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## Carcinogenicity of mercury and mercury compounds

by Paolo Boffetta, MD,<sup>1</sup> Enzo Merler, MD,<sup>2</sup> Harri Vainio, MD<sup>3</sup>

BOFFETTA P, MERLER E, VAINIO H. Carcinogenicity of mercury and mercury compounds. *Scand J Work Environ Health* 1993;19:1-7. Mercury and mercury compounds are widely used in modern society, but only sparse data are available on their carcinogenicity. Methylmercury chloride causes kidney tumors in male mice. Mercury chloride has shown some carcinogenic activity in male rats, but the evidence for female rats and male mice is equivocal. Other mercury compounds and metallic mercury have not been tested adequately in experimental animals. Epidemiologic data are available for chloralkali workers, dentists and dental nurses, and nuclear weapons workers, three groups occupationally exposed to low levels of mercury and its compounds, but those highly exposed in the past, such as miners, or populations which have suffered massive environmental exposure have not been adequately studied. However, the sparse epidemiologic data point toward the possibility of a risk of lung, kidney, and central nervous system tumors. Better data are needed on the carcinogenicity of mercury and mercury compounds in humans and experimental animals.

**Key terms:** cancer, central nervous system, chloralkali workers, kidney, lung, methyl mercury, neoplasms, review.

Mercury and its compounds have been used since ancient times, but the uses have changed profoundly since the industrial revolution as a consequence of the greater availability of the metal and the recognition of the health effects of occupational exposure and the hazards due to environmental pollution and accumulation (1).

The chemical forms of mercury can be classified as inorganic and organic. Mercury assumes three oxidation states; namely, it can be metallic, mercurous, and mercuric. Inorganic and organic compounds contain mercury in the latter two oxidation states.

Organic forms are those in which mercury is attached covalently to at least one carbon atom. Methylmercury is the most important in terms of human exposure.

### Production

A comparison of estimates of the worldwide production of mercury during this century suggests a shift from a strong concentration in Italy and Spain in the early part of the century to a much wider range of producing countries, including newly industrialized countries such as China and Algeria (table 1).

Two types of mercury mines exist. There are ores containing native mercury (free metal in minute droplets or quicksilver), to which miners are exposed during quarrying; such ore is found in the mines of Idrija in Slovenia, Almaden in Spain, and Huancauelica in Peru. In other mines mercury is present as cinnabar (crystalline mercury sulfide), as in the mine of Monte Amiata in Italy and in North American mines.

The technology used in the mines and the levels of exposure have not been well documented, although data on air levels of mercury have been published for a few mines and furnaces. In Idrija, airborne mercury levels in 1950 were in the range 0.05-5.9 mg · m<sup>-3</sup> in the mine and 0.17-1.1 mg · m<sup>-3</sup> in the smelter (4). Similar values were found in 1963 (5).

In several mines, reduced shifts and the rotation of workers between mining and roasting are measures that have been taken to mitigate the harmful effect

**Table 1.** Production of mercury in selected countries, in 1925, 1955 and 1979.<sup>a</sup> (NA = not available)

Country	Annual production (t)		
	1925	1955	1979
Algeria	1	NA	1034
China	3	NA	600
Czechoslovakia	74	NA	196
Italy	1846	1845	5
Mexico	39	1030	76
Spain	1286	1249	1070
Turkey	3	29	59
Soviet Union	10	NA	2070
United States	314	653	834
Yugoslavia	NA	503	108 <sup>b</sup>

<sup>a</sup> Based on references 1-3. Other producers include Australia, Canada, Chile, Colombia, Finland, Germany, Ireland, Japan, Peru, Philippines, Romania, Tunisia.

<sup>b</sup> 1978 production.

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of mercury exposure. The extent of past health effects on miners can be indirectly deduced from the fact that some mines have established local hospitals to treat affected workers.

## Uses

An estimate of the consumption of mercury and mercury compounds in the early 1970s in industrialized countries is as follows: chloralkali industry 25%, electrical instruments 20%, paints 15%, medical and precision instruments 10%, dental amalgams 3%, laboratories 2%, other uses 20% (6).

The main industrial uses of mercury are presented in table 2. One of the most important uses is in the chloralkali industry, where airborne and urinary or blood mercury levels have been monitored for decades. A decrease in exposure over time has been observed (13, 14). Factories differ greatly, however, in exposure levels even in the same country (15, 16), and exposure varies greatly among jobs (17, 18). Massive mercury intoxication occurred in Minamata Bay, Japan, between 1953 and 1965, due to the discharge of large quantities of methylmercury into a river as a result of a side reaction in the synthesis of acetaldehyde from acetylene (19).

Other major uses include dental amalgam and organic mercury pesticides. A number of epidemics of mercury poisoning occurred after the consumption of products derived from grain treated with ethyl- or methylmercury pesticides. The most important intoxication occurred in Iraq in 1971–1972, and it was due to the consumption of grain treated with methylmercury-based antifungal agents (20).

## Mercury toxicity

Detailed reviews of the metabolism of mercury and methylmercury have been published (21, 22). Inhaled

mercury vapor reaching the alveoli passes nearly completely into the blood stream, where it is oxidized in red blood cells, the liver, and the kidney to the divalent form (ionic mercury) by the hydrogen peroxide catalase complex (21). Deposition and accumulation occur primarily in the brain and kidney, but also in several other organs (thyroid, pituitary gland, brain, liver, pancreas, testes or ovary, prostate). The oxidative capacity of red blood cells can be overwhelmed by a high rate of entry or inhibited by ethanol. In such cases, mercury remains available for transport to the brain. Elimination appears to be slower (taking even years) from the brain and kidney (23). The central nervous system is the principal target organ of methylmercury, which affects mainly specific areas of the brain, such as cerebellum and temporal lobes.

Acute and chronic toxic effects of mercury and mercury compounds in high- and low-level doses caused by poisonings or occupational exposures have been reviewed extensively (1, 7, 21, 22). The critical organs are the central nervous system and the kidneys.

## Genetic and related effects

### *Inorganic mercury*

The most obvious genotoxic effect of inorganic mercury compounds is the induction of C-mitosis with inactivation of the mitotic spindle. This phenomenon results in aneuploidy and polyploidy and is probably due to the action of the mercury ion on sulfhydryl groups in the spindle apparatus (24–26). The ability of inorganic mercury to induce genetic mutations appears, however, to be low (25).

Cytogenetic studies on exposed humans have generally shown no effects on chromosomes in the peripheral blood lymphocytes (27–30). In a recent study on 26 chloralkali workers exposed to inorganic

**Table 2.** Major industrial uses of mercury (1, 7).

Use	Comments
Production of electrical devices and batteries	For example, fluorescent lamps, rectifiers, power cells, switches
Production of industrial and control instruments	For example, barometers, thermometers, hygrometers
Chemical industry	Production of acetaldehyde from acetylene; production of chlorine and caustic soda (chloralkali industry)
Fire gilding of metals	Mainly replaced by electroplating
Gold extraction	Important source of environmental contamination (8)
Hat manufacture	Used in fur carroting; has caused many cases of severe intoxication (9, 10); has been replaced by hydrogen peroxide or sulfuric acid
Nuclear weapons industry	Used in the lithium isotope separation process (11)
Medicine	Main uses include dental amalgam, treatment of syphilis, antiseptic and diuretic drugs and brain scintigrams; most uses have been discontinued
Paint and color industry	Used in antifouling and mildew proofing paints for boats, ships and wood houses (12); used in paints for pottery and porcelain
Pesticides	Methylmercury and other alkyl mercurials; mainly used for the prevention of seedborne cereal diseases; banned in many countries
Wood pulp industry	Used as slime control agent (7); use discontinued in the 1970s

mercury, no increase in lymphocyte micronuclei was observed (31). However, a significant correlation was reported between previous exposure to mercury (cumulative exposure or number of blood mercury peaks) and the frequency of lymphocyte micronuclei (31); this finding suggests an accumulation of cytogenetic effects in T-lymphocytes.

In one study, an increase in chromosome aberrations and micronuclei in peripheral lymphocytes was found among workers exposed to mercury fulminate when the workers were compared with referents (32).

In human whole-blood cultures, mercuric chloride has caused a dose-dependent increase in sister chromatid exchanges (33).

### *Methylmercury*

Organic mercury is more toxic than inorganic mercury in cultured mammalian and human cells (34, 35). Organic mercurials, including methylmercury, have been shown to be about 10 times more effective than mercury chloride in inducing abnormal mitosis and single-strand breaks in cellular deoxyribonucleic acid (DNA) (35, 36).

The dose of methylmercury required to increase the frequency of sister chromatid exchanges in cultures of human whole blood cells in vitro was found to be about one-fifth of that of mercury chloride (33). Methylmercury can cause spindle disturbances in mammalian cells in culture, an effect which appears to be mediated by the interaction of mercury with sulfhydryl ions (37). In *Drosophila melanogaster*, the induction of nondisjunction (38) and gender-linked recessive lethal mutations has been found after treatment with methylmercury (39).

## **Long-term carcinogenicity studies**

### *Metallic mercury*

One study has reported the occurrence of local sarcomas in rats after intraperitoneal injections of metallic mercury (40).

### *Mercury chloride*

One large study was carried out by the National Toxicology Program in the United States to investigate the carcinogenicity of mercury chloride in rats and mice at concentrations of 2.5 and 5 mg · kg<sup>-1</sup> (rats) and 5 and 10 mg · kg<sup>-1</sup> (mice) (41). Male rats had an increased incidence of papillary hyperplasia and squamous cell papilloma of the forestomach. Two of the 50 female rats in the highest dose group had a squamous cell papilloma of the forestomach (none in the remaining groups). Among the male mice, there were three adenocarcinomas of the renal tubule in the two treated groups [two in one group (N = 49) and one in the other (N = 49)] and no such tumors in the reference group. No tumor increase was found among the female mice. Therefore, mercury chloride

showed some evidence of carcinogenic activity in male rats, equivocal evidence for female rats and male mice, and no evidence for female mice.

### *Methylmercury chloride*

**Rats.** Only limited data on the carcinogenicity of methylmercury chloride in rats are available. A study on weaning animals reported no increase in tumor incidence at concentrations up to 2.5 mg · kg<sup>-3</sup> (42). Another study on adult rats also failed to detect any increase in tumors among animals treated with up to 10 mg · kg<sup>-3</sup> (43, 44). Another study in which methylmercury chloride was given to pregnant rats, together with increasing concentrations of ethylurea, exposure to methylmercury did not affect the incidence of neurological tumors in progeny (45). However, the tumors in the progeny of the methylmercury-treated rats tended to appear earlier than those in the progeny of rats not treated with methylmercury.

**Mice.** Four studies on the long-term carcinogenicity of methylmercury chloride among mice have been reported (46–49). All of them showed an increased incidence of renal tumors among treated males (the minimal dose that led to a significant increase was 10 mg · kg<sup>-1</sup>), but not among treated females. The possible hormonal dependence of renal tumors induced by methylmercury chloride in male mice was investigated in detail in one of these studies, in which a significant increase in kidney tumors was seen among noncastrated mice treated with methylmercury chloride, but not in castrated treated mice or in referents (48). Another study on female mice found an increase in the incidence of pulmonary adenomas in the group treated with methylmercury chloride and urethane, as compared with animals treated with urethane only (50). In conclusion, methylmercury chloride is clearly carcinogenic in male mice, and a carcinogenic effect in female mice cannot be excluded at present.

## **Cancer epidemiology studies**

Only a few epidemiologic studies have analyzed cancer mortality or incidence in relation to occupational or environmental exposure to mercury. The studied occupations possibly exposed to mercury are miners (51), workers in chloralkali plants (13, 52, 53), dentists (54–58), workers in the nuclear weapons industry (11), disinfectant applicators (59), and hat makers (60). The design of these studies, as well as their main results, are presented in table 3. Two population-based case-referent studies provided additional information (61, 62). They are summarized in table 4.

Although farmers are probably the largest occupational group with exposure to mercury and mer-

**Table 3.** Epidemiologic studies that investigated specific groups of mercury-exposed workers. (US = United States, SMR = standardized mortality ratio, 95% CI = 95% confidence interval, UK = United Kingdom, SIR = standardized incidence ratio, CNS = central nervous system, PMR = proportionate mortality ratio)

Study	Population	Results <sup>a</sup>	Comments
<i>Miners</i>			
Amandus & Costello (51) <sup>b</sup>	US mercury miners, employed in 1959–1961, follow-up 1959–1975, 263 nonsilicotics, 11 silicotics	Nonsilicotics, 8 lung cancers (SMR 2.66, 95% CI 1.15–5.24); silicotics, 3 lung cancers (SMR 14.0, 95% CI 2.89–41.0)	Low radon exposure; SMR values for miners from 38 mines: 1.18 (nonsilicotics) and 1.73 (silicotics)
<i>Chloralkali workers</i>			
Duffield et al (52) <sup>c</sup>	466 death certificates of UK employees who died in 1945–1960	Excess of deaths from genitourinary tract diseases	No data on cancer
Barregård et al (13) <sup>b</sup>	1190 men monitored ≥ 1 years during 1946–1984 at eight Swedish plants, follow-up 1958–1982	64 cancers [SIR 1.0, 95% CI 0.8–1.3], 13 lung cancers [SIR 1.8, 95% CI 0.9–3.0], 1 pleural mesothelioma (0.1 expected), 4 kidney cancers (3.0 expected), 4 brain cancers (2.2 expected)	Similar results for workers with ≥ 10 years' latency; no trend in lung cancer risk according to cumulative mercury exposure determined on the basis of biological measurements; excess of cardiovascular mortality
Ellingsen et al (53) <sup>b</sup>	799 men employed in two Norwegian plants, follow-up 1953–1985	19 lung cancers (SIR 1.66, 95% CI 1.0–2.6), 3 kidney cancers [SIR 0.94], 2 CNS cancers [SIR 0.83]	No trend in lung cancer risk according to duration of employment, latency, or cumulative mercury exposure
<i>Dentists</i>			
Ahlbom et al (54) <sup>b</sup>	9201 dentists and dental nurses, Sweden, in 1960 census, follow-up 1961–1979	18 glioblastomas (SIR 2.1, 95% CI 1.3–3.4), 4 gliomas (SIR 1.8, 95% CI 0.5–4.7), 6 meningiomas (SIR 1.3, 95% CI 0.5–2.8)	Excess of glioblastomas among both dentists and dental nurses; no excess among other physicians or nurses
Milham (55) <sup>c</sup>	~ 300 000 deaths, males, Washington, US, 1950–1971; 734 deaths among dentists	4 brain cancers (PMR 162), 12 pancreas cancers (PMR 153), 17 lymphohematopoietic cancers (PMR 145)	No excess of total cancers or, lung or kidney cancers
Walrath et al (56) <sup>b</sup>	~ 290 000 males, US veterans, follow-up 1954–1970, 2498 dentists	3 brain cancers [SMR 63], 16 pancreas cancers (SMR 140), 6 oral cancers [SMR 240]	Deficit of total cancers; no excess of lung and kidney cancers
Gallagher et al (57) <sup>c</sup>	~ 320 000 deaths, males, British Columbia, Canada, 1950–1984, 441 deaths among dentists	5 brain cancers (PMR 236, 95% CI 76–552), 4 kidney cancers (PMR 194, 95% CI 52–496)	Deficit of total cancers; no excess of lung and pancreas cancers; excess of mortality from nonneoplastic diseases of the CNS
Petersen & Milham (58) <sup>c</sup>	~ 200 000 deaths, males, California, US, 1959–1961, 514 deaths among dentists	Excess of pancreas cancer and lymphosarcoma	Detailed data and results for other sites not presented
<i>Workers in nuclear weapons industry</i>			
Cragle (11) <sup>b</sup>	US plant; workers employed 1953–1963, follow-up 1953–1978, 2133 workers exposed to mercury, 270 workers potentially exposed to mercury, 3260 unexposed workers	Exposed: 42 lung cancers (SMR 1.34 [95% CI 1.0–1.8]), 4 kidney cancers (SMR 1.65), 4 brain cancers (SMR 1.22); potentially exposed: 8 lung cancers, (SMR 1.61); unexposed: 71 lung cancers (SMR 1.34 [95% CI 1.0–1.7]), 13 brain cancers (SMR 2.30 [95% CI 1.2–3.9])	Among exposed, no site showed any trend according to level of exposure or duration of employment
<i>Seed disinfectant applicators</i>			
Wiklund et al (59) <sup>b</sup>	1657 applicators, Sweden, licensed 1965–1976, follow-up 1965–1982	5 brain cancers (SIR 1.00, 95% CI 0.33–2.34)	Applicators of mercury-based disinfectants not separated from applicators of other disinfectants
<i>Hat makers</i>			
Buiatti et al (60) <sup>d</sup>	376 lung cancer cases, 892 hospital referents, Florence, Italy, 1981–1983	6 female cases/0 referents ever employed as hat makers (P = 0.01)	Possible exposure to arsenic

<sup>a</sup> Figures in square brackets were calculated from the raw data presented in the original publication.<sup>b</sup> Historical cohort study.<sup>c</sup> Proportionate mortality study.<sup>d</sup> Case-referent study.

cury compounds, no epidemiologic study has analyzed exposure to mercury-containing pesticides separately from exposure to other groups of pesticides.

Cancer risk has also been investigated among individuals who, in the 1950s, suffered acute mercury poisoning from their intake of polluted fish in Minamata, Japan. No overall excess risk of cancer was found in the follow-up of this population, either

among over 700 poisoned persons or among inhabitants (about 4000) of the polluted area (63–65). However, excesses of cancer of the esophagus, liver, breast, and lung, as well as leukemia (based on small numbers of cases) were detected (64).

Other populations have been exposed to high environmental concentrations of mercury compounds: people from Niigata, Japan, where an episode simi-

**Table 4.** Population-based case-referent studies that provided information on mercury carcinogenicity. (OR = odds ratio, 95% CI = 95% confidence interval, 90% CI = 90% confidence interval)

Study	Population	Mercury exposure	Results	Comments
Siemiatycki (61)	3730 cases of cancer from various sites, 533 referents, Montreal, Canada, 1979–1985	Occupational exposure estimated from occupational history (prevalence 0.6% mercury, 2% mercury compounds)	Mercury: lung cancer (OR 4.0, 90% CI 1.2–13.0), prostate cancer (OR 6.2, 90% CI 1.2–33.2); mercury compounds: prostate cancer (OR 1.7, 90% CI 1.0–3.0), bladder cancer (OR 1.5, 90% CI 0.9–2.6)	Higher risk of prostate cancer for substantial exposure
Ryan et al (62)	110 gliomas, 60 meningiomas, 417 population referents, Adelaide, Australia, 1987–1990	Number of dental amalgam fillings	Any filling: glioma (OR 0.5, 95% CI 0.3–0.9), meningioma (OR 1.0, 95% CI 0.4–2.5)	No trend with number of fillings

lar to the one in Minamata occurred; the victims of a mass poisoning that took place in Iraq in 1971–1972, when seed grain treated with a methylmercury fungicide was used to prepare homemade bread in rural communities (22); and groups of Canadian Indians, who had been exposed seasonally over a long period of time to methylmercury through fish consumption (22). Cancer occurrence in these populations has not been studied.

Finally, a study from a rural area in Poland showed a higher mercury hair content in acute leukemia patients than in referents, but no difference between persons with chronic granulocytic or lymphocytic leukemia and referents (66).

#### *Lung cancer*

A study (51) on miners in the United States suggested that the risk of lung cancer is higher among mercury miners than among other miners, both among silicotics and nonsilicotics. Two prospective studies on chloralkali workers found an overall increased risk of lung cancer (13, 53), but no trend according to latency, duration of employment, or estimated cumulative exposure to mercury. The data on hat makers support an association between mercury exposure and lung cancer (60). A population-based study from Montreal found an increased risk of lung cancer for any exposure to mercury, but not for substantial exposure (61). Studies on dentists have not found an excess risk of lung cancer (54–58).

Mercury miners can also be exposed to other known or suspected lung carcinogens, such as radon and silica, but no apparent confounder has been identified for chloralkali workers. Potential confounders such as smoking and social class cannot be ruled out however. They might have either increased the risk of lung cancer among miners and chemical workers or decreased it among dentists. The consistency of the findings on lung cancer in different industries suggests a true carcinogenic effect of mercury on the human lung. However, this suggestion is limited by the lack of a dose-response relationship in analyses by latency, duration of employment, or estimated cumulative mercury exposure.

#### *Kidney cancer*

On the basis of the evidence from human toxicology and animal carcinogenicity studies, the kidney is among the most likely target organs of a carcinogenic effect of mercury. No evidence of an increased risk of kidney cancer can be derived from the studies on chloralkali workers (13, 53), and only one study on dentists (57) and a study on nuclear weapons workers (11) reported small increases in risk, on the basis of four deaths in each study. Therefore, the data available do not suggest a strong carcinogenic effect of mercury on the human kidney, but they are not sufficient to exclude it either.

#### *Tumors of the central nervous system*

Great concern about the carcinogenicity of mercury on the central nervous system has been raised by the results of a study on Swedish dentists and dental nurses (54). Although some studies have suggested a similar effect among other groups of dentists (55, 57) and among nuclear weapons workers (11), the studies on chloralkali workers (13, 53), seed disinfectant applicators (59), and a population-based study from Australia (62) do not support this association. Possible explanations for the inconsistency of these results are the different effects of metallic mercury as compared with organic or inorganic species and the existence of other risk factors for tumors of the central nervous system among dentists.

#### *Tumors in other organs*

Three studies on dentists found an increased risk of pancreas cancer (55, 56, 58), and two studies described an increased risk of lymphohematopoietic neoplasms (55, 58). Although the consistency of the results on dentists suggests the presence of a risk factor, the lack of positive findings in other groups exposed to mercury does not support the hypothesis of a role of mercury.

Increased risks of tumors from other sites have been sporadically reported among groups exposed to mercury, for example, prostate cancer among individuals exposed to mercury in the study from Mon-



treval (61). Although these results may have occurred by chance, they should be kept in mind in future investigations.

## Concluding remarks

Occupational and environmental exposure to mercury and mercury compounds occurs in most countries. However, data on the possible carcinogenicity of mercury and its compounds are sparse. The few studies available strongly suggest a genetic activity of mercury compounds in human and other species. Data on long-term animal experiments on methylmercury exposure strongly suggest a carcinogenic response in the kidneys of male mice. Data for other species and other sites are of insufficient quality to exclude other carcinogenic effects. Among other mercury compounds, only mercury chloride has been extensively studied in long-term experiments, and increased tumors were found in the kidney and forestomach of male rats and, to a less extent, female rats and male mice. Metallic mercury has not been adequately tested in experimental animals.

Epidemiologic results are not sufficient, at present, to allow a conclusion to be drawn about the carcinogenicity of mercury and its compounds in humans. Some of the populations that have been studied (chloralkali workers, dentists and dental nurses, and nuclear weapons workers) have probably been exposed to relatively low levels of mercury compounds. Few data are available on groups of workers exposed to high levels of mercury and its compounds, such as hat manufacturing workers and miners. Overall, the possibility of an increased risk of cancer of the lung, the kidney, and the central nervous system cannot be ruled out. Better epidemiologic and experimental studies are clearly needed. In particular it seems important to test metallic mercury adequately in experimental animals and to study occupational groups with substantial exposure (eg, mercury miners).

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