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INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

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Volume 58
Beryllium, Cadmium, Mercury, and Exposures in the Glass Manufacturing Industry

Summary of Data Reported and Evaluation

Last Updated 08/22/1997

BERYLLIUM AND BERYLLIUM COMPOUNDS
(Group 1)

For definition of Groups, see Preamble Evaluation.

VOL.: 58 (1993) (p. 41)

CAS No.: 7440-41-7
Chem. Abstr. Name: Beryllium metal

CAS No.: 12770-50-2
Chem. Abstr. Name: Beryllium-aluminium alloy

CAS No.: 11133-98-5
Chem. Abstr. Name: Beryllium-copper alloy

CAS No.: 1302-52-9
Chem. Abstr. Name: Beryl

CAS No.: 7787-47-5
Chem. Abstr. Name: Beryllium chloride

CAS No.: 7787-49-7
Chem. Abstr. Name: Beryllium fluoride

CAS No.: 13327-32-7
Chem. Abstr. Name: Beryllium hydroxide

CAS No.: 13510-49-1
Chem. Abstr. Name: Beryllium sulfate

CAS No.: 7787-56-6
Chem. Abstr. Name: Beryllium sulfate tetrahydrate

CAS No.: 1304-56-9
Chem. Abstr. Name: Beryllium oxide

CAS No.: 1319-43-3
Chem. Abstr. Name: Beryllium carbonate basic

CAS No.: 13597-99-4
Chem. Abstr. Name: Beryllium nitrate

CAS No.: 7787-55-5
Chem. Abstr. Name: Beryllium nitrate trihydrate

CAS No.: 13510-48-0
Chem. Abstr. Name: Beryllium nitrate tetrahydrate

CAS No.: 13598-15-7

Chem. Abstr. Name: Beryllium phosphate

CAS No.: 13598-00-0
Chem. Abstr. Name: Beryllium silicate

CAS No.: 39413-47-3
Chem. Abstr. Name: Zinc beryllium silicate

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Beryllium is found at low concentrations in the Earth's crust. Since the early twentieth century, it has been produced and used in a variety of applications as the metal, in alloys and as its oxide.

Although only a relatively small number of workers worldwide are potentially exposed to high levels of beryllium, mainly in the refining and machining of the metal and in production of beryllium-containing products, a growing number of workers are potentially exposed to lower levels of beryllium in the aircraft, aerospace, electronics and nuclear industries. Although the range of industrial processes with potential occupational exposure to beryllium has expanded over the past two decades, exposures have generally decreased over the same period.

The most important source of exposure to beryllium in the general environment is the burning of coal.

5.2 Human carcinogenicity

In an early series of cohort mortality studies of workers at two beryllium extraction, production and fabrication facilities in the USA, a consistent, marginally significant excess of deaths from lung cancer was observed. The excess increased with time since first exposure. In a more recent mortality analysis of some 9000 workers at seven beryllium plants in the USA, including the two plants studied previously, a small but significant excess in mortality from lung cancer was found in the total cohort. The risks for lung cancer were consistently higher in those plants in which there was also excess mortality from nonmalignant respiratory disease. Also, the risk for lung cancer increased with time since first exposure and was greater in workers first hired in the period when exposures to beryllium in the work place were relatively uncontrolled. Mortality from cancers at other sites was not increased. The association between lung cancer risk and exposure to beryllium was judged not to be confounded by smoking.

Follow-up of deaths among workers entered into the US Beryllium Case Registry (which registered cases of acute beryllium-related pneumonitis and chronic beryllium-related nonmalignant lung disease, including cases from the plants mentioned above) revealed excess mortality from lung cancer; the excess was greater in those who were entered into the Registry with acute beryllium pneumonitis. Potential confounding by smoking was addressed in several ways and did not appear to explain the increased risk for lung cancer. The results of the follow-up of the Case Registry subjects yielded a higher risk for lung cancer than had been found in the previous cohort mortality study of the seven production facilities.

In a nested case-control study of cancers of the central nervous system among workers at two nuclear facilities in the USA, an increasing risk of cancer of the central nervous system was suggested with longer duration of employment in jobs with more highly ranked exposure to beryllium.

Several aspects of the two most recent cohort studies support the conclusion that the work environment of workers involved in refining, machining and producing beryllium metal and alloys was causally associated with an increased risk of lung cancer: the large number of lung cancer cases, providing a stable estimate of the mortality ratio; the consistency of the lung cancer excess in most of the locations; the greater excess in workers hired before 1950, when exposures to beryllium in the work place were relatively uncontrolled and much higher than in subsequent decades; the highest risk for lung cancer being found in the plant from which the greatest proportion of cases of acute beryllium pneumonitis was provided to the Beryllium Case Registry; the increasing risks with increasing latency; the greater lung cancer risk observed in the Beryllium Case Registry cohort, the highest risk for lung cancer being observed among individuals diagnosed with acute beryllium-induced pneumonitis, who represent a group that had the most intense exposure to beryllium; and the highest risks for lung cancer occurring in the plants where the risk for pneumoconiosis and other respiratory diseases was highest. Aspects of the studies which limit their interpretation are: the absence of any individual measurements of exposures to beryllium, the relatively low excess risk for lung cancer and the absence of any mention of exposure of workers to other lung carcinogens in the work place, although there is no evidence that other lung carcinogens were present.

5.3 Animal carcinogenicity data

Beryl ore and bertrandite ore were tested for carcinogenicity in rats, hamsters and monkeys by inhalation exposure in three experiments in one study. Beryl ore was shown to produce malignant and benign lung tumours in rats. The experiments in hamsters and monkeys were inadequate for evaluation, as were all experiments with bertrandite ore.

In one study in rats by single intratracheal instillation, beryllium metal, passivated beryllium metal (99% beryllium, 0.26% chromium as chromate) and beryllium-aluminium alloy (62% beryllium) produced dose-related increases in the incidence of lung tumours, which were mostly adenocarcinomas and adenomas.Various beryllium compounds were tested by inhalation in five studies in rats, rabbits and monkeys. In two studies in rats, beryllium sulfate tetrahydrate produced lung tumours, which were mostly adenocarcinomas. In one study, both beryllium oxide and beryllium chloride produced dose-related increases in the incidence of malignant epithelial lung tumours in rats. The studies in rabbits and monkeys were considered to be inadequate for evaluation. Beryllium hydroxide and low- and high-temperature-fired beryllium oxide were tested in rats by intratracheal instillation; beryllium hydroxide produced lung adenocarcinomas and adenomas in one study, and low-temperature-fired (below 900 ^{o}C) beryllium oxide produced malignant lung tumours in two studies.

Rabbits given intravenous injections of beryllium metal and various compounds of beryllium (zinc beryllium silicate, beryllium silicate, beryllium oxide and beryllium phosphate) developed osteosarcomas. Similar findings were obtained in rabbits treated by implantation or injection into the bone of beryllium oxide, zinc beryllium silicate and beryllium carbonate.

5.4 Other relevant data

Increased levels of beryllium have been found in the lungs of people exposed up to 20 years previously. In dogs and rats, the lung clearance of beryllium oxide calcined at high temperatures is slower than for that calcined at low temperatures. After inhalation, beryllium also accumulates in tracheobronchial lymph nodes. Gastrointestinal absorption of beryllium and beryllium compounds is very limited. Beryllium accumulates in bone and, to a lesser extent, in the liver. Absorbed beryllium is excreted mostly in the urine.

Beryllium may cause a fatal acute pneumonitis and, after long-term exposure, a chronic, non-caseating granulomatous pulmonary disease with a high rate of fatality; the pathogenesis of the latter disease involves cell-mediated immunological reactions. Susceptibility to chronic beryllium disease varies between individuals, and the disease may develop after low environmental exposures in some people. A similar disease is seen in exposed dogs, guinea-pigs and sensitized rats. Beryllium causes contact dermatitis, which is also associated with cell-mediated immunological reactions.

Beryllium sulfate did not induce micronuclei in the bone marrow of mice treated *in vivo*. Beryllium salts induced sister chromatid exchange and possibly chromosomal aberrations in mammalian cells *in vitro*. Beryllium sulfate induced morphological transformation in a number of different systems. In one report, beryllium chloride induced gene mutation in mammalian cells. In bacteria, beryllium chloride was comutagenic with 9-aminoacridine but not with ultraviolet radiation. Beryllium compounds are not mutagenic in most bacterial systems. In assays of differential toxicity, beryllium salts gave mixed results. In cultured mammalian cells, low-temperature-fired beryllium oxide induced single-strand breaks in DNA and morphological transformation; an unspecified beryllium oxide did not induce sister chromatid exchange in mammalian cells or differential toxicity or mutation in bacteria.

5.5 Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of beryllium and beryllium compounds.

There is *sufficient evidence* in experimental animals for the carcinogenicity of beryllium and beryllium compounds.

Overall evaluation

Beryllium and beryllium compounds are *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Suppl. 7 (1987) (p. 127)

Synonyms for Beryllium metal

- Beryllium
- Beryllium-9
- Beryllium element
- Beryllium metallic
- Glucinium
- Glucinum

Synonyms for Beryllium-aluminium alloy

- Aluminium alloy, nonbase, Al,Be
- Aluminium-beryllium alloy

Synonyms for Beryllium-copper alloy

- Copper alloy, base, Cu, Be
- Copper-beryllium alloy

Synonyms for Beryl

- Beryllium aluminosilicate
- Beryllium aluminium silicate

Synonym for Beryllium chloride

- Beryllium dichloride

Synonym for Beryllium fluoride

- Beryllium difluoride

Synonym for Beryllium hydroxide

- Beryllium dihydroxide

Synonym for Beryllium sulfate

- Sulfuric acid, beryllium salt (1:1)

Synonym for Beryllium sulfate tetrahydrate

- Sulfuric acid, beryllium salt (1:1), tetrahydrate

Synonyms for Beryllium oxide

- Beryllia
- Beryllium monoxide
- Thermalox™

Synonym for Beryllium carbonate basic

- Carbonic acid, beryllium salt, mixture with beryllium hydroxide ($Be(OH)_2$)

Synonyms for Beryllium nitrate

- Beryllium dinitrate
- Nitric acid, beryllium salt

Synonym for Beryllium nitrate trihydrate

- Nitric acid, beryllium salt, trihydrate

Synonyms for Beryllium nitrate tetrahydrate

- Beryllium dinitrate tetrahydrate
- Nitric acid, beryllium salt, tetrahydrate

Synonym for Beryllium phosphate

- Phosphoric acid, beryllium salt (1:1)

Synonyms for Beryllium silicate

- Phenazite
- Phenakite

Synonym for Zinc beryllium silicate

- Silicic acid, beryllium zinc salt

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CADMIUM AND CADMIUM COMPOUNDS
(Group 1)

For definition of Groups, see Preamble Evaluation.

VOL.: 58 (1993) (p. 119)

CAS No.: 7440-43-9
Chem. Abstr. Name: Cadmium

CAS No.: 543-90-8
Chem. Abstr. Name: Cadmium acetate

CAS No.: 513-78-0
Chem. Abstr. Name: Cadmium carbonate

CAS No.: 10108-64-2
Chem. Abstr. Name: Cadmium chloride

CAS No.: 21041-95-2
Chem. Abstr. Name: Cadmium hydroxide

CAS No.: 10325-94-7
Chem. Abstr. Name: Cadmium nitrate

CAS No.: 2223-93-0
Chem. Abstr. Name: Cadmium stearate

CAS No.: 10124-36-4
Chem. Abstr. Name: Cadmium sulfate

CAS No.: 1306-23-6
Chem. Abstr. Name: Cadmium sulfide

CAS No.: 1306-19-0
Chem. Abstr. Name: Cadmium oxide

Cadmium-copper alloys

CAS No.: 37364-06-0

CAS No.: 12685-29-9

CAS No.: 132295-56-8

CAS No.: 132295-57-9

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Cadmium is found at low concentrations in the Earth's crust, mainly as the sulfide in zinc-containing mineral deposits. Since the early twentieth century, it has been produced and used in a variety of applications in alloys and in compounds. Among the important compounds of cadmium are cadmium oxide (used in batteries, as an intermediate and catalyst and in electroplating), cadmium sulfide (used as a pigment), cadmium sulfate (used as an intermediate and in electroplating) and cadmium stearate (used as a plastics stabilizer).

Occupational exposure to cadmium and cadmium compounds occurs mainly in the form of airborne dust and fume. Occupations in which the highest potential exposures occur include cadmium production and refining, nickel-cadmium battery manufacture, cadmium pigment manufacture and formulation, cadmium alloy production, mechanical plating, zinc smelting, soldering and polyvinylchloride compounding. Although levels vary widely among the different industries, occupational exposures generally have decreased in the last two decades.

Urinary and blood cadmium concentrations are generally much lower in non-occupationally exposed people, for whom the most important sources of exposure are cigarette smoking and, especially in polluted areas, eating certain foods (e.g. rice). Acidification of cadmium-containing soils and sediments may increase the concentrations of cadmium in surface waters and crops.

5.2 Human carcinogenicity data

Following a report of the occurrence of prostatic cancers in a small group of workers employed before 1965 in a plant manufacturing nickel-cadmium batteries in the United Kingdom, a series of cohort analyses were undertaken, which did not confirm the excess among the remaining workers; however, an increase in mortality rates from lung cancer was detected. A small cohort working in the same industry was studied in Sweden: no excess of prostatic cancer was detected, but a nonsignificant increase in mortality from lung cancer was found among workers who had the longest duration of employment and latency.

Two small copper-cadmium alloy plants were studied in the United Kingdom. The rate of mortality from lung cancer was increased in one of them but decreased in the other. A case-control analysis of lung cancer did not show any association with exposure to cadmium. No increase in mortality from prostatic cancer was found in these two plants, while in a similar plant in Sweden a nonsignificant excess was detected.

Excess mortality from lung cancer was reported among workers employed in a US cadmium recovery plant, and a dose-response relationship was demonstrated between estimated cumulative exposure to cadmium and lung cancer risk. The latter was unlikely to be due to confounding by cigarette smoking and persisted among workers employed after 1940, when little arsenic was present in feedstock. Excess mortality from prostatic cancer was found initially, but the relative risk diminished and became nonsignificant with further follow-up.

In a large cohort of workers from 17 cadmium processing plants in the United Kingdom, decreased mortality from prostatic cancer was observed, while that from lung cancer was increased in the overall cohort and there were suggested trends with duration of employment and with intensity of exposure. The increase in lung cancer risk was stronger in the small proportion of workers with high cadmium exposure. Confounding by concomitant exposure to other cancer determinants, including arsenic, was not controlled for. Excess mortality from stomach cancer, which was not related to intensity of cadmium exposure, was also reported among these workers.

A number of early studies reported an increased risk for prostatic cancer among cadmium workers, but the results of later studies were not consistent. Early and recent studies provide consistent evidence that the risk for lung cancer is increased among workers exposed to cadmium.

Constraints that influence the assessment of both lung and prostatic cancer risk are that the number of long-term, highly exposed workers is small, the historical data on exposure to cadmium are limited, particularly for the non-US plants, and the ability to define and examine a gradient of cumulative exposure varies across studies. Additionally, for cohort studies, prostatic cancer poses special difficulties in that it is subject to the possibility of detection bias. Confounding by cigarette smoking in relation to lung cancer was addressed directly only in the study from the USA, but some other studies provided analyses based on internal comparisons, which are not likely to be affected by this problem. Control of the confounding effect of co-exposure to other metals, particularly arsenic and nickel, was limited; however, the analyses in which an attempt was made to distinguish US cadmium-exposed workers with different levels of exposure to arsenic indicated that the increase in lung cancer risk was unlikely to be explained by exposure to arsenic.

5.3 Animal carcinogenicity data

Cadmium chloride, cadmium sulfate and cadmium acetate have been tested by oral administration in several studies in mice and rats. Most of the studies were inadequate for an evaluation of carcinogenicity. Two adequate studies on cadmium chloride in rats are available. In one study with controlled dietary zinc levels in male rats, cadmium chloride produced dose-related increases in the incidences of leukaemia, interstitial-cell tumours of the testis and proliferative lesions of the prostate. In another study on cadmium chloride in rats, in which zinc levels in diet were not controlled, no increase in tumour incidence was seen.

In two inhalation studies in rats, malignant lung tumours were produced by cadmium chloride, cadmium sulfide/sulfate, cadmium sulfate and cadmium oxide fume and dust at low levels of exposure for short durations. In one study in rats by intratracheal instillation, malignant pulmonary tumours were produced by cadmium sulfide and cadmium chloride, but not by cadmium oxide. In one inhalation study in mice of cadmium chloride, cadmium sulfide/sulfate, cadmium sulfate and cadmium oxide fume and dust, some groups exposed to cadmium oxide fume or dust had increased incidences of lung tumours. In one inhalation study in hamsters of cadmium chloride, cadmium sulfide/sulfate, cadmium sulfate and cadmium oxide fume and dust, no increase in the incidence of lung tumours was found.

In several studies, single or multiple subcutaneous injections of cadmium chloride, cadmium sulfide, cadmium sulfate and cadmium oxide and of cadmium-containing rat liver ferritin caused local sarcomas in rats. Mice appear to be generally less susceptible than rats to induction of local tumours by cadmium compounds. Cadmium powder, cadmium chloride and cadmium sulfide produced local sarcomas in rats following intramuscular administration. In a single study by intraperitoneal injection in rats, cadmium sulfide induced malignant tumours within the peritoneal cavity. Cadmium chloride in mice and rats and cadmium sulfate and cadmium-precipitated rat liver ferritin in rats produced testicular interstitial tumours after subcutaneous administration. Dietary zinc deficiency enhanced the multiplicity of cadmium-induced interstitial-cell tumours of the testis and increased the incidence of local tumours at the site of subcutaneous cadmium injections. Subcutaneous injection of cadmium chloride to rats produced tumours of the prostate but only at doses below the level that induced cadmium-induced testicular degeneration or when such degeneration was prevented by concurrent exposure to zinc. Intramuscular administration of cadmium chloride also induced prostatic tumours in rats. Subcutaneous administration of cadmium chloride increased the incidence of pancreatic tumours in rats in one study and decreased the incidence in another.

In limited studies in rats, injection of cadmium chloride into the prostate produced malignant prostatic tumours.

Administration of excess zinc by inhalation, parenteral and oral routes has been shown to reduce the carcinogenic potential of cadmium after exposure systemically or by inhalation. When combined with known carcinogens, cadmium enhanced, suppressed or had no effect on tumour incidence, depending on a complex set of circumstances including, at least in part, the dose, time sequence of administration, site of tumour and route of administration.

5.4 Other relevant data

Cadmium enters the body mainly by inhalation and by ingestion. Fractional intestinal absorption is influenced by dietary factors and increases with dietary cadmium concentration. Pulmonary fractional absorption depends partly on the solubility *in vivo* of the compound. Cadmium induces synthesis of metallothionein, a low-molecular-weight protein that binds cadmium primarily in the liver and kidney. Metallothionein production can also be induced by e.g. zinc. When metallothionein-bound cadmium is released into the blood, it is filtered through the glomeruli and then reabsorbed in the proximal tubules. In certain mammalian tissues, such as rat ventral prostate, hamster ovary and rat, mouse and monkey testis, the concentrations of metallothionein are low and its synthesis is not induced by exposure to cadmium. Most of the body burden of cadmium is retained in the kidneys and the liver. The half-life of cadmium in human kidneys is probably 10-20 years. Cadmium concentrations in whole blood are affected by both recent exposure and body burden. Excretion occurs mainly via the urine. Urinary excretion of cadmium by individuals without renal dysfunction primarily reflects the amount of cadmium retained in the kidneys.

The target organs for cadmium toxicity depend on the type of exposure. Inhalation of cadmium can lead to chronic obstructive airway disease. Following long-term exposure, renal tubular and glomerular dysfunction can develop. Renal function can deteriorate further, even after cessation of exposure to cadmium. Cadmium can suppress cell-mediated immune responses *in vitro*.

Parenteral administration of cadmium salts produces adverse effects on the testes, ovaries, placenta and embryo in experimental animals; many of these effects have been shown to be preventable by administration of zinc compounds. Administration of cadmium at doses that affect placental morphology or function induces fetal anaemia, growth retardation, teratogenicity and embryonic and fetal death in experimental animals. Reproductive and developmental toxicity have been reported following exposure to cadmium compounds by oral and inhalation routes, but the effects are generally much less severe than after parenteral administration.

In three of five studies, the frequencies of chromosomal aberration were increased in peripheral blood lymphocytes of workers exposed to cadmium in the metal industry, where they were usually also exposed to other metals. No effect of cadmium was observed in a limited study of workers from a Swedish alkaline battery factory. In two studies of cadmium pigment plant workers, no increase in the frequency of chromosomal aberrations was observed. No increase in the frequency of sister chromatid exchange was seen in one study of workers exposed to cadmium.

In one of two limited studies of *itai-itai* patients, increased frequency and severity of chromosomal aberrations were observed. In one study, no increase in sister chromatid exchange frequency was observed in people living in a cadmium-polluted region of Japan. In a study of subjects living in a cadmium-polluted region of China, there were small but significant increases in chromosomal aberration frequency. A significant dose-effect relationship between urinary levels of cadmium and chromosomal aberration frequency was also observed, and more severe aberration types were observed in individuals with high urinary levels of cadmium.

In those studies in which significant responses were observed, the chromosomal aberrations tended to occur in the more heavily exposed groups and were of more complex types.

Chromosomal aberrations and aneuploidy were observed in animals exposed to cadmium chloride *in vivo*. Dominant lethal mutations were generally not induced in mice.

Cadmium chloride damages DNA of human cells *in vitro*. In the few studies available, chromosomal aberrations were observed in human cells treated with cadmium sulfide but not in those treated with cadmium chloride. Indications of aneuploidy were observed in human fibroblasts after treatment with cadmium chloride.

Studies using cultured animal cells show that exposure to cadmium compounds damages genetic material. DNA strand breaks, mutations, chromosomal damage and cell transformation have been observed *in vitro*. Cadmium compounds inhibit the repair of DNA damaged by other agents, thereby enhancing their genotoxicity.

Mutations have generally not been observed in *Drosophila* or bacteria; however, a weak response was observed in some studies in bacteria and there is evidence for cadmium-induced DNA damage in bacteria.

5.5 Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of cadmium and cadmium compounds.

There is *sufficient evidence* in experimental animals for the carcinogenicity of cadmium compounds.

There is *limited evidence* in experimental animals for the carcinogenicity of cadmium metal.

In making the overall evaluation, the Working Group took into consideration the evidence that ionic cadmium causes genotoxic effects in a variety of types of eukaryotic cells, including human cells.

Overall evaluation

Cadmium and cadmium compounds are *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Suppl. 7 (1987) (p. 139)

Synonyms for Cadmium

- Cadmium metal
- CI 77180

Synonyms for cadmium acetate

- Acetic acid, cadmium salt
- Bis(acetoxy)cadmium
- Cadmium(II)acetate
- Cadmium diacetate
- Cadmium ethanoate
- CI 77185

Synonyms for cadmium carbonate

- Carbonic acid, cadmium salt
- Cadmium carbonate ($CdCO_3$)
- Cadmium monocarbonate
- Chemcarb
- Kalcit
- Mikrokalcit
- Supermikrokalcit

Synonyms for Cadmium chloride

- Cadmium dichloride
- Dichlorocadmium

Synonyms for Cadmium hydroxide

- Cadmium hydroxide ($Cd(OH)_2$)
- Cadmium dihydroxide

Synonyms for Cadmium nitrate

- Nitric acid, cadmium salt
- Cadmium dinitrate
- Cadmium(II) nitrate
- Cadmium nitrate ($Cd(NO_3)_2$)

Synonyms for Cadmium stearate

- Alaixol II
- Cadmium distearate
- Cadmium octadecanoate
- Cadmium(II) stearate
- Octadecanoic acid
- Cadmium salt
- SCD
- Stabilisator SCD
- Stabilizer SCD
- Stearic acid, cadmium salt

Synonyms for Cadmium sulfate

- Cadmium monosulfate
- Sulfuric acid, cadmium salt (1:1)

Synonyms for Cadmium sulfide

- Cadmium monosulfide
- Cadmium orange
- Cadmium yellow
- CI 77199

Synonym for Cadmium oxide

- Cadmium monoxide

Synonyms for cadmium-copper alloys

- Copper alloy base, Cu 99.60-100, CD 0.1-0.3
- Coper alloy, base, Cu 99.75-100, Cd 0.05-0.15
- Cadmium nonbase, Cd,Cu
- Copper base, Cu,Cd
- IMI 143
- UNS C14300
- UNS C14310

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MERCURY AND MERCURY COMPOUNDS
Methylmercury compounds (Group 2B)
Metallic mercury and inorganic mercury compounds (Group 3)

For definition of Groups, see Preamble Evaluation.

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CAS No.: 7439-97-6
Chem. Abstr. Name: Mercury metal

CAS No.: 1600-27-7
Chem. Abstr. Name: Mercuric acetate

CAS No.: 7487-94-7
Chem. Abstr. Name: Mercuric chloride

CAS No.: 21908-53-3
Chem. Abstr. Name: Mercuric oxide

CAS No.: 593-74-8
Chem. Abstr. Name: Dimethylmercury

CAS No.: 115-09-3
Chem. Abstr. Name: Methylmercury chloride

CAS No.: 62-38-4
Chem. Abstr. Name: Phenylmercury acetate

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.

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 phenyl-mercury 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

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.

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)*.

For definition of the italicized terms, see Preamble Evaluation.

Synonyms for Mercury metal

- Colloidal mercury
- Hydrargyrum
- Liquid silver
- Quecksilber
- Quicksilver

Synonyms for Mercuric acetate

- Acetic acid, mercury (2+) salt
- Bis(acetyloxy)mercury
- Diacetoxymercury
- Mercuri, diacetic acid
- Mercury acetate
- Mercuric diacetate
- Mercury diacetate

Synonyms for Mercuric chloride

- Abavit B
- Bichloride of mercury
- Calochlor
- Corrosive sublimate
- Corrosive mercury chloride
- CRC
- Dichloromercury
- Mercuric bichloride
- Mercuric dichloride
- Mercury bichloride
- Mercury chloride
- Mercury(2+) chloride
- Mercury(II) chloride
- Mercury dichloride
- Mercury perchloride
- Sublimate
- Sulem

Synonyms for Mercuric oxide

- Mercuric oxide (HgO)
- Mercury monoxide
- Mercury oxide
- Mercury oxide (HgO)
- Mercury(II) oxide
- Mercury(2+) oxide
- Red mercuric oxide
- Santar
- Yellow mercuric oxide

Synonym for Dimethylmercury

- Methyl mercury

Synonyms for Methylmercury chloride

- Caspan
- Chloromethylmercury
- Mercury methyl chloride
- Methylmercuric chloride
- Methylmercury monochloride
- Monomethyl mercury chloride

Synonyms for Phenylmercury acetate

- Acetato-*O*-phenylmercury
- Acetatophenylmercury
- Acetic acid, phenyl mercury derivative
- (Acetoxymercurio)benzene
- Acetoxyphenylmercury
- Mercuriphenyl acetate
- Phenylmercuric acetate
- Phenylmercury(II) acetate

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EXPOSURES IN THE GLASS MANUFACTURING INDUSTRY
Manufacture of art glass, glass containers and pressed ware (Group 2A)
Occupational exposures in flat-glass and special glass manufacture (Group 3)

For definition of Groups, see Preamble Evaluation.

4. Summary of Data Reported and Evaluation

4.1 Exposure data

There are five main sectors in the glass manufacturing industry: flat glass, container and pressed ware, art glass, special glass (e.g. optical, ophthalmic, electronic) and fibre glass (which is not considered here). The basic steps in the manufacture of glass products are melting, fining, homogenization, annealing and forming. Art and special glasses are produced by pot processes, involving manual batch handling. Art glass production has changed little with time and, for the most part, still involves blowing by mouth. During the twentieth century, the production of flat glass and container glass has evolved from traditional batch processes to highly automated processes. The modern production of flat glass is the most highly automated and usually utilizes tank melting with the continuous feeding of batch ingredients and the float (Pilkington) process for forming. The production of containers and pressed ware has also become increasingly mechanized, with mechanical blowing or pressing of the molten glass.

Exposure to lead, arsenic and antimony oxides occurs primarily in sectors of the industry where traditional, non-mechanized techniques are used, such as in the production of crystal and other art glasses. Other potential exposures in glass manufacture include silica, asbestos, other metal oxides and polycyclic aromatic hydrocarbons.

4.2 Human carcinogenicity data

Four cohort studies of workers involved in glass manufacture - at a plant in Italy producing glass containers, among ceramics and glass workers in Austria, at two glass factories in Finland and among art glass-workers in Sweden - found increased risks for lung cancer. Population-based case-control studies in Sweden and Canada also found increased risks for lung cancer in glass-workers; a population-based case-control study in China found a significantly increased risk for lung cancer in female glass-workers and a nonsignificantly decreased risk in male glass, ceramics and enamelled product workers. None of the studies was specifically informative with respect to work in the flat-glass manufacturing industry. It is unlikely that the increased risk for lung cancer can be explained by nonoccupational risk factors such as smoking, in view of the consistency and magnitude of the findings, which were obtained in studies of various designs in different countries. When smoking habits were addressed in one of the studies, the estimated relative risk for lung cancer was increased.

In general, no distinction was made in these studies between different components of the glass manufacturing industry. The only subgroup of glass-workers for whom specific findings were available was glass-blowers. Population-based case-control studies in Sweden on glass-workers and in Canada on people exposed to glass dust found small increased risks for stomach cancer, whereas in three cohort studies of glass-workers in Italy, Austria and Finland the risks for stomach cancer were not increased; in two of the cohort studies, the numbers of cases were small. Only the cohort study in Finland and the case-control study in Sweden specifically reported findings on stomach cancer in glass-blowers; both showed stronger increases in risk in glass-blowers than in glass-workers in general.

The three cohort studies in Austria, Finland and Sweden showed little evidence of an increased risk for intestinal cancer. A Swedish population-based case-control study of colon cancer found a small increase in risk in glass-workers in general but a stronger increase in glass-blowers.

Two population-based case-control studies, in Canada and the USA, showed non-significantly increased risks for urinary bladder cancer in glass-workers, but the numbers of cases were small. An Italian cohort study showed an increased risk for laryngeal cancer in glass-workers. In the Finnish cohort study, an increased risk was seen for basal-cell carcinomas of the skin in male workers.

The evidence that favours a causal association between exposures in the glass manufacturing industry and cancer is: a reasonably consistent association with lung cancer in all four cohort studies; a similar though less consistent association with lung cancer in three case-control studies; a larger lung cancer risk than can reasonably be explained by non-occupational confounding factors; the presence of human lung carcinogens in some components of the glass manufacturing industry; and the finding of an increased risk for stomach cancers in several cohort and case-control studies. Findings that limit the interpretation of causality include: the poorly characterized and heterogeneous exposures of workers in the glass manufacturing industry, which are likely to result in a weak or null association between exposure and cancer risk in some studies; the absence of demonstrated dose-response relationships; the fact that, in some studies, risk estimates were made for the combination of glass-workers and workers in other industries, thereby diminishing the degree to which results can be interpreted for the glass manufacturing industry itself; and the relatively few studies of workers in the glass manufacturing industry.

4.3 Other relevant data

A single study reported an increased frequency of chromosomal aberrations in peripheral blood lymphocytes of subjects working in a glass factory in the Czech Republic.

4.4 Evaluation

There is *limited evidence* that occupational exposures in the manufacture of art glass, glass containers and pressed ware are carcinogenic.
This evaluation does not apply to glass fibre, which was evaluated previously (Vol. 43, 1988). The Working Group could not identify the specific exposure, process or activity that is most likely to be responsible for the excess risk.

There is *inadequate evidence* that occupational exposures in flat-glass and special glass manufacture are carcinogenic.

Overall evaluations

The manufacture of art glass, glass containers and pressed ware entails exposures that are *probably carcinogenic to humans (Group 2A)*.

Occupational exposures in flat-glass and special glass manufacture are *not classifiable as to their carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Vol. 43 (1988) (p. 39)

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