury in blood ranged from not detected to 1.10 nmol/L (not detected–0.22 μg/L); those of inorganic

mercury compounds in urine ranged from 96 to 1560 nmol/L (19.2–312 μg/L); and those of metallic mercury in urine ranged from 0.05 to 1.22 nmol/L (0.01–0.24 μg/L) (Yoshida, 1985).

In a thermometer factory in the USA, 17 personal samples showed mean air concentrations of mercury of 75.6 μg/m^3 (range, 25.6-270.6); 11 area samples showed a mean of 56.7 μg/m^3 (range, 23.7–118.5). The mean urinary mercury concentration in 79 workers employed for 65 ± 48.9 months was 73.2 ± 69.7 μg/g creatinine (range, 1.3–344.5) (Ehrenberg *et al.*, 1991).

In a thermometer factory in Sweden, where filling with mercury was done inside a ventilated hood but with spillage of mercury during temperature conditioning and testing, the mean concentration of mercury in the air was 39 μg/m^3 (range, 15–58). In seven workers, the median blood mercury concentration was 57 nmol/L (11.4 μg/L), and in six workers, the median urinary concentration was 21 nmol/mmol (37.5 μg/g) creatinine (Sällsten *et al.*, 1992).

(*c*) *Hospitals*

In Belgium, a group of 40 chemical and biological laboratory technicians employed for < 1–15 years were exposed to an average airborne mercury concentration of 28 μg/m^3 (range, 2–124). The mean mercury concentration in urine was 10.72 ± 1.49 μg/g creatinine, and that in whole blood was 10.0 ± 0.9 μg/L. The mean mercury concentrations in a group of 23 unexposed technicians were 2.30 ± 1.49 μg/g creatinine in urine and 6.5 ± 1.1 μg/L in blood (Lauwerys & Buchet, 1973).

In a study in Scotland, use of mercuric chloride as a histological fixative was associated with high atmospheric concentrations of mercury vapour (up to 100 μg/m^3) and of all mercury compounds (200 μg/m^3). Twenty-one technicians exposed to this environment had a median urinary mercury output of 265 nmol (53 μg)/24 h. The median urinary output among a control group of 21 subjects was 72 nmol (14.4 μg)/24 h (Stewart *et al.*, 1977).

Hospital employees who repair sphygmomanometers or work in areas in which such machines are repaired are potentially exposed to mercury. In 13 hospitals in the USA, in which most employees had worked for less than 10 years, the airborne concentrations of mercury in repair rooms ranged from 1 to 514 μg/m^3, and 86 employees tested had a mean urinary mercury concentration of 12.4 μg/L (range, 1–200) (Goldberg *et al.*, 1990).

(*d*) *Dental personnel*

Special interest has focused on occupational exposure to mercury in dentistry. Several studies conducted during 1960–80 reported average concentrations of mercury vapour in dental clinics ranging between 20 and 30 μg/m^3 air; in certain clinics concentrations of 150–170 μg/m^3 were measured (WHO, 1991). In some of these studies, urinary mercury concentrations of dental personnel were also reported.

An average urinary mercury concentration of 40 μg/L was found among 50 dentists in the USA, with some values exceeding 100 μg/L (Joselow *et al.*, 1968). In a nationwide US study, the average mercury concentration in the urine of 4272 dentists sampled between 1975 and 1983 was 14.2 μg/L (range, 0–556 μg/L). In 4.9% of the samples, the concentrations were ≥ 50 μg/L, and in 1.3% they were > 100 μg/L. The wide range of values was probably due to variations in occupational exposure to amalgams with time, in addition to variations in

sampling techniques and other methodological problems (Naleway *et al.*, 1985). At the annual sessions of the American Dental Association, on-site screening for exposure to mercury showed mean urinary concentrations of 5.8 μg/L in 1042 dentists in 1985 and 7.6 μg/L in 772 dentists in 1986; 10% contained concentrations above 20 μg/L (Naleway *et al.*, 1991).

Blood samples from a group of 130 dentists in Denmark in 1986 contained a median mercury concentration of 4.0 μg/L (range, 1.2–19.2); 2.0 μg/L (1.1–4.6) were found in controls. Practice characteristics, as stated on questionnaires, were not significantly related to blood mercury concentration, but 49 dentists who ate one or more fish meals per week had a median concentration 47% higher than that of dentists who seldom consumed fish (Möller-Madsen *et al.*, 1988).

In 82 dental clinics in northern Sweden, the median concentration of mercury vapour in air was 1.5 μg/m^3 in public surgeries and 3.6 μg/m^3 in private ones. The urinary mercury concentrations in 505 occupationally exposed subjects ranged from 1.4 to 2.9 nmol/mmol (2.5–5.13 μg/g) creatinine, which are of the same order of magnitude as those of the Swedish population as a whole. The load derived from the amalgam fillings of the exposed subjects was estimated to be of the same order of magnitude as that from the working environment (Nilsson *et al.*, 1990). In the offices of six dentists in Sweden, the mean concentration of mercury in air was 4.5 μg/m^3 (range, 1.7–24); the mean concentrations in 12 subjects were 17 nmol/L (range, 6–29) (3.4 μg/L; range, 1.2–5.8 μg/L) in blood and 2.6 nmol/mmol (4.6 μg/g) creatinine (range, 1.1–5.4 nmol/mmol; 2.00–9.65 μg/g) (Sällsten *et al.*, 1992). In 224 dental personnel in Sweden, the levels of mercury in urine (1.8 nmol/mmol [3.19 μg/g] creatinine) were not significantly higher than those of 81 referents (1.1 nmol/mmol [1.95 μg/g] creatinine), and no difference was seen for the plasma or blood levels. When adjustment was made, however, for amalgam fillings in the mouths of the personnel, significant differences in urinary, plasma and blood mercury concentrations were seen (Akesson *et al.*, 1991).

Urinary excretion of inorganic mercury compounds was determined in 50 individuals attached to Madras Dental College, India. The lowest concentration observed was 3 μg/L and the highest, 136.6 μg/L. Of those subjects who handled mercury, 70% had urinary concentrations > 20 μg/L (Karthikeyan *et al.*, 1986).

(*e*) *Others*

The airborne concentrations of mercury in Idrija, Slovenia, in 1950 were reported to be 0.05–5.9 mg/m^3 in a mine and 0.17–1.1 mg/m^3 in a smelter (Vouk *et al.*, 1950). Similar values were reported during a survey conducted in 1963: 0.1–2.0 mg/m^3 in both the mine and the smelter. The average concentration of mercury in blood from 57 asymptomatic miners in Idrija was 77 μg/L (range, 0–450); the corresponding value in 16 workers with symptoms of intoxication was 110 μg/L (range, 0–510). The concentrations in urine were 276 μg/L (range, 0–1275) in the asymptomatic miners and 255 μg/L (range, 2.0–601) in those with symptoms (Ladd *et al.*, 1966).

Concentrations > 2.0 mg/m^3 were detected in 1964 in a mine and smelter on Palawan Island, the Philippines (Ladd *et al.*, 1966).

The average concentrations of mercury in the air in various departments in the Italian hat manufacturing industry in 1942–52 were 0.09–2.21 mg/m^3. The concentrations were > 0.2 mg/m^3 in 13 of the 17 departments studied, and concentrations as high as 4 mg/m^3 were measured in specific locations (Baldi *et al.*, 1953).

In a mercury distillation plant in Italy, airborne mercury concentrations ranged from 0.005 to 0.278 mg/m^3; the mean urinary concentration in 19 workers was 108.26 ± 55.61 µg/L and the mean blood concentration, 77 ± 28 µg/L. In 13 subjects in a control group, the urinary mercury concentration was < 10 µg/L, while in 11 other subjects, the mean value was 15.27 µg/L (range, 11–21) (Angotzi *et al.*, 1980).

In a recycling distillation plant in Germany, the concentration of mercury in air in February 1984 ranged from 115 to 379 µg/m^3; in 12 workers in the plant, mercury was found at 28–153 µg/L in blood and 128–609 µg/g creatinine in urine. In previous years, the levels of both biological indicators (determined since 1978) were decidedly higher: 44–255 µg/L in blood and 143–1508 µg/g creatinine in urine. The authors cited the 'normal' values for mercury as 0.2–7.2 µg/L (mean, 0.6) in blood and 0.2–5.0 µg/g creatinine (mean, 0.8) in urine (Schaller *et al.*, 1991).

Individual external exposure in a dry alkaline battery plant in Belgium was to 40 µg/m^3 mercury, ranging from 10 to 106 µg/m^3. Urinary mercury concentrations were usually < 50 µg/g creatinine in some parts of the plant and between 50 and 100 µg/g creatinine in others (Roels *et al.*, 1987).

In a plant for the manufacture of fluorescent lamps in Italy, the mercury concentrations in air in maintenance areas in 1984–85 were between 2 and 5 µg/m^3; 27 workers employed for 10.96 ± 1.14 years in those areas had mean urinary concentrations of 5.15 ± 2.2 µg/L (range, 2–11). In the same plant, the concentrations in the air of production areas varied between 6 and 44 µg/m^3, and 22 workers employed for 10.34 ± 1.43 years in those areas showed mean urinary concentrations of 4.94 ± 1.62 µg/L (range, 1.9-8) (Assennato *et al.*, 1989).

In a study of reproductive function among women employed at a mercury vapour lamp factory (described in detail on pp. 296–297), De Rosis *et al.* (1985) reported that time-weighted average concentrations exceeded 50 µg/m^3 in 1972–76; after modification of the ventilation system, the concentrations dropped to < 10 µg/m^3.

1.3.3 *Air*

The most important sources of mercury in the atmosphere are degassing of the Earth's crust, emissions from volcanoes and evaporation of mercury vapours from natural bodies of water. Recent estimates indicate that these natural emissions amount to 2700–6000 tonnes per year; however, it is difficult to determine the relative contributions of natural and anthropogenous sources to the general emission of mercury in the biosphere, since some may have been deposited in water from the atmosphere and produced by human activities (WHO, 1990). Traditional municipal solid-waste incinerators may have a significant impact on the ambient air concentration as well as on the deposition rates of mercury. Rates of emission of mercury from traditional incinerators in Europe, Canada and the USA range from 100 to 2200 µg/m3 and those from advanced incinerators, 30–200 µg/m^3. Such emissions could result in deposition rates of 0.2–4.0 and 0.02–1.0 µg/m^2 per day, respectively (WHO, 1988).

Table 8. Occupational exposure to mercury in various industries and occupations

Industry and activity (country) [year, when available]	No. of workers	Air (μg/m³)		Urine (μg/L, except where noted)		Blood (μg/L)		Reference
		Mean±SD	Range	Mean±SD	Range	Mean±SD	Range	
Chloralkali plants (USA and Canada; 21 plants) Cell room	567	65±85	< 10–270 (TWA) < 1–2640					Smith *et al.* (1970)
Chloralkali plant (Italy) Cell rooms Miscellaneous	72 55 17		60–300	157.79±120.94 40.29±26.16	0–762 0–96			Foà *et al.* (1976)
Chloralkali plant [1975] (Sweden) [1977]	13 16	64±21.8 22.6±7	36–112 15–43	161.6±62.8 39.2±14.4	74–306 23–65	47.6±23.8 18.4±6.8		Lindstedt *et al.* (1979)
Chloralkali plant (Sweden)	26	NR	25–50	50.4	5–186	NR		Barregård *et al.* (1991)
Chloralkali plant (Sweden) [1985–86]	89	NR	NR	25.5[a]	0.5–84[a]	11		Langworth *et al.* (1991)
Chloralkali plant (Sweden) Normal maintenance	NR	65 (14 samples)	24–123	57[a] (8 samples)	29–77[a]	14.6 (8 samples)	9–30	Sällsten *et al.* (1992)
Special maintenance	NR	131 (16 samples)	38–437	10.9[a] (5 samples)	8.4–15[a]	29.6 (7 samples)	17–48	
Thermometer factory (Israel) [1979]	5 3 7	NR	50–99 100–149 150–200	59.8 89.8 125.6		21 24.4 28.6		Richter *et al.* (1982)
Thermometer factories (Japan; 4 factories)	27	NR	25–226	NR	19–312	NR	16–230	Yoshida (1985)
Thermometer factory (USA)	84	75.6 (17 samples)	25.6–271	73.2±69.7[a] (79 samples)	1.3–344.5[a]			Ehrenberg *et al.* (1991)
Thermometer factory (Sweden)	NR	39 (13 samples)	15–58	37.5[a] (6 samples)	1.96–91[a]	11.4 (7 samples)	6–20	Sällsten *et al.* (1992)
Pathology laboratory (Belgium)	40	28	2–124	10.72±1.49[a]	NR	10.0±0.9		Lauwerys & Buchet (1973)

Table 8 (contd)

Industry and activity (country) [year, when available]	No. of workers	Air (μg/m³)		Urine (μg/L, except where noted)		Blood (μg/L)		Reference
		Mean±SD	Range	Mean±SD	Range	Mean±SD	Range	
Pathology laboratory (United Kingdom)	21	200		26.5		NR		Stewart *et al.* (1977)
Sphygmomanometer repair (USA; 13 facilities)	93	86	1–514	12.4±22.2 (86 samples)	1–200	NR		Goldberg *et al.* (1990)
Dental staff (USA) [1975–83]	4272	NR	NR	14.2±25.4	0–556	NR		Naleway *et al.* (1985)
Dental staff (India)	50	NR	NR	NR	3–136.6	NR		Karthikeyan *et al.* (1986)
Dental staff (Sweden; 82 clinics) [1983]	505	NR	1.5–3.6	NG	2.5–5.13	NG		Nilsson *et al.* (1990)
Dental staff (USA) [1985]	1042	NR	NR	5.8±8.5	max, 84	NR		Naleway *et al.* (1991)
[1986]	772			7.6±11.8	max, 115			
Dental staff (Denmark) [1986]	130	NR	NR	NR	NR	4.0	1.2–19.2	Möller-Madsen *et al.* (1988)
Dental staff (Sweden; 6 offices)	NR	4.5 (36 samples)	1.7–24	4.6	1.96–9.65	3.4	1.2–5.8	Sällsten *et al.* (1992)
Mercury distillation (Italy) [1976–78]			5–279					Angotzi *et al.* (1980)
Distillation	19	NR		108.26±55.61	NR	77±28		
Maintenance	19	NR		84.11±45.54	NR	53±16		
Recycling plant (Germany) [1984]	12		115–379		128–609[a]	28–153		Schaller *et al.* (1991)
Dry alkaline battery plant (Belgium) [1984]	10	40 (46 samples)	10–106	< 100[a] (10 samples)				Roels *et al.* (1987)
Fluorescent lamps (Italy) [1984–85]								Assennato *et al.* (1989)
Maintenance	27	NR	2–5	5.15±2.2	2–11	NR		
Production	22	NR	6–44	4.94±1.62	1.9–8	NR		

NR, not reported
[a]μg creatinine

Table 9. Concentration of mercury in the air of work places in Finland during 1977–88 and in blood in 1987

Industrial code or work	Air concentrations (μg/m^3)			Concentration in blood (μg/L)			
	No. of measurements	Mean	Range	No. of workplaces	No. of measurements	Mean	Range
Seed dressing and packing	11	4	1–13	10	27	3.6	1–9
Pesticide manufacture	8	58	29–105	1	24	10.4	3–46
Mercury production	NR	32	13–157	NR	NR	NR	NR
Welding	24	88	2–150	NR	NR	NR	NR
Manufacture of light bulbs, fluorescent tubes and batteries	133	30	1–250	5	17	5.8	2–8
Laboratory work	26	15	1–120	NR	NR	NR	NR
Dentistry	136	10	1–100	21	42	4.4	1–9
Chlorine industry	NR	NR	NR	3	518	13.6	1–69

From Anttila *et al.* (1992). NR, not reported

Mercury concentrations in the atmosphere range from a few nanograms per cubic metre over remote, uncontaminated areas to about 20 ng/m^3 in urbanized areas. Concentrations have been estimated to be 2 ng/m^3 in the northern hemisphere and about 1 ng/m^3 in the southern hemisphere. Concentrations of mercury up to 18 ng/m^3 have been reported in the atmosphere close to active volcanoes (Berlin, 1986; Clarkson *et al.*, 1988a).

Mercury vapour is believed to be the predominant form in the atmosphere. There is evidence that some of the mercury in ambient air is in the form of alkylmercury, and the presence of methylmercury compounds has been reported. The particulate fraction of mercury in air (as a percentage of total mercury) is usually 4% or less (WHO, 1990).

Another source of mercury in the atmosphere is the release of metallic mercury vapour during the cremation of cadavers, when all the mercury from amalgam fillings vaporizes as the temperature reaches above 800 °C. It is difficult to estimate the global release of mercury from cremation because of the uncertainties about dental status at the time of death and about the frequency of cremation (WHO, 1991).

1.3.4 *Water*

Mercury is removed from the atmosphere mainly by precipitation. The chemical species of mercury in water is mainly ionic mercury[II]. Concentrations of mercury in surface water are very low, and accurate analysis is still a problem. Total mercury concentrations range from 0.5 to 3 ng/L in open oceans, from 2 to 15 ng/L in coastal seawater and from 1 to 3 ng/L on average in freshwater rivers and lakes (WHO, 1990). The bottom sediment of lakes and oceans may contain 20–250 µg/kg mercury (Berlin, 1986). Concentrations in drinking-water are generally less than 25 ng/L (WHO, 1990).

Concentrations of mercury in inland waters of gold-mining areas in Rondônia, Brazil, were between < 0.1 and 8.6 µg/L (Pfeiffer *et al.*, 1989). A study of water from the Madeira River and its tributaries, in the centre of the gold rush area in Brazil, showed an average mercury level of 24.6 ng/L (Nriagu *et al.*, 1992).

1.3.5 *Soil and plants*

The commonest form of mercury in soil is the bivalent ion. Concentrations measured in soils are generally less than 1 ppm (mg/kg). Methylation of mercury has been demonstrated in soil and is influenced by humidity, temperature and the mercury concentration of the soil (Sequi, 1980; Simon *et al.*, 1990).

The accumulation of mercury in plants increases with increasing soil concentration. Soil type has a considerable influence on this process: a high content of organic matter decreases the uptake. Generally, the highest concentrations of mercury are found at the roots, but translocation to other organs (e.g. leaves) occurs. In contrast to higher plants, mosses take up mercury from the atmosphere (WHO, 1989a).

Mercury concentrations in bottom sediments of Brazilian polluted rivers ranged between 50 and 19 800 µg/kg (Pfeiffer *et al.*, 1989).

1.3.6 *Food*

Environmental contamination with mercury leads to a critical concentration effect in animals that occupy higher positions in the food chain (large fish and fish-eating sea fowl)

(Simon *et al.*, 1990). The factors that determine the methylmercury concentration in fish are the mercury content of the water and bottom sediments, the pH and redox potential of the water and the species, age and size of fish (Berlin, 1986).

The concentrations of mercury in most foods are generally below the reported limit of detection, which is usually 20 μg/kg fresh weight. A large proportion of the mercury in food—at least in animal products—is likely to be in the form of methylmercury compounds. Most of the mercury in fish is as methylmercury compounds, which are formed in the bottom sediment of the ocean and in freshwater systems and are enriched to a high degree in the aquatic food chain, with the highest levels occurring in the predatory fish: The concentrations of total mercury in edible tissues of shark and swordfish are > 1200 μg/kg, whereas anchovies and smelt have average values of < 85 μg/kg (Berlin, 1986; WHO, 1990).

In a survey sponsored by the Ministry of Food, Agriculture and Forestry of Germany, the average mercury contamination of 759 specimens of fish from German fishing grounds was < 100 μg/kg (Jacobs, 1977). The mercury concentrations in edible parts of fish from polluted rivers in Brazil were between 70 and 2700 μg/kg wet wt (Pfeiffer *et al.*, 1989).

The average daily intake of mercury can be estimated by assuming that intake from non-fish food sources is negligible in comparison with that from fish. FAO estimated an average worldwide fish intake of 16 g per person per day but an average daily intake of 300 g in populations that are largely dependent on fish; therefore, the average daily intake of total mercury will result in 3 μg, of which 80% is methylmercury compounds and 20% inorganic mercury. The average intake of methylmercury compounds can thus be calculated as 2.4 μg per day, with 2.16 μg retained (90% absorption), and the average daily intake of inorganic mercury is 0.6 μg per day, with 60 ng retained (10% absorption) (Clarkson *et al.*, 1988a; Table 10). Daily intake from the consumption of fish from polluted water, however, can rise to toxic levels, as occurred in Minamata and Niigata in Japan around 1953–66: Concentrations of 1–20 mg/kg in fish resulted in daily intake, in people with frequent fish consumption (200–500 g per day), of 5 mg per day (Berlin, 1986).

Table 10. Estimated average daily intake and retention of various forms of mercury in populations not occupationally exposed to mercury

Source	Estimated daily intake and retention (ng mercury/day)					
	Mercury vapour		Inorganic mercury compounds		Methylmercury compounds	
	Intake	Absorbed	Intake	Absorbed	Intake	Absorbed
Atmosphere	40	32				
Water			50	5		
Food			600	60	2400	2160
Total intake	40		650		2400	2160
Absorbed		32		65		

From Clarkson *et al.* (1988a)

Toxic levels have also been reached following consumption of bread prepared from wheat treated with methylmercury dicyandiamide fungicide, as occurred in Iraq in the winter of 1971–72 (Bakir *et al.*, 1973; Greenwood, 1985).

1.3.7 *Dental amalgam*

Dental amalgams are a potential source of exposure to mercury vapour not only for dental staff but also for the general population. Hardening of the amalgam continues over many months, so that stress on the amalgam surface, produced by chewing or grinding of the teeth, causes breakdown of a surface barrier and release of mercury vapour into the mouth. This results in the deposition of mercury in body tissues like kidney and brain and increased urinary excretion. The release of mercury from amalgams makes a significant contribution to human exposure to inorganic mercury, including mercury vapour (Clarkson *et al.*, 1988b; WHO, 1991; US Department of Health and Human Services, 1993).

Different concentrations of mercury are released from unstimulated amalgams (3.3–7.4 ng/min) and stimulated amalgams (16.3–163.2 ng/min) (Clarkson *et al.*, 1988b). Average daily intake of metallic mercury vapour can thus range from 3.8 to 21 μg/day, with corresponding retentions of 3–17 μg/day (WHO, 1990, 1991).

In 147 individuals in an urban Norwegian population, correlations were found between the concentrations of mercury in urine (mean, 17.5 nmol/L [3.5 μg/L]) and in exhaled air (mean, 0.8 $\mu g/m^3$) and between both urinary and air concentrations and the number of amalgam restorations, the number of amalgam-restored surfaces and the number of amalgam-restored occlusal surfaces. The results suggested that individuals with more than 36 restored surfaces absorb 10–12 μg of mercury per day (Jokstad *et al.*, 1992).

1.3.8 *Mercury-containing creams and soaps*

The mean concentration of mercury in the urine of 60 African women who used skin-lightening creams, containing 5–10% ammoniated mercury, was 109 μg/L (range, 0–220). Those in the urine of six women who had used skin-lightening creams containing 1–3% ammoniated mercury for two years ranged from 28 to 600 μg/L (WHO, 1991).

Mercury was found in the blood (91.1 μg/L) and urine (784 μg/g creatinine) of a woman who had been using soap containing 1% mercuric iodide for about 15 years. Mercury was also present in the blood (19 μg/L) and urine (274 μg/g creatinine) of her three-month-old child, who was not directly exposed to mercury (Lauwerys *et al.*, 1987).

1.3.9 *Mercury-containing paint*

Air samples from 19 homes recently painted with an interior latex paint with a median mercury concentration of 754 mg/L contained a median of 2 $\mu g/m^3$ mercury, while concentrations in 10 uncoated houses were below the detection limit of 0.1 $\mu g/m^3$. The median concentration in urine was higher for 65 exposed inhabitants (8.4 μg/g creatinine) than for 28 unexposed people (1.9 μg/g creatinine) (Agocs *et al.*, 1990; WHO, 1991).

1.3.10 *Human tissues and secretions*

In order to establish reference values for mercury concentrations in whole blood, blood cells and plasma, 98 publications in the international scientific literature presenting

biological data on individuals not occupationally exposed to mercury were reviewed critically and graded for quality (Brune *et al.*, 1991). The mean levels of mercury in non-fish eaters were 2.0 μg/L (10th-90th percentiles, 0–4.3) in whole blood, 3.8 (2.8–4.8) in blood cells and 1.3 (0.3–2.3) μg/L in plasma. Although the authors recognized the importance of retrieving information on the number of amalgam restorations, few data were available.

In 380 Italian subjects non-occupationally exposed to mercury, the mean urinary concentration of mercury was 3.5 μg/L (range, 0.1–6.9) (Minoia *et al.*, 1990). Average urinary mercury concentrations in 50 male and 54 female residents of the Monte Amiata mercury mine area in Italy were greater than those in 104 controls from other regions of the country: men, 2.3 μg/g creatinine (95% CI, 1.7–3.0); women, 3.9 μg/g creatinine (95% CI, 2.2–5.6); men and women combined, 3.1 μg/g creatinine (95% CI, 2.2–4.1) (Cicchella *et al.*, 1968).

Mercury levels in the hair of unexposed populations are generally between 0.5 and 4 mg/kg. Hair mercury is indicative of blood mercury concentration at the point of growth, so that sequential analysis of hair segments provides information on past exposure to mercury and particularly to organomercury compounds (Bakir *et al.*, 1973; Kazantzis *et al.*, 1976).

In Sweden, increased concentrations of mercury were found in samples from former dental staff (seven dentists and one dental assistant) of the pituitary gland (average, 9.8 μmol [1.96 mg]/kg wet weight; range, 0.7–28 [0.14–5.6]), occipital cortices (average, 0.33 μmol [0.07 mg]/kg wet weight; range, 0.07–1.43 [0.014–0.3]), renal cortices (average, 8.6 μmol [1.7 mg]/kg wet weight; range, 4.7–11.3 [0.9–2.3]), and thyroid gland (range, 0.32–140 μmol [0.06–28 mg]/kg wet weight). Mercury was found together with selenium at a rough stoichiometric ratio of 1:1. In the general population, the average concentrations were 0.12 (0.03–5.83) μmol/kg wet weight in pituitary gland, 0.053 (0.012–0.114) in occipital cortices, 1.4 (0.11–4.04) in renal cortices and 0.019 (0.004–0.047) in abdominal muscles (Nylander & Weiner, 1991).

1.4 Regulations and guidelines

Occupational exposure limits and guidelines established in different parts of the world are given in Table 11. The recommended health-based occupational exposure limit is 0.05 mg/m^3 (WHO, 1980; Simon *et al.*, 1990). The recommended health-based limit for long-term occupational exposure to mercury vapours is 50 μg/g creatinine in urine (WHO, 1980).

The American Conference of Governmental Industrial Hygienists (1992) gave notice of their intent to establish biological exposure indices for mercury in blood and urine. The values proposed are 35 μg/g creatinine for total inorganic mercury in urine in preshift samples and 15 μg/L for total inorganic mercury in blood at the end of a working week. The German biological tolerance values for metallic mercury and inorganic mercury compounds are 50 μg/L in blood and 200 μg/L in urine; that for organomercury compounds is 100 μg/L in blood (Deutsche Forschungsgemeinschaft, 1992). The Finnish guideline values for biological measurements are 10 μg/L in blood and 25 μg/L in urine (Anttila *et al.*, 1992).

The WHO recommended guideline for all forms of mercury in drinking-water is 1 μg/L (WHO, 1992). The maximum contaminant level of mercury in drinking-water and the

permissible level in bottled water in the USA is 2 μg/L (US Environmental Protection Agency, 1991; US Food and Drug Administration, 1992).

Table 11. Occupational exposure limits and guidelines for mercury and mercury compounds

Country or region	Year	Concentration (mg/m^3)	Substances affected	Interpretation[a]
Australia	1990	0.01	Alkyl mercury compounds (as Hg)	TWA, S
		0.03	Alkyl mercury compounds (as Hg)	STEL, S
		0.05	Mercury and mercury vapour	TWA, S
		0.1	Aryl mercury compounds, inorganic mercury compounds (as Hg)	TWA, S
Austria	1982	0.1	Mercury and mercury vapour	TWA
		0.01	Organic mercury compounds (as Hg)	TWA, S
Belgium	1990	0.01	Alkyl mercury compounds (as Hg)	TWA, S
		0.03	Alkyl mercury compounds (as Hg)	STEL, S
		0.05	Mercury and mercury vapour, mercury compounds except alkyls (as Hg)	TWA, S
		0.1	Aryl mercury compounds, inorganic mercury compounds (as Hg)	TWA, S
Brazil	1978	0.04	Inorganic mercury compounds (as Hg)	TWA
Bulgaria	1984	0.01	Mercury and mercury vapour, inorganic mercury compounds (as Hg)	TWA
Chile	1983	0.008	Alkyl mercury compounds (as Hg)	TWA, S
		0.04	Mercury and mercury vapour	TWA
China	1979	0.01	Mercury and mercury vapour	TWA
		0.005	Organic mercury compounds (as Hg)	TWA, S
Former Czechoslovakia	1991	0.05	Mercury and mercury vapour, mercury compounds except mono- and dialkyls (as Hg)	TWA
		0.15	Mercury and mercury vapour, mercury compounds except mono- and dialkyls (as Hg)	Ceiling
Denmark	1990	0.01	Alkyl mercury compounds (as Hg)	TWA, S
		0.05	Mercury and mercury vapour, mercury compounds except alkyls (as hg)	TWA
Egypt	1967	0.1	Mercury and mercury vapour	TWA
Finland	1992	0.01	Alkyl mercury compounds (as Hg)	TWA, S
		0.05	Mercury and mercury vapour, inorganic mercury compounds (as Hg)	TWA
France	1990	0.01	Alkyl mercury compounds (as Hg)	TWA, S
		0.05	Mercury and mercury vapour	TWA, S
		0.1	Aryl mercury compounds, inorganic mercury compounds (as Hg)	TWA, S
Germany	1992	0.1	Mercury and mercury vapour	TWA, S
		0.01	Organic mercury compounds except methylmercury (as Hg) (total dust)	TWA, S, sensitizer
		0.01	Methylmercury (total dust)	TWA, PR1, S, sensitizer

Table 11 (contd)

Country or region	Year	Concentration (mg/m^3)	Substances affected	Interpretation[a]
Hungary	1990	0.02	Mercury and mercury vapour, inorganic mercury compounds (as Hg)	TWA, sensitizer
		0.04	Mercury and mercury vapour, inorganic mercury compounds (as Hg)	STEL
		0.01	Inorganic mercury compounds (as Hg)	STEL
		0.01	Organic mercury compounds except mono- and dialkyl compounds (as Hg)	TWA, STEL
India	1983	0.01	Alkyl mercury compounds (as Hg)	TWA, S
		0.03	Alkyl mercury compounds (as Hg)	STEL, S
		0.05	Mercury and mercury vapour	TWA
		0.15	Mercury and mercury vapour	STEL
Indonesia	1978	0.01	Organic mercury compounds (as Hg)	TWA, S
		0.1	Alkyl mercury compounds (as Hg)	TWA, S
Italy	1978	0.01	Organic mercury compounds (as Hg)	TWA, S
		0.05	Inorganic mercury compounds (as Hg)	TWA, S
Japan	1991	0.05	Mercury and mercury vapour, mercury compounds except alkyl compounds (as Hg)	TWA
Mexico	1991	0.05	Mercury compounds except alkyl compounds (Hg)	TWA
		0.01	Alkyl mercury compounds (as Hg)	TWA
		0.03	Alkyl mercury compounds (as Hg)	15-min, 4 ×/day, 1-h interval
Netherlands	1986	0.05	Inorganic mercury compounds (as Hg)	TWA
		0.01	Alkyl mercury compounds (as Hg)	TWA, S
Poland	1990	0.01	Mercury and mercury vapour, organic mercury compounds (as Hg)	TWA
		0.05	Inorganic mercury compounds (as Hg)	TWA
Republic of Korea	1983	0.05	Mercury and mercury vapours	TWA
		0.03	Alkyl mercury compounds (as Hg)	TWA
Romania	1975	0.05	Mercury and mercury vapour	TWA, S
		0.15	Mercury and mercury vapour	STEL, S
		0.01	Organic mercury compounds (as Hg)	STEL, S
Sweden	1992	0.01	Alkyl mercury compounds (as Hg)	TWA, S
		0.05	Mercury and mercury vapour, mercury compounds except alkyl compounds (as Hg)	TWA, S
Switzerland	1990	0.05	Mercury and mercury vapour	TWA, S
		0.01	Organic mercury compounds (as Hg)	TWA, S, sensitizer
		0.1	Inorganic mercury compounds (as Hg)	TWA, PR1, S, sensitizer
Taiwan	1981	0.01	Organic mercury compounds (as Hg)	TWA, S
		0.05	Inorganic mercury compounds (as Hg)	TWA, S

Table 11 (contd)

Country or region	Year	Concentration (mg/m^3)	Substances affected	Interpretation[a]
United Kingdom	1992	0.01	Alkyl mercury compounds (as Hg)	TWA, S
		0.03	Alkyl mercury compounds (as Hg)	STEL, S
		0.05	Mercury and mercury vapour, mercury compounds except alkyls (as Hg)	TWA
		0.15	Mercury and mercury vapour, mercury compounds except alkyls (as Hg)	STEL (10 min)
USA				
OSHA	1992	0.01	Alkyl mercury compounds (as Hg), organic mercury compounds (as Hg)	TWA, PEL, S
		0.03	Alkyl mercury compounds (as Hg), organic mercury compounds (as Hg)	STEL, PEL, S
		0.05	Mercury and mercury vapour	TWA, PEL, S
		0.1	Aryl mercury compounds, inorganic mercury compounds (as Hg)	Ceiling, PEL, S
NIOSH	1990	0.01	Alkyl mercury compounds (as Hg), organic mercury compounds (as Hg)	TWA, REL, S
		0.03	Alkyl mercury compounds (as Hg), organic mercury compounds (as Hg)	STEL, REL, S
		0.05	Mercury and mercury vapour	TWA, REL, S
ACGIH	1992	0.01	Alkyl mercury compounds (as Hg)	TWA, TLV, S
		0.03	Alkyl mercury compounds (as Hg)	STEL, TLV, S
		0.05	Methylmercury, all forms except alkyl vapours	TWA, TLV, S
		0.1	Aryl mercury compounds, inorganic mercury compounds (as Hg)	TWA, TLV, S
Former USSR	1990	0.005	Mercury and mercury vapour	TWA
		0.05	Inorganic mercury compounds (as Hg)	TWA
		0.2	Inorganic mercury compounds (as Hg)	STEL
Venezuela	1978	0.01	Alkyl mercury compounds (as Hg)	TWA, S
		0.03	Alkyl mercury compounds (as Hg)	Ceiling, S
		0.05	Inorganic mercury compounds (as Hg)	TWA
		0.15	Inorganic mercury compounds (as Hg)	Ceiling
Former Yugoslavia	1971	0.1	Mercury and mercury vapour	TWA
		0.01	Alkyl mercury compounds (as Hg)	TWA, S

From Arbeidsinspectie (1986); Cook (1987); US Occupational Safety and Health Administration (OSHA) (1992); US National Institute for Occupational Safety and Health (1990); International Labour Office (1991); American Conference of Governmental Industrial Hygienists (ACGIH) (1992); Arbejdstilsynet (1992); Deutsche Forschungsgemeinschaft (1992); Health & Safety Executive (1992); UNEP (1993)

[a]The concentrations given may or may not have regulatory or legal status in the various countries; for interpretation of the values, the original references or other authoritative sources should be consulted. PR1, a risk of damage to the developing embryo or fetus has been demonstrated unequivocally, even when exposure limits have been adhered to; S, absorption through the skin may be a significant source of exposure; TWA, time-weighted average; STEL, short-term exposure limit; PEL, permissible exposure limit; REL, recommended exposure limit; TLV, threshold limit value.

The Joint FAO/WHO Expert Committee on Food Additives set a provisional tolerable weekly intake of 300 μg total mercury per person, of which no more than 200 μg (3.33 μg/kg bw for a 60-kg individual) should be present as methylmercury compounds (WHO, 1989b). In Japan, a provisional tolerable weekly intake of 250 μg mercury per week, with no more than 170 μg as methylmercury, was calculated from the WHO values on the basis of 50 kg body weight. This weekly intake is considered to be one-tenth of the minimum toxic dose of adults and is therefore expected to give protection against fetal damage (WHO, 1990).

Stationary sources in the USA where mercury ore is processed to recover mercury, where mercury chloralkali cells are used to produce chlorine gas and alkali metal hydroxide and where wastewater treatment plant sludge is incinerated or dried are subject to the US national emission standard for mercury. Thus, atmospheric emissions from mercury ore processing facilities and mercury-cell chloralkali plants cannot exceed 2300 g of mercury per 24-h period. Atmospheric emissions from sludge incineration plants, sludge drying plants, or a combination of these, where wastewater treatment plant sludges are processed cannot exceed 3200 g of mercury per 24-h period (US Environmental Protection Agency, 1992).

In the countries of the European Communities, no detectable quantity of mercury is allowed in colouring matter authorized for use in food intended for human consumption (Commission of the European Communities, 1981). The threshold value for mercury in tuna fish in Denmark is 0.5 mg/kg (Rasmussen, 1984). In Sweden, it was recommended that the consumption of fish caught in areas of high contamination (but below 1.0 mg/kg) be restricted to one meal per week (Swedish Expert Group, 1970).

Use of mercury compounds as cosmetic ingredients in the USA is limited to eye-area cosmetics, at concentrations not exceeding 65 ppm (0.0065%) of mercury calculated as the metal (about 100 ppm or 0.01% phenylmercury acetate or nitrate) (US Department of Health and Human Services, 1992). In the European Communities, mercury and its compounds must not be used in cosmetic products, except that thiomerosal (mercurothiolate) and phenylmercury salts (including borate) can be used for eye make-up or eye make-up remover, with a maximum concentration of 0.007% mercury (Commission of the European Communities, 1990, 1991).

2. Studies of Cancer in Humans

Many populations have low-grade or infrequent exposure to metallic mercury or mercury compounds. The Working Group restricted their review to studies specific to metallic mercury or mercury compounds and to groups who are known to have considerable exposure.

2.1 Inorganic mercury compounds

2.1.1 *Descriptive studies*

In a study in Poland, mercury was determined in the hair of leukaemia patients and in healthy relatives and unrelated healthy subjects (Janicki *et al.*, 1987). The mean content of total mercury was 1.24 ± 1.93 mg/kg hair from 23 cases of acute leukaemia and 0.49

± 0.41 mg/kg hair from 79 healthy control subjects. In 47 cases of acute leukaemia (chronic granulocytic as well as chronic lymphocytic), the mercury content was 0.92 ± 1.44 mg/kg hair. For 19 leukaemia cases of all groups and their 52 relatives, the corresponding figures were 0.69 ± 0.75 mg/kg and 0.43 ± 0.24 mg/kg, respectively. These differences between cases and control subjects were significant. [The Working Group noted that comparisons of means are inappropriate, as the distributions were highly skewed, and that the distribution of mercury may have been affected by the disease.]

In Washington State, USA, occupational mortality was studied for the period 1950–71 on the basis of death certificates (Milham, 1976). For male dentists, the proportionate mortality ratio (PMR) for all malignant neoplasms was 1.05 (127 cases [95% confidence interval (CI), 0.88–1.25]). When sites with more than five cases were considered, the PMR was 1.53 for pancreatic cancer based on 12 cases [95% CI, 0.79–2.69), 1.32 for prostatic cancer based on 20 cases [95% CI, 0.80–2.03] and 1.45 for neoplasms of the lymphatic and haematopoietic tissues based on 17 cases [95% CI, 0.84–2.33).

Occupational mortality was studied in British Columbia, Canada, by the proportionate mortality method and based on 320 423 deaths for which valid records were available among men over 20 years of age (Gallagher *et al.*, 1985). The occupational codes were those used in conjunction with the censuses of 1951 and 1961. Among dentists, there were four cases of kidney cancer (PMR, 1.94; 95% CI, 0.52–4.96) and five tumours of the brain and central nervous system (PMR, 2.36; 95% CI, 0.76–5.52). There were even fewer cases at other sites, or no more than slightly elevated PMRs.

2.1.2 *Cohort studies* (see Table 12, p. 272)

(a) Nuclear weapons industry workers

A cohort of 2133 white men from Oak Ridge, TN, USA, who were exposed to metallic mercury and an unexposed cohort of 3260 workers from the same plant were studied with regard to mortality in comparison with national rates for white men (Cragle *et al.*, 1984). Exposure to mercury occurred in the context of lithium production in a nuclear weapons plant, which earlier had also produced a fissionable isotope of uranium; anyone in whom mercury had ever been found in the urine, regardless of the concentration, was considered to have been exposed. A mercury monitoring programme was started in mid-1953 and became effective in late 1954. The cohorts were followed-up from 1 January 1953 until 1 January 1979, when vital status was assessable for at least 95.5% of the cohort and death certificates were available for 98% or more. Total mortality was lower than expected for both groups, and there was no excess of any non-cancer death possibly related to mercury exposure (target organs were thought to be liver, lung, brain and other central nervous system, and kidney). The cancer mortality rate was lower than expected for the exposed cohort (standardized mortality ratio [SMR], 0.94 [95% CI, 0.75–1.16]; based on 85 cases) but not for the unexposed (SMR, 1.10 [0.94–1.28]; based on 175 cases). An excess of lung cancer was seen in both cohorts (SMR, 1.34 [0.97–1.81], based on 42 cases among exposed; and 1.34 [1.05–1.69], based on 71 cases among unexposed). For cancers of the brain and central nervous system, the corresponding figures were 1.22 ([0.33–3.12]; based on 4 cases) for the exposed cohort and 2.30 ([1.22–3.94]; based on 13 cases) for the unexposed; for kidney cancer, the SMRs were reported to be 1.65 ([0.45–4.23]; based on 4 cases) for the exposed

cohort and 0.72 ([0.15–2.10]; based on 3 cases) for the unexposed. In subgroups with mercury levels in urine exceeding 0.3 mg/L at least once or with more than one year of exposure, there was also no clear increase in cancer mortality rates. No definite explanation could be given for the excess of lung cancer observed in both cohorts, but life-style factors or some factor other than mercury present in the plant were mentioned.

(b) Dentists

Cohorts of 3454 male and 1125 female dentists and 4662 dental nurses identified from the Swedish census in 1960 were followed for cancer development in the period 1961–79 by linkage with cancer register data (Ahlbom *et al.*, 1986). The overall standardized incidence ratio (SIR) was 2.1 (95% CI, 1.3–3.4) for glioblastoma (astrocytoma III–IV) in comparison with national incidence rates, based on 18 cases. The SIRs for the various cohorts were 2.0 for male dentists, 2.5 for female dentists and 2.2 for dental nurses. In the combined cohorts, there were also four gliomas (astrocytoma I–II) (SIR, 1.8; 95% CI, 0.5–4.7) and six meningiomas (SIR, 1.3; 95% CI, 0.5–2.8). There was no excess of all tumours in these cohorts. For comparison, physicians and female nurses were also studied; no indication was found of an excess of glioblastomas. Exposures to amalgam, chloroform and X-radiation were mentioned as possible occupational factors.

In another analysis of this population, occupational risks for intracranial gliomas in Sweden were studied by linking cancer incidence data from the national cancer registry during 1961–79 with census data on occupation from 1960 (McLaughlin *et al.*, 1987). The expected number of cases for each occupational category was calculated on the basis of the general population in the study period, and regional adjustment was applied. There were 3394 gliomas in men and 1035 in women who had been employed in 1960. An excess risk was found for male dentists, with an SIR of 2.1 ($p < 0.05$) based on 12 cases; for female dental assistants, nine cases (SIR, 2.1; $p = 0.09$) were reported. For comparison, it may be noted also that among male physicians there were 14 cases (SIR, 1.4; nonsignificant) and among female physicians, four cases (SIR, 3.7; $p < 0.05$). Male chemists, physicists, veterinary surgeons, agricultural research scientists and pharmacists also had SIRs greater than 2.0. [The Working Group noted that no distinction was made between the various subtypes of glioma.]

Mortality risks by occupation have been studied among veterans who served in the US Armed Forces between 1917 and 1940 (Hrubec *et al.*, 1992). Occupation and smoking status were assessed through questionnaires in 1954 and 1957. Follow-up to 1980 was done using insurance and pension systems (96% complete for First World War veterans). The smoking-adjusted relative risk (RR) for each occupation was estimated by using all other occupations as the standard, and Poisson regression modelling was applied. In a subcohort of 2498 dentists with a total of 1740 deaths, there were 299 cancer deaths (RR, 0.9; 90% CI, 0.80–0.97). The risk for pancreatic cancer was 1.4 (90% CI, 0.98–1.86; 27 deaths). No excess of brain or kidney tumours was detected (RR, 0.9; 90% CI, 0.45–1.74; 6 cases; and RR, 0.8; 90% CI, 0.39–1.50; 6 cases, respectively). For a group of 267 medical and dental technicians, there was an elevated risk for all cancers among 40 nonsmokers (RR, 2.5; 90% CI, 1.36–4.73; 7 deaths). For nonsmokers and smokers in this group, the risk for all cancers was only slightly

elevated (RR, 1.2; 90% CI, 0.87–1.54; 34 deaths), but there was an excess of colon cancer (RR, 1.9; 90% CI, 1.01–3.53; 7 deaths).

(*c*) *Chloralkali workers*

Mortality and cancer incidence were reported for a group of 1190 male Swedish chloralkali workers in whom mercury had been measured in the blood or urine for at least one year between 1946 and 1984 (Barregård *et al.*, 1990). Their mortality and cancer incidence were compared with those of the general male population for the periods 1958–84 and 1958–82, respectively, and the follow-up was complete. The mean level of mercury excreted in the urine had been about 200 μg/L in the 1950s, 150 μg/L in the 1960s and less than 50 μg/L in the 1980s. On the basis of crude estimates, 26% of the cohort was estimated to have had an accumulated urinary mercury dose of 1000 years·μg/L or more, 457 subjects also had some (mostly low-grade) asbestos exposure; exposure to static magnetic fields was reported to have occurred. Mortality from all causes was not significantly increased, the observed to expected mortality being 1.1 (95% CI, 0.9–1.3) based on 147 deaths with 10 or more years of latency. There were 51 incident cases of cancer observed *versus* 42 expected with a latency of 10 years or more, i.e. a rate ratio of 1.2 (95% CI, 0.9–1.6). Lung cancer was the only type of tumour in clear excess, with 10 observed and 4.9 expected with a latency of 10 years or more (rate ratio, 2.0; 95% CI, 1.0–3.8). There were slight excesses of some other cancers with a latency of 10 years or more, namely three brain tumours *versus* 1.1 expected (RR, 2.7; 95% CI, 0.5–7.7), three kidney cancers *versus* 1.9 expected (1.6; 0.3–4.7), five urinary bladder cancers *versus* 2.9 expected (1.7; 0.6–4.1) and 10 prostatic cancers *versus* 8.6 expected (1.2; 0.6–2.1). The excess of lung cancer was thought to be due to exposure to asbestos; one case of mesothelioma was observed. Smoking was considered to explain 10% of the excess of lung cancer, although information on smoking habits was available for only a 7% random sample of the cohort. The authors noted that chloralkali workers have five to 10 times the mercury exposure of dental personnel.

In a cohort study of 674 male Norwegian chloralkali workers exposed to inorganic mercury for more than one year prior to 1980, who had a mean cumulative urinary concentration of 740 μg/L, there were 204 deaths *versus* 210.7 expected (SMR, 0.97; 95% CI, 0.84–1.11) and 89 incident cases of cancer *versus* 85.0 expected (SIR, 1.05; 95% CI, 0.84–1.29) (Ellingsen *et al.*, 1993). During the follow-up period (1953–89 for incidence and 1953–88 for mortality), there were 19 incident cases of lung cancer, with 11.5 expected (SIR, 1.66; 95% CI, 1.00–2.59) on the basis of national rates. There was no correlation with cumulative mercury dose, employment or latency; a somewhat increased frequency of smoking and exposure to asbestos (one mesothelioma was found) were considered to explain the excess of lung cancer. Three kidney cancers and two brain tumours were observed *versus* 3.2 and 2.45 expected, respectively. These two sites were considered by the authors to be of primary interest with regard to exposure to mercury.

(*d*) *Mercury miners*

In a cohort study of the relationship between silicosis and mortality from lung cancer in US metal miners, the difference in risk for silicotic miners compared with nonsilicotic white metal miners was greater for mercury miners than for other miners (Amandus & Costello,

Table 12. Cohort studies of populations exposed to inorganic mercury compounds

Study population Period of follow-up	End-point		Site	No. of cases	SMR	95% CI	Reference
Nuclear weapons industry workers							
2133 Mercury exposed,	Mortality	Exposed	Lung	42	1.34	[1.0–1.8]	Cragle *et al.*
3260 unexposed male workers,			Kidney	4	1.65	[0.4–4.2]	(1984)
USA, 1953–79			Brain	4	1.22	[0.3–3.1]	
		Unexposed	Lung	71	1.34	[1.0–1.7]	
			Kidney	3	0.72	[0.1–2.1]	
			Brain	13	2.30	[1.2–3.9]	
Dentists							
9201 Dentists and dental	Incidence		Glioblastoma	18	2.1	1.3–3.4	Ahlbom *et al.*
nurses, Sweden, 1961–79			Glioma	4	1.8	0.5–4.7	(1986)
			Meningioma	6	1.3	0.5–2.8	
2498 Dentists, US veterans,	Mortality		Pancreas	27	1.4	0.96–1.86	Hrubec *et al.*
1954–80			Brain	6	0.9	0.45–1.74	(1992)
			Kidney	6	0.8	0.39–1.50	
267 Medical and dental	Mortality		Colon	7	1.9	1.01–3.53	Hrubec *et al.*
assistants, US veterans,			Brain	1	1.5	NR	(1992)
1954–80			Kidney	2	2.8	NR	
Chloralkali workers							
1190 Males, Sweden,	Incidence		Lung	13	[1.8]	[0.9–3.0]	Barregård *et al.*
1946–82			Kidney	4	[1.3]	[0.4–3.4]	(1990)
			Brain	4	[1.8]	[0.5–4.7]	
674 Males, Norway,	Incidence		Lung	19	1.66	1.00–2.59	Ellingsen *et al.*
1953–89			Kidney	3	0.95	0.2–2.8	(1993)
			Brain	2	0.8	0.1–3.0	
Mercury miners							
274 Males, USA,	Mortality	11 Silicotics	Lung	3	14.0	2.89–41.0	Amandus &
1959/61–75		263 Nonsilicotics	Lung	8	2.66	1.15–5.24	Costello (1991)

NR, not reported

1991). The follow-up was from date of examination in 1959–61 to 31 December 1975. For the 11 silicotic mercury miners, the SMR was 14.0 (95% CI, 2.89–41.0) based on three lung cancer deaths, whereas the SMR for the 263 nonsilicotic mercury miners was 2.66 (95% CI, 1.15–5.24) based on eight cases. For other miners (copper, lead–zinc, iron and others), the corresponding figures were 1.39 [95% CI, 0.70–2.49] based on 11 silicotic lung cancer deaths and [1.14; 95% CI, 0.93–1.37] based on 110 deaths from nonsilicotic lung cancer. The reference for calculating the SMRs was death rates in white US males. No explanation was offered for the differences seen between mercury and other miners. [The Working Group noted that the small numbers of silicotic mercury miners may make the estimate unstable.]

2.1.3 *Case–control studies* (see Table 13, p. 274)

In a case–control study of incident cases of lung cancer admitted during 1981–83, 340 male and 36 female cases and 817 male and 75 female hospital controls, all residents of metropolitan Florence, Italy, were drawn from the regional general hospital for the analyses (Buiatti *et al.*, 1985). Occupational histories were collected from each subject directly; six female cases but no control had ever worked as felt-hat makers ($p = 0.01$). Heavy exposure to mercury but also to arsenic and other chemicals was reported to have occurred in the Italian hat-making industry.

In a study described in detail in the monograph on beryllium (pp. 73–74; Carpenter *et al.*, 1988), based on 29 cases identified from information on death certificates as ever exposed to mercury, the odds ratio for cancer of the central nervous system was 1.77 [95% CI, 0.5–5.8] when compared with unexposed cases. The matched analysis by highest rank ever held *versus* rank 0 yielded odds ratios of 2.01, 1.33 and 1.19 for ranks 1, 2 and 3, respectively (all odds ratios had a p value of 0.26 or greater). When risk estimates were calculated with a 10-year latency, the odds ratios were 1.58, 0.77 and 1.57 for ranks 1, 2 and 3, respectively, with a p value of 0.47 or greater. A further analysis based on time spent in ranks 2 and 3, assuming a 10-year latency, yielded odds ratios of 0.00, 0.96, 0.00 and 1.86 for workers with > 1 year and < 3 years, 3–10 years, 11–20 years and 21 years or more in ranks 2 and 3 compared with ranks 0 and 1. The authors concluded that their study does not support the hypothesis that occupational exposures to any of the 26 chemicals studied increase appreciably the risk for cancers of the central nervous system.

The effects of a great number of exposures were considered in a case–control study from Montréal, Canada, involving all major cancer forms and population controls as well as two hospital control series, i.e. cancer cases and other cases (Siemiatycki, 1991). In total, 4576 incident cancer cases were recruited through local informants at the hospitals. Completed questionnaires and interviews on occupational exposures (293 agents were considered) were obtained for 3730 of these (response rate, 81.5%). A total of 740 population controls were drawn from electoral lists or obtained by random-digit dialling. Of these, exposure was successfully assessed for 533 (72.0%). The prevalence of exposure to metallic mercury was 0.6% and that to any mercury compound (including metallic mercury), 2%. For prostatic cancer, 14 of 449 cases were exposed to mercury compounds, resulting in an odds ratio of 1.7 (90% CI, 1.0–3.0); five cases had been exposed to metallic mercury, giving an odds ratio of 6.2 (90% CI, 1.2–33.2). For lung cancer, four of the 857 cases had been exposed to metallic mercury (odds ratio, 4.0; 90% CI, 1.2–13.0). For bladder cancer, 14 of the 484 cases had been

Table 13. Case–control studies of populations exposed to inorganic mercury compounds

Study population	End-point	Exposure	Sex	No. of exposed cases	Odds ratio	95% CI	Reference
Lung cancer							
Hospital-based, Italy	Incidence	Hat makers	F	6		$p = 0.01$	Buiatti *et al.* (1985)
Population-based, Canada	Incidence	Mercury, metallic	M	4	4.0	1.2–13.0[a]	Siemiatycki (1991)
Prostatic cancer							
Population-based, Canada	Incidence	Mercury, metallic	M	5	6.2	1.2–33.2[a]	Siemiatycki (1991)
		Mercury and mercury compounds[b]	M	14	1.7	1.0–3.0	
Bladder cancer							
Population-based, Canada	Incidence	Mercury and mercury compounds[b]	M	14	1.5	0.9–2.6[a]	Siemiatycki (1991)
Brain tumours							
Population-based, USA	Mortality	Nuclear facilities	Central nervous system	29	1.77	[0.5–5.8]	Carpenter *et al.* (1988)
Population-based, Australia	Incidence	Amalgam fillings	Glioma		0.47	0.25–0.91	Ryan *et al.* (1992)
			Meningioma		1.04	0.43–2.47	

[a]90% CI

[b]Including organomercury compounds

exposed to mercury compounds (odds ratio, 1.5; 90% CI, 0.9–2.6). Significant results were not obtained for cancers at other sites. [The Working Group noted that although several potential confounding factors were considered not all possible occupational confounders were addressed.]

A case–control study from Adelaide, Australia, considered incident brain tumours and exposure to amalgam fillings and diagnostic dental X-rays (Ryan *et al.*, 1992). Cases aged 25–74 were notified by neurosurgeons in Adelaide, and there was a further check for cases in cancer and brain tumour registries. Controls were selected from the Australian electoral roll, covering 95% of the adult population. In total, 190 cases of brain tumours were identified, together with 662 controls; of these, 110 glioma cases, 60 meningioma cases and 417 controls were included in the analyses. There was a decreased odds ratio (0.47; 95% CI, 0.25–0.91) for glioma in association with self-reported amalgam fillings (at least one filling) and with diagnostic X-rays (at least one X-ray) (odds ratio, 0.42; 95% CI, 0.24–0.76); the corresponding results for meningioma were 1.04 (95% CI, 0.43–2.47) in relation to fillings, whereas the risk associated with diagnostic X-rays was slightly increased (odds ratio, 1.37; 0.68–2.73). No dose–response pattern was seen for either glioma or meningioma with regard to amalgam fillings. The authors considered a biological protective mechanism unlikely.

2.2 Organomercury compounds

2.2.1 *Descriptive studies*

Direct SMRs for biliary tract cancer in the Japanese prefectures in 1975 were correlated with an environmental pollution index related to use of agricultural chemical products for the years 1962–66 (Yamamoto *et al.*, 1986). In both men and women, only weak, non-significant correlations were found for exposure to mercuric compounds (such as phenylmercury acetate, used as a fungicide in Japan until 1971) converted to the dose of inorganic mercury, whereas positive and significant correlations were obtained, especially for DDT and some phenoxy herbicides.

The mortality pattern was studied in the population of a small area of the city of Minamata, Kumamoto Prefecture, Japan, which consisted mainly of fishermen and their families (Tamashiro *et al.*, 1986) and where 70% of the 1612 confirmed cases (including 527 deaths) of Minamata disease (see pp. 291–292) in the Prefecture through 1983 were known to have occurred. SMRs were computed for different causes of death in 1970–81 by using age-specific rates for the entire city for 1972–78. The total population of the study area in 1975 was 3887 *versus* 36 782 in the city. Some migration took place during the study period, and, in particular, young adults moved out of the area and former residents returned. The SMR for all causes of death was 1.05 (95% CI, 0.95–1.15, based on 412 deaths) and that for all cancers was 1.18 (95% CI, 0.96–1.46, based on 84 deaths). For the various cancers reported, the corresponding figures were: oesophagus, 2.05 (95% CI, 0.67–4.78; 5 cases); stomach, 0.77 (95% CI, 0.42–1.29; 14 cases); liver, 2.07 (95% CI, 1.16–3.42; 15 cases); pancreas, 0.99 (95% CI, 0.20–2.88; 3 cases); trachea–bronchus–lung, 1.52 (95% CI, 0.79–2.65; 12 cases); breast, 2.64 (95% CI, 0.54–7.71; 3 cases); uterus, 0.89 (95% CI, 0.24–2.28; 4 cases); leukaemia, 1.82 (95% CI, 0.50–4.66; 4 cases); and other cancers, 0.98 (95% CI, 0.63–1.46; 24 cases). An elevated SMR was also seen for chronic liver disease and cirrhosis

(2.16; 95% CI, 1.41–3.17; based on 26 cases). There was some evidence that alcohol consumption in the area was above the Japanese average. [The Working Group noted that the increased risk for liver cancer seems consistent with the increased occurrence of chronic liver disease and cirrhosis and with a higher than average alcohol consumption; the latter might also have affected the risk for oesophageal cancer.]

The effects on life expectancy of elevated exposure to methylmercury compounds were studied in five coastal towns of southern Japan in comparison with a surrounding control area (Tamashiro *et al.*, 1987). The average hair concentrations of mercury were reported to be three to six times higher in the exposed area than in the control area. The study period was from 1969 through to 1982. The crude RR for death from malignant neoplasms was [1.05].

2.2.2 *Cohort study*

It was reported in letter to the Editor that 1657 people with a licence for seed disinfection using organomercury compounds and other agents, issued between 1965 and 1976, were followed through the Swedish Cancer Registry from the date of licencing until death or December 1982 (Wiklund *et al.*, 1988). The mean follow-up time was 14.7 years, resulting in 24 429 person-years of observation. Five tumours of the nervous system were observed *versus* 4.98 expected (SIR, 1.0; 95% CI, 0.33–2.34); rates of tumours at other sites were not reported. The authors noted that the use of alkylmercury compounds was banned in Sweden in the mid-1960s, and limitations were placed on mercury disinfection.

2.2.3 *Case–control studies* (see Table 14, p. 277)

Three similarly designed studies on soft-tissue sarcomas in different parts of Sweden, mainly focusing on exposure to phenoxyacetic acid herbicides and chlorophenols, also provide data on exposure to organomercury seed dressings and other pesticides (Eriksson *et al.*, 1981; Hardell & Eriksson, 1988; Eriksson *et al.*, 1990). The first study encompassed 110 cases and 219 population controls in the five southernmost counties. The second study involved 55 cases and 220 living and 110 dead controls and a third group of 190 other cancer controls in the three northernmost counties. In the third study, there were 237 cases and 237 controls from the seven central counties, matched on vital status. Information on exposure was obtained from questionnaires to the subjects or their next-of-kin, supplemented with telephone interviews. Exposure to mercury seed dressings was reported for 8.2% of cases and 4.6% of controls in the first study; for 1.9% of cases and 3.5% of living and 2.8% of dead controls in the second study; and for 4.6% of cases and 5.2% of controls in the third study. The resulting odds ratio in the first study [not given] was said to have a 90% CI that included unity. [A calculation results in a crude odds ratio of 1.9 (95% CI, 0.65–5.3) for the first study and, for the second study, 0.52 (95% CI, 0.01–4.3) with regard to living controls and 0.66 (95% CI, 0.08–5.74) using dead controls.] The odds ratio in the third study was given as 0.89 (95% CI, 0.40–1.96).

In a study from northern Sweden on malignant lymphomas, which mainly considered exposure to organic solvents, chlorophenols and phenoxyacetic acid herbicides, exposure frequencies to organomercury seed dressings were also reported (Hardell *et al.*, 1981). The study included 169 cases (60 Hodgkin's lymphomas, 109 non-Hodgkin lymphomas) and 338

(335 used in the calculation) population controls. Information on exposure was obtained through questionnaires. For the cases and controls, 5.3 and 3.0%, respectively, exposure to mercury seed dressings co-varied with exposure to phenoxyacetic acid herbicides, whereas asbestos and glass fibre exposure co-varied with chlorophenol exposure. Exposure to phenoxyacetic acid herbicides as well as to chlorophenols appeared to be strong risk factors for lymphomas, but after exclusion of subjects with exposure to phenoxy herbicides, 128 cases and 311 controls remained, with exposure frequencies to mercury seed dressings of 4.7 and 2.9%, respectively; for DDT, the corresponding figures were 5.5 and 3.5%. [For the restricted material, a calculation results in a crude odds ratio of 1.78 (95% CI, 0.62–5.11) for mercury seed dressings and 1.6 (95% CI, 0.51–4.6) for DDT.]

Table 14. Population-based case–control studies of populations of men exposed to organomercury seed dressings in Sweden

No. of exposed cases	Odds ratio	95% CI	Reference
Soft-tissue sarcomas			
[9]	[1.9]	[0.65–5.3]	Eriksson *et al.* (1981)
[1]	[0.52][a] [0.66][b]	[0.01–4.3] [0.08–5.7]	Hardell & Eriksson (1988)
[10]	0.89	0.40–1.96	Eriksson *et al.* (1990)
Lymphomas			
[6]	1.78	[0.62–5.1]	Hardell *et al.* (1981)

[a] Living controls

[b] Dead controls

3. Studies of Cancer in Experimental Animals

3.1 Metallic mercury

Intraperitoneal administration

Rat: A group of 39 male and female BDIII and BDIV rats, three months old, received two intraperitoneal injections of 0.05 ml **metallic mercury** [purity unspecified] over 14 days (total dose, 0.1 ml); mean survival was 580 days in treated rats and 780 days in controls. Only gross lesions were investigated histopathologically. At 22 months, when 12/39 animals were still alive, one female rat had a spindle-cell sarcoma in the abdominal cavity. Two females and two males of the 11 remaining rats developed similar tumours (Druckrey *et al.*, 1957). [The Working Group noted the incomplete reporting of the study and the possibility that the lesions seen were the result of a solid-state effect.]

3.2 Mercuric chloride

3.2.1 *Oral administration*

(*a*) *Mouse*

A group of 54 male and 54 female Swiss mice (Charles River CD strain), 20 days old, were given drinking-water containing **mercuric chloride** (5 ppm [mg/L] mercury) [purity unspecified] for life. A control group of 54 male and 54 female mice was given the drinking-water alone. Of the controls, 50% of the males were still alive at 602 days and 10% at 789 days, and 50% of females were still alive at 539 days and 10% at 691 days. Of the treated mice, 50% of males were still alive at 540 days and 10% at 697 days, and 50% of females at 575 days and 10% at 736 days. The numbers of mice autopsied were 38 control males and 47 control females and 48 male and 41 female treated mice. The authors reported that 11/41 treated female mice and 3/47 control females developed lymphoma or leukaemia [$p = 0.09$, Fisher exact test] (Schroeder & Mitchener, 1975). [The Working Group noted the incomplete reporting of the study and that only some of the animals were autopsied.]

Groups of 60 male and 60 female B6C3F1 mice, six weeks old, received 0, 5 or 10 mg/kg bw **mercuric chloride** (purity > 99%) in deionized water by gavage (10 ml/kg bw) on five days a week for 103–104 weeks. Ten animals from each group were killed at 15 months for evaluation. Survival at the end of the two-year study was 36/50, 36/50 and 31/50 in the control, low-dose and high-dose male groups and 41/50, 35/50 and 31/50 in the corresponding female groups. Body weights of both female and male treated mice were similar to those of controls throughout. Of the high-dose male mice, 2/49 developed renal tubular adenomas and 1/49 a renal tubular adenocarcinoma. No such tumour was seen in either the control or low-dose groups. No increase in the incidence of tumours was seen in the treated female mice (US National Toxicology Program, 1993).

(*b*) *Rat*

Groups of 60 male and 60 female Fischer 344/N rats, six weeks old, received 0, 2.5 or 5 mg/kg bw **mercuric chloride** (purity, > 99%) in deionized water by gavage (5 ml/kg bw) on five days a week for 103–104 weeks. Ten animals from each group were killed at 15 months for evaluation. Body weights of low- and high-dose males and high-dose females were lower than those of controls. Survival at two years was 26/50 male controls, 10/50 low-dose and 5/50 high-dose rats and 35/50, 28/49 and 30/50 in the females. The decrease in survival in male rats was due, in part, to an increased incidence of treatment-related renal disease. High-dose males had a greater incidence of renal tubular hyperplasia than control males (12/50 *versus* 3/50; $p = 0.005$), but the incidence of renal tubular adenomas was similar (control, 4/50; high-dose, 5/50). In female rats, renal tubular hyperplasia occurred in 5/50 high-dose rats and 2/50 controls; two high-dose female rats had renal tubular adenomas, but none was seen in controls. Treated male rats had a dose-related increase in the incidence of forestomach hyperplasia compared to controls (control, 3/49; low-dose, 16/50; high-dose, 35/50), as did high-dose female rats (control, 5/50; low-dose, 5/49; high-dose, 20/50). In addition, there was a dose-related increase in the incidence of squamous-cell papilloma of the forestomach in treated males (control, 0/50; low-dose, 3/50; high-dose, 12/50); such tumours also occurred in 2/50 high-dose female rats. High-dose males also had an increased

incidence of thyroid follicular-cell carcinoma (control, 1/50; low-dose, 2/50; high-dose, 6/50), but not of hyperplasia (control, 2/50; low-dose, 4/50; high dose, 2/50) or adenoma (control, 1/50; low-dose, 4/50; high-dose, 0/50) (US National Toxicology Program, 1993). [The Working Group noted the low survival rate of male animals.]

3.2.2 *Administration with known carcinogens*

As the purpose of the investigations described below was to study interactions with known carcinogens, the studies were limited to specific target sites, were often of short duration and were not intended to address the carcinogenicity of mercury *per se*.

(*a*) *Mouse*

Twenty female Sencar mice [age unspecified] received single topical applications of 0.2 ml of 10 nmol [2.6 μg] 7,12-dimethylbenz[*a*]anthracene (DMBA) followed by twice weekly topical applications of 200 μg **mercuric chloride** in 0.2 ml of a 90% acetone solution for 26 weeks. A positive control group of 20 mice, initiated with DMBA, received promotion with 12-*O*-tetradecanoylphorbol 13-acetate [dose and dosing regime unspecified]. All mice in the positive control group developed skin papillomas, and two developed carcinomas. No skin tumour occurred in the mercuric chloride-treated mice (Kurokawa *et al.*, 1989). [The Working Group noted the incomplete reporting of the study.]

(*b*) *Rat*

A group of 15 male Fischer 344 rats, seven weeks old, was administered *N*-nitroso-*N*-hydroxydiethylamine (NHDEA) at 500 ppm [mg/L] in the drinking-water for two weeks followed by drinking-water containing 40 ppm [mg/L] **mercuric chloride** (99.5% pure) for 25 weeks. A further group of 15 rats received only mercuric chloride at 40 ppm for 25 weeks; a control group of 15 rats received drinking-water for the 27-week experimental period; and a further group of 15 rats was given NHDEA for two weeks followed by 25 weeks of drinking-water alone. There was no significant difference in the number of renal-cell tumours in rats receiving NHDEA and mercuric chloride (5/15) and those receiving NHDEA alone (2/15), but there was a significant ($p < 0.01$, Student's t test) increase in the mean number of dysplastic foci/cm^2 in the NHDEA- plus mercuric chloride-treated group (1.09) over that in the group treated with NHDEA alone (0.23). No renal-cell tumour or dysplastic focus was reported in the group receiving mercuric chloride alone (Kurokawa *et al.*, 1985).

Groups of 20 male Fischer 344 rats [age unspecified] were given drinking-water containing 50 ppm [mg/L] *N*-nitrosodiethylamine (NDEA) for four weeks to initiate liver carcinogenesis, followed by 30 weeks of treatment with drinking-water containing 40 ppm [mg/L] **mercuric chloride** [purity unspecified], water alone or 1000 ppm [1 g/L] phenobarbital (positive control). All animals were killed at week 34. Mercuric chloride treatment did not increase the number of hepatocellular carcinomas, adenomas or hyperplastic nodules over that in rats treated with NDEA alone (Kurokawa *et al.*, 1989). [The Working Group noted the incomplete reporting of the study.]

Groups of 20 male Wistar rats [age unspecified] were given *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine in the drinking-water at 100 ppm [mg/L], together with a diet supplemeted with 10% sodium chloride for eight weeks to initiate gastroduodenal carcinogenesis,

followed by 32 weeks of treatment with drinking-water containing 40 ppm [mg/L] **mercuric chloride** and basal diet without the 10% sodium chloride; controls were given the nitrosamine and basal diet containing sodium chloride for eight weeks then basal diet and standard drinking-water. The incidences of carcinoma and hyperplasia of the fundic and pyloric regions of the glandular stomach and of carcinoma of the duodenum were not increased by treatment with mercuric chloride over those caused by the nitrosamine alone (Kurokawa *et al.*, 1989). [The Working Group noted the incomplete reporting of the study.]

(*c*) *Hamster*

A group of 20 female Syrian golden hamsters [age unspecified] received three weekly injections [site unspecified] of *N*-nitrosobis(2-oxopropyl)amine (NBOPA) at a dose of 10 mg/kg bw to initiate pancreatic carcinogenesis, followed by treatment with drinking-water containing 40 ppm [mg/L] **mercuric chloride** for a further period [presumed to be 30 weeks]. A further group of 32 hamsters received NBOPA followed by drinking-water alone for 30 weeks. At the end of the study [duration unspecified], there was no difference in the multiplicity of either pancreatic adenocarcinomas or dysplastic lesions between the two groups (Kurokawa *et al.*, 1989). [The Working Group noted the incomplete reporting of the study.]

3.3 Methylmercury chloride

3.3.1 *Oral administration*

(*a*) *Mouse*

Groups of 60 male and 60 female ICR mice, five weeks of age, were fed a diet containing 0, 15 or 30 ppm [mg/kg] **methylmercury chloride** (99.3% purity) for 78 weeks. All animals were examined macroscopically, but histopathological examination was carried out only on kidneys of animals that died after week 53 and on lungs of mice with renal masses. The first renal tumour was detected in a male treated with 15 ppm and necropsied at week 58. Most mice given 30 ppm had severe neurotoxic effects and died or became moribund by week 26; similar, but less marked toxic effects occurred in the group treated with 15 ppm. At 78 weeks, survival among male mice was 24/60 given 0 ppm, 8/60 given 15 ppm and 0/60 given 30 ppm; survival among female mice was 33/60 given 0 ppm, 18/60 given 15 ppm and 0/60 given 30 ppm. The numbers of male mice that died after 53 weeks with renal tumours were: 1/37 (an adenoma) in the group given 0 ppm, 13/16 (total numbers of tumours: 11 adenocarcinomas [$p < 0.001$] and five adenomas [$p < 0.01$]) in the group given 15 ppm and none in the one surviving animal treated with 30 ppm. No renal tumour was reported in the female mice (Mitsumori *et al.*, 1981). [The Working Group noted the poor survival in the groups exposed to high doses of methylmercury chloride and the limited number of tissues subjected to histopathological evaluation.]

Groups of 60 male and 60 female ICR mice, five weeks of age, were administered diets containing 0, 0.4, 2 or 10 ppm (mg/kg) **methylmercury chloride** (99.3% pure) for 104 weeks. Six males and six females from each group were killed at 26-week intervals and subjected to histological examination, as were all other animals. No neurotoxic effect was observed in the

treated animals, and, although all male mice given 10 ppm were dead by week 98, there was no difference in survival rates between the control and treated groups. The first renal tumour occurred in a male treated with 10 ppm at 58 weeks. Epithelial degeneration of the renal proximal tubules was seen in both males (40/59) and females (19/60) given 10 ppm, and similar but milder degeneration was seen in males given 2 ppm (12/58). The incidence of renal tumours in male mice was 1/58 (an adenoma) at 0 ppm, 0/59 at 0.4 ppm, 0/58 at 2.0 ppm and 13/59 (10 adenocarcinomas and three adenomas) at 10 ppm. [The effective numbers of animals at risk for renal tumours could not be determined.] No such tumour was seen in treated female mice (Hirano *et al.*, 1986).

Groups of 60 male and 60 female specific-pathogen-free (SPF) B6C3F1 mice, five weeks of age, were fed diets containing 0, 0.4, 2.0 or 10 ppm [mg/kg] **methylmercury chloride** (99.3% pure) for 104 weeks. All animals were subjected to histopathological examination. In the group treated with 10 ppm, neurotoxicity was recorded in male mice at week 59 and in females at week 80; at termination, neurological signs were seen in 33/60 males and 3/60 females. Survival was similar to that of controls (48%) in all groups except males treated with 10 ppm, which had 17% survival. The incidence of chronic nephropathy was increased in male mice treated with 2 ppm (27/60) or 10 ppm (59/60) and in females given 10 ppm (56/60). The first renal tumour was seen in a male given 10 ppm and killed at week 70. Renal epithelial tumours occurred in 0/60 control males, 0/60 given 0.4 ppm, 1/60 (an adenoma) given 2 ppm and 16/60 (13 adenocarcinomas and five adenomas) given 10 ppm; among female mice, a single adenoma (1/60) was found in those given 10 ppm (Mitsumori *et al.*, 1990). [The Working Group noted the lower survival of high-dose males after 60 weeks.]

(*b*) *Rat*

Groups of 25 male and 25 female weanling SPF Wistar rats were administered diets containing 0, 0.1, 0.5 or 2.5 ppm [mg/kg] **methylmercury chloride** (100% pure) for two years. Apart from a slight reduction in growth of females treated with 2.5 ppm, there was no effect of treatment on growth. No clinical or neurological sign of methylmercury chloride toxicity was reported during the study; mortality at 104 weeks was: 6/25 female and 7/25 male controls, 10/25 females and 8/25 males at 0.1 ppm, 9/25 females and 13/25 males at 0.5 ppm and 11/25 females and 13/25 males at 2.5 ppm. Histopathological examination was carried out on the control and 2.5 ppm-treated animals and on all animals that died. The authors reported no difference in tumour incidence or latency among the groups [no further detail reported] (Verschuuren *et al.*, 1976a,b). [The Working Group noted the limited nature of the study.]

Groups of 56 male and 56 female SPF Sprague–Dawley rats, five weeks of age, were administered diets containing 0, 0.4, 2 or 10 ppm [mg/kg] **methylmercury chloride** (99.3% purity) for 130 weeks. Ten animals of either sex were killed at 13 and 26 weeks and 10 at 52 and 78 weeks. Neurological signs of methylmercury chloride toxicity were apparent in the 10 ppm-treated group from week 22 in males and from week 46 in females. All animals were subjected to necropsy and histopathological examination. Survival in the groups given 10 ppm was lower than in controls or in the other two treated groups; the cause of death was related to nephrotoxicity. The incidence of tumours did not differ significantly among the

treated and control groups. A single renal adenoma was found in a high-dose female (Mitsumori *et al.*, 1983, 1984).

3.3.2 *Administration with known carcinogens*

As the purpose of the investigations described below was to study interactions with known carcinogens, the studies were limited to specific target sites, were often of short duration and were not intended to address the carcinogenicity of mercury *per se*.

Mouse: Groups of 16–20 female Swiss-cross mice, 21–24 days old, were given 0, 0.2, 0.5, or 2.0 μg/ml (mg/L) **methylmercury chloride** [purity unspecified] in deionized drinking-water for 15 weeks and then killed. After the first three weeks of the exposure, mice received intraperitoneal injections of 1.5 mg/g [g/kg bw] urethane in normal saline [volume unspecified] or saline alone. The lung tumour incidence in the mice injected with saline was reported to be less than one tumour per mouse in all test groups [no further detail reported]. The number of pulmonary adenomas induced by urethane alone (21.5 ± 3.0) was exceeded only in the group that received the high dose of methylmercury chloride (33.1 ± 3.8) (Blakley, 1984).

Groups of 20 female W rats were maintained either on basal diet or on basal diet containing 10 ppm [mg/kg] **methylmercury chloride** [purity unspecified] dissolved in corn oil, from weaning until they delivered pups. They were also given either 0.159, 0.318 or 0.636% ethylurea in the diet from day 14 of the breeding period to parturition or 50 or 100 mg/kg bw by gavage on days 17, 18 and 19 of gestation; at the same time, they received 0.5, 1.0 or 2.0 g/L sodium nitrite in drinking-water or 25 or 50 mg/kg bw by gavage. Control groups received either the basal diet alone or the methylmercury chloride diet alone. All dams were returned to the basal diet at parturition, and progeny (generally about 25: 13 males and 12 females) were maintained on the basal diet for their lifespan. Survival was poor in some treatment groups. The incidence of neurogenic tumours was nearly 100% in some ethylurea/sodium nitrite-treated groups; there were 0/25 neurogenic tumours in the methylmercury chloride control group. Methylmercury chloride did not increase the incidence of neurogenic tumours in the groups receiving ethylurea/sodium nitrite, but schwannomas of the central nervous system tended to appear earlier than in the group given ethylurea/sodium nitrite alone (Nixon *et al.*, 1979). [The Working Group noted the reduced sensitivity of the study, due to the very high incidence of neurogenic tumours in ethylurea/sodium nitrite-treated groups, and the poor survival.]

3.3.3 *Hormonal influences*

Mouse: Groups of 50 intact male and 50 intact female SPF ICR mice, seven weeks of age, were fed basal diet or basal diet containing 10 ppm [mg/kg] **methylmercury chloride** (purity, 99.3%) for 80 weeks. Groups of 50 orchiectomized male and 50 ovarectomized female mice, operated at five weeks of age, were fed basal diet containing 10 ppm methylmercury chloride only or also received weekly subcutaneous injections of 0.2 mg/mouse testosterone propionate in a 0.2% suspension (w/v) of sesame oil for 80 weeks. All groups receiving methylmercury chloride had nephrotoxic changes and caecal ulceration. No renal tumour was seen in intact males receiving basal diet alone, but one renal adenoma was seen in an

intact female mouse; renal adenocarcinomas (14/50) and an adenoma (1/50) were seen in intact male mice given the basal diet with methylmercury chloride but not in intact female mice. In addition, 6/50 intact male mice given methylmercury chloride in the diet had tubular-cell hyperplasia, a lesion that the authors considered to be preneoplastic. No renal tumour was seen in orchiectomized or ovarectomized mice receiving methylmercury chloride only, but two adenocarcinomas occurred in males and three in females that received methylmercury chloride together with testosterone propionate (Hirano *et al.*, 1988).

4. Other Relevant Data

4.1 Absorption, distribution, metabolism and excretion

The absorption, distribution, metabolism and excretion of inorganic mercury (Nordberg & Skerfving, 1972; WHO, 1976; Berlin, 1986; Clarkson *et al.*, 1988a; WHO, 1991; Clarkson, 1992), methylmercury compounds (Nordberg & Skerfving, 1972; WHO, 1976; Berlin, 1986; Magos, 1987; Clarkson *et al.*, 1988a; WHO, 1990) and phenylmercury acetate (Nordberg & Skerfving, 1972; WHO, 1976; Berlin, 1986; Clarkson *et al.*, 1988a) have been reviewed.

4.1.1 *Humans*

(a) Metallic mercury and inorganic mercury compounds

In five human volunteers who inhaled radioactive metallic mercury-197 or mercury-203 vapour for 14–24 min, an average of 74% was absorbed in the respiratory tract (Hursh *et al.*, 1976). The half-time for whole-body elimination averaged 58 days; however, elimination rates varied for different parts of the body: lung, 1.7 days; head, 21 days; kidney region, 64 days; chest, 43 days.

Absorbed metallic mercury is dissolved in the blood. Addition of metallic mercury-203 vapour to blood *in vitro* resulted in oxidation to mercuric mercury, but rather slowly (Hursh *et al.*, 1988). The authors concluded that metallic mercury may pass the blood–brain barrier. A man who accidentally ingested 135 g of liquid metallic mercury had raised mercury concentrations in blood, but to an extent indicating only minimal absorption (Suzuki & Tanaka, 1971). The average ratio of mercury in erythrocytes:plasma was about 2 during the first few days after a 14–24-min exposure of five volunteers by inhalation of metallic mercury-197 and mercury-203 vapour (Cherian *et al.*, 1978).

Studies in five volunteers who exposed their forearms to metallic mercury-203 vapour for 27–43 min indicated absorption of mercury through the skin of 0.01–0.04 ng/cm^2 per min per ng Hg/cm^3 air (Hursh *et al.*, 1989).

In five human volunteers who inhaled metallic mercury-197 vapour for 11–21 min, the kidney region accumulated the highest levels of mercury (Hursh *et al.*, 1980). In autopsy samples from seven dentists and one dental assistant, particularly high levels of mercury were found in the renal cortex (average, 8.6 μmol [1.7 mg]/kg wet weight) and pituitary glands (average, 9.8 μmol [2 g]/kg wet weight). In 24 controls, the values were 1.4 μmol [280 μg]/kg wet weight in renal cortex and 0.12 μmol [24 μg]/kg wet weight in pituitary (Nylander & Weiner, 1991). High levels have also been recorded in the thyroid glands of deceased mercury miners (average, 35 mg/kg fresh weight) (Kosta *et al.*, 1975).

Equimolar ratios of mercury:selenium were found in pituitary and thyroid glands, kidney and brain in subjects with occupational exposure to metallic mercury vapour (Kosta *et al.*, 1975; Nylander & Weiner, 1991). Renal biopsy samples from two patients with inorganic mercury poisoning had inclusion bodies which contained mercury and selenium (Aoi *et al.*, 1985).

The blood mercury concentration of nine men who had been exposed to high levels (> 100 μg/m^3) of metallic mercury vapour for three days decreased with a half-time of three days for a fast phase and 18 days for a slow phase; the half-times in the urine were 28 and 141 days, respectively (Barregård *et al.*, 1992).

Analysis of brain samples from a deceased subject who had been exposed to metallic mercury vapour for 18 months 16 years before death showed high levels of mercury, indicating that the brain has a compartment with very slow turnover of mercury. Most of the deposited mercury was in colloidal form (Hargreaves *et al.*, 1988).

The concentration of mercury in the blood of the infants of two women who had been exposed accidentally to metallic mercury vapour during pregnancy was similar to that in maternal blood at the time of delivery, indicating transplacental passage (WHO, 1991).

An average urinary mercury concentration of about 50 μg/g creatinine was seen in 10 workers exposed to 40 μg/m^3 of air in a dry alkaline battery factory; the concentration in blood was about 18 μg/L (Roels *et al.*, 1987).

In 10 volunteers who received single oral doses of either ^{203}Hg-mercuric nitrate as such or added to calf-liver protein, 75–92% of the dose was excreted in the faeces during the first four to five days. The average whole-body half-time for mercury (slow component) was 42 days. No difference was seen between the two forms of administration. The ratio of mercury in red blood cells to that in plasma was 0.4 over at least the first 50 days of the experiment. At that time, approximately equal amounts of mercury were excreted in faeces and urine (Rahola *et al.*, 1973).

In a study of two men who had accidentally inhaled aerosols of neutron-activated ^{203}Hg-mercuric oxide, the lung clearance pattern displayed two phases, with biological half-times of two and 24 days, respectively, in one man; in the second, lung clearance appears to have been more rapid. The authors stated that absorption may have occurred from the lung, gastrointestinal tract or both. The major site of systemic deposition was the kidney, the content of which decreased with half-times of 60 and 37 days, respectively, in the two subjects. After 40 days, excretion was mainly urinary (Newton & Fry, 1978).

In five human volunteers who inhaled metallic mercury-197 vapour for 11–21 min, mercury was excreted by exhalation of metallic mercury and excretion of mercury in faeces and urine (Hursh *et al.*, 1980).

(*b*) *Methylmercury compounds*

After a single oral dose of ^{203}Hg-methylmercury nitrate was given to three volunteers, methylmercury was almost completely absorbed. A maximum of 10% of the dose was deposited in the head region, presumably in the brain. Whole-body radiolabel decline followed a first-order process, with half-times of 70–74 days. The decline in radiolabel in the head was less rapid than in the rest of the body. In two of the subjects, faecal excretion accounted for about 87 and 90% of the total elimination during the 49 days that followed

administration (Åberg *et al.*, 1969). Gastrointestinal absorption was similarly high, whether methylmercury was given as the nitrate or bound to protein (Åberg *et al.*, 1969; Miettinen, 1973).

In six volunteers who ate a single meal of fish containing methylmercury, the ratio of the concentration of mercury in erythrocytes and plasma was 21. Incorporation of methylmercury into hair was proportional to the concentration in blood at the time of formation of the hair strand; the ratio hair:blood was 292. The average half-times in blood were 7.6 h and 52 days (Kershaw *et al.*, 1980).

In a study of 162 subjects who had been exposed to methylmercury through consumption of contaminated fish in Sweden in 1967–72, intake was associated with concentrations of mercury in blood and hair. After cessation of eating the contaminated fish, the concentration of mercury in the blood cells of four subjects decreased with a half-time of 58–87 days; in one subject, the half-time was 164 days (Skerfving, 1974). The ratio of mercury in blood cells and in plasma was 2–12 (Skerfving, 1988).

Individuals with long-term intake of around 200 μg methylmercury per day were estimated to have blood mercury concentrations of about 200 μg/L and hair concentrations of about 50 μg/g (WHO, 1990).

After consumption of bread contaminated with methylmercury for two months in Iraq, the molar fraction of total mercury as inorganic mercury in several people was 7% in whole blood, 22% in plasma, 39% in breast milk, 73% in urine and 16–40% in liver (WHO, 1990).

The average ratio of methylmercury in cord blood and in maternal blood was 1.66 (Suzuki *et al.*, 1984). The infants of 10 fishermen's wives who were exposed to methylmercury through consumption of fish in Sweden had about 47% higher mercury levels in erythrocytes and similar levels in plasma in comparison with their mothers. The concentration of total mercury in breast milk from 15 women was similar to that in plasma; only about 20% of the total mercury in the milk was methylmercury (Skerfving, 1988).

(*c*) *Phenylmercury compounds*

In 509 infants in Buenos Aires, Argentina, who were exposed to phenylmercury fungicide through contaminated diapers, the average urinary excretion of total mercury was about 20 times higher than in 166 matched controls; over 90% of the mercury was inorganic (Gotelli *et al.*, 1985).

4.1.2 *Experimental systems*

(*a*) *Metallic mercury and inorganic mercury compounds*

Kostial *et al.* (1983) observed that the retention of orally administered ^{203}Hg-mercuric chloride in the carcass, gut and whole body was higher in newborn rats (60–70%) than in weaned rats (14–15%).

Absorption of an aqueous solution of ^{203}Hg-mercuric chloride applied under occlusion onto about 3 cm^2 of the shaved skin of guinea-pigs was dependent on the mercury concentration. A maximal rate of about 0.02% per min was recorded during 5 h after application of 16 mg/ml (as mercury) (Friberg *et al.*, 1961).

In rats, rabbits and monkeys exposed for 4 h to 1 mg/m^3 of metallic mercury vapour or injected intravenously with an equivalent dose of mercuric nitrate, the main accumulation

was in the kidney, but 10 times more mercury entered the brain after exposure to mercury vapour than after injection of mercuric nitrate (Berlin *et al.*, 1969).

In rats exposed to metallic mercury vapour, mercury deposits were found by a histochemical technique in the nerve cells in the cerebellum and hypothalamus (Møller-Madsen, 1992). In frog nerve–muscle preparations treated with mercuric chloride (3 μM [600 μg]), mercuric ions penetrated the nerve-cell membrane through sodium and calcium channels (Miyamoto, 1983).

Khayat and Dencker (1982) found four-fold higher fetal mercury concentrations in mice after exposure to metallic mercury vapour by inhalation than after intravenous injection of mercuric chloride. The passage of metallic mercury through the blood–brain barrier is usually ascribed to its lipophilicity.

In studies of cell suspensions of erythrocytes from humans, ducks and mice exposed *in vitro* to mercury vapour, uptake was proportional to catalase activity, which shows that this enzyme is involved in oxidation of mercury vapour in the erythrocyte (Halbach & Clarkson, 1978). Catalase-mediated oxidation of the vapour has also been demonstrated in other tissues, e.g. liver (Magos *et al.*, 1978).

Intravenous injection of rats with mercuric chloride at 0.7 mg/kg bw induced metallothionein in kidney tissue, which resulted in the binding of mercury (Nishiyama *et al.*, 1987).

After administration of 12 or 25 daily doses of mercury at 1 mg/kg bw as ^{203}Hg-mercuric chloride, the mitochondria in the proximal convoluted tubules were found to be enlarged and there were many very fine, dense, small particles. After fragmentation of the renal tissue and centrifugation at high speed, the radiolabel was found in two fractions, corresponding to mitochondria and microsomes (Bergstrand *et al.*, 1959).

Mice given parenteral doses of mercuric chloride exhaled metallic mercury vapour; exhalation was proportional to the body burden of mercury (Dunn *et al.*, 1978). Following intravenous treatment of rats with mercuric chloride, mercury was excreted into bile as a low-molecular-weight complex which had gel filtration properties similar to those of a mercury–glutathione complex (Ballatori & Clarkson, 1984).

In guinea-pigs exposed for a short time to metallic mercury vapour after parturition, the mercury concentration in milk was slightly lower than that in plasma. Neonates had increased concentrations of mercury in tissues and particularly in the kidney (Yoshida *et al.*, 1992). In rats given mercuric acetate orally, a linear relationship was observed between mercury concentrations in plasma and in milk (Sundberg *et al.*, 1991).

Selenium affects the tissue distribution and excretion of mercuric mercury. For example, three weeks' administration of sodium selenite or seleno-L-methionine (7.5, 37.5 or 75 μmol/L in drinking water) to BOM:NMRI mice increased the whole-body retention of a single oral dose (5 or 25 μmol [1 or 5 mg]/kg bw of ^{203}Hg-mercuric chloride. The effect on organ distribution varied with the dose of mercury and the type and dose of selenium compound (Nielsen & Andersen, 1991).

Human oral bacteria caused some methylation of mercuric chloride *in vitro* (Heintze *et al.*, 1983).

(*b*) *Methylmercury compounds*

Exposure of rats to ^{203}Hg-methylmercury chloride vapour at 10–28 mg/m^3 for 6–24 h was followed by efficient uptake of methylmercury through the lungs (0.6–7 nmol/g fresh tissue) [no data on absorbed fraction given]. Rats given a single oral dose of 0.75–2.3 mg/kg bw had several times higher mercury concentrations in organs (18.6–107.6 nmol/g fresh tissue). In liver and kidney, 42–50% of the mercury was in the soluble fraction, 32–43% in the crude nuclear fraction, 6–9% in the mitochondria and 9–11% in the microsomal fraction. In brain, 29% was in the soluble and 27% in the nuclear fraction, 31% was in mitochondria and 10% in microsomes (Fang, 1980).

Absorption of an aqueous solution of ^{203}Hg-methylmercury dicyandiamide applied under occlusion onto about 3 cm^2 of the shaved skin of guinea-pigs was dependent on concentration. A maximal disappearance of 5.9% was recorded during 5 h after application of 16 mg/ml (as mercury) (Friberg *et al.*, 1961).

Significant species differences have been observed in the distribution of methylmercury compounds in the body: The ratio between mercury concentrations in erythrocytes and plasma is about 20 in monkeys (17 in squirrel, 25 in rhesus), 25 in guinea-pigs, 7 in mice and more than 100 in rats (for review, see Magos, 1987). After prolonged administration of methylmercury compounds, the brain:blood ratios are 3–6 in squirrel monkeys (for review, see Berlin, 1986), 3.3 in pigs, 1.2 in guinea-pigs, 1.2 in mice and 0.06 in rats (for review, see Magos, 1987).

Following intraperitoneal injection of 1 mg/kg bw methylmercury chloride into four strains of mice, a significant difference in mercury concentrations was observed among strains, particularly in the blood. The rate of elimination from organs also differed: the biological half-time in blood (days) was 5.03 in BALB/c, 5.52 in C3H, 7.79 in C57Bl and 3.81 in CD-1 mice; that in kidneys was 8.73, 7.73, 7.47 and 4.54, respectively (Doi & Kobayashi, 1982). Eight days after intraperitoneal administration of ^{203}Hg-methylmercury chloride (0.4 mg/kg bw as Hg) to two strains of mice, males had significantly higher mercury concentrations in kidney than had females (C129F$_1$ strain: 5.33 and 3.34%; 129 strain: 7.47 and 3.57% of the dose in males and females, respectively). There was no sex difference in whole-body mercury retention (Doherty *et al.*, 1978).

The percentage of inorganic mercury in total mercury in tissues of squirrel monkeys that received single or repeated weekly doses of methylmercury nitrate by stomach tube at about 0.8 mg/kg bw Hg, was about 20% in liver, about 50% in kidney, 30–85% in bile and < 5% in brain, showing that methylmercury is demethylated (Berlin *et al.*, 1975). Similarly, inorganic mercury was demonstrated in the kidney and to a lesser extent in the liver of rats given daily doses of methylmercury dicyandiamide (Magos & Butler, 1972).

The relative concentration of inorganic mercury in mice increased gradually after a single intravenous injection of 25 μg methylmercury chloride and was about 30% after 22 days; the author concluded that mice obtain a lower fraction of inorganic mercury in the kidney than rats (Norseth, 1971). Cats fed either methylmercury-contaminated fish or methylmercury hydroxide added to fish accumulated inorganic mercury in the liver and kidney; 62% was recovered as methylmercury in kidney and 80% in liver. The metabolism of the methylmercury in the contaminated fish and of the added hydroxide was similar (Albanus

et al., 1972). Similar results were found in cats fed methylmercury-contaminated fish or methylmercury chloride (Charbonneau *et al.*, 1976), and no difference in metabolism was seen in rats given four different salts of methylmercury orally or subcutaneously (Ulfvarson, 1962).

Methylmercury added as the chloride *in vitro* to erythrocytes from humans, rabbits and mice was complexed to a low-molecular-weight compound—probably glutathione. In rats, such binding was minimal (Naganuma *et al.*, 1980). Following the addition of methylmercury chloride to erythrocytes from mice, rats and humans in another study, mercury was found to be bound to haemoglobin—probably cysteinyl residues (Doi & Tagawa, 1983). In rats, L-cysteine enhanced the uptake of mercury by the brain after administration of methylmercury chloride by intracarotid injection. There were indications of a transport system carrying methylmercury over the brain capillary endothelial cell membrane (Aschner & Clarkson, 1988).

In rats injected intravenously with methylmercury chloride, methylmercury was present in the bile as a low-molecular-weight compound complex, which was identified as methylmercury glutathione on the basis of thin-layer chromatography, gel filtration and ionic exchange (Refsvik & Norseth, 1975).

After intravenous injection into rats, methylmercury was excreted into the bile, predominantly as methylmercury cysteine, which is largely reabsorbed from the intestine. There is thus enterohepatic circulation of methylmercury (Norseth & Clarkson, 1971). In rat gut, however, a fraction of methylmercury is converted to inorganic mercury, which is then excreted mainly in the faeces (Rowland *et al.*, 1980).

Hamsters administered a single oral dose of 10 mg/kg bw methylmercury chloride excreted about 50% of the mercury (only about 10% of which was inorganic mercury) in the urine within one week. In rabbits given 0.4 mg/kg bw intravenously, < 2% was excreted in the urine (Petersson *et al.*, 1989).

After addition of 250 ng methylmercury chloride to three hydroxyl radical producing systems, copper ascorbate, xanthine oxidase hypoxanthine–ferric monosodium ethylenediaminetetraacetate and hydrogen peroxide–ultraviolet B light, analysis of inorganic mercury revealed significant dealkylation, which appeared to be unrelated to either superoxide or hydrogen peroxide production alone (Suda *et al.*, 1991). In rat liver microsomes treated with 500 ng methylmercury chloride, both inorganic mercury and hydroxy radical contents increased after addition of NADPH and were further increased by KCN (Suda & Hirayama, 1992).

Selenium affects the tissue distribution and excretion of methylmercury. For example, selenite increased the brain levels of mercury in rats treated with methylmercury (Magos & Webb, 1977).

(*c*) *Phenylmercury and methoxyethylmercury compounds*

Faecal excretion of 0.120 mg/kg bw Hg as phenylmercury acetate in rats was 65% during 48 h after a single oral dose and 30% after intravenous administration of the same dose, indicating that more than half of the phenylmercury salt was absorbed (Prickett *et al.*, 1950).

In rats given an intraperitoneal injection of phenylmercury acetate, the compound was metabolized rapidly to mercuric mercury (Magos *et al.*, 1982).

Daniel *et al.* (1971) administered a single subcutaneous dose of methoxy-^{14}C-ethylmercury chloride to rats. Within three days, about half of the radiolabel appeared in exhaled air, with 44% in ethylene and 5% in carbon dioxide (44% after pyrolysis of air). Mercury was accumulated in kidney: A few hours after dosing, inorganic mercury constituted about one-half of the total mercury in that organ; after one day, all of the mercury was inorganic. About 25% of the radiolabel was excreted in urine over 4 days and about 10% after 8 days.

4.2 Toxic effects

The toxic effects of inorganic mercury (WHO, 1976; Kark, 1979; Berlin, 1986; Clarkson *et al.*, 1988a; Dayan *et al.*, 1990; WHO, 1991; Clarkson, 1992), methylmercury compounds (WHO, 1976; Berlin, 1986; Clarkson *et al.*, 1988a; Dayan *et al.*, 1990; WHO, 1990) and phenylmercuric acetate (Skerfving & Vostal, 1972; WHO, 1976; Berlin, 1986; Clarkson *et al.*, 1988a) have been reviewed.

4.2.1 *Humans*

(*a*) *Inorganic mercury*

Workers accidentally exposed for 4–8 h to metallic mercury at levels estimated to have ranged from 1 to 44 mg/m^3 developed chest pain, dyspnoeic cough, haemoptysis, impairment of pulmonary function and interstitial pneumonitis (McFarland & Reigel, 1978). Acute massive exposure to metallic mercury vapour can result in psychotic reactions with delirium (for review, see Kark, 1979).

Troen *et al.* (1951) reported 18 cases of human poisoning by ingestion of single doses of mercuric chloride. In nine fatal cases, the lowest estimated dose was 2 g. Gastrointestinal and renal lesions were observed at autopsy.

Roels *et al.* (1985) examined 131 male and 54 female workers exposed to metallic mercury vapour in several factories in Belgium and 114 and 48 unexposed control male and female workers. In responses to a questionnaire, several symptoms of central nervous system disorder (memory disturbances, depressive feelings, fatigue and irritability) were more prevalent among exposed subjects than controls. A significantly increased prevalence of hand tremor was recorded in the group of exposed men, as compared to male controls (15 *versus* 5%). The average concentrations of mercury in urine were 52 μg/g creatinine in exposed men and 37 μg/g creatinine in women; the corresponding levels in controls were 0.9 and 1.7 μg/g creatinine.

In a study of 89 chloralkali workers with a median urinary mercury concentration of 25 μg/g creatinine (range up to 83) and a control group of 75 workers from other industries (median concentration, 2 μg/g creatinine), an association was observed between urinary mercury concentration, self-reported symptoms—tiredness, confusion and degree of neuroticism (Langworth *et al.*, 1992a)—and urinary excretion of *N*-acetyl-β-glucosaminidase, a lysosomal enzyme originating from tubular epithelial cells. No significant effect on serum titres of autoantibodies (including antiglomerular basement membrane and antilaminin) was observed (Langworth *et al.*, 1992b). Elevated excretion of *N*-acetyl-β-glucosaminidase was also reported by Barregård *et al.* (1988) in chloralkali workers.

Of 44 African women with nephrotic syndrome, 70% used or had used mercury-containing skin-lightening creams; the corresponding fraction among other general medical female in-patients was 11% (Barr *et al.*, 1972). In eight other cases of nephrotic syndrome, IgG and C3 complement deposits were observed in glomeruli (Lindqvist *et al.*, 1974). Proteinuria and the nephrotic syndrome have also been described in workers exposed to mercury compounds (Kazantzis *et al.*, 1962).

Lauwerys *et al.* (1983) studied 62 workers in a chloralkali plant and a zinc–mercury amalgam factory with a mean urinary mercury concentration of 56 μg/g creatinine. Eight exposed workers, but none of 60 control workers who were not occupationally exposed to heavy metals but were matched to the exposed group with respect to age and socioeconomic status, had serum antibodies towards laminin, a non-collagen glycoprotein found *inter alia* in the glomerular basal membrane. No alterations were seen in a large battery of renal function tests.

In studies of dentists and chloralkali workers exposed to metallic mercury vapour (mean urinary mercury concentration, 1.3 nmol/mmol [2.3 μg/g] creatinine in dentists and 26 nmol/mmol [46 μg/g] creatinine in chloralkali workers), no significant effect on endocrine function (pituitary, thyroid and adrenal glands, testis) was observed as compared to controls (0.4–0.6 nmol/mmol [0.7–1.06 mg/g] creatinine) without occupational exposure (Erfurth *et al.*, 1990). Similar results were reported by Langworth *et al.* (1990) in dental personnel.

In a study reported in detail on p. 271, Barregård *et al.* (1990) studied mortality among 1190 chloralkali workers who had been monitored biologically for exposure to metallic mercury vapour for at least one year in 1946–84. For workers with > 10 years of latency, mortality from all causes was not significantly increased (SMR, 1.1; 95% CI, 0.9–1.3), but mortality from circulatory disease was slightly increased (SMR, 1.3; 95% CI, 1.0–1.5). No such elevation was reported in another study of workers exposed to metallic mercury (Cragle *et al.*, 1984; see p. 269).

Contact dermatitis with sensitization against metallic mercury has been reported. For example, Ancona *et al.* (1982) reported such a case in a dentist who had a positive epicutaneous patch test. Finne *et al.* (1982) performed patch tests on 29 patients with amalgam fillings and oral lichen planus. Positive reactions to mercury were found in 62% as compared with 3% of controls (2300 eczema cases). After the amalgam fillings had been removed from four patients, an improvement in the oral changes was recorded.

In the 1940s, 'pink disease' (acrodynia), presenting as irritation, insomnia, sweating, photophobia and general rash in children, was reported to be associated with exposure mainly to calomel (mercurous chloride) in, e.g. teething powder and ointments (Warkany, 1966). Cases have also been associated with exposure to other chemical forms of mercury, e.g. metallic mercury vapour from broken fluorescent tubes (Tunnessen *et al.*, 1987). The mechanism by which the condition occurs has not been elucidated. Three of six children with mucocutaneous lymph node syndrome (Kawasaki disease), including increased serum IgE and eosinophilia, had urinary concentrations of mercury (16–25 μg/24 h) higher than established normal levels (< 10 μg/24 h). The syndrome may represent a hypersensitivity reaction to environmental pollution with mercury (Orlowski & Mercer, 1980).

(*b*) *Methylmercury compounds*

The first case of 'methylmercury poisoning' was described in a worker exposed to methylmercury phosphate and nitrate for a period of four months (Hunter & Russell, 1954). Since then, numerous descriptions have been published, mainly in connection with outbreaks of poisoning in subjects consuming contaminated fish in Japan (Minamata disease) (Igata, 1991) or seeds treated with methylmercury dicyandiamide, e.g. in Iraq (Bakir *et al.*, 1973). Its main features are that: (i) the target organ is the central nervous system; (ii) there is a latent period between exposure and onset of clinical disease; (iii) the symptoms and signs include paraesthesia in the hands, feet and lips, concentric constriction of visual fields and ataxia; and (iv) morphological changes occur in the visual and precentral cortical areas as well as in the cerebellum. There is also evidence of peripheral neuropathy (Rustam *et al.*, 1975).

In the cohort study in two administrative subunits in the vicinity of Minamata City, Japan (Tamashiro *et al.*, 1986; see pp. 275–276), significantly elevated SMRs were observed for cerebral haemorrhage (1.67, 95% CI; 1.24–2.24), liver disease (2.00; 1.33–2.89), senility (2.34; 1.67–3.26) and violent death (accident, poisoning, suicide) (1.48; 1.12–1.97).

(*c*) *Phenylmercury, ethylmercury and methoxyethylmercury compounds*

A study of 509 infants exposed to phenylmercury acetate from contaminated diapers showed a clear dose–response relationship between the concentration of organomercury compounds in urine and urinary excretion of γ-glutamyl transpeptidase, an enzyme in the brush borders of renal tubular cells. Children with the highest mercury excretion also had increased 24-h urine volumes. Some of the children also had 'pink disease' (Gotelli *et al.*, 1985).

A few cases of systemic poisoning by ethylmercury and methoxyethyl compounds have been reported (for review, see Skerfving & Vostal, 1972). Most patients showed symptoms and signs of disorders in the gastrointestinal tract and kidneys (albumin, red cells and casts in urine).

4.2.2 *Experimental systems*

(*a*) *Metallic mercury and inorganic mercury compounds*

Application of 2 ml of a solution containing 0.24 mol [65 g] mercuric chloride resulted in the death of 3/20 guinea-pigs after two days (Wahlberg, 1965).

Ashe *et al.* (1953) reported damage to brain, liver, kidney, heart and lungs of rabbits exposed to mercury vapour at a concentration of 29 mg/m^3 air. Damage was seen after exposure as short as 1 h. Microscopic changes were observed in mitochondria of the renal proximal tubule after 12 or 25 daily doses of 1 mg/kg bw Hg as mercuric chloride to rats (Bergstrand *et al.*, 1959).

In a susceptible strain of rats (Brown–Norway), subcutaneous injections of mercuric chloride caused a systemic autoimmune nephritis characterized by the production of various antibodies to self and non-self antigens and an increase in total serum IgE concentrations. A biphasic autoimmune glomerulonephritis occurred: initially, anti-glomerular basement membrane antibodies were produced, resulting in linear IgG deposition along the glomerular capillary walls. Later, granular IgG deposits appeared which are responsible for

an immune-complex type glomerulonephritis (Druet *et al.*, 1978). Mercuric chloride appears to induce a T cell-dependent polyclonal activation of B cells in Brown–Norway rats (Pelletier *et al.*, 1986); most animals develop proteinuria, which in some animals progresses to a nephrotic syndrome that is sometimes lethal (Druet *et al.*, 1978), while in other animals the condition is transient. There is a striking strain difference. By crossing susceptible rats with unsusceptible Lewis rats, susceptibility was shown to depend on three or four genes, one of which is located within the major histocompatibility complex (Druet *et al.*, 1982). Certain strains of mice may develop similar glomerular conditions after injection with mercuric chloride (Hultman & Enestrom, 1987).

In Lewis rats injected subcutaneously with mercuric chloride (1 mg/kg bw three times a week for up to 4 weeks), no autoimmune disorder was observed. Instead, animals showed proliferation of suppressor/cytotoxic T cells in the spleen and lymph nodes. As a consequence, they developed a non-antigen-specific immunosuppression and responded to neither classical mitogens nor alloantigens (Pelletier *et al.*, 1987a). Mercuric chloride could also inhibit the development of an organ-specific autoimmune disorder, Heymann's nephritis (Pelletier *et al.*, 1987b).

Micromolar concentrations of mercury have been shown to increase the release of acetylcholine in frog neuromuscular preparations (Manalis & Cooper, 1975) and that of dopamine in adult mouse brain homogenates (Bondy *et al.*, 1979).

Significant decreases in the activities of several enzymes of the glutathione (GSH) metabolic pathway in kidney—GSH disulfide reductase, GSH-peroxidase, γ-glutamyl-cysteine synthetase and γ-glutamyl transpeptidase—were seen 24 h after subcutaneous administration of 10 μmol[2.5 ml]/kg bw mercuric chloride to Sprague–Dawley rats; in the liver, only the activity of GSH disulfide reductase was decreased. After administration of 30 μmol [7.5 mg]/kg bw, the decreases in specific enzyme activities were accompanied by large losses of cellular protein and decreased GSH concentrations in both kidney and liver. The effects could be blocked by sodium selenite (Chung *et al.*, 1982). The mercuric ion binds to reduced sulfhydryl groups in proteins and inhibits a wide range of enzymes (for review, see Kark, 1979).

In Holtzman rats given a lethal intravenous dose of 3 mg/kg bw Hg as mercuric chloride and sacrificed after 4 h, there was extensive renal haemorrhage. Kidney mitochondria contained mercury at 4–5 nmol[0.8–1 μg]/mg protein and showed uncoupling of oxidative phosphorylation.

In mitochondrial preparations of kidney cortex from Sprague–Dawley rats, mercury at concentrations of 2 nmol/mg protein and above affected mitochondrial respiration: clear stimulation of state 4, mild stimulation of state 3 and inhibition of the 2,4-dinitrophenol-induced uncoupled respiration rate. These effects were both preventable and reversible by addition of albumin or dithioerythritol to the in-vitro system (Weinberg *et al.*, 1982a), but not in mitochondria isolated 3 h after subcutaneous administration of mercuric chloride at 5 mg/kg bw, when the concentration of mercury in mitochondrial protein was 0.72 ± 0.10 nmol/mg (Weinberg *et al.*, 1982b).

Addition of mercuric chloride at concentrations of 1–6 μm [0.2–1.2 mg] mercury to preparations of mitochondria from rat kidney cortex and heart in the presence of antimycin

A decreased the production of superoxide but increased hydrogen peroxide production. The authors concluded that mercuric ion caused dismutation of the superoxide, leading to increased hydrogen peroxide formation, which could lead to oxidative tissue damage. Addition of mercurous ions did not affect superoxide production (Miller *et al.*, 1991). [The Working Group noted that the mercury concentrations employed were high.]

Mercuric ions from mercuric chloride, added at 1 mM (270 mg), reacted *in vitro* with isolated DNA (Eichhorn & Clark, 1963). [The Working Group noted the very high concentration used.] No study has shown covalent binding to DNA, e.g. by isolating such an adduct from DNA after complete hydrolysis to nucleosides.

Inhibition of protein synthesis was observed in cell-free systems prepared from mouse glioma after addition of mercuric chloride at a concentration of 2×10^{-5} M [5 mg] (Nakada *et al.*, 1980). [The Working Group noted the high concentration used.] Mercuric chloride at a concentration of 10 μM [2.3 mg] reduced lipid synthesis in isolated mouse sciatic nerve (Clöez *et al.*, 1987).

Sodium selenite dramatically decreased the acute nephrotoxicity of mercuric chloride in rats, when given simultaneously or even 1 h after mercury (Pařízek & Oštádalová, 1967).

(*b*) *Methylmercury compounds*

There are clear species differences in symptoms and signs of poisoning by methylmercury compounds. Blindness has been reported in man, rats, monkeys and pigs, but not in cats (for reviews, see WHO, 1976, 1990). Man, monkeys and cats develop ataxia; but in rats dosed orally with methylmercury chloride reduced conduction velocities and histopathological changes occurred in peripheral nerves, while the central nervous system was not affected (Fehling *et al.*, 1975).

Renal damage is a typical finding in rats. Male Wistar rats fed mercury at 0.250 mg/kg bw per day as methylmercury chloride for up to 26 months developed severe renal tubular damage. The estimated mercury level in kidney was 30.2 mg/kg in males and 60 mg/kg in females (Munro *et al.*, 1980). Nuclear swelling and vacuolar degeneration of the cytoplasm were seen in SPF ICR mice fed a diet containing 10 ppm methylmercury chloride for 26 weeks (Hirano *et al.*, 1986). Treatment of monkeys with daily oral doses of 80–125 μg/kg bw methylmercury hydroxide for 3–12 months did not appear to affect the general well-being of the animals, but ultrastructural changes occurred in the kidneys, with intracytoplasmic vacuoles and electron-dense inclusion bodies in the proximal tubuli (Chen *et al.*, 1983).

In mice fed mercury at 3.9 mg/kg diet as methylmercury chloride for 12 weeks, thymus weight and cell number were decreased, the lymphoproliferative response to T and B mitogens was increased in thymus and spleen, and natural killer cell activity was decreased in the spleen and blood (Ilbäck, 1991). Mice fed methylmercury chloride at doses of 1–10 mg/kg diet for 84 days had significantly higher mortality rates when inoculated with encephalomyelitis virus (nononcogenic) than did animals not given methylmercury (Koller, 1975).

Impairment of adrenal and testicular function occurred in rats given 23 intraperitoneal injections of 0.26 mg methylmercury chloride over six weeks (Burton & Meikle, 1980); thyroid function was impaired in mice given two intraperitoneal doses of 5 mg/kg bw (Kawada *et al.*, 1980).

Female Charles River CD rats were given 3–10 mg/L methylmercury hydroxide in drinking-water four weeks prior to mating and through day 19 of pregnancy. With concentrations of 3–5 mg/L, there was decreased synthesis of mitochondrial structural proteins in the livers of the fetuses and inhibition of several mitochondrial enzymes (Fowler & Woods, 1977a). In male rats of the same strain treated similarly for six weeks, electron microscopy revealed swelling of the renal proximal tubule cell mitochondria at a dose of 5 mg/L. The respiratory control ratios were decreased (mitochondrial respiratory dysfunction), and effects were seen on enzyme activities, including decreased monoamine oxidase and cytochrome oxidase and increased δ-aminolaevulinic acid synthetase. The rats had increased urinary excretion of porphyrins but no deterioration in standard renal function tests (Fowler & Woods, 1977b).

Mouse glioma cell cultures treated with methylmercury chloride (5×10^{-6} M for 4 h) showed inhibition of cell mitosis, by blockage of the polymerization of tubulin to microtubuli, with accumulation of cells during mitosis. Electron microscopy showed an absence of microtubuli as mitotic spindle fibres and disorganization of chromosomes (Miura *et al.*, 1978).

Sodium selenite, and possibly also the chemically unknown form of selenium found in marine foods, delayed the onset of the toxic effects of methylmercury chloride in rats and reduced the severity of its effects (Chang & Suber, 1982).

Methylmercury hydroxide added to fish homogenate and methylmercury-contaminated fish were equally neurotoxic to cats (Albanus *et al.*, 1972). Similar results (ataxia, loss of balance or motor incoordination, loss of nerve cells) were found in cats fed either methylmercury chloride or methylmercury-contaminated fish (Charbonneau *et al.*, 1976).

(*c*) *Phenylmercury, ethylmercury and methoxyethylmercury*

Renal damage was observed in mice, rats and rabbits given phenylmercury nitrate and chloride intraperitoneally or intravenously (Weed & Ecker, 1933). Ethylmercury poisoning has been described in rats, rabbits, cats, sheep, swine and calves. The symptoms are similar to those of methylmercury poisoning (Skerfving & Vostal, 1972). In rats administered the fungicide methoxyethyl mercury chloride (2 mg/kg bw for 50 days or 0.2 mg/kg bw for 80 days) intraperitoneally, impaired weight gain, renal damage and signs of nervous system damage (e.g. tremor, ataxia) were seen (Lehotzy & Bordas, 1968).

4.3 Reproductive and prenatal effects

4.3.1 *Humans*

The effects of inorganic and organomercury compounds on human reproduction and development have been reviewed (Khera, 1979; Inskip & Piotrowski, 1985; Schardein, 1985; Burbacher *et al.*, 1990; Roeleveld *et al.*, 1990; Shepard, 1992).

(*a*) *Metallic mercury and inorganic mercury compounds*

(i) *Exposure of women*

Adverse pregnancy outcomes have been reported following exposure to mercuric chloride tablets (Afonso & de Alvarez, 1960), to mercuric iodide-containing soap (Lauwerys

et al., 1987) and in a dental surgery unit where the concentration of mercury exceeded the threshold limit value of 0.05 mg/m^3 (Gelbier & Ingram, 1989). After exposure of a woman prior to week 17 of pregnancy to metallic mercury in a contaminated carpet (24-h urinary concentration of mercury, 230 μg/L), no adverse effect was seen on birth weight, growth or on acquisition of developmental milestones in the child at the age of two (Thorp *et al.*, 1992).

Heidam (1984) conducted a historical prospective study of pregnancy outcomes in women in 12 selected occupations in the Danish county of Funen. Controls were employed in occupations with less exposure to chemicals. Dental assistants returned 94% of the 772 mailed questionnaires on pregnancy history. The incidence of spontaneous abortions in dental assistants in private clinics was 11.2% in 259 pregnancies, yielding a crude odds ratio of 1.1 (95% CI, 0.7–1.8). After control for confounding variables, including age at gravidity, pregnancy order and maternal age at pregnancy, the odds ratio was 1.0 (0.6–1.6). Dichotomization of dental assistants according to whether they reported exposure to inorganic mercury compounds also showed no increase in the spontaneous abortion rate in the exposed subgroup.

Brodsky *et al.* (1985) conducted a postal survey of 30 272 female dental assistants in California (USA) regarding the use of anaesthetic agents and mercury amalgams and health and pregnancy histories for the years 1968–78. The response rate was 70%. Exposure was categorized on the basis of the number of amalgam restorations prepared per week into no, low (0–40) or high (> 40) . Outcomes were adjusted for maternal age and cigarette smoking. No relationship was observed between exposure and spontaneous abortion or congenital abnormalities.

Sikorski *et al.* (1987) evaluated reproductive function and outcome in 81 women (45 dentists, 36 dental assistants) exposed occupationally to metallic mercury and in 34 unexposed women [occupational details not given] recruited at random in the Lublin region of Poland. Exposure was ascertained by determination of mercury in samples of scalp and pubic hair; the mercury content in hair was related to duration of employment and to the number of amalgams used per week. A total of 57 exposed women had 117 pregnancies, 24% of which ended in spontaneous abortion, stillbirth or congenital malformations (including five cases of spina bifida). Thirty unexposed women had 63 pregnancies, 11% of which ended in an adverse outcome. Reproductive failure was associated with the mercury content of the hair. The frequency of menstrual disorders was also high in exposed women and was related to the number of years employed and to the mercury content of scalp hair. [The Working Group noted that temporal matching of exposure and pregnancy was not carried out, that no mention of potential confounders was made and that hair mercury levels poorly reflect exposure to metallic mercury.]

Ericson and Källén (1989) evaluated 8157 infants born to dentists, dental assistants and dental technicians in Sweden between 1976 and 1986. Outcomes were standardized for maternal age and parity, year of birth and sex of the infant. There was no suggestion of an increased rate of stillbirths or congenital malformations. The risk ratio for low birth weight (< 2500 g) was 0.9 (95% CI, 0.7–1.2) for dentists, 1.2 (1.0–1.3) for dental assistants and 0.8 (0.5–1.4) for dental technicians. Data on spontaneous abortions were available only for 1980–81, and the rates for dentists, dental assistants and dental technicians corresponded to expected figures. The authors also reported no increase in the rates of spontaneous abortion

or neural tube defects among women working in dentistry, as ascertained in a small prospective study in Malmö in 1964–65. [The Working Group noted that no marker of exposure to mercury was used.]

De Rosis *et al.* (1985) studied the possible effects on reproductive function and outcome in women of exposure to mercury vapour in two mercury vapour lamp factories in Italy. Workers were exposed to mercury in only one plant, where time-weighted averages exceeded 0.05 mg/m^3 in 1972–76; they were subsequently reduced to < 0.01 mg/m^3. Workers in a second plant were used as the reference group. Participation was 79% (153 women) in the exposed plant and 88% (293) in the reference plant. Past health events were ascertained by interview. The prevalence and incidence of menstrual cycle disorders were higher in the exposed group, with an age-standardized ratio of abnormal cycles of 1.4. Exposed married women also had a higher prevalence of primary subfecundity. No difference in the rates of spontaneous abortion was found, but the malformation rate, particularly of dislocations of the hip, was higher in the exposed group (6/106 births) than in the unexposed group (0/218 births); however, the authors noted that the prevalence of the condition differed between northern and southern Italy.

(ii) *Exposure of men*

A questionnaire on fertility was distributed to the total male work force of three factories in which workers were exposed to mercury vapour and of two control plants with comparable work characteristics in Belgium (Lauwerys *et al.*, 1985). Blood and urine mercury concentrations were used as indices of exposure. The mercury-exposed group consisted of 17 workers in a zinc–mercury amalgam factory, 35 workers in a chloralkali plant and 51 workers in plants for the manufacture of electrical equipment. The 50th and 95th percentiles of mercury in the urine were 36.9 and 147.1 μg/g creatinine. No difference was noted between the observed and expected numbers of children in the mercury-exposed group.

Alcser *et al.* (1989) conducted a retrospective study of reproductive function in 247 white male workers who had been employed for at least four months between 1953 and 1966 at a US Department of Energy plant where large quantities of metallic mercury were used in 1953–1963. Intermittent periods of potentially high exposure occurred, especially between 1955 and 1956, and a quarterly programme of urine analysis charted worker exposure from 1953 onwards. A control group was selected from unexposed workers at the same plant. Most measures of reproductive health (fertility rates, incidence of major malformations and childhood illnesses) did not differ between the two groups. The wives of the exposed men had a higher rate of miscarriages; however, this effect was also present prior to exposure to mercury.

Cordier *et al.* (1991) studied the rate of spontaneous abortions in wives of workers exposed to mercury vapour at a chloralkali plant in France and compared it with that of the wives of controls from the same plant. Reproductive history was ascertained by questionnaire in 1984, and exposure history was provided by a plant physician. Urinary mercury levels were measured in most potentially exposed workers at least once a year from 1968. The response to the questionnaire was about 75%, resulting in the inclusion of 118 exposed and 283 unexposed workers. Results were adjusted for maternal age, gravidity, tobacco use and

alcohol consumption. The risk for spontaneous abortion increased significantly with increasing urinary mercury concentration in the three months preceding pregnancy. For example, for urinary mercury concentrations in excess of 50 μg/ml in the three-month period prior to the initiation of pregnancy, the spontaneous abortion rate was 18.4/100 pregnancies, as compared with 8.6/100 in the wives of unexposed men [RR, 2.1; 95% CI, 1.1–4.1]. No relationship between exposure to mercury and birth weight or the frequency of malformations was found.

(*b*) *Methylmercury compounds*

In a review of the literature, Inskip and Piotrowski (1985) found no evidence that miscarriage, stillbirth, major deficits in birthweight, chromosomal damage or hormonal imbalances in infants were associated with exposure to methylmercury compounds; microcephaly appeared to be the only congenital malformation associated with exposure. Most effects were expressed as clinical symptoms, such as delay in disappearance of primitive reflexes, mental disturbances, retardation of physical development, retardation in emergence of behaviour patterns, disturbances in chewing and swallowing, motility disturbances, impairment of voluntary movements and coordination (ataxia) and constriction of the visual field. Manifestations of toxicity were not always evident at birth but sometimes developed later in childhood.

In a review of autopsy reports on children exposed *in utero* to methylmercury compounds, Burbacher *et al.* (1990) concluded that high concentrations in the brain (12–20 ppm [mg/kg]) decreased brain size, damaged the cortex, basal ganglia and cerebellum and resulted in ventricular dilatation, ectopic cells, gliosis, disorganized layers, misorientated cells and loss of cells. At those tissue concentrations, the neurobehavioural effects included blindness, deafness, cerebral palsy, spasticity, mental deficiency and seizures. At concentrations of 3–11 ppm (mg/kg), mental deficiency, abnormal reflexes and muscle tone and retarded motor development occurred [no data were presented on neuropathological effects]. At low levels (< 3 ppm), delayed psychomotor development was reported.

Foldspang and Hansen (1990) studied reproductive outcomes in Godthaab (365 infants; 45.9% of total births in the period) and Thule (11 infants; 100% of total births), Greenland, between January 1983 and December 1986. Women were invited to participate in the study when they entered maternity clinics at the beginning of labour; nonparticipation was attributed to the difficulty of collecting data in the Arctic. Socioeconomic data, cigarette consumption, consumption of traditional Greenlandic foods (eating whale and seal meat was widespread) and other data were obtained by interview or from hospital records. Maternal and umbilical blood samples were collected at delivery and assayed for total mercury. The average blood mercury concentration of the infants was 21 μg/ml (range, 2–136 μg/L), while maternal levels averaged 14.9 μg/ml (range, 2–128 μg/L). Birth weights were inversely proportional to maternal and offspring blood mercury concentrations. [The Working Group noted that maternal height was not taken into account although birthplace was.]

Grandjean and Weihe (1993) studied birthweight in relation to fish consumption in residents of the Faroe Islands. A total of 1024 births that occurred between March 1986 and December 1987 were included. The average birthweights of the infants of nonsmoking

mothers were 3400 g in 13 infants whose mothers consumed no fish and 3600 g (n = 83), 3850 (n = 220), 3800 (n = 183) and 3750 g (n = 114) in women who consumed 1, 2, 3 and > 4 fish dinners per week, respectively. The average total mercury concentrations in cord blood were 20, 118, 105, 133 and 138 nmol/L [4, 23.6, 21, 26.6 and 27.6 μg/L] in the same groups. Thus, elevated cord blood mercury concentrations were associated with increased birth-weight, but the authors attributed this correlation to the content of (n-3)-poly-unsaturated fatty acids in fish.

4.3.2 *Experimental systems*

(*a*) *Metallic mercury and inorganic mercury compounds*

The reproductive and developmental effects of metallic mercury and its salts in laboratory animals have been reviewed (Khera, 1979; Barlow & Sullivan, 1982; Léonard *et al.*, 1983; Schardein, 1985; Shepard, 1992). In a review, Barlow and Sullivan (1982) concluded that exposure to metallic mercury (e.g. inhalation of 0.3 ppm [2.5 mg/m^3] by rats for 6 h per day for three weeks prior to pregnancy and again on gestation days 7–20) and to inorganic mercury (e.g. intravenous injections of 2–4 mg/kg bw mercury into hamsters on gestation day 8) can cause fetal growth retardation and prenatal and postnatal mortality.

Altered oocyte maturation was reported after exposure of hamsters to mercuric chloride on day 1 of the oestrous cycle. The effective dose levels were as low as 1 mg/kg bw per day (Lamperti & Printz, 1973; Watanabe *et al.*, 1982).

When mercuric chloride (at 5–80 μM [1.2–18.8 mg]) was added to freshly prepared human semen samples *in vitro*, a dose- and time-dependent decrease in sperm motility was observed. In addition, morphological changes and silver-enhanced mercury deposits in the sperm were noted (Ernst & Lauritsen, 1991).

Exposure of mice to mercuric chloride as 1.5 or 2.0 mg/kg bw Hg by intravenous injection on day 0 resulted in a high incidence of abnormal blastocysts when cells were examined on day 3.5 of gestation (Kajiwara & Inouye, 1986). The minimal effective doses of mercuric acetate that reduced embryonic viability and increased the incidence of malformations and growth retardation in hamsters treated on day 1 of gestation were 35, 25 and 8 mg/kg by oral administration, 8 mg/kg by subcutaneous injection, 4 mg/kg by intravenous injection and 2 mg/kg by intraperitoneal injection (Gale, 1974). Subcutaneous injection of 15 mg/kg bw mercuric acetate to six strains of hamsters on gestation day 8 caused increased resorptions and abnormal and growth retarded fetuses, the incidence of which varied slightly from strain to strain (Gale, 1981).

Exposure of mice to doses of 7.5–25 mg/kg mercuric chloride by subcutaneous injection on day 16 of gestation resulted in a 40% reduction in fetal accumulation of vitamin B_{12} and α-aminobutyric acid within 4 h; no overt fetal toxicity was observed with doses up to 15 mg/kg, although some fetal deaths occurred with 20 mg/kg and maternal lethality was seen at 25 mg/kg (Danielsson *et al.*, 1984). Reduced levels of fetal zinc, copper and iron were reported 4–24 h after exposure of pregnant rats to 0.79 mg/kg mercury by intravenous injection on gestation day 12 (Holt & Webb, 1986a). Intravenous injections of 0.5–0.6 mg/kg mercuric chloride on gestation day 7 were reported to cause fetal malformations. A slightly higher dose (0.79 mg/kg) caused resorptions when given on day 12 and growth retardation

when given on days 8, 10, 12, 14 or 16. The authors attributed the fetal effects to alterations in maternal renal function resulting from exposure to mercury (Holt & Webb, 1986b).

Subcutaneous administration of 1 mg/kg bw mercuric chloride to Sprague–Dawley rats on the last eight days of gestation induced a transient increase in urinary excretion of β_2-microglobulin and albumin in both mothers and offspring. In male offspring, these effects reappeared at 180 days of age. A follow-up experiment in which females were dosed throughout pregnancy showed an effect on male offspring renal function at 3–4 months of age, but not at 10 months (Bernard *et al.*, 1992).

Decreased embryonic growth was observed after exposure *in vitro* of day-10 rat embryos to 4 μM mercuric chloride for 48 h or to 20 μM for 24 h; the concentrations required to affect morphogenesis were 1 μM and 20 μM, respectively (Kitchin *et al.*, 1984; Saillenfait *et al.*, 1990).

(*b*) *Methylmercury compounds*

The literature on the effects of exposure to methylmercury compounds on prenatal development in experimental animals, including effects on the function of several organ systems in postnatal animals following exposure *in utero*, is extensive (for reviews, see Khera, 1979; Reuhl & Chang, 1979; Léonard *et al.*, 1983; Inskip & Piotrowski, 1985; Mottet *et al.*, 1985; Schardein, 1985; Burbacher *et al.*, 1990; Shepard, 1992).

Subcutaneous injection of hamsters with 6.4 or 12.8 mg/kg bw mercury as methylmercury chloride on day 1 of the oestrous cycle did not affect the number of oocytes released (Watanabe *et al.*, 1982).

Albino male rats received 0, 5 or 10 μg/kg bw per day methylmercury chloride by intraperitoneal injection for 15–90 days. Time- and dose-dependent decrease in seminiferous tubular diameter, numbers of Sertoli cells per tubular cross section, and numbers of spermatogonia, preleptotene spermatocytes, pachytene spermatocytes and step-7 spermatids were found. Zygotenes at stages XII through XIII and pachytenes at stages XII through early XIV of seminiferous tubules were most affected. The Sertoli cell was suggested as the target of toxicity (Vachhrajani *et al.*, 1992). [The Working Group noted that the testes were immersed, fixed and embedded in paraffin.] In freshly prepared human semen samples to which methylmercury chloride was added *in vitro*, similar, but less rapid and pronounced changes than those seen with mercuric chloride (see above) were present; however, no silver-enhanced mercury deposition was seen in sperm (Ernst & Lauritsen, 1991).

No effect on the ability to inseminate females or produce viable young was noted in male mice exposed by oral intubation for five to seven days to up to 5 mg/kg mercury as methylmercury chloride in seven consecutive five-day breeding trials. When male Wistar rats were exposed by oral intubation at the same dose regimen for seven days and followed over 14 consecutive five-day breeding trials, a reduced incidence of pregnancy was seen at 5 mg/kg on days 0–15 after treatment and reduced numbers of viable implants were seen on days 5–20 after 2.5 or 5 mg/kg. With longer-term exposures (up to 125 days), reduced numbers of viable implants were seen 25–30 days after exposure to 1 mg/kg and 85–90 days after exposure to 0.5 mg/kg (Khera, 1973a).

A three-generation study showed a lower viability index in F_1 and F_2 generations of rats following dietary exposure to 2.5 but not to 0.5 ppm (mg/kg) methylmercury chloride.

Growth retardation was observed in F_{2a} females at 0.1, 0.5 and 2.5 ppm and in F_{2a} males at 2.5 ppm; and increased relative kidney weights were observed in P males and females, F_{1a} males and F_{2a} females and males at 2.5 ppm, in F_{2a} males and females at 0.5 ppm and in F_{2a} females and F_{1a} males at 0.1 ppm (Verschuuren *et al.*, 1976c).

The development of mouse blastocysts *in vitro* was affected by exposure to methylmercury chloride at 1 μM (Matsumoto & Spindle, 1982) and 0.3 μM (Müller *et al.*, 1990). Intravenous injections of 2 mg/kg bw mercury or more as methylmercury chloride to mice on day 0 of gestation (Kajiwara & Inouye, 1986) or intraperitoneal injection of 5 mg/kg bw to rats during the pre-implantation period (Giavini *et al.*, 1985) affected embryonic development and/or viability.

Prenatal effects on offspring were reported following exposure of mice *in vivo* to methylmercuric chloride during pregnancy at doses as low as 5 mg/kg (fetal weight, Fuyuta *et al.*, 1978; embryonic death, Curle *et al.*, 1983, 1987); malformations commonly seen at this dose or at slightly higher doses included cleft palate and hydronephrosis. The effective dose levels in the rat fetus appear to be similar to those that cause effects in mice (Fuyuta *et al.*, 1979); however, the manifestations vary somewhat (e.g. cleft palate is observed less frequently at 7.5 mg/kg). Reductions in embryonic growth and viability were seen in rat embryos taken on gestation day 10 and exposed *in vitro* to 30 μM methylmercury chloride for 48 h; effects on morphogenesis were reported at the lowest dose tested (3 μM) (Kitchin *et al.*, 1984). Histological damage to the developing brain was observed following exposure *in utero* to methylmercury chloride of hamsters (10 mg/kg on gestation day 10; 2 mg/kg on gestation days 10–15; Reuhl *et al.*, 1981), guinea-pigs (7.5 mg/kg on day 21, 28, 35, 42 or 49; Inouye & Kajiwara, 1988) and cats (0.25 mg/kg on gestation days 10–58; Khera, 1973b). Monkeys (*Macacca fascicularis*) exposed to 50 or 90 μg/kg bw methylmercury hydroxide by oral intubation for 124 days before mating appeared to have lower conception rates and smaller offspring, but small sample sizes precluded statistical significance (Burbacher *et al.*, 1984).

Exposure of mice *in utero* to doses as low as 8 mg/kg of methylmercury compounds on single days of gestation resulted in neonatal mortality and growth impairment (Gates *et al.*, 1986, using the chloride), hydrocephaly (Choi *et al.*, 1988, chloride), changes in activity in the open field (Spyker *et al.*, 1972, dicyandiamide [$CH_3HgNHC(NH)NHCN$]; Su & Okita, 1976, hydroxide) and altered swimming behaviour (Spyker *et al.*, 1972, dicyandiamide). Snell *et al.* (1977, chloride) reported lower concentrations of liver glycogen in fetal (two-day prenatal) rats but higher concentrations in six-day-old rats exposed to 4 or 8 mg/kg on gestation day 9. Robbins *et al.* (1978, chloride) found decreased levels of cytochrome P450 and certain xenobiotic metabolizing enzymes in 26–36-week-old male but not female offspring exposed by oral intubation to 5 mg/kg on gestation day 0 or to 2.75 mg/kg on gestation day 7. Chang and Sprecher (1976a,b) reported morphological evidence of renal tubular damage (degenerative changes in epithelial cells of the proximal tubule, hyperplastic changes in distal convoluted tubules and thickening of the tubular epithelial linings) in neonatal rats after injection of dams with 1 or 4 mg/kg methylmercury chloride on day 8 of gestation. Smith *et al.* (1983) exposed rats to 4 mg/kg methylmercury chloride on days 8, 10 and 12 of gestation and observed reduced uptake of an organic anion (*para*-aminohippurate) by renal slices on postnatal day 42, but not on days 1 or 7, and reduced ability to eliminate sodium and water in volume-loaded rats when measured on postnatal day 42. Slotkin *et al.* (1986) reported slightly

reduced growth rates after weaning, alteration of renal function, an increased level of liver ornithine decarboxylase and altered renal ornithine decarboxylase response to isoproterenol and vasopressin in rats injected subcutaneously with 0.5 or 1.0 mg/kg methylmercury hydroxide on days 8–21 of gestation.

Bornhausen *et al.* (1980) reported impaired operant behaviour performance in the offspring of rats exposed to daily doses as low as 0.01 mg/kg methylmercury chloride on days 6–9 of gestation. A large, multilaboratory evaluation of behavioural effects in rat offspring exposed to 2 or 6 mg/kg methylmercury chloride on days 6–9 of gestation found increased auditory startle response at the high dose in young offspring and dose-related effects on figure-8 maze exploratory activity and in the pharmacological response to d-amphetamine challenge in older animals (Buelke-Sam *et al.*, 1985). In rats exposed to mercury at 3.9 mg/kg diet as methylmercury chloride *via* their dams during gestation and lactation and *via* the diet up to the age of 50 days, no histological change occurred in the brain, but increased noradrenaline levels were observed in the cerebellum (Lindström *et al.*, 1991). Rice (1992) found deficits in fixed interval performance, but not in discrimination reversal or activity patterns, in offspring of *Macaca fascicularis* exposed to steady-state levels during gestation and subsequently of 0, 10, 25 or 50 μg/kg per day mercury as methylmercury chloride. One infant in the high-dose group showed overt signs of methylmercury toxicity.

4.4 Genetic and related effects

4.4.1 *Humans* (see also Table 15, pp. 304–305 and Appendices 1 and 2)

(*a*) *Dietary exposures*

Skerfving *et al.* (1970) examined nine Swedish subjects who ate methylmercury-contaminated fish (containing 1–7 ppm [mg/kg] mercury) at least three times a week for more than five years and four controls who ate uncontaminated fish (containing $\leq$ 0.05 ppm [mg/kg] mercury] less than once a week. There was no significant difference in the frequency of chromosomal aberrations between exposed subjects and controls nor any correlation between aneuploidy or polyploidy rates and concentrations of mercury in red blood cells, which were in the range of 5–17 ng/g in controls and 21–370 ng/g in exposed subjects. Mercury concentrations were, however, significantly correlated with the frequency of structural rearrangements. The study was expanded to include a total of 23 exposed subjects (including the nine subjects already reported in 1970) and 16 controls (Skerfving *et al.*, 1974). Small differences were observed in the frequency of chromosomal aberrations in the exposed groups, and a significant correlation was seen between chromatid-type aberrations, 'unstable' chromosome-type aberrations or aneuploidy and mercury concentrations in red blood cells, which were in the range of 3–17 ng/g in controls and 12–1100 ng/g in exposed subjects. There was no correlation between the frequency of chromosomal aberrations and variations in mercury concentrations in repeated samplings.

Wulf *et al.* (1986) investigated the frequency of sister chromatid exchange in the lymphocytes of 147 Eskimos living in Greenland or Denmark, who were divided into three groups according to their intake of seal meat: subjects who ate seal meat at least six times a week and had an average concentration of mercury in the blood of 62.5 μg/L (range, 41.9–

65.4); subjects who ate seal meat two to five times per week and had mercury concentrations of 23.2–51.0 μg/L; subjects who ate seal meat once a week or less and had an average mercury concentration in the blood of 22.2 μg/L (range, 5.4–26.4). The mean frequency of sister chromatid exchange was 1.7-fold higher in the group that ate seal meat at least six times a week than in those who ate it less than once a week and 10.7-fold higher in the intermediary group. An increase of 10 μg/L in blood mercury corresponded to an increase of 0.2–0.3 sister chromatid exchanges per cell. [The Working Group noted that the reported results are difficult to interpret because only a series of statistical analyses is provided in the article, with limited original cytogenetic data.]

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 who ate fish from an uncontaminated area. The blood mercury ranges were 2.2–25.8 μg/L in unexposed and 10.2–97.3 μg/L in the exposed people. The frequency of structural chromosomal aberrations was increased only when achromatic lesions (chromatid and chromosome gaps) were included (Monsalve & Chiappe, 1987).

(*b*) *Occupational exposures*

Verschaeve *et al.* (1976) examined seven control subjects (blood mercury concentration, 2.5–8.4 μg/L) and 28 mercury-exposed subjects (blood mercury concentration, < 0.1–13 μg/L; urinary mercury concentration, < 0.1–114.12 μg/L) in Belgium, 10 of whom were under medical supervision for mercury intoxication, and 18 subjects working with mercury at Brussels University. An increased frequency of aneuploidy was seen in those subjects exposed to metallic mercury (14), amalgams (3), phenylmercury (8) and ethylmercury (3), while the incidence of structural chromosomal aberrations was increased only in the last (small) group. An increased rate of hyperploidy was also reported by Verschaeve *et al.* (1978) in 16 workers exposed to phenylmercury acetate (blood mercury concentration, 0–5.6 μg/L), compared to 12 unexposed controls (0–3.5 μg/L). In an abstract, Verschaeve and Susanne (1979) reported an increased rate of aneuploidy, with no increase in the frequency of structural chromosomal aberrations in 10 subjects exposed to mercury-containing amalgams in a dental practice and compared with 10 controls, but they could not rule out other factors such as X-rays. Verschaeve *et al.* (1979) failed to detect any chromosomal effect in 28 workers exposed to metallic mercury (urinary mercury concentration, 7–175 μg/L) in a chloralkali plant, as compared with 20 unexposed controls (eight from the same plant [< 5–15 μg/L] and 12 from the general population). In the discussion of the report, the authors questioned the positive findings in their previous three studies, stating that they might have been due to lack of information on exposures to agents other than mercury in the subjects. Negative results were also reported in a more recent Belgian study (Mabille *et al.*, 1984) involving cytogenetic analyses of 25 unexposed subjects (urinary mercury, < 5 μg/g creatinine, and blood mercury, < 6 μg/L) and of 22 workers exposed to metallic mercury in a chloralkali plant and in a plant in which mercury is amalgamated with zinc (urinary mercury, 8.2–286 μg/g creatinine, and blood mercury, 7.5–105.2 μg/L).

Popescu *et al.* (1979) examined peripheral blood lymphocytes from 22 workers in two departments of a chemical plant in Romania, four of whom were exposed to vapours of

metallic mercury and 18 to a mixture of mercuric chloride, methylmercury chloride and ethylmercury chloride. During the year before the study, atmospheric mercury concentrations ranged from 0.15 to 0.44 mg/m3. Urinary analysis demonstrated high concentrations of mercury (100–896 μg/L). When compared with 10 unexposed controls, neither exposed group had an increased rate of aneuploidy or of total structural chromosomal aberrations; however, both had a significant increase in the frequency of acentric fragments.

In an abstract, Mottironi *et al.* (1986) reported an increased rate of sister chromatid exchange in somatic cells [presumably lymphocytes] from 29 workers exposed to metallic mercury and inorganic mercury in two plants [presumably in the USA] (blood mercury, 6.7–103.9 μg/L) over that in 26 unexposed controls (blood mercury, 1.5–6.1 μg/L). The increase was significant in 'exposed workers with high mercury levels' in the blood [no detail given] and was enhanced by cigarette smoking. An increased rate of sister chromatid exchange, related to time since exposure, was detected in Argentina in the lymphocytes of 38 children, aged one month to five years, who had been intoxicated by the use of phenylmercury acetate to disinfect diapers. Nineteen unexposed children served as controls. The increased rate of sister chromatid exchange disappeared nine months after exposure ceased (Mudry de Pargament *et al.*, 1987).

Barregård *et al.* (1991) compared the incidence of lymphocytic micronuclei in 26 chloralkali workers (air mercury concentration, 25–50 μg/m^3) and 26 unexposed controls in Sweden. No difference was found between the two groups, and no correlation was found with current mercury concentrations in erythrocytes, plasma or urine (exposed, 4.8–64.6 μg/L, 2.8–40 μg/L and 5–186 μg/L; controls, 2.4–20.2 μg/L, 0.8–2.6 μg/L and 0.2–9.6 μg/L, respectively). A significant association was found between the number of micronuclei in phytohaemagglutinin-stimulated blood and previous exposure to mercury (measured either by a cumulative exposure index, i.e. integrated yearly mean blood mercury over employment time, or number of occasions when blood mercury peaks were > 150 nmol/L [30 μg/L]), suggesting an accumulation of cytogenetic effects in T lymphocytes. No such association was seen in pokeweed mitogen-stimulated blood. Anwar and Gabal (1991) examined 29 workers in an explosives factory in Egypt (mean urinary mercury concentration, 123 μg/L) who were exposed to mercury fulminate [$Hg(CNO)_2$] (which results from the reaction between mercuric nitrate, ethanol and nitric acid) and 29 controls (mean urinary mercury concentration, 39 μg/L). The frequencies of both micronuclei and chromosomal aberrations (gaps, breaks and fragments) were increased in the exposed group. The authors reported, however, that the increases were not correlated with urinary concentration of mercury or duration of exposure, putting in question the role of mercury in the observed clastogenic effect. In addition, there was no increased incidence of either aneuploidy or polyploidy.

4.4.2 *Experimental systems*

The genetic and related effects of mercury compounds have been reviewed (Ramel, 1972; Léonard *et al.*, 1983; Kazantzis & Lilly, 1986).

(*a*) *Inorganic mercury compounds* (see also Table 16, pp. 307–309 and Appendices 1 and 2)

Almost all of the studies reported were carried out with mercuric chloride.

Table 15. Genetic and related effects of mercury in humans

Test system	Result without exogenous metabolic system	Dose[a] (LED/HID)	Reference
Food contaminated with organomercury compounds[b]			
SLH, Sister chromatid exchange, human lymphocytes *in vivo*	(+)[c]	0.042	Wulf *et al.* (1986)
SLH, Sister chromatid exchange, human lymphocytes *in vivo*	-	0.040	Monsalve & Chiappe (1987)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	(+)	0.126	Skerfving *et al.* (1970)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	(+)	0.12	Skerfving *et al.* (1974)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	-[d]	0.040	Monsalve & Chiappe (1987)
AVH, Aneuploidy, human lymphocytes *in vivo*	-	0.126	Skerfving *et al.* (1970)
AVH, Aneuploidy, human lymphocytes *in vivo*	(+)	0.12	Skerfving *et al.* (1974)
Occupational and environmental exposures to mercury			
Metallic mercury			
SLH, Sister chromatid exchange, human lymphocytes *in vivo*[e]	+	0.027	Mottironi *et al.* (1986) abstract
MVH, Micronucleus induction, phytohaemaglutinin-stimulated human (T) lymphocytes *in vivo*	(+)	0.025	Barregård *et al.* (1991)
MVH, Micronucleus induction, pokeweed mitogen-stimulated human (T/B) lymphocytes *in vivo*	-	0.025	Barregård *et al.* (1991)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	-	NR	Verschaeve *et al.* (1976)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	+	NR	Popescu *et al.* (1979)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	-	NR	Verschaeve *et al.* (1979)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	-	0.031	Mabille *et al.* (1984)
AVH, Aneuploidy, human lymphocytes *in vivo*	?	NR	Verschaeve *et al.* (1976)
AVH, Aneuploidy, human lymphocytes *in vivo*	-	NR	Popescu *et al.* (1979)
AVH, Aneuploidy, human lymphocytes *in vivo*	-	NR	Verschaeve *et al.* (1979)
Amalgams			
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	-	NR	Verschaeve *et al.* (1976)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	-	NR	Verschaeve & Susanne (1979) abstract
AVH, Aneuploidy, human lymphocytes *in vivo*	?	NR	Verschaeve *et al.* (1976)
AVH, Aneuploidy, human lymphocytes *in vivo*	?	NR	Verschaeve & Susanne (1979) abstract

Table 15 (contd)

Test system	Result without exogenous metabolic system	Dose[a] (LED/HID)	Reference
Ethylmercury compounds [unspecified]			
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	?	NR	Verschaeve *et al.* (1976)
AVH, Aneuploidy, human lymphocytes *in vivo*	?	NR	Verschaeve *et al.* (1976)
Mercury fulminate [$Hg(CNO)_2$]			
MVH, Micronuclei, human lymphocytes *in vivo*	?	NR	Anwar & Gabal (1991)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	?	NR	Anwar & Gabal (1991)
AVH, Aneuploidy, human lymphocytes *in vivo*	-	NR	Anwar & Gabal (1991)
Methylmercury chloride/ethylmercury chloride/mercuric chloride mixture			
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	+	NR	Popescu *et al.* (1979)
AVH, Aneuploidy, human lymphocytes *in vivo*	-	NR	Popescu *et al.* (1979)
Phenylmercury compounds [unspecified]			
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	-	0.008	Verschaeve *et al.* (1976)
AVH, Aneuploidy, human lymphocytes *in vivo*	(+)	0.008	Verschaeve *et al.* (1976)
Phenylmercury acetate			
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	-	0.002	Verschaeve *et al.* (1978)
AVH, Aneuploidy, human lymphocytes *in vivo*	?	0.002	Verschaeve *et al.* (1978)
SCE, Sister chromatid exchange, human lymphocytes *in vivo*	+	NR	Mudry de Pargament *et al.* (1987)

+, positive; (+), weakly positive; +?, positively questioned by the authors themselves; -, negative; ?, inconclusive

[a]Mean concentration of Hg in blood; μg/ml. NR, not reported

[b]Organic mercury of alimentary source (seal or fish meat)

[c]Also contaminated with lead, cadmium and selenium

[d]Excluding gaps; positive if gaps are included

[e]Exposure to metallic mercury mixed with organic mercury

In bacteria, assays for differential toxicity suggest that mercuric chloride induces DNA damage very weakly in *Bacillus subtilis* and not in *Escherichia coli*. No studies of bacterial mutation were available to the Working Group.

Mercuric chloride weakly induced mitotic recombination and induced mitochondrial mutations in *Saccharomyces cerevisiae*. It induced various types of mutations in the plant, *Anacharis canadensis*.

Mercuric chloride did not increase the frequency of micronuclei in cultured fish cells, even when tested at doses 10 times higher than those that were effective for some organomercury compounds.

In cultured mammalian cells, mercuric chloride inhibited DNA repair induced by X-rays but not that induced by ultraviolet radiation. Gene mutations at the *tk* locus were induced in a single study with mouse lymphoma L5178Y cells, but only in the presence of an exogenous metabolic system from rat liver. Sister chromatid exchange was induced in cultured Chinese hamster ovary cells and in human lymphocytes. Spindle disturbance and chromosomal aberrations were induced by mercuric chloride in most studies with cultured mammalian cells, including human lymphocytes, and by mercuric acetate in mouse oocytes *in vitro*.

Mercuric chloride enhanced cell transformation produced by simian adenovirus SA7 in Syrian hamster embryo primary cell cultures. Mercuric acetate did not induce anchorage-dependent growth of human fibroblasts.

In larvae of the newt, *Pleurodeles waltl*, mercuric chloride induced chromosomal aberrations and micronuclei in erythrocytes. Studies of mammals exposed to mercuric chloride *in vivo* have given negative or conflicting results. Neither chromosomal aberrations nor aneuploidy were observed in Syrian hamster bone marrow or oocytes following a single subcutaneous dose of 12.8 mg/kg mercuric chloride. In mice, the frequency of chromosomal aberrations in bone-marrow cells was increased in one study after a single oral dose of 3 mg/kg but not in another study by intraperitoneal injection of a dose of 6 mg/kg. In a second study in mice, chromosomal aberrations were not induced in spermatogonia. Weak dominant lethal effects have been described in rats and mice. Mercuric acetate did not induce chromosomal aberrations in mouse oocytes after subcutaneous or intravenous dosing.

(*b*) *Organomercury compounds* (see also Table 17, pp. 312–320 and Appendices 1 and 2)

Very weak differential toxicity was induced in *B. subtilis* by methylmercury chloride, but negative results were obtained with phenylmercury chloride and bis(ethylmercury)hydrogen phosphate. Mutations were not induced in *Salmonella typhimurium* by methylmercury chloride or methylmercury acetate.

Methylmercury chloride did not induce gene conversion or mitotic recombination in *S. cerevisiae*, but conflicting results were obtained for induction of mutations, mitochondrial mutations and aneuploidy.

Phenylmercury nitrate induced mutations in seedlings of *Zea mays*, and phenylmercury hydroxide induced mutations in seedlings of a number of different plants. Chromosomal aberrations and/or spindle disturbances were induced in *Allium cepa* roots by all of eight compounds tested.

Table 16. Genetic and related effects of inorganic mercury compounds in experimental systems

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Mercuric chloride (74% Hg)				
PRB, Lambda-prophage induction, *E. coli*	-	0	0.036	Rossman *et al.* (1991)
BSD, *Bacillus subtilis rec* strains, differential toxicity	(+)	0	10 000	Kanematsu *et al.* (1980)
ERD, *Escherichia coli rec* strains, differential toxicity	-	0	0.5	Brandi *et al.* (1990)
SCH, *Saccharomyces cerevisiae* D7, mitotic crossing-over	(+)	0	60	Fukunaga *et al.* (1981)
SCR, *Saccharomyces cerevisiae* N123, petite mutation	(+)	0	20	Fukunaga *et al.* (1981)
PLM, *Anacharis canadensis*, mutation	+	0	740	MacFarlane & Messing (1953)
***, Micronuclei, fish (*Lepomis macrochirus*)[b] cells *in vitro*	-	0	0.8	Babich *et al.* (1990)
***, Inhibition of X-ray-induced DNA repair, Chinese hamster ovary cells *in vitro*	+	0	0.2	Christie *et al.* (1986)
***, Inhibition of UV-induced DNA repair, Chinese hamster ovary cells *in vitro*	-	0	10	Christie *et al.* (1986)
DIA, DNA strand breaks, Chinese hamster ovary cells *in vitro*	+	0	5.0	Cantoni *et al.* (1982)
DIA, DNA strand breaks, Chinese hamster ovary cells *in vitro*	+	0	2.0	Robison *et al.* (1982)
DIA, DNA strand breaks, Chinese hamster ovary cells *in vitro*	+	0	5.0	Cantoni & Costa (1983)
DIA, DNA strand breaks, Chinese hamster ovary cells *in vitro*	+	0	5.0	Cantoni *et al.* (1984a)
DIA, DNA strand breaks, Chinese hamster ovary cells *in vitro*	+	0	1.0	Cantoni *et al.* (1984b)
DIA, DNA strand breaks, Chinese hamster ovary cells *in vitro*	+	0	10	Robison *et al.* (1984)
DIA, DNA strand breaks, mouse embryo fibroblasts *in vitro*	+	0	0.02	Zasukhina *et al.* (1983)
DIA, DNA strand breaks, rat embryo fibroblasts *in vitro*	+	0	0.02	Zasukhina *et al.* (1983)
RIA, DNA repair, Syrian hamster cells *in vitro*	(+)	0	2.0	Robison *et al.* (1984)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus, *in vitro*	-	(+)	4.44	Oberly *et al.* (1982)
SIC, Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	(+)	0	2.0	Howard *et al.* (1991)
CIC, Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	+	0	0.2	Howard *et al.* (1991)

Table 16 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Mercuric chloride (contd)				
***, Spindle disturbances, Indian muntjac fibroblasts *in vitro*	+	0	0.1	Verschaeve *et al.* (1984)
***, Spindle disturbances, human lymphocytes *in vitro*	+	0	0.2	Verschaeve *et al.* (1984)
T7S, Cell transformation, SA7/Syrian hamster embryo cells *in vitro*	+	0	10	Casto *et al.* (1979)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	0	0.08	Morimoto *et al.* (1982)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	+	0	4.0	Verschaeve *et al.* (1985)
CHT, Chromosomal aberrations, human HeLa cells *in vitro*	-	0	7.4	Umeda *et al.* (1969)
***, Chromosomal condensation, human lymphocytes *in vitro*	+	0	2.0	Andersen *et al.* (1983)
***, Micronuclei in red blood cells, newt larvae *in vivo*	+		0.012	Zoll *et al.* (1988)
CBA, Chromosomal aberrations, mouse bone-marrow cells *in vivo*	-		4.44, ip × 1	Poma *et al.* (1981)
CBA, Chromosomal aberrations, Syrian hamster bone-marrow cells *in vivo*	(+)		4.74, sc × 1	Watanabe *et al.* (1982)
CBA, Chromosomal aberrations, mouse bone-marrow cells *in vivo*	+		2.22, po × 1	Ghosh *et al.* (1991)
CGG, Chromosomal aberrations, mouse spermatogonia *in vivo*	-		4.44, ip × 1	Poma *et al.* (1981)
COE, Chromosomal aberrations, Syrian hamster oocytes *in vivo*	-		9.47, sc × 1	Watanabe *et al.* (1982)
***, Chromosomal aberrations, newt larvae and embryos *in vivo*	+		0.06, water × 4 days	Zoll *et al.* (1988)
AVA, Aneuploidy, Syrian hamster bone-marrow cells *in vivo*	-		9.47, sc × 1	Watanabe *et al.* (1982)
AVA, Aneuploidy, Syrian hamster oocytes *in vivo*	-		9.47, sc × 1	Watanabe *et al.* (1982)
DLM, Dominant lethal mutation, mice	(+)		1.48, ip × 1	Suter (1975)
DLR, Dominant lethal mutation, rats	(+)		0.0003, po/day × 12 months	Zasukhina *et al.* (1983)
Mercurous chloride				
BSD, *Bacillus subtilis rec* strains, differential toxicity	+	0	10 000	Kanematsu *et al.* (1980)

Table 16 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Mercuric acetate (63% Hg)				
CIA, Chromosomal aberrations, mouse oocytes *in vitro*	+	0	35	Jagiello & Lin (1973)
TIH, Anchorage-independent growth, human foreskin fibroblasts *in vitro*	-	0	2.0	Biedermann & Landolph (1987)
COE, Chromosomal aberrations, mouse oocytes *in vivo*	-		2, iv × 1	Jagiello & Lin (1973)
COE, Chromosomal aberrations, mouse oocytes *in vivo*	-		10, sc × 1	Jagiello & Lin (1973)

+, 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; ip, intraperitoneally; sc, subcutaneously; iv, intravenously; po, orally by gavage

[b]Bluegill sunfish

***Not displayed on profile

Methylmercury hydroxide induced sex-linked recessive lethal mutations, but not chromosomal aberrations or meiotic crossing-over, in *Drosophila melanogaster*. It induced chromosomal aberrations in *Stethophyma grossum*. Methylmercury chloride, methylmercury hydroxide, phenylmercury hydroxide and phenylmercury acetate consistently induce aneuploidy in *D. melanogaster*. Methylmercury chloride did not induce aneuploidy in silkworms.

Studies of gene mutations in cultured mammalian cells have yielded varying responses. In one study, both methylmercury chloride and methoxyethylmercury chloride induced ouabain-resistance and *hprt* locus mutations in Chinese hamster V79 cells, whereas in another study with the same cells methylmercury hydroxide did not induce mutations at the *hprt* locus.

The induction of spindle disturbances and chromosomal aberrations has been studied extensively in cultured mammalian cells, including human lymphocytes. Significant responses were obtained consistently with methylmercury chloride in a number of studies of both end-points. In addition, chromosomal aberrations and/or spindle disturbances have been induced by methylmercury hydroxide, methoxyethylmercury chloride, dimethyl mercury, ethylmercury chloride and phenylmercury chloride in independent studies using Chinese hamster V79 cells, human HeLa cells and lymphocytes *in vitro*. The frequency of micronuclei, which may be an expression of either spindle disturbances or chromosomal breakage, was increased in cultured cells from *Lepomis macrochinus* (bluegill sunfish) after treatment with methylmercury chloride, ethylmercury chloride or phenylmercury chloride.

Methylmercury chloride induced chromosomal aberrations in larvae and embryos of the newt, *Pleurodeles waltl*, and micronuclei in peripheral erythrocytes of the larvae. Treatment of pregnant rats with methylmercury chloride induced chromosomal aberrations in the livers of the fetuses, but it did not induce chromosomal aberrations in the bone marrow of Syrian hamsters and rats or in oocytes of Syrian hamsters. Intraperitoneal injection of methylmercury acetate did not induce micronuclei in mouse bone-marrow cells. Spindle disturbances were induced by methylmercury chloride in fetal lung and liver cells after treatment of mice *in vivo* in two studies and in killifish (*Fundulus heteroclitus*) embryo cells. Aneuploidy was seen in bone-marrow cells and oocytes of Syrian hamsters in one study but not in another. Methylmercury chloride appears therefore to be more active as a clastogen in fetal than in adult tissues of mice and more active as a spindle poison in Syrian hamster bone marrow than in Syrian hamster oocytes.

Dominant lethal mutation has been demonstrated in male rats and female mice, but not in male mice, treated with methylmercury chloride. Methylmercury hydroxide induced either weak or no dominant lethal effect in male mice. Methylmercury acetate did not induce sperm-head abnormalities in mice.

Few studies have been conducted on nonionized organomercury compounds; those that have been performed reflect the properties described above. Thus, dimethylmercury induced DNA fragmentation in the slime mould *Physarum polycephalum* and chromosomal aberrations and aneuploidy in cultured human lymphocytes; it induced chromosomal aberrations in mouse oocytes *in vitro* but not *in vivo*.

Several fungicides containing organomercury compounds have been tested for genotoxic activity in various plant systems. Spindle disturbances were induced by Panogen 5, 8 and 15, while chromosomal aberrations were induced by Agrimax M, Granosan, Ceresan M, Betoxin and New Improved Ceresan. [The Working Group noted that the different results may not reflect different properties, as various authors were involved.] In *D. melanogaster*, sex-linked recessive lethal mutation was induced by Ceresan and Ceresan M, but not by Agallol 3, and neither Ceresan nor Agallol 3 induced dominant lethal effects.

The azo dye, mercury orange, was not mutagenic to strains of *S. typhimurium*.

Considerations with regard to genotoxic mechanisms

Mercury has not only a direct effect on chromosomes, resulting in clastogenic effects in eukaryotes, but also causes disturbance of the spindle mechanism, owing to its high affinity for the sulfhydryl groups contained in spindle fibre proteins. Organomercury compounds inhibit the spindle mechanism even more strongly than colchicine, but, in contrast to colchicine, produce a gradual transition to c-mitosis at sub-lethal doses, which may result in aneuploidy and/or polyploidy.

In general, inorganic mercury compounds are less effective than ionizable organomercury compounds in inducing genetic effects *in vitro*. Similarities in the effects of different mercury compounds may suggest similar modes of action, while differences may be due to variations in solubility and bioavailability and in the rate of formation of a common toxic entity.

The possible contribution of reactive oxygen species to the genotoxicity of inorganic mercury compounds has also been addressed. ^{203}Hg-Mercuric chloride is taken up by Chinese hamster ovary cells and was reported to bind to the DNA in these cells in a temperature-dependent manner; however, DNA strand breaks were induced at 37 °C, but not at 4 °C, even though there was uptake and DNA binding of mercury at the lower temperature. It therefore appears that DNA strand breaks induced by Hg^{2+} require cellular metabolic processes. Mercuric chloride induced single-strand breaks in DNA of Chinese hamster ovary cells, and the effect was related linearly to leakage of superoxide into the medium. DNA damage induced by mercuric chloride can be increased by the addition of diethyldithiocarbamate, which inhibits superoxide dismutase, as well as by diethyl maleate, which depletes glutathione. Single strand breakage was inhibited by superoxide dismutase, catalase, glycerol and ascorbate (Cantoni *et al.*, 1984b).

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)

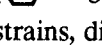
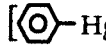
Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Bis(ethylmercury)hydrogen phosphate [$(CH_3CH_2Hg)_2HPO_4$]				
BSD, *Bacillus subtilis rec* strains, differential toxicity	-	0	14.4	Shirasu *et al.* (1976)
Butylmercury bromide [$(CH_3(CH_2)_3HgBr$]				
***, *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)

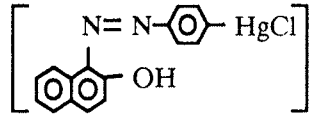
Table 17 (contd)

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).*

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